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S3 Leitlinie
Epidemiologie, Diagnostik, Therapie, Prävention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei Erwachsenen (HWI)

Aktualisierung 2024
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AWMF-Register-Nr. 043/044
Version 3.0

Erstellungsdatum	2010
Überprüfung	2017
Überprüfung	2023
Nächste geplante Überprüfung	2029

Evidenztabellen

DGU Deutsche Gesellschaft für Urologie e.V.

Das dieser Veröffentlichung zugrundliegende Projekt wurde mit Mitteln des Innovationsausschusses beim Gemeinsamen Bundesausschuss unter dem Förderkennzeichen 01VSF21020 gefördert.

Inhaltsverzeichnis

1. Informationen zum Leitlinienreport

1.1 Herausgeber und Federführung

Herausgeber dieses Leitlinienreports ist die Deutsche Gesellschaft für Urologie e. V. (DGU). Der DGU oblag die Federführung und Erstellung der Leitlinie.

1.2 Finanzierung der Leitlinie

Das dieser Veröffentlichung zugrundliegende Projekt wurde mit Mitteln des Innovationsausschusses beim Gemeinsamen Bundesausschuss (G-BA) unter dem Förderkennzeichen 01VSF21020 gefördert. Alle ärztlichen Mitglieder der Leitliniengruppe arbeiteten ehrenamtlich ohne Vergütung. Reisekosten und anderweitige Auslagen wurden entsprechend über die Drittmittelgelder des Innovationsfonds abgerechnet. Die wissenschaftliche und organisatorische Unterstützung erfolgte durch das Team UroEvidence der DGU-Geschäftsstelle Berlin.

1.3 Kontakt

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1.4 Zitierweise

Deutsche Gesellschaft für Urologie e. V. (Hrsg.): S3 Leitlinie: Epidemiologie, Diagnostik, Therapie, Prävention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei Erwachsenen – Aktualisierung 2024. Langversion, 3.0, AWMF Register-nummer: 043/044, https://register.awmf.org/de/leitlinien/detail/043-044
(Zugriff am: TT.MM.JJ).

1.5 Weitere Dokumente zur Leitlinie

Bei diesem Dokument handelt es sich um die Langversion der S3-Leitlinie Epidemiologie, Diagnostik, Therapie, Prävention und Management

unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei Erwachsenen, welche über folgende Seiten zugänglich ist:

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): http://www.awmf.org/leitlinien/aktuelle-leitlinien.html

Die Evidenztabellen sind u. a. die methodische Grundlage zu folgenden Dokumenten:

- Kurzfassung der Leitlinie
- Langfassung der Leitlinie
- Leitlinienreport

1.6 Abkürzungsverzeichnis

Tabelle 1: Abkürzungen

Abkürzung	Bedeutung
ACSS	Acute cystitis symptom score
AE	Adverse Events
AGV	Abwendbar gefährliche Verläufe
ARESC	An international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections
ASB	Asymptomatische Bakteriurie
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BF	Blickfeld
CI	Confidence intervall
CFU	colony-forming units
CLED-Agar	Cystine Lactose Electrolyte Deficient-Agar
CLSI	Clinical and Laboratory Standards Institute
CPSI	Chronischer Prostatitis Symptomen Index
CS	Chondroitin Sulfate
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin
DHFR	Dihydrofolat-Reductase

DHPS	Dihydropteroat-Synthetase
DMPA	Depot-Medroxyprogesteron-Acetat
DOR	Diagnostic Odds Ratio
EAU	European Association of Urology
ECO.SENS	An International Survey of the Antimicrobial Susceptibility of Urinary Pathogens.
EMA	European Medicines Agency
ESBL	Extended-spectrum beta-lactamases
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	U.A. Food and Drug Administration
GAG	Glucosaminglykan
GBA	Gemeinsamer Bundesausschuss
GCP	Good clinical practice
GF	Glomeruläre Filtration
GI	Gastrointestinal
HA	Hyaluronic Acid
HMO	Health Maintenance Organisation
HWI	Harnwegsinfektion
I	increased („sensibel bei erhöhter Exposition“)
ICSI	Institute for Clinical System Improvement
IPSS	Internationaler Prostata Symptomen Score
IRR	Inzidenz Rate Ratio
IVA	Intravesical Antimicrobials
k.A.	Keine Angaben
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KBE	Kolonie bildende Einheiten
KI	Konfidenzintervall

KPC	Klebsiella pneumoniae Carbapenemasen
LOE	Level of Evidence
LL	Leitlinie
LORE	Lokales Resistenzprofil bei unkomplizierten Harnwegsinfektionen
LR	Likelihood Ratio
MD	Mean Difference
MHK	Minimale Hemmkonzentration
MRSA	Methicillinresistenter Staphylococcus aureus
MSCC	midstream clean-catch technique
MSU	midstream urine
n.a.	Not applicable
ND	Not detected, not determined
NICE	National Institute for Health and Care Excellence
NNH	Number needed to harm
NNT	Number needed to treat
NPG	Nominaler Gruppenprozess
NPV	Negative predictive value (negativ prädiktiver Wert)
OR	Odds Ratio (Chancenverhältnis)
PBP	Penicillinbindeproteine
PLZ	Postleitzahl
PPV	Positive predictive value (positiv prädiktiver Wert)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
R	Resistent
RCT	randomized controlled trial (randomisiert kontrollierte Studie), Plural: RCTs
REDARES	Reduktion von Antibiotikaresistenzen durch leitliniengerechte Behandlung von Patienten mit unkompliziertem Harnwegsinfekt in der ambulanten Versorgung

REHIP	Resitenzsituation bei unkomplizierten Harnwegsinfektionen in der Primärversorgung
RoB	Risk of Bias
RR	Risk Ratio
rUTI	Recurrent Urinary Tract Infection
S	Sensibel
Sens.	Sensitivität
SHV	SHV-Betalactamase
SIGN	Scottish Intercollegiate Guidance Network
SMD	Standardized Mean Difference
SMZ	Sulfamethoxazole
Spez.	Spezifität
STD	Sexually transmitted disease
TEM	TEM-Betalactamase
TMP	Trimethoprim
TMP-SMZ	Trimethoprim-sulfamethoxazole
UAW	Unerwünschte Arzneimittelwirkung
UTI	Urinary tract infection
VRE	Vancomycin-resistente Enterokokken
VUR	Vesikouretraler Reflux
WBC	White blood counts
y	year

2. Schema der Evidenzklassifikation

Die Bewertung des Evidenzlevels der herangezogenen Literatur, erfolgte in der alten Leitlinie nach den Oxford Centre for Evidence-based Medicine Kriterien von 2009 (siehe Tabelle 2), weshalb auch bei dieser Aktualisierung weiterhin so verfahren wurde https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009.

Die Einstufung des jeweiligen Evidenzlevels einer Empfehlung oder Statements richtete sich jeweils nach der Quelle des höchsten Evidenzlevels.

Tabelle 2: Evidenzgrad (I-V) nach Oxford Centre of Evidence Based Medicine [1] (Übersetzt durch UroEvidence)

Studien zu Therapie/Prävention/Ätiologie	
Evidenz-grad	**Evidenzgraduierung 2023: Beschreibung**
Ia	Systematische Übersichtsarbeit (mit hohem Homogenitätsgrad) mit randomisierten klinischen Studien (RCTs)
Ib	Einzelne RCT (mit engem Konfidenzintervall)
Ic	Alle-oder-Keiner-Prinzip
IIa	Systematische Übersichtsarbeit (mit hohem Homogenitätsgrad) mit Kohortenstudien
IIb	Einzelne Kohortenstudie (einschließlich RCT von minderer Qualität, z. B. <80 % Follow-up)
IIc	Wirkungsstudien, ökologische Studien
IIIa	Systematische Übersichtsarbeit (mit hohem Homogenitätsgrad) mit Fall-Kontroll-Studien
IIIb	Eine Fall-Kontrollstudie
IV	Fallserien oder Kohorten- und Fall-Kontroll-Studien minderer Qualität)
V	Expertenmeinung ohne explizite kritische Bewertung der Evidenz oder basierend auf physiologischen Modellen/Laborforschung
Studien zu Diagnostik	
Evidenz-grad	**Evidenzgraduierung 2023: Beschreibung**
Ia	Systematische Übersichtsarbeit mit Level 1 Diagnostik (mit hohem Homogenitätsgrad), diagnostische Entscheidungsregel begründet auf Ib Studien, validiert in verschiedenen klinischen Zentren
Ib	Validierungs- Kohortenstudie mit gutem Referenzstandard oder diagnostische Entscheidungsregel, validiert in einem Zentrum
Ic	Alle-oder-Keiner-Prinzip (absolute SpPins und SnNouts)
IIa	Systematische Übersichtsarbeit mit Level >2 Diagnostikstudien (mit hohem Homogenitätsgrad)
IIb	Explorative Kohortenstudie mit gutem Referenzstandard, diagnostische Entscheidungsregel nach Herleitung oder nur validiert nach split-sample oder Datenbanken
IIIa	Systematische Übersichtsarbeit mit Level 3b Diagnostikstudien (mit hohem Homogenitätsgrad)
IIIb	Nicht-konsekutive Studie; oder ohne Konsistenz der angewendeten Referenzstandards
IV	Fall-Kontrollstudie, schlechte oder nicht unabhängige Referenzstandards
V	Expertenmeinung ohne explizite kritische Bewertung der Evidenz oder basierend auf physiologischen Modellen/Laborforschung

3. Klinische Studien

3.1 Abgeschlossene Studien

Einschluss n= 83 Studien (n=79 in Clinicaltrials.gov, n=4 WHO-Register)

Nummer	Name	Status	Studienplan	Ergebnis
Clinicaltrials.gov				
NCT04055675	Urinalysis Results in Healthy Individuals	Recruitment Status: Completed Last Update Posted: June 18, 2020	Condition: Asymptomatic Bacteriuria Asymptomatic Pyuria Intervention/treatment: • Diagnostic Test: Urine dipstick test Allocation: Observational, cohort Primary Purpose: dignostic Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: all	Results published.
NCT03151603	Reducing Antibiotic Use for Uncomplicated Urinary Tract Infection in General Practice by Treatment With Uva Ursi (UU)- a Comparative Effectiveness Trial (REGATTA)	Recruitment Status: Completed Last Update Posted : November 27, 2019	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Arctuvan • Drug: Fosfomycin • Drug: Placebo to Arctuvan • Drug: Placebo to Fosfomycin Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 Years to 75 Years (Adult, Older Adult) Sexes: Female	Ergebnisse bereits publiziert.
NCT03543436	Temocillin Versus a Carbapenem as Initial Intravenous Treatment	Recruitment Status: Completed	Condition: Urinary Tract Infections Intervention/treatment:	No results published.

	for ESBL Related Urinary Tract Infections (TEMO-CARB)	Last Update Posted: April 19, 2021	• Drug: Temocillin • Drug: meropenem or imipenem Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: all	
NCT04731090	Standard Antibiotic Versus Enhanced Prophylactic Measures on Rate of Urinary Tract Infection After Flexible Ureteroscopy	Recruitment Status: Completed Last Update Posted: January 29, 2021	Condition: Urinary Tract Infections Intervention/treatment: • Drug: IV fluoroquinolone 1 hour preoperatively and oral antibiotics for 24h postoperatively. • Other: Urine culture, antibiotic prophylaxis and hydrophilic-coated ureteral access sheaths Allocation: randomized Primary Purpose: prevention Ages Eligible for Study: 20 Years to 80 years (Adult, Older Adult) Sexes: all	No results published.
NCT03497598	Preventing Recurrent Urinary Tract Infections With α-D-mannose (PUTIM)	Recruitment Status: Terminated (not enough patients) Last Update Posted: September 2, 2020	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Mannose • Drug: Lactose Allocation: randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: female	No results published.
NCT03256825	Rapid Urinary Tract Infection Diagnosis and Real-time Antimicrobial Stewardship Decision	Recruitment Status: Completed Last Update Posted:	Condition: Urinary Tract Infections Intervention/treatment: • Diagnostic Test: Rapid diagnostics alone	No results published.

	Support (RUDE)	May 12, 2020	• Other: Real-time antimicrobial stewardship decision support Allocation: Non-Randomized Primary Purpose: diagnostic Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	
NCT03042273	High Strength Cranberry Supplementation for Prevention of Recurrent Urinary Tract Infection	Recruitment Status: Completed Last Update Posted: March 18, 2020	Condition: Urinary Tract Infections Intervention/treatment: • Dietary Supplement: High Strength Cranberry • Dietary Supplement: Placebo Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 18 years to 65 years (Adult, Older Adult) Sexes: female	No results published.
NCT02959957	Disturbance of the Intestinal Microbiota by Temocillin vs Cefotaxime in Treatment of Febrile Urinary Tract Infections	Recruitment Status: Completed Last Update Posted: September 16, 2019	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Temocillin • Drug: Cefotaxime Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.
NCT02835456	Does Micropattern on Urinary Catheter Surface Reduce Urinary Tract Infections? (SHARKLET)	Recruitment Status: Completed Last Update Posted: January 4, 2017	Condition: Catheter Associated Urinary Tract Infections Intervention/treatment: • Device: Sharklet Catheter insertion • device: Silicone Foley Catheter insertion	Abstract publication: https://university.auanet.org/abstract_detail.cfm?id=PD12-

			Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	12&meetingID=17 BOS
NCT04315129	Smart Catheter: A Novel Biosensor for Early Detection of Catheter Associated Urinary Tract Infection	Recruitment Status: Completed Last Update Posted: September 2, 2021	Condition: Catheter Associated Urinary Tract Infections Intervention/treatment: • Diagnostic Test: Smart Catheter Biosensor Allocation: N/A Primary Purpose: dignostic Ages Eligible for Study: 18 years to 99 years (Adult, Older Adult) Sexes: all	No results published.
NCT03354598	Oral Sulopenem-etzadroxil/Probenecid Versus Ciprofloxacin for Uncomplicated Urinary Tract Infection in Adult Women	Recruitment Status: Completed Last Update Posted: January 12, 2021	Condition: uncomplicated Urinary Tract Infections Intervention/treatment: • Drug: Sulopenem-Etzadroxil/Probenecid • Drug: Ciprofloxacin Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: female	Results are published. https://pubmed.ncbi.nlm.nih.gov/36069202/
NCT02474706	Evaluation of the Non-inferiority of Cefoxitin Versus Imipenem/Cilastatin in the Treatment of Urinary Tract Infections Caused by ESBL-producing Escherichia Coli (COLIFOX)	Recruitment Status: Terminated (Lack of recruitment) Last Update Posted: August 11, 2017	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Cefoxitin • Drug: imipenem Allocation: Randomized Primary Purpose: treatment	No results published.

			Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	
NCT03140085	Bacteriophages for Treating Urinary Tract Infections in Patients Undergoing Transurethral Resection of the Prostate	Recruitment Status: Completed Last Update Posted: March 21, 2019	Condition: Intravesical Bacteriophage Treatment for Urinary Tract Infections Intervention/treatment: • Biological: PYO Phage • Drug: Antibiotics • Other: Sterile bacteriology media Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.
NCT03395288	Nutraceutical Efficacy for rUTI	Recruitment Status: Terminated (Performed a futility analysis and determined that study objectives could not be met.) Last Update Posted: February 4, 2022	Condition: Urinary Tract Infections Intervention/treatment: • Drug: D-Mannose Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 20 years and older (Adult, Older Adult) Sexes: female	Results published.
NCT03235947	Perioperative Fosfomycin in the Prophylaxis of Urinary Tract Infection in Kidney Transplant Recipients (PERIFOS)	Recruitment Status: Completed Last Update Posted: November 13, 2017	Condition: Urinary Tract Infections, Asymptomatic Bacteriuria Intervention/treatment: • Drug: Fosfomycin disodium • Drug: Trimethoprim / Sulfamethoxazole • Drug: Intravenous placebo Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.

NCT03218800	Ertapenem Administered Subcutaneously Versus Intravenously	Recruitment Status: Terminated (not enough participants due to COVID19 pandemia) Last Update Posted: August 11, 2022	Condition: Urinary Tract Infections Intervention/treatment: • Combination Product: Ertapenem Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.
NCT03840148	Safety and Efficacy Study of Cefepime/VNRX-5133 in Patients With Complicated Urinary Tract Infections (CERTAIN-1)	Recruitment Status: Completed Last Update Posted: December 12, 2022	Condition: Urinary Tract Infections, Acute Pyelonephritis Intervention/treatment: • Drug: Cefepime/VNRX-5133 (taniborbactam) • Drug: Meropenem Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.
NCT04832581	Developing Self-care Behaviors for Urinary Tract Infections	Recruitment Status: Completed Last Update Posted: April 6, 2021	Condition: Urinary Tract Infections, During Pregnancy Intervention/treatment: • Behavioral: The Self-Care Behavior Development Program Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 22 years to 49 years (Adult, Older Adult) Sexes: female	No results published.
NCT03508921	Comparison of Methods for Prevention of Urinary Tract Infection Following Botox	Recruitment Status: Completed Last Update Posted:	Condition: Overactive Bladder, Urinary Tract Infections Intervention/treatment: • Procedure: Periprocedural Antibiotics	No results published.

	Injection	August 1, 2022	• Drug: Extended Antibiotics • Procedure: Injection of OnabotulinumtoxinA (BTX-A) Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	
NCT03190421	Expanded Quantitative Urinary Culture (EQUC) vs Standard Culture (SUC) Techniques in the Clinical Care	Recruitment Status: Completed Last Update Posted: June 16, 2020	Condition:, Urinary Tract Infections Intervention/treatment: • Dietary Supplement: Uqora • Dietary Supplement: Group1 • Dietary Supplement: Group 2 Allocation: Randomized Primary Purpose: diagnostic Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: female	No results published.
NCT03680612	Cefepime/AAI101 Phase 2 Study in Hospitalized Adults With cUTI	Recruitment Status: Completed Last Update Posted: September 21, 2018	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Cefepime 1G - 2G / AAI101 0.5G - 0.75G • Drug: cefepime 1 g or cefepime 2 g Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years to 90 years (Adult, Older Adult) Sexes: all	No results published.
NCT04272437	TRA for Preventing Symptomatic Urinary Tract Infection Among High-risk Elderly Residing in Nursing	Recruitment Status: Completed Last Update Posted: February 17, 2020	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Concentrated herbal extract granules TRA • Drug: Placebo	No results published.

	Homes		Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 65 years and older (Older Adult) Sexes: all	
NCT03970356	Improving Antibiotic Prescribing for Urinary Tract Infections in Frail Elderly (ImpresU-WP2)	Recruitment Status: Completed Last Update Posted: May 24, 2022	Condition: Urinary Tract Infections Intervention/treatment: • Other: antibiotic stewardship intervention Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 70 years and older (Older Adult) Sexes: all	No results published.
NCT03715062	Reducing Antibiotic Prescriptions for Urinary Tract Infection in Long-Term Care Facilities	Recruitment Status: Completed Last Update Posted: June 4, 2019	Condition: Urinary Tract Infections Intervention/treatment: • Other: Dialogue tool Allocation: Randomized Primary Purpose: Health Services Research Ages Eligible for Study: 65 years and older (Older Adult) Sexes: all	No results published.
NCT03077711	Methenamine Hippurate Versus Trimethoprim in the Prevention of Recurrent UTIs	Recruitment Status: Completed Last Update Posted: January 14, 2020	Condition: Recurrent Urinary Tract Infections Intervention/treatment: • Drug: Trimethoprim • Drug: Methenamine hippurate Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 years to 99 years (Adult, Older	Results published. https://pubmed.ncbi.nlm.nih.gov/34115162/

			Adult) Sexes: female	
NCT03019172	Clinical Trial of L. Reuteri in Urinary Tract Infections in Non Pregnant Women (UTIReuteri)	Recruitment Status: Completed Last Update Posted: November 29, 2017	Condition: Urinary Tract Infections Intervention/treatment: • Combination Product: Lactobacillus reuteri • Dietary Supplement: Sachet with cranberry + placebo Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 years to 45 years (Adult) Sexes: female	No results published.
NCT02623179	Conventional and Molecular Diagnostic Method for Patients With Suspected UTI	Recruitment Status: Completed Last Update Posted: October 5, 2017	Condition: Urinary Tract Infections Intervention/treatment: • culture versus Molecular diagnostics Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 years to 89 years (Adult, older adult) Sexes: all	No results published.
NCT03050515	Fecal Microbiota Transplantation for the Treatment of Recurrent Urinary Tract Infections	Recruitment Status: Completed Last Update Posted: June 18, 2020	Condition: Recurrent Urinary Tract Infections Intervention/treatment: • Biological: Fecal Microbiota Transplantation Allocation: N/A Primary Purpose: Treatment Ages Eligible for Study: 18 years to 100 years (Adult, older Adult) Sexes: female	No results published.
NCT03645967	Efficacy of a Prepackaged Cleansing Cloth and Standardized	Recruitment Status: Completed	Condition: catheter associated Urinary Tract Infections Intervention/treatment:	No results published.

	Cleansing Protocol for Catheter Care at Reducing CAUTI Rates	Last Update Posted: October 14, 2021	• Device: ReadyCleanse Cloths Allocation: N/A Primary Purpose: Prevention Ages Eligible for Study: 18 years and older (Adult, older Adult) Sexes: all	
NCT03366077	Double-blinded, Randomized, Placebo-controlled Study Evaluating the Effect of the Probiotic on Recurrent Urinary Tract Infection	Recruitment Status: Completed Last Update Posted: January 5, 2021	Condition: Recurrent urinary tract infection in adult women Intervention/treatment: • Dietary Supplement: Probiotic Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 years to 50 years (Adult) Sexes: female	No results published.
NCT04191148	Safety, Tolerability, and PK of LBP-EC01 in Patients With Lower Urinary Tract Colonization Caused by E. Coli	Recruitment Status: Completed Last Update Posted: March 16, 2022	Condition: urinary tract infection Intervention/treatment: • Drug: LBP-EC01 • Drug: Placebo Allocation: Randomized Primary Purpose: basic science Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	Results published. https://pubmed.ncbi.nlm.nih.gov/33310655/
NCT05513677	Characterisation of Biofilm Growth on Coated vs. Uncoated Urinary Catheter Surfaces in Normal Clinical Use (PRO30CSP)	Recruitment Status: Completed Last Update Posted: August 31, 2022	Condition: urinary tract infection, urosepsis Intervention/treatment: • Other: urine culture and susceptibility testing Allocation: Non-Randomized Primary Purpose: other	No results published.

			Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	
NCT03346603	Prevalence of Antimicrobial-resistant Pathogens in Patients Admitted for UTIs	Recruitment Status: Completed Last Update Posted: July 8, 2021	Condition: urinary tract infection Intervention/treatment: • Other: urine culture and susceptibility testing Allocation: Obervational, case-only Primary Purpose: ? Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	No results published.
NCT04371159	A Comparative, Controlled Study to Evaluate the Clinical Accuracy of the Velieve U.S. UTI Urine Analysis Test System	Recruitment Status: Completed Last Update Posted: June 23, 2020	Condition: urinary tract infection Intervention/treatment: • Device: Velieve U.S. Allocation: N/A Primary Purpose: diagnostic Ages Eligible for Study: 18 years to 80 years (Adult, older adult) Sexes: all	No results published.
NCT03526484	The Utility of Urinalysis Prior to In-Office Procedures	Recruitment Status: Completed Last Update Posted: December 2, 2021	Condition: urinary tract infection Intervention/treatment: • Behavioral: Standard of Care • Behavioral: Experimental Allocation: Randomized Primary Purpose: health service research Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	No results published.
NCT03488355	Modified Reporting From Indwelling Catheters	Recruitment Status: Completed Last Update Posted: August 13, 2019	Condition: urinary tract infection Intervention/treatment: • Other: Modified laboratory report	Results published.

			Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	
NCT04616352	Cefuroxime Resistance in Pyelonephritis	Recruitment Status: Completed Last Update Posted: August 3, 2021	Condition: urinary tract infection Intervention/treatment: • Other: Resistance to cefuroxime Allocation: Observational, cohort Primary Purpose: ? Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	No results published.
NCT03379389	Clinical Assessment of Urinary Antiseptics Methenamine and Methylthioninium in Recurrent Cystitis	Recruitment Status: Completed Last Update Posted: December 14, 2021	Condition: urinary tract infection Intervention/treatment: • Drug: Methenamine + Methylthioninium • Drug: Methenamine + Methylthioninium + Acriflavine + Atropa belladona • Drug: Antibiotics Allocation: randomized Primary Purpose: treatment Ages Eligible for Study: 18 years to 80 years (Adult, older adult) Sexes: all	No results published.
NCT04020341	A Study to Evaluate Efficacy and Safety of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (UTI)	Recruitment Status: Completed Last Update Posted: December 15, 2022	Condition: urinary tract infection Intervention/treatment: • Drug: Gepotidacin • Drug: Placebo matching nitrofurantoin • Drug: Nitrofurantoin • Drug: Placebo matching gepotidacin Allocation: randomized	No results published.

			Primary Purpose: treatment Ages Eligible for Study: 12 years and older (Adult, older adult) Sexes: all	
NCT05254808	EXtended Use of FOsfomycin for the Treatment of CYstitis in Primary Care (EXFOCY)	Recruitment Status: Terminated (Insufficient participating sites, and insufficient participants from participating sites mainly due to COVID-19 workload. The number of necessary participants could not be reached within the anticipated timelines and the allocated budget.) Last Update Posted: March 15, 2022	Condition: urinary tract infection Intervention/treatment: • Drug: Fosfomycin • Drug: Nitrofurantoin Allocation: randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: female	No results published.
NCT04187144	Comparative Study to Evaluate Efficacy and Safety of Gepotidacin to Nitrofurantoin in Treatment of Uncomplicated Urinary Tract Infection (UTI)	Recruitment Status: Completed Last Update Posted: December 16, 2022	Condition: urinary tract infection Intervention/treatment: • Drug: Gepotidacin • Drug: Placebo matching nitrofurantoin • Drug: Nitrofurantoin • Drug: Placebo matching gepotidacin Allocation: randomized Primary Purpose: treatment Ages Eligible for Study: 12 years and older (Adult, older adult) Sexes: female	No results published.
NCT02698332	Effect of a Diagnostic Algorithm for Urinary Tract Infection in General Practice	Recruitment Status: Completed Last Update Posted: July 26, 2016	Condition: urinary tract infection Intervention/treatment: • Device: Algorithm for UTI	No results published.

			Allocation: randomized Primary Purpose: diagnostic Ages Eligible for Study: Cild, Adult, older adult Sexes: all	
NCT03520010	Facilitated Implementation of Antibiotic Stewardship in Wisconsin Nursing Homes (IMUNIFI)	Recruitment Status: Completed Last Update Posted: December 23, 2021	Condition: urinary tract infection Intervention/treatment: • Behavioral: Externally-facilitated implementation • Behavioral: Internally-driven implementation Allocation: randomized Primary Purpose: prevention Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	No results published.
NCT03716804	Establish the Relationship Between Shift in Prescribing Pattern and Associated Shift in Sensitivity Pattern of Causative Microbes in UTI Patients in a Closed Community (UTI)	Recruitment Status: Completed Last Update Posted: August 5, 2020	Condition: uncomplicated urinary tract infection, Antibiotic Resistant Infection Intervention/treatment: • Drug: Tablet Nitrofurantoin • Drug: Tablet Ciprofloxacin/ Tablet Cefixime/ Tablet Cefuroxime Allocation: non-randomized Primary Purpose: health service research Ages Eligible for Study: 18 years to 65 years (Adult, older adult) Sexes: all	No results published.
NCT04488770	Safety, Tolerability and Pharmacokinetic Investigation of GSK3882347 in Healthy Participants.	Recruitment Status: Completed Last Update Posted: July 28, 2021	Condition: urinary tract infection Intervention/treatment: • Drug: GSK3882347 • Drug: Placebo Allocation: Randomized Primary Purpose: treatment	No results published.

			Ages Eligible for Study: 18 years to 50 years (Adult) Sexes: all	
NCT02966977	Extending Urine Analysis By Direct Mass Spectrometry	Recruitment Status: Completed Last Update Posted: July 17, 2020	Condition: urinary tract infection Intervention/treatment: • Device: disposable urinary catheter • Device: super smooth antibacterial urinary catheter Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years to 80 years (Adult, older adult) Sexes: all	No results published.
NCT04108910	Morbidity Rate for UTI Through Use of PCR-Based Diagnosis and Management	Recruitment Status: Completed Last Update Posted: July 17, 2020	Condition: urinary tract infection Intervention/treatment: • Diagnostic Test: Guidance UTI Allocation: observational, cohort Primary Purpose: ? Ages Eligible for Study: Child, Adult, older adult Sexes: ?	No results published.
NCT03080389	Sensitivity of Extended Cultures in Diagnosing Urinary Tract Infections	Recruitment Status: Terminated (Study staff not available to complete the trial) Last Update Posted: September 4, 2018	Condition: Overactive Bladder, Overactive Detrusor, Urgency-Frequency Syndrome, UTI Intervention/treatment: • Procedure: Extended Urine Culture Allocation: observational, cohort Primary Purpose: ? Ages Eligible for Study: 18 years to 70 years (Adult, older adult) Sexes: female	No results published.
NCT04408976	Implementation Study With Decision Support	Recruitment Status: Completed	Condition: urinary tract infection	No results published.

	Based on Data	Last Update Posted: June 1, 2020	Intervention/treatment: • ? Allocation: observational, cohort Primary Purpose: ? Ages Eligible for Study: 12 years and older (Child, Adult, older adult) Sexes: all	
NCT03362697	Lactobacillus Reuteri for Treatment of Uncomplicated UTI in Pregnant Women (UTIPregnant)	Recruitment Status: Completed Last Update Posted: June 20, 2019	Condition: urinary tract infection in pregnancy Intervention/treatment: • Dietary Supplement: Probiotics • Drug: Antibiotics Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years to 40 years (Adult) Sexes: female	No results published.
NCT02808000	BIP Foley in Prevention of CAUTI at Rehab Station (CDOC)	Recruitment Status: Completed Last Update Posted: January 22, 2021	Condition: Complications; Catheter, Urinary Infection or Inflammation Intervention/treatment: • Device: BIP Foley (latex) or BIP Foley -silicone • Device: Standard catheter Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	No results published.
NCT02695173	Complications of UTI in Patients on Dapagliflozin	Recruitment Status: Completed Last Update Posted: December 7, 2021	Condition: Severe Complications of Urinary Tract Infections Intervention/treatment: • ?	No results published.

			Allocation: observational, cohort Primary Purpose: ? Ages Eligible for Study: Cild, Adult, older adult Sexes: all	
NCT02797613	Restricted Reporting for Positive Urine Cultures	Recruitment Status: Completed Last Update Posted: February 27, 2020	Condition: Urinary Tract Infection, Bacteriuria Intervention/treatment: • Behavioral: Restricted Reporting Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	Results published. https://pubmed.ncbi.nlm.nih.gov/29804552/
NCT04575493	Clinical Efficacy of Crano-cure in Treatment of Urinary Tract Infection	Recruitment Status: Completed Last Update Posted: June 24, 2021	Condition: Urinary Tract Infection Intervention/treatment: • Dietary Supplement: Crano-cure • Drug: Ciprofloxacin 500 mg Allocation: Randomized Primary Purpose: other Ages Eligible for Study: 15 years to 60 years (Adult, older adult) Sexes: all	No results published.
NCT03282006	Treating Pyelonephritis an Urosepsis With Pivmecillinam (MePUr)	Recruitment Status: Completed Last Update Posted: April 22, 2020	Condition: Pyelonephritis, Urinary Tract Infection Intervention/treatment: • Drug: pivmecillinam Allocation: N/A Primary Purpose: treatment Ages Eligible for Study: 18 years to 110 years (Adult, older adult)	No results published.

			Sexes: all	
NCT03729336	PEEZY Midstream Urine Device Compared to Catheterized Urine Sample (PEEZY)	Recruitment Status: Completed Last Update Posted: June 5, 2019	Condition: Lower Urinary Tract Symptoms, Lower Urinary Tract Infection Intervention/treatment: • Device: Midstream urine collection device • Device: Catheter for urine collection Allocation: Non-Randomized Primary Purpose: diagnostic Ages Eligible for Study: 18 years to 95 years (Adult, older adult) Sexes: female	No results published.
NCT03425396	Oral Omadacycline vs. Oral Nitrofurantoin for the Treatment of Cystitis	Recruitment Status: Completed Last Update Posted: June 9, 2020	Condition: Uncomplicated Urinary Tract Infection, Cystitis Intervention/treatment: • Drug: Omadacycline tablets • Drug: Nitrofurantoin capsules Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: female	Ergebnisse wurden extrahiert. Siehe Dokument: Unveröffentlichte Studienergebnisse
NCT03655548	Optimization Management Study of Community Urinary Tract Infections Spectrum (OPTICUR-EBLSE)	Recruitment Status: Completed Last Update Posted: August 31, 2018	Condition: Urinary Tract Infections, Resistant Infection, Community-Acquired Infections, Beta Lactam Resistant Bacterial Infection Intervention/treatment: • ? Allocation: observational, cohort Primary Purpose: ? Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	No results published.
NCT03700060	Communication and	Recruitment Status:	Condition: Urinary Tract Infections, Communication,	No results

	Compliance for Antibiotic Prescribing by General Practice to Nursing Home Residents With Suspected UTI	Completed Last Update Posted: October 9, 2018	Compliance, Medication Intervention/treatment: • ? Allocation: observational Primary Purpose: ? Ages Eligible for Study: Child, Adult, older adult Sexes: all	published.
NCT02753946	Safety and Efficacy of ZTI-01 (IV Fosfomycin) vs Piperacillin/Tazobactam for Treatment cUTI/AP Infections (ZEUS)	Recruitment Status: Completed Last Update Posted: March 7, 2019	Condition: Urinary Tract Infection Symptomatic, Acute Pyelonephritis, Urinary Tract Infection Complicated Intervention/treatment: • Drug: ZTI-01 • Drug: Piperacillin-tazobactam Allocation: randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, older adult) Sexes: all	Results published. https://pubmed.ncbi.nlm.nih.gov/30861061/
NCT03554603	Modified Reporting of Positive Urine Cultures Collected From Long Term Care	Recruitment Status: Completed Last Update Posted: February 27, 2020	Condition: Urinary Tract Infections, Asymptomatic Bacteriuria Intervention/treatment: • Behavioral: Modified Report Allocation: randomized Primary Purpose: treatment Ages Eligible for Study: Child, Adult, older adult Sexes: all	Results published. https://pubmed.ncbi.nlm.nih.gov/36262767/
NCT03445312	Safety and Effectiveness of a Laboratory Intervention to Effectively NOT Treat Asymptomatic Bacteriuria (Salient)	Recruitment Status: Completed Last Update Posted: June 1, 2020	Condition: Asymptomatic Bacteriuria, Urinary Tract Infections Intervention/treatment: • Behavioral: not processing urine cultures Allocation: observational, cohort	No results published.

			Primary Purpose: ? Ages Eligible for Study: Child, Adult, older adult Sexes: all	
NCT02882256	Video Discharge Instructions (VDI) as Adjuncts to Written Discharge Instructions in the Emergency Department	Recruitment Status: Completed Last Update Posted: December 7, 2018	Condition: Urinary Tract Infection, Head Injury, Laceration Intervention/treatment: • Other: Video discharge instructions Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: all	No results published.
NCT03535558	Fluoroquinolone Associated Disability	Recruitment Status: Completed Last Update Posted: January 29, 2019	Condition: Bronchitis Sinusitis, Urinary Tract Infections Intervention/treatment: • Drug: Fluoroquinolone (FQ) • Drug: Azithromycin (AZ) • Drug: Sulfamethoxazole/Trimethoprim (ST) Fixed Dose Combination Allocation: Observational, cohort Primary Purpose: ? Ages Eligible for Study: 18 years to 65 years (Adult, Older Adult) Sexes: all	No results published.
NCT02869165	Vaginal and Urinary Microbiome Trial	Recruitment Status: Completed Last Update Posted: May 18, 2021	Condition: Atrophic Vaginitis, Menopause, Recurrent Urinary Tract Infections Intervention/treatment: • Drug: Conjugated equine estrogen topical cream • Drug: Apricot kernel oil Allocation: Randomized Primary Purpose: Basic science	No results published.

			Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	
NCT03143920	Hyperbaric Oxygen Therapy for Inflammatory Conditions of the Urinary Bladder (HBOTCICrUTI)	Recruitment Status: Terminated (No funding to continue) Last Update Posted: July 11, 2022	Condition: Chronic Interstitial Cystitis, Painful Bladder Syndrome, Recurrent Urinary Tract Infection Intervention/treatment: • Combination Product: Hyperbaric Oxygen Therapy- Allocation: N/A Primary Purpose: treatment Ages Eligible for Study: 35 years to 70 years (Adult, Older Adult) Sexes: female	No results published.
NCT03147807	BetaLACTA® Test for Early De-escalation of Empirical Carbapenems in Pulmonary, Urinary and Bloodstream Infections in ICU (BLUE-CarbA)	Recruitment Status: Completed Last Update Posted: December 19, 2022	Condition: Pneumonia, Urinary Tract Infections, Bloodstream Infection Intervention/treatment: • Device: betaLACTA® rapid diagnostic test Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.
NCT03379194	Routine Antibiotic Prescription Monitoring in Primary Care Physicians: A Nationwide Trial	Recruitment Status: Completed Last Update Posted: November 18, 2022	Condition: Acute Respiratory Tract Infection, Urinary Tract Infections Intervention/treatment: • Behavioral: Antibiotic stewardship program Allocation: Randomized Primary Purpose: Health Service Research Ages Eligible for Study: Child, Adult, Older Adult Sexes: all	No results published.

NCT03178734	Foley Catheter vs a Self-contained Valved Urinary Catheter	Recruitment Status: Completed Last Update Posted: July 28, 2020	Condition: Catheter-Related Infections, Urinary Tract Infections, Urogynecologic Surgery Intervention/treatment: • Device: Foley Catheter vs Self-Contained Valved Catheter Allocation: Randomized Primary Purpose: other Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.
NCT03818321	Urinary Track Infection Prevention After Urogynecological Surgery	Recruitment Status: Completed Last Update Posted: November 14, 2022	Condition: Urinary Tract Infections, Urinary Retention Postoperative, Pelvic Organ Prolapse Intervention/treatment: • Drug: Methenamine Hippurate 1 g tablet • Drug: Placebo tablet Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 18 years to 80 years (Adult, Older Adult) Sexes: female	Results published. https://pubmed.ncbi.nlm.nih.gov/35272334/
NCT02864420	Hospitalization at Home: The Acute Care Home Hospital Program for Adults	Recruitment Status: Completed Last Update Posted : July 11, 2017	Condition: Pneumonia, Heart Failure, Cellulitis, Urinary Tract Infections Intervention/treatment: • Other: Home hospitalization • Other: Inpatient Hospitalization Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.

NCT03833752	Flexible V/S Rigid Cystoscopy In Men With Urinary Tract Infection	Recruitment Status: Completed Last Update Posted: February 12, 2019	Condition: Lower Urinary Tract Symptoms Intervention/treatment: • Diagnostic Test: Diagnostic Flexible Cystosocpy • Diagnostic Test: Diagnostic Rigid Cystoscopy Allocation: Randomized Primary Purpose: diagnostic Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	No results published.
NCT04140669	Automated Myocardial Performance Index Using Samsung HERA W10	Recruitment Status: Terminated (Sponsor support and funding was terminated due to pandemic) Last Update Posted: July 13, 2022	Condition: Twin to Twin Transfusion Syndrome, Congenital Diaphragmatic Hernia, Neural Tube Defects, Lower Urinary Tract Infection Intervention/treatment: • Device: Automated Myocardial Performance Index (MPI) Allocation: observational, cohort Primary Purpose: ? Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: female	No results published.
NCT04651244	Diagnostic Imaging of Acute Pyelonephritis	Recruitment Status: Completed Last Update Posted: September 16, 2022	Condition: Pyelonephritis Acute Intervention/treatment: • Diagnostic Test: MRI • Diagnostic Test: Ultrasound performed by a radiologist • Diagnostic Test: Point of care ultrasound Allocation: Observational, cohort Primary Purpose: ? Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: all	No results published.
NCT03275623	Management of Sub-Clinical Bacteriuria in Pregnancy	Recruitment Status: Completed	Condition: Cystitis, Cystitis;Puerperium, Pyelonephritis Intervention/treatment:	Ergebnisse wurden extrahiert. Siehe Dokument:

		Last Update Posted: April 3, 2020	• Drug: Antibiotic • Other: Standard Prenatal Care Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: female	Unveröffentlichte Studienergebnisse
NCT04361864	Cross-sectional Survey on Patients With Urinary Tract Infections in Puy-de-Dôme : Epidemiology of Recurrent Urinary Tract Infections and Risk Factors (IUR63)	Recruitment Status: Completed Last Update Posted: May 7, 2021	Condition: Urinary Tract Infections Intervention/treatment: • ? Allocation: Observational, cohort Primary Purpose: to estimate the proportion of patients in Puy-de-Dôme with recurrent urinary tract infections among patients with at least one UTI during 2019 Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: all	No results published.
NCT05651217	Clinical Study on Disposable Sterile Urinary Catheter	Recruitment Status: Completed Last Update Posted: December 14, 2022	Condition: Urinary Catheters, Urinary Tract Infections Intervention/treatment: • Device: disposable urinary catheter • Device: super smooth antibacterial urinary catheter Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 Years to 80 years Adult, Older Adult) Sexes: all	No results published.
NCT05015400	Female Urogenital Nutrition- Health Study (FUN-Health)	Recruitment Status: Completed Last Update Posted: May 6, 2022	Condition: Bacterial Urinary Tract Infection Intervention/treatment: • Other: Plain Water	No results published.

			Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 18 Years to 34 years Adult) Sexes: female	
NCT04680325	Impact of Cranberry Juice Consumption on Gut and Vaginal Microbiota in Post-menopausal Women	Recruitment Status: Completed Last Update Posted: December 22, 2020	Condition: Urinary Tract Infection Intervention/treatment: • Dietary Supplement: Juice daily consumption Allocation: Randomized Primary Purpose: basic science Ages Eligible for Study: (Child, Adult, older Adult) Sexes: female	No results published.
WHO-Register (https://trialsearch.who.int)				
TCTR20200408003	Antibiotic prophylaxis for patients with asymptomatic urinary tract infection undergoing urodynamic study: a randomized-controlled trial	Date of registration: 08/04/2020	Condition: Patients with asymptomatic urinary tract infection undergoing urodynamic study in Srinagarind hospital Intervention/treatment: Patients that were assigned to the antibiotic prophylaxis group received a 30-minute intravenous (IV) infusion of gentamicin 5 mg/kg and a 1-hour IV infusion of ampicillin within 1 hour before UDS if their CrCl more than 60 mL/min. Patients with CrCl less than 60 mL/min received a 2-gram IV infusion of ceftriaxone instead of ampicillin plus gentamicin. Patients who were assigned to the non-antibiotic prophylaxis group did not receive antibiotics before urodynamic study. Allocation: Randomized Ages Eligible for Study: 18 Years Sexes: Both	No results published.
EUCTR2018-003671-35-EE	Multicenter study to assess the efficacy, safety and pharmacokinetics of the study drug tebipenem pivoxil	Date of registration: 14/03/2019	Condition: Complicated Urinary Tract Infection or Acute Pyelonephritis Intervention/treatment: tebipenem pivoxil hydrobromide Allocation: Randomized	keine Ergebnisse zu finden

	hydrobromide compared with ertapenem in complicated urinary tract infections.		Ages Eligible for Study: at least 18 years of age Sexes: Both	
JPRN-jRCTs061180053	Effectiveness of Lactobacillus vaginal suppositories in patients with recurrent urinary tract infection	Date of registration: 2019-03-14	Condition: Recurrent urinary tract infection, Urinary tract infection Intervention/treatment: For 1 year, Lactobacillus vaginal supposite is inserted into the vagina once every 2 days or 3 times a week before going to bed Allocation: single arm study Ages Eligible for Study: >= 20 age old Sexes: Female	https://pubmed.ncbi.nlm.nih.gov/34258813/
EUCTR2016-004486-37-NL	Fosfomycin as stepdown treatment for ascending urinary tract infections	Date of registration: 14/08/2017	Condition: Acute febrile urinary tract infection Intervention/treatment: Monuril 3000 mg vs. Ciprofloxacine 500 mg Ages Eligible for Study: 18 years Sexes: Female	https://pubmed.ncbi.nlm.nih.gov/34791074/

3.2 Laufende Studien

Einschluss n= 56 Studien (n=30 in Clinicaltrials.gov, n=26 WHO-Register)

Nummer	Name	Status	Studienplan	Geplanter Studienabschluss
Clinicaltrials.gov				
NCT04859621	Phase II Clinical Trial of Vitamin D3 for Reducing Recurrence of Recurrent Lower Urinary Tract Infections	Recruiting	Condition: Recurrent Urinary Tract Infection Intervention/treatment: • Drug: Vitamin D3 4000 IU • Drug: Vitamin D3 2000 IU • Drug: Placebo • Other: standard antibiotic therapy	Estimated Primary Completion Date: April 30, 2023 Estimated Study Completion Date: July 30, 2023

			Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 Years to 75 Years (Adult, Older Adult) Sexes: All	
NCT04301934	Fractional CO2 Vaginal LASER Therapy for Recurrent Urinary Tract Infection	Recruiting	Condition: Urinary Tract Infection Intervention/treatment: • Device: Mona Lisa Touch • Drug: Conjugated estrogen • Drug: Estradiol Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: December 2022 Estimated Study Completion Date: December 2022
NCT04095572	Alternative Prophylaxis in Female Recurrent Urinary Tract Infections	Recruiting	Condition: Urinary Tract Infection Intervention/treatment: • Drug: intravesical instillation with HA-CS • Drug: intravesical instillation of sterile purified water Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 Years to 70 Years (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: December 2022 Estimated Study Completion Date: December 2022
NCT04880343	Clinical Study to Evaluate the Efficacy	Recruiting	Condition: Lower Urinary Tract Infection	Estimated Primary Completion Date: January 26, 2021

	of the Dietary Supplement UROMANNOSA® in Women With Recurrent Lower Urinary Tract Infections		Intervention/treatment: • Dietary Supplement: Group (A) • Dietary Supplement: Group (B) Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 Years to 80 Years (Adult, Older Adult) Sexes: Female	Estimated Study Completion Date: January 26, 2021
NCT02246270	Recurrent Urinary Tract Infections and Heparin (RUTIH Trial)	Recruiting	Condition: Recurrent Urinary Tract Infection Intervention/treatment: • Drug: Intravesical Heparin • Other: Placebo Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 Years to 85 Years (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: November 28, 2017 Estimated Study Completion Date: May 2023
NCT04831840	Recurrent Urinary Tract Infections and the Microbiome	Recruiting	Condition: Recurrent Urinary Tract Infection Intervention/treatment: • Drug: Intravesical Heparin • Other: Placebo Allocation: Observational Primary Purpose: to determine if polymerase chain reaction (PCR) (UTIP™) is more sensitive in identifying urinary tract infections (UTI's) than standard urine cultures. Ages Eligible for Study: 18 Years to 90 Years	Estimated Primary Completion Date: May 26, 2021 Estimated Study Completion Date: June 1, 2023

			(Adult, Older Adult) Sexes: Female	
NCT05309317	Preventing Catheter-Associated Urinary Tract Infections With a Virtual Simulation Game	Not yet recruiting	Condition: Catheter-Associated Urinary Tract Infection, Nurse's Role Intervention/treatment: • Other: Virtual Simulation Game for the Prevention of Catheter-Associated Urinary Tract Infections • Other: Ongoing education Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: All	Estimated Primary Completion Date: April 2022 Estimated Study Completion Date: May 2022
NCT04959331	Clinical Effectiveness and Bacteriological Eradication of 4 Short-course Antibiotics for Uncomplicated UTIs in Women.	Recruiting	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Fosfomycin Trometamol Salt • Drug: Nitrofurantoin • Drug: Pivmecillinam Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: May 15, 2023 Estimated Study Completion Date: May 30, 2023
NCT04096820	Uromune in Treating Recurrent Urinary Tract Infections in Women	Active, not recruiting	Condition: Recurrent UTI Intervention/treatment: • Biological: Uromune Allocation: N/A	Estimated Primary Completion Date: October 31, 2022 Estimated Study Completion Date: January 1, 2023

			Primary Purpose: Prevention Ages Eligible for Study: 18 Years to 75 Years (Adult, Older Adult) Sexes: Female	
NCT04100980	A Non-Interventional Pilot Study to Explore the Role of Gut Flora in Chronic Urinary Tract Infections (UTI)	Recruiting	Condition: Chronic UTI Chronic Urinary Tract Infection Intervention/treatment: • Other: No Intervention Allocation: Observational Primary Purpose: Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: All	Estimated Primary Completion Date: March 2023 Estimated Study Completion Date: July 2023
NCT04287478	Bacteriophage Therapy in Patients With Urinary Tract Infections	Active, not recruiting	Condition: Urinary Tract Infection Bacterial Intervention/treatment: • Biological: Bacteriophage Therapy Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: Sexes:	Estimated Primary Completion Date: February 2023 Estimated Study Completion Date: February 2023
NCT05219877	Effectiveness of Preurodynamic With Posturodynamic Levofloxacin on the Incidence of UTI	Enrolling by invitation	Condition: Urinary Tract Infection Intervention/treatment: • Drug: Pre-urodynamic Levofloxacin • Drug: Post-urodynamic Levofloxacin Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 Years and older	Estimated Primary Completion Date: March 1, 2022 Estimated Study Completion Date: December 1, 2022

			(Adult, Older Adult) Sexes: All	
NCT05399797	Management of Acute Uncomplicated UTIs in Adults by Community Pharmacists	Recruiting	Condition: Urinary Tract Infections Urinary Tract Infection Lower Acute Intervention/treatment: • Other: Educational training Allocation: Randomized Primary Purpose: Health Services Research Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: All	Estimated Primary Completion Date: September 2022 Estimated Study Completion Date: November 2022
NCT04798365	Antimicrobial Stewardship in UTIs in Nursing Homes	Recruiting	Condition: Urinary Tract Infections Intervention/treatment: • Behavioral: Intervention group Allocation: Non-Randomized Primary Purpose: Other Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: All	Estimated Primary Completion Date: December 2022 Estimated Study Completion Date: December 2022
NCT04913753	Relevance of the Urine Bacterial Culture Performed Before Double J Ablation for Post-operative Urinary Tract Infection Prevention	Recruiting	Condition: Urinary Infections Intervention/treatment: • Procedure: CBEU • Procedure: No CBEU Allocation: Randomized Primary Purpose: Diagnostic Ages Eligible for Study: 18 Years to 100 Years (Adult, Older Adult)	Estimated Primary Completion Date: March 31, 2023 Estimated Study Completion Date: April 30, 2023

			Sexes: All	
NCT04077580	The Effect of Methenamine Hippurate to Reduce Antibiotic Prescribing in Elderly Women With Recurrent UTI	Enrolling by invitation	Condition: Recurrent Urinary Tract Infection Intervention/treatment: • Drug: Methenamine Hippurate 1000 MG Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 70 Years to 99 Years (Older Adult) Sexes: Female	Estimated Primary Completion Date: November 30, 2022 Estimated Study Completion Date: November 30, 2022
NCT05520684	Asymptomatic Bacteriuria, Urinalysis Abnormality at the Initiation of SGLT2 Inhibitors and UTI Risk	Recruiting	Condition: Type2diabetes, SGLT2 Inhibitor, Urinary Tract Infection Intervention/treatment: • Diagnostic Test: urine culture and urinalysis Allocation: Observational Primary Purpose: Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: November 1, 2022 Estimated Study Completion Date: January 1, 2023
NCT05141188	Extended Spectrum Beta Lactamase Producing Organisms In Urinary Tract Infections	Not yet recruiting	Condition: Urinary Tract Infections Intervention/treatment: • ? Allocation: Observational Primary Purpose: Ages Eligible for Study: Child, Adult, Older Adult Sexes: All	Estimated Primary Completion Date: May 1, 2022 Estimated Study Completion Date: November 1, 2022
NCT04285320	Antibiotic Bladder Instillations vs. Oral	Not yet recruiting	Condition: Recurrent Urinary Tract Infection	Estimated Primary Completion Date: April 2023

	Suppression for the Treatment of Recurrent Urinary Tract Infections		Intervention/treatment: • Drug: Intravesical antibiotic instillation • Drug: Antibiotic oral suppressive therapy Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: Child, Adult, Older Adult Sexes: Female	Estimated Study Completion Date: April 2023
NCT04496726	Cranberry and Quillaja on Symptoms of Uncomplicated UTI	Recruiting	Condition: Urinary Tract Infections UTI UTI - Lower Urinary Tract Infection Intervention/treatment: • Other: Pacran and Sapnov P quillaja Allocation: N/A Primary Purpose: Treatment Ages Eligible for Study: 18 Years to 65 Years (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: June 1, 2023 Estimated Study Completion Date: December 1, 2023
NCT05702762	Single Dose Aminoglycosides for Acute Uncomplicated Cystitis in the Emergency Department Setting	Recruiting	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Gentamicin • Drug: Standard of Care Allocation: Randomized Primary Purpose: Treatment Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: June 30, 2023 Estimated Study Completion Date: June 30, 2024
NCT04815369	Evaluating UTI Diagnosis in Nursing Homes	Active, not recruiting	Condition: Urinary Tract Infections Intervention/treatment:	Estimated Primary Completion Date: March 2023

			• ? Allocation: Observational Primary Purpose: Ages Eligible for Study: 65 Years and older (Older Adult) Sexes: All	Estimated Study Completion Date: May 2023
NCT04305808	Characterization of Vaginal, Urinary and Fecal Microbiomes in Women With Recurrent Urinary Tract Infections	Recruiting	Condition: Urinary Tract Infections Menopause Intervention/treatment: • ? Allocation: Observational Primary Purpose: Ages Eligible for Study: Child, Adult, Older Adult Sexes: Female	Estimated Primary Completion Date: August 30, 2022 Estimated Study Completion Date: December 30, 2022
NCT05365906	UTI Reference Standard: Delphi Method	Recruiting	Condition: Urinary Tract Infections Intervention/treatment: • Other: Delphi-procedure consisting of four survey rounds Allocation: Observational Primary Purpose: Ages Eligible for Study: Child, Adult, Older Adult Sexes: All	Estimated Primary Completion Date: November 12, 2022 Estimated Study Completion Date: November 12, 2022
NCT05376670	Patient Satisfaction and Long-term Safety of Intravesical Aminoglycoside	Recruiting	Condition: Urinary Tract Infections Recurrent Urinary Tract Infection Intervention/treatment:	Estimated Primary Completion Date: September 20, 2022 Estimated Study Completion

	Instillations in UTI Prevention		• Drug: Intravesical aminoglycoside instillations Allocation: Observational Primary Purpose: Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: All	Date: September 20, 2022
NCT04987164	Incidence of Cystitis in Women Consuming a Mixture of Cranberry, Cinnamon, Probiotics	Active, not recruiting	Condition: Cystitis Urinary Tract Infections Intervention/treatment: • Dietary Supplement: Feminabiane CBU Allocation: Observational Primary Purpose: Ages Eligible for Study: 18 Years to 65 Years (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: August 30, 2022 Estimated Study Completion Date: October 30, 2022
NCT05227937	Single Dose Amikacin for Uncomplicated Cystitis in the ED: A Feasibility Study	Recruiting	Condition: Urinary Tract Infections Intervention/treatment: • Drug: Amikacin Allocation: Observational Primary Purpose: Ages Eligible for Study: 14 Years to 110 Years (Child, Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: June 30, 2023 Estimated Study Completion Date: December 31, 2023
NCT05039203	Bacteriuria and Indwelling Urinary Catheter.	Not yet recruiting	Condition: Bacteriuria Asymptomatic Urinary Tract Infections Intervention/treatment:	Estimated Primary Completion Date: September 2022 Estimated Study Completion

			• Device: Indwelling urinary catheter Allocation: Observational Primary Purpose: Ages Eligible for Study: 65 Years and older (Older Adult) Sexes: All	Date: September 2023
NCT03672214	Caesarean Delivery With or Without an Indwelling Bladder Catheter	Not yet recruiting	Condition: Urinary Tract Infections Cesarean Section; Infection Intervention/treatment: • Procedure: Without placement of indwelling catheter • Procedure: With placement of indwelling catheter Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: Female	Estimated Primary Completion Date: June 1, 2023 Estimated Study Completion Date: November 1, 2023
NCT03274960	Screening and Treating Asymptomatic Bacteriuria Every Trimester and Preterm Birth	Active, not recruiting	Condition: Preterm Birth Asymptomatic Bacteriuria in Pregnancy Intervention/treatment: • Combination Product: Griess, Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: Child, Adult, Older Adult Sexes: Female	Estimated Primary Completion Date: December 30, 2021 Estimated Study Completion Date: December 30, 2021
WHO-Register (https://trialsearch.who.int)				
ISRCTN11092188	Clinical and cost-effectiveness of alternative urinary catheter design	2022-06-07, ongoing	Condition: clinical and cost-effectiveness of a novel urinary catheter design in reducing catheter-associated urinary tract infection Intervention/treatment:	Date of first enrolment: January 9, 2023 Estimated Study Completion Date: November 30, 2024

			• receive either the intervention or control catheter design at their next planned catheter change and will continue to receive the assigned catheter (Optitip or Foley) for 12 months in addition to all other standard catheter-related care. Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: >=18 years Sexes: all	
EUCTR2021-003466-12-DE	A double-blind, randomised, multi-centre, controlled clinical trial to compare D-mannose versus antibiotic in the treatment of acute uncomplicated lower urinary tract infections in female patients	2021-12-16, Authorised-recruitment may be ongoing or finished	Condition: acute uncomplicated lower urinary tract infections in female patients Intervention/treatment: • Fosfomycin HEXAL Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 to 70 years Sexes: female	Date of first enrolment: March 25, 2022 Estimated Study Completion Date:
EUCTR2019-002768-28-BG	A Phase 3 study of an Investigational Drug, Cefepime-zidebactam versus Meropenem in patients with Complicated Urinary Tract Infection or Acute Pyelonephritis	2021-12-10, Authorised-recruitment may be ongoing or finished	Condition: Complicated urinary tract infection or acute pyelonephritis Intervention/treatment: • Cefepime-zidebactam Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years or older Sexes: all	Date of first enrolment: March 11, 2022 Estimated Study Completion Date:
EUCTR2019-002768-28-LT	A Phase 3 study of an Investigational Drug, Cefepime-zidebactam	2021-11-22, Authorised-recruitment	Condition: Bacterial Infections and Mycoses Intervention/treatment:	Date of first enrolment: January 4, 2022

	versus Meropenem in patients with Complicated Urinary Tract Infection or Acute Pyelonephritis	may be ongoing or finished	• Cefepime-zidebactam Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 years or older Sexes: all	Estimated Study Completion Date:
JPRN-jRCT2031210272	A Study of Vaccination with 9-valent Extraintestinal Pathogenic Escherichia coli Vaccine (ExPEC9V) in the Prevention of Invasive Extraintestinal Pathogenic Escherichia coli Disease in Adults Aged 60 Years And Older with a History of Urinary Tract Infection in the Past 2 Years	2021-08-25, Recruiting	Condition: Invasive extraintestinal pathogenic Escherichia coli disease (IED) prevention Intervention/treatment: • ExPEC9V:Participants of Part 1 and Part 2 will receive a single intramuscular (IM) injection of 9-valent extraintestinal pathogenic Escherichia coli vaccine (ExPEC9V) on Day 1. • Placebo:Participants of Part 1 and Part 2 will receive a single IM injection of matching placebo on Day 1. Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: >= 60age old Sexes: all	Date of first enrolment: September 3, 2021 Estimated Study Completion Date:
IRCT20210617051604N1	Evaluation of the effect of vitamin E in women with urinary tract infection	2021-07-11, Recruiting	Condition: Lower urinary tract infection Intervention/treatment: • Intervention 1: Intervention group: Vitamin E softgel 100 units daily for 6 months. • Intervention 2: Control group: Vitamin E softgel placebo 100 units daily for 6 months. Allocation: Randomized Primary Purpose: prevention	Date of first enrolment: July 23, 2023 Estimated Study Completion Date:

			Ages Eligible for Study: over 18 years Sexes: female	
EUCTR2021-001332-26-ES	Clinical effectiveness and bacteriological eradication of 3 short-course antibiotic regimens and single-dose of fosfomicyn trometamol for lower urinary tract infections in adult women [SCOUT study]	2021-07-02, Authorised-recruitment may be ongoing or finished	Condition: Uncomplicated Lower urinary tract infections Intervention/treatment: • Nitrofurantoína • Pivmecillinam • Fosfomicina trometamol Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: over 18 years Sexes: female	Date of first enrolment: September 6, 2021 Estimated Study Completion Date:
EUCTR2020-000553-27-PL	Phase III, Double-Blind, Parallel-Group, Comparator-Controlled, Efficacy and Safety Study of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis)	2021-06-09, Authorised-recruitment may be ongoing or finished	Condition: Urinary Tract Infection (Acute Cystitis) Intervention/treatment: • Gepotidacin • Macrobid Allocation: Randomized Primary Purpose: therapeutic response Ages Eligible for Study: over 12 years Sexes: female	Date of first enrolment: September 24, 2021 Estimated Study Completion Date:
ChiCTR2100046520	A Multicenter, Randomized, Placebo-controlled, Phase II Trial of Vitamin D3 for Reducing Recurrence of Recurrent Lower Urinary Tract Infections	2021-05-19, Recruiting	Condition: Recurrent urinary tract infections Intervention/treatment: • Treatment group A:2000IU per tablet, 2 tablet per time, qd, oral administration with the first meal, continuous use for 48 weeks; • Treatment group B:2000IU per tablet, 1 tablet per time, qd, oral administration with the first meal, continuous use for 48 weeks;	Date of first enrolment: April 15, 2021 Estimated Study Completion Date:

			• placebo group:0 IU per tablet, 1 tablet per time, qd, oral administration with the first meal, continuous use for 48 weeks; Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 to 75 years Sexes: all	
EUCTR2020-005559-19-DE	Furazidin for resolution or improvement of all clinical symptoms of Urinary Tract Infections	2021-05-19, Authorised-recruitment may be ongoing or finished	Condition: Female diseases of the urinary and reproductive systems and pregancy complications Intervention/treatment: • Furazidin prolonged-release tablets, 200 mg • Uvamin Retard, 100 mg capsules Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: = 18 < 65 years of age Sexes: female	Date of first enrolment: May 23, 2022 Estimated Study Completion Date:
ChiCTR2100045775	Treatment of female urinary tract infection with faecal bacteria transplantation	2021-04-24, Recruiting	Condition: Women's urinary tract infection Intervention/treatment: • Experimental group:Fecal bacteria transplantation; • Healthy control group :None; Allocation: Interventional, single arm study Primary Purpose: treatment Ages Eligible for Study: over 18 years Sexes: female	Date of first enrolment: May 1, 2021 Estimated Study Completion Date:
ISRCTN13032419	Urinary tract infection diagnosis in	2021-04-22, Ongoing	Condition: Urinary tract infections in pregnancy	Date of first enrolment: April 12, 2021

	pregnancy by volatile organic compound analysis		Intervention/treatment: • Volatile organic compound analysis of a midstream urine sample, • compared to microscopy culture and sensitivity testing of midstream urine sample and chemical dipstick test results Allocation: Observational Primary Purpose: diagnostic Ages Eligible for Study: Sexes: female	Estimated Study Completion Date: December 31, 2023
EUCTR2019-002747-14-CZ	Study to investigate efficacy, safety and tolerability of Furamag in the treatment of urinary tract infections	2021-04-12, Authorised-recruitment may be ongoing or finished	Condition: Microbiologically confirmed acute uncomplicated lower urinary tract infections in women. Intervention/treatment: • Furamag • Furantoina Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: aged between 18 and 55 years Sexes: female	Date of first enrolment: May 3, 2021 Estimated Study Completion Date:
EUCTR2020-005559-19-PL	Furazidin for resolution or improvement of all clinical symptoms of Urinary Tract Infections	2021-01-04, Authorised-recruitment may be ongoing or finished	Condition: Female diseases of the urinary and reproductive systems and pregancy complications Intervention/treatment: • Furazidin prolonged-release tablets, 200 mg • Uvamin Retard, 100 mg capsules Allocation: Randomized Primary Purpose: treatment	Date of first enrolment: February 23, 2021 Estimated Study Completion Date:

			Ages Eligible for Study: =< 12 years Sexes: female	
ChiCTR2000040867	A multicenter, randomized, open, positive controlled, non inferiority study of Pseudomonas aeruginosa injection in the prevention of recurrent urinary tract infection (Ruti)	2020-12-12, Recruiting	Condition: RUTI Intervention/treatment: • experimental group:V1 (Day 1)-Inject 0.5ml of "Pseudomonas aeruginosa injection" for the first time. For the next 4 weeks, take 1ml/time every week for 5 times. • control group::V1 (Day 1)-One dose of fosfomycin tromethamine for 10 days, 9 consecutive doses (serving Usage: add water (50~70ml) or other non-alcoholic beverage to each bottle, take it immediately after dissolution; follow-up 0.5-1 Years (the follow-up period starts from the day of medication) Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: Aged 18 to 70 years Sexes: female	Date of first enrolment: December 23, 2021 Estimated Study Completion Date:
ChiCTR2000032512	Pidomod dispersible tablets for the efficacy and safety of adjuvant treatment of recurrent urinary tract infections: a Randomized, double-blind, parallel placebo-controlled, multicenter clinical trial	2020-04-30, Recruiting	Condition: Used for adjuvant treatment of chronic or recurrent respiratory and urinary tract infections Intervention/treatment: • experimental group:Give conventional treatment medicines while taking Pidimod dispersible tablets.; • control group:Give conventional treatment drugs while taking placebo Allocation: Randomized Primary Purpose: treatment	Date of first enrolment: April 30, 2020 Estimated Study Completion Date:

			Ages Eligible for Study: Aged 18 to 70 years Sexes: all	
EUCTR2019-003282-17-DK	Comparison of the effect of shortened versus standard antibiotic treatment in patients infected with Gram negative bacteria with a urinary tract source of infection	2019-12-05, Authorised-recruitment may be ongoing or finished	Condition: Gram-negative bacteremia Intervention/treatment: • Ampicillin, Tablet • Ampicillin, Injection • Piperacillin, Injection • Cefuroxime, Injection • Cefuroxime, Tablet • Cefotaxime SODIUM, Injection • Meropenem, Injection • Ertapenem, Injection Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: >18 years Sexes: all	Date of first enrolment: Febuary 11, 2020 Estimated Study Completion Date:
EUCTR2018-001801-98-GB	Phase III, Double-Blind, Parallel-Group, Comparator-Controlled,Efficacy and Safety Study of Gepotidacin in the Treatment of Uncomplicated Urinary Tract Infection (Acute Cystitis).	2019-09-16, Authorised-recruitment may be ongoing or finished	Condition: Female diseases of the urinary and reproductive systems and pregancy complications Intervention/treatment: • Gepotidacin • Macrobid Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: >12 years Sexes: female	Date of first enrolment: Febuary 27, 2020 Estimated Study Completion Date:
IRCT20160110025929N24	The effect of cranberry gavage on prevention catheter related urinary tract infection	2019-07-10, Recruiting	Condition: Urinary tract infection Intervention/treatment: • Intervention 1: Intervention group: In the intervention group, in addition to	Date of first enrolment: Juli 23, 2019 Estimated Study Completion Date:

			rutine care from the Foley catheter , the cranberry tablet(500mg) will be given twice a day by gavage. • Intervention 2: Control group: Control group will receive only routine care from the catheter foley(Washing the perineal area). Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: Age over 18 years Sexes: all	
EUCTR2018-001481-42-ES	Clinical trial to evaluate the efficacy of a 0.005% estriol vaginal gel in the prevention of recurrent urinary tract infections in postmenopausal women with vaginal atrophy.	2018-09-17, Authorised-recruitment may be ongoing or finished	Condition: Female diseases of the urinary and reproductive systems and pregancy complications Intervention/treatment: • BLISSEL, Vaginal gel, ESTRIOL Allocation: Randomized Primary Purpose: prevention Ages Eligible for Study: 55 and 75 years Sexes: female	Date of first enrolment: October 4, 2018 Estimated Study Completion Date:
ChiCTR1800018350	A multi-center, randomized, controlled trial for Tailinfang in the treatment of recurrent urinary tract infection	2018-09-12, Recruiting	Condition: Recurrent urinary tract infection Intervention/treatment: • Group 1:Tailinfang; • Group 2:Bacteriostatic therapy Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: Aged 18 to 75 years Sexes: all	Date of first enrolment: September 17, 2018 Estimated Study Completion Date:
IRCT20170417033483N2	Comparison the effect	2018-02-13,	Condition: Urinary tract infection	Date of first enrolment: May

	of two days interval amikacin with standard therapy in treatment of urinary tract infection	Recruiting	Intervention/treatment: • Intervention 1: Intervention group ESBL: Each 48 hours of amikacin is given 3mg / kg / Q48 hours for 7 days, and then treatment of Ofloxacin 300 mg twice daily for 7 days is continued. • Intervention 2: ESBL control group: INn ESBL control group patients Maropenem is given at a dose of 1 g three times a day for one week, followed by treatment with ofloxacin 300 mg twice daily for 7 days. • Intervention 3: Control group NON ESBL: In non-ESBL control group patients Maropenem is given at a dose of 1 g three times a day for one week, followed by treatment with ofloxacin 300 mg twice daily for 7 days. • Intervention 4: Non ESBL intervention group: Each 48 hours of amikacin is given 3mg / kg / Q72 hours for 7 days, then treatment with ofloxacin 300 mg twice daily for 7 days. Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: Sexes: all	22, 2017 Estimated Study Completion Date:
DRKS00011042	Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with Uva ursi - a comparative effectiveness trial	2017-09-15, Recruiting	Condition: Other disorders of urinary system Intervention/treatment: • Intervention 1: day 0: placebo granules: 1x1 orally (day 0); UU (Uva ursi) 105 mg (Arctuvan®) 3x2 tablets orally from day 0 for 5 days; if the patient returns with persistent/recurrent symptoms, antibiotic therapy according to the sensitivity test	Date of first enrolment: May 3, 2017 Estimated Study Completion Date:

			• Intervention 2: 2nd arm: day 0: fosfomycin (Monuril®) 3 g granules orally 1x1 (day 0), placebo tablets 3x2 from day 0 for 5 days; if the patient returns with persistent/recurrent symptoms, antibiotic therapy according to the sensitivity test • Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18-75 years Sexes: female	
DRKS00010357	A Double-blind, Controlled, Parallel-group, Randomized, Multicenter Clinical Trial to Assess the Efficacy and Safety of a Herbal Drug Containing Centaury, Lovage Root and Rosemary Leaf (CLR) in Comparison to Fosfomycin Trometamol for the Treatment of Acute Lower Uncomplicated Urinary Tract Infections (uUTIs) in Women	2017-05-08, Recruiting	Condition: Urinary tract infection Intervention/treatment: • Intervention 1: Drug: Canephron® N • Intervention 2: Drug: Fosfomycin trometamol • Intervention 3: Drug: Canephron® N-placebo • Intervention 4: Drug: Fosfomycin trometamol-placebo Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: 18 to 70 years Sexes: female	Date of first enrolment: December 31, 2015 Estimated Study Completion Date:
EUCTR2016-004842-27-DE	Clinical Trial to investigate the efficacy and safety of ANGOCIN® Anti-Infekt N against placebo preventing urinary tract infections in	2017-03-16, Authorised-recruitment may be ongoing or finished	Condition: Bacterial Infections and Mycoses Intervention/treatment: • Angocin Anti-Infekt N, Film-coated tablet Allocation: Randomized Primary Purpose: prophylaxis	Date of first enrolment: July 17, 2018 Estimated Study Completion Date:

	catheterized patients		Ages Eligible for Study: over 18 years Sexes: all	
CTRI/2016/11/007513	A clinical study of Bio-Kult Pro-Cyan probiotic in recurrent urinary tract infections (UTI) in adult females.	2016-11-30, Open to Recruitment	Condition: Recurrent Urinary Tract Infections Intervention/treatment: • Intervention1: Bio-Kult Pro-Cyan: Vegetable Capsule two probiotic bacteria (Lactobacillus acidophilus PXN 35, Lactobacillus plantarum PXN 47), cranberry extract (18mg), vitamin A (160mcg). Administered orally, one capsule two times a day (BD) , for 26 weeks. • Control Intervention1: Placebo: Matched placebo vegetable capsule Administered orally, one capsule two times a day (BD) , for 26 weeks Allocation: Randomized Primary Purpose: treatment Ages Eligible for Study: between 18 and 55 years Sexes: female	Date of first enrolment: August 31, 2016 Estimated Study Completion Date:

3.3 Unveröffentlichte Studienergebnisse

n= 2 Studien (aus den abgeschlossenen Studien der Clinicaltrials.gov-Suche)

Referenz	Studiencharakteristika	Studienziel	Patientenmerkmale	Intervention	Kontrolle	Ergebnisse
Eziefule, 2020 NCT03275623	Interventional study (clinical trial) • Allocation: Randomized; • Intervention	The purpose of the study is to determine if treatment of pregnant women with	N= 60 pregnant women (18 years and older) who seek prenatal care within the University of Texas	Antibiotic treatment (n=30 participants) Those randomized	No Antibiotic Treatment (n=30 participants) Standard	Number of Participants Who Have Cystitis (>100,000 CFU at any point during antenatal care) after 10 months • No antibiotic treatment 4/28, 14.3% • Antibiotic treatment 4/25, 16 %

	Model: Parallel Assignment; • Masking: None (Open Label)	urine cultures with a low level of bacteria (less than 100,000 colony forming units (CFU)) may decrease adverse pregnancy outcomes.	Health System with UT Physicians. Urine culture of less than 100,000 CFU Participant's age (n=17 participant: <20y, n=31 participants: 20-34y, n=12 participants: >= 35y)	for treatment will be prescribed the most commonly used antibiotic for urinary tract infections in pregnancy. This includes: Nitrofurantoin, Cephalexin, Amoxicillin It is unsure which antibiotic the participant will receive but a majority of the time it will be one of the above named antibiotic. The choice will be determined by the physician, but will accommodate participants' prior medication history and adverse events.	prenatal care without treatment for any urine culture with growth of 1-100,000 CFU of any organism. Continued surveillance of urinary cultures	Number of Participants Who Have Pyelonephritis (>100,000 CFU with fever at any point during antenatal care) after 10 months • No antibiotic treatment 3/28, 10.7% • Antibiotic treatment 4/25, 16 % Adverse events during antenatal care (about 10 months) All-cause Mortality • No antibiotic treatment 0/30, 0% • Antibiotic treatment 0/30, 0% Serious adverse events • No antibiotic treatment 0/30, 0% • Antibiotic treatment 0/30, 0% Other adverse events • No antibiotic treatment 0/30, 0% • Antibiotic treatment 0/30, 0%
Paratek Pharmaceuticals	Interventional study (clinical trial)	The purpose of this study is to evaluate the	N=225 female participants, (18 years and older)	Omadacycline tablets	Nitrofurantoin capsules (100/100	**Primary Outcome – Number of Participants with an Investigator Assessment of Clinical Response at the Post Therapy Evaluation**

Inc, 2020 NCT03425396	Allocation: Randomized	safety and efficacy of oral omadacycline as compared to oral nitrofurantoin in the treatment of female adults with cystitis.	that must have a qualifying uncomplicated urinary tract infection, not pregnant at the time of enrollment	(300/300) once every 24h; (450/300) once every 24h; 450/300 once every 24h; 450/450 once every 24h; 450/450 once every 12h	Once Every 12 Hours)	**(PTE) Visit (ITT Population)** Clinical success • Omadacycline 300/300 Once Every 24 Hours: 48/55 87.3% • Omadacycline 450/300 Once Every 24 Hours: 42/54, 77.8% • Omadacycline 450/450 Once Every 24 Hours: 46/54, 85.2% • Omadacycline 450/450 Once Every 12 Hours: 7/8, 87.5% • Nitrofurantoin 100/100 Once Every 12 Hours: 49/54, 90.7% **Secondary outcome – Number of Participants with an Investigator Assessment of Clinical Response at the End of Treatment (EOT) Visit (ITT Population)** (End of Treatment (EOT): 1 to 2 days following the last dose of study drug) Clinical success • Omadacycline 300/300 Once Every 24 Hours: 49/55 89.1% • Omadacycline 450/300 Once Every 24 Hours: 47/54, 87% • Omadacycline 450/450 Once Every 24 Hours: 49/54, 90.7% • Omadacycline 450/450 Once Every 12 Hours: 7/8, 87.5% • Nitrofurantoin 100/100 Once Every 12 Hours: 49/54, 90.7% **Secondary outcome – Number of Participants with an Investigator Assessment of Clinical Response at the Final Follow-up (FFU) Visit (ITT Population)** (Final Follow-up (FFU): occurred 30 to 37 days following the first dose of study drug) Clinical success • Omadacycline 300/300 Once Every 24 Hours: 47/55 85.5%

						• Omadacycline 450/300 Once Every 24 Hours: 41/54, 75.9% • Omadacycline 450/450 Once Every 24 Hours: 44/54, 81.5% • Omadacycline 450/450 Once Every 12 Hours: 7/8, 87.5% • Nitrofurantoin 100/100 Once Every 12 Hours: 49/54, 90.7% Data obtained on bacterial cure were not shown **Adverse events** <u>All-cause mortality</u> • Total of all intervention and control measures: 0% <u>Serious adverse events</u> • Serious adverse events reported for the intervention Omadacycline 450/450 Once Every 24 Hours: 1/54, 1.85% • No other serious adverse events reported <u>Other adverse events</u> • Omadacycline 300/300 Once Every 24 Hours, total: 16/55 29.9% (n=2/55 Diarrhoea, n=12/55 Nausea, n=3/55 Vomitting, n=1/55 Asyptomatic bacteriuria, n=1/55 UTI, n=3/55 Headache, n=2/55 Dysuria) • Omadacycline 450/300 Once Every 24 Hours, total: 13/54, 24.7% (n=1/54 Diarrhoea, n=8/54 Nausea, n=3/54 Vomitting, n=2/54 Asyptomatic bacteriuria, n=1/54 UTI, n=2/54 Headache) • Omadacycline 450/450 Once Every 24 Hours, total: 15/54, 27.78% (n=3/54 Diarrhoea, n=10/54 Nausea, n=3/54 Vomitting, n=1/54 Asyptomatic bacteriuria, n=2/54 UTI, Headache, n=4/54 Dysuria) • Omadacycline 450/450 Once Every 12

						Hours, total: 4/8, 50% (n=1/8 Abdominal discomfort, n=4/8 Nausea, n=1/8 Vomitting, n=1/8 Hordeolum, n=1/8 Dysgeusia, n=2/8 Headache) • Nitrofurantoin 100/100 Once Every 12 Hours, total: 9/54, 16.76% (n=2/54 Diarrhoea, n=4/54 Nausea, n=2/54 Bronchitis, n=1/54 Headache)

3.4 Zurückgezogene Studien

Einschluss n= 12 Studien (Clinicaltrials.gov)

Nummer	Name	Studienplan	Ergebnis
Clinicaltrials.gov			
NCT02637986	The Efficacy of Orally Administrated Probiotic Formula in Preventing a Recurrence of a Urinary Tract Infection During Pregnancy	Condition: Urinary Tract Infections (UTIs) Intervention/treatment: • Dietary Supplement: Urex Plus - containing L. rhamnosus GR-1 and L. reuteri RC-14 • Other: Placebo - capsule with no active ingredient Allocation: Randomized Primary Purpose: Prevention Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: Female	The investigator decided not to proceed with this study. Last posted: November 8, 2022
NCT03299387	INtravesical Antimicrobial Agents v STANDard Oral Antibiotics for the Treatment of Acute UTI in Women With rUTI (INSTANT)	Condition: Urinary tract infection Intervention/ treatment: • Nitrofurantoin • Gentamicin Allocation: Randomized Primary purpose: Treatment	Study never recruited Last update posted: June 6, 2019

		Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: Female	
NCT04077749	Probiotic Bladder Instillation for Prevention of Catheter Associated UTIs in Chronically Catheterized Patients	Condition: Urinary tract infection Intervention/ treatment: • Biological: Femdophilus probiotic • Other: Normal Saline Allocation: Randomized Primary purpose: Prevention Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: all	The study never started. It was withdrawn from the IRB. Last update posted: July 8, 2021
NCT02509403	An Open-label Trial to Evaluate the Safety of an Essential Oil Infused Perineal Towel (WIPEAWAY)	Condition: Urinary tract infection Intervention/ treatment: • Essential oils infused Perineal Hygiene wipe Allocation: N/A Primary purpose: Other Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: female	The company responsible for funding has filed for bankruptcy Last update posted: April 1, 2020
NCT03854396	Clinical Trial on the Preventive Effect of Intravaginal Prasterone on Recurrent Urinary Tract Infections in Postmenopausal Women	Condition: recurrent Urinary tract infection, Postmenopause, Postmenopausal Syndrome, Postmenopausal Symptoms, Menopause Intervention/ treatment: • Prasterone • Placebo Allocation: Randomized Primary purpose: Prevention Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: female	Due to termination of ISR by PI with agreement by grant sponsor Last update posted: June 30, 2021
NCT03800667	Vitamin C for the Prevention of UTI in Women Who Undergo	Condition: Catheter-Associated Urinary Tract Infection Intervention/ treatment:	No funds Last update posted: July 15,

	Elective GYN Surgeries	• Ascorbic Acid 1000 MG Allocation: Randomized Primary purpose: Prevention Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: female	2019
NCT03861260	GAG Replacement vs URethral DIlAtatioN (GUARDIAN)	Condition: recurrent Urinary tract infection Intervention/ treatment: • Rigid cystoscopy with urethral dilatation • Flexible cystoscopy and installation of Glycosaminoglycan layer replacement (laluril) Allocation: Randomized Primary purpose: treatment Ages Eligible for Study: Child, Adult, Older Adult Sexes: female	Withdrawn no participants enrolled Last update posted: September 27, 2021
NCT03996057	Methenamine in a Non-antibiotic, Multimodal Approach to UTI Prevention	Condition: Urinary tract infection, lower UTI Intervention/ treatment: • Methenamine Hippurate 1000 MG • Vaginal estrogen • Dietary Supplement: D-mannose Allocation: Randomized Primary purpose: prevention Ages Eligible for Study: 18 Years and older (Adult, Older Adult) Sexes: female	Project cancelled due to PI leaving institution, staff changes and COVID Last update posted: July 8, 2022
NCT04700787	Safety, Tolerability, and Pharmacokinetics of Sulopenem in Adolescents	Condition: Urinary tract infection, Pyelonephritis Acute, Intraabdominal Infections Intervention/ treatment: • Sulopenem Allocation: N/A	Enrolment challenges and change in development plan necessitating a change in study design Last update posted: June 13,

		Primary purpose: treatment Ages Eligible for Study: 12 Years to 18 Years (Child, Adult) Sexes: all	2022
NCT02697162	Antiseptic-coated Intermittent Urinary Catheter (GuardianCath)	Condition: Neurogenic Bladder, Catheter-Related Infections Intervention/ treatment: • Device: Antiseptic-coated catheter • Device: Hydrophilic catheter • Drug: Octenidine chloride Allocation: randomized Primary purpose: prevention Ages Eligible for Study: 1 month to 18 Years (Child, Adult) Sexes: all	Withdrawal of research institution from participating Last update posted: February 9, 2021
NCT04171388	Enhancing Nutrition and Antenatal Infection Treatment for Maternal and Child Health in Ethiopia (ENAT)	Condition: Low Birthweight, Preterm Birth, Maternal; Malnutrition, Affecting Fetus, Sexually Transmitted Diseases, Urinary Tract Infections, Pregnancy and Infectious Disease Intervention/ treatment: • Drug: Azithromycin 500 mg • Dietary Supplement: Multiple Micronutrient or Fortified Balanced Energy Protein Supplement • Drug: Placebo oral tablet 500 mg • Other: Enhanced Infection Management Package (EIMP) Allocation: randomized Primary purpose: prevention Ages Eligible for Study: Child, Adult, Older Adult Sexes: female	Trial withdrawn due to COVID-19 Last update posted: August 17, 2020
NCT04230746	Effect of Antibiotics on Urinary Microbiome	Condition: Microtia, UTI, Bacteriuria, Antibiotic Resistant Infection, Antibiotics Causing Adverse Effects in Therapeutic Use Intervention/ treatment: • Drug: Bactrim DS 800Mg-160Mg Tablet	Funding, recruitment issues Last update posted: November 3, 2021

		• Drug: Placebo oral tablet Allocation: randomized Primary purpose: basic science Ages Eligible for Study: 18 years and older (Adult, Older Adult) Sexes: all	

4. HTA-Berichte

Referenz	Studiencharakteristika	Studienziel	Patientenmerkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
IQWiG, 2022 HT20-01	HTA-Bericht n=15 RCTs Letztes Suchdatum: 27.11.2021	Helfen pflanzliche Mittel bei wiederkehrender Blasenentzündung?	Patientinnen ab 16 Jahren mit unkomplizierter rezidivierender Urozystitis Mittlere bzw. Mediane Alter: 25-63 y	• Phytopräparate (n=14) • Phytopräparate+Antibiotika (n=1)	• Placebo (n=10) • Antibiotika (n=3) • Phytopräperate (n=2)	**Spezifische Symptome** Liebstöckelwurzel, Rosmarinblätter und Tausendgüldenkraut + Ofloxacin vs. Ofloxacin (n=1) • kein Anhaltspunkt für einen höheren oder geringeren Nutzen **Entwicklung komplizierter Infekte** • Keine Studien berichtete Daten zur Entwicklung komplizierter	Der präventive Einsatz von Cranberry-Präparaten kann bei Frauen mit unkomplizierter wiederkehrender Blasenentzündung sinnvoll sein, da es einen Hinweis auf einen Nutzen zur Rezidivvermeidung im Vergleich zu Placebo gibt und der präventive Einsatz von Antibiotika gemäß S3-Leitlinie nur in seltenen Fällen empfohlen ist. Ob der präventive Einsatz von anderen	Unklar, ob eine unabhängige Kontrolle der extrahierten Daten durchgeführt wurde und ob mehrere Personen unabhängig voneinander das Verzrrungspozenzial erhoben haben. Es wurden keine Interessenkonflikte festgestellt, die die fachliche Unabhängigkeit im Hinblick auf	1a RoB: un-clear

						Infekte. **Zeitraum bis zum Rezidiv** <u>Cranberry-Präparate vs. Placebo</u> (n=5) Anhaltspunkt für einen Nutzen von Cranberry-Präparaten im Vergleich zu Placebo: • statistisch signifikanter Unterschied zugunsten der Intervention (n=3) • nicht statistisch signifikant (n=2) <u>Cranberry-Präparate vs. Antibiotika</u> (n=2) • Trimethoprim: kein signifikanter Unterschied • Trimethoprim-Sulfamethoxazol: statistisch signifikant unterschiedliche mediane Zeit bis zum Rezidiv in der Cranberry-Gruppe berichtet	Phytopräparaten sinnvoll sein kann, lässt sich aufgrund der sehr wenigen verfügbaren Daten nicht ausreichend beurteilen. Zum Einsatz von Cranberry-Präparaten oder anderen Phytopräparaten zur Akutbehandlung von symptomatischen Episoden bei Frauen mit unkomplizierter wiederkehrender Blasenentzündung sind keine Daten verfügbar.	eine Bearbeitung des vorliegenden Auftrags gefährden.	

						(122 Tage vs. 244 Tage; p = 0,03) <u>Cranberry-Monopräperat vs. Cranberry-Kombipräperat</u> (n=1) • längere Zeit bis zum Rezidiv beim Kombinationspräperat berichtet (98,6 Tage vs. 84,6 Tage), statistische Signifikanz nicht angegeben **Rezidivrate** <u>Cranberry-Präparate vs. Placebo</u> (n=6) • Metaanalyse min. 1 Rezidiv (n=6): Vorteil von Cranberry-Präparaten IRR = 0,58 [95 %-KI = 0,38-0,89]; n = 1151 • Metaanalyse Gesamtrezidive (n=3): Vorteil von Cranberry-Präparaten IRR = 0,47 [95 %-KI =			

						0,34-0,65]; n = 645 • Cranberry -Extrakt, Propolis und Zink vs Placebo: statistisch signifikanter Unterschied bzgl. mittlere Anzahl an Rezidivien in 3 Monaten • 6 Studien ohne Ergebnisse im Register identifiziert: potenzielle Publikationsbias <u>Cranberry-Präparate vs. Antibiotika</u> (n=2) • Trimetho prim: kein Anhaltspunkt für einen höheren oder geringeren Nutzen von Cranberry • Trimetho prim-Sulfamethoxazol: Anhaltspunkt für einen geringeren Nutzen von Cranberry <u>Bärentraubenblätter und Löwenzahnwurzel</u>			

						und –kraut vs. Placebo (n=1) • Intervention: 0%; Placebo: 23% (statistisch signifikant) Meerrettichwurzel und Kapuzinerkressekraut vs. Placebo (n=1) • nicht signifikant (3 Monate: p = 0,28; 6 Monate: p = 0,26; n = 174). Liebstöckelwurzel, Rosmarinblätter und Tausendgüldenkraut + Ofloxacin vs. Ofloxacin (n=1) • statistisch signifikante Unterschiede nach 6 und 12 Monaten zugunsten der Kombination Cranberry-Präparate vs. andere Phytopräperate (n=1) Vergleichsgruppe			

						n: Bärentrauben, Birke und Berberitzen in Kombination mit D-Mannose vs. Bärentrauben, Birke, Berberitzen und Makandi in Kombination mit D-Mannose vs. Cranberry und D-Mannose: • kein Anhaltspunkt für einen höheren oder niedrigeren Nutzen <u>Cranberry-Monopräperat vs. Cranberry-Kombipräperat</u> (n=1) • statistische signifikanter Unterschied zugunsten des Kombipräperates (p = 0,002; n = 184). **Gesundheitsbezogene Lebensqualität** <u>Cranberry-Extrakt, Propolis und Zink vs. Placebo</u> (n=1) • keine signifikanten			

						Unterschiede in der Lebensqualität festgestellt wurden **Unerwünschte Ereignisse** <u>Cranberry-Präperate vs. Placebo</u> (n=8) • keine berichtet (n=2 Studien) • nicht behandlungsbedürfig (n=2 Studien) Stothers 2002 • Kopfschmerzen (2/50) • Übelkeit (2/50) • häufiger Stuhlgang (1/50) Takahasi 2013 • starkes Brennen (1/106) Koradia 2019 • behandlungsbedürftige Ergebnisse (3/44; 2 Durchfall, 1 Blähungen) Stapleton 2012 • Cranberry			

						29/120 vs. Placebo 7/56; p=0,7 (hauptsächlich gastrointestinale und vaginale Beschwerden und Migräne) Fazit: • Es ergibt sich kein Anhaltspunkt für einen Schaden durch Cranberry im Vergleich zu Placebo <u>Cranberry-Präperate vs. Antibiotika</u> (n=2) • Es ergibt sich kein Anhaltspunkt für einen geringeren oder höheren Schaden durch Cranberry im Vergleich zu Trimethoprim oder Trimethoprim-Sulfamethoxazol. <u>Bärentraubenblätter und Löwenzahnwurzel und –kraut vs. Placebo</u> (n=1) • keine			

						unerwünschten Ereignisse beobachtet <u>Meerrettichwurzel und Kapuzinerkressekraut vs Placebo</u> (n=1) • kein statistisch signifikanter Unterschied zwischen den beiden Gruppen <u>Cranberry-Präparate vs. andere Phytopräperate</u> (n=1) Vergleichsgruppen: Bärentrauben, Birke und Berberitzen in Kombination mit D-Mannose vs. Bärentrauben, Birke, Berberitzen und Makandi in Kombination mit D-Mannose vs. Cranberry und D-Mannose: • keine unerwünschten Ereignisse beobachtet <u>Cranberry-</u>			

						Monopräparat vs. Cranberry-Kombipräparat (n=1) • Monopräparat 19/94; Kombipräparat 12/90; Ereignisse unterschieden sich nicht wesentlich **Mortalität** Cranberry-Präperat vs. Placebo (n=1) • keine Todesfälle berichtet			
GBA, 2019 Mutterschafts-Richtlinien: Screening auf asymptomatische Bakteriurie	Verfahren nach §§ 135, 137c und 137e SGB V: Bewertung und Erprobung von Untersuchungs- und Behandlungsmethoden Letztes Suchdatum • Primärliteratur: 21.10.2014 • Leitlinien:	Ziel der vorliegenden Überprüfung war es, den patientenrelevanten Nutzen eines Screenings auf asymptomatische Bakteriurie bei Schwangeren unter besonderer Berücksichtigung der Testmethoden zu bewerten.	Schwangere	Screening auf asymptomatische Bakteriurie	kein Screening auf asymptomatische Bakteriurie	**Ergebnisse Recherche Primärliteratur (IQWIQ)** Screening vs. kein Screening • keine Studien identifiziert Antibiotische Therapie bei asymptomatischer Bakteriurie • 3 RCTs aus den 1960er und 1970ern: mangelnden Übertragbarkeit auf die heutige Versorgungssitua	**Beschluss des GBA:** Eine regelhafte Urinuntersuchung auf asymptomatische Bakteriurie bei allen Schwangeren wird nicht empfohlen. Das bisher geforderte Urinsediment wird gestrichen. Gleichzeitig wird der Hinweis auf ggf. erforderliche bakteriologische Untersuchungen konkretisiert,	-	-

	September 2017					tion keine Belege für den Nutzen einer Antibiose bei asymptomatischer Bakteriurie • 1 RCT abgebrochen, welche antibiotischen Therapie der asymptomatischen Bakteriurie bei Frauen mit geringem Risiko durchführte, da angenommene Pyelonephritisinzidenz weit unterschritten wurde, anscließende Observationsstudie deutet nicht auf einen Vorteil der antibiotischen Behandlung hin <u>Identifikation asymptomatische Bakteriurie</u> • keine RCTs, bei denen das Urinsediment oder Papierstreifentests zur Identifikation von asymptomatischen Bakteriurien	indem beispielhaft besondere Risiken genannt werden, bei denen die Durchführung bakteriologischer Urinuntersuchungen erforderlich sein kann.		

						verwendet wurde <u>Laufende Studien</u> • eine Studie aus Zimbabwe, welche nicht auf den deutschen Versorgungskontext übertragbar ist <u>Zusammenfassung</u> Der Nutzen der antibiotischen Therapie einer asymptomatischen Bakteriurie in der Schwangerschaft, ermittelt durch Kultur aus Mittelstrahlurin, ist aus heutiger Sicht nicht belegt ist. Zum Nutzen des in der Mutterschafts-Richtlinien geforderten Urinsediments wurden keine Studien gefunden. **Ergebnisse Recherche Leitlinien (GBA)** <u>S3 HWI LL 2017</u>			

						• kein systematisches Screening • kein alleiniger Einsatz von Streifentest zur Diagnose • Behandlung empfohlen <u>EAU 2017</u> • Eingeschränkte Empfehlung zum systematisches Screening • Mittelstrahlurin • Behandlung eingeschränkt empfohlen <u>Südaustralien 2017</u> • Empfehlung zum systematisches Screening • Mittelstrahlurin beim ersten Arztbesuch • Behandlung mit 5 Tage orale Antibiotika <u>NICE 2013</u> • Empfehlung zum systematisches Screening			

						• Urinkultur in der Frühschwangerschaft • Behandlung empfohlen <u>ICSI 2012</u> • Empfehlung zum systematisches Screening • Urinkultur beim ersten Arztbesuch (12.-16. Schwangerschaftswoche) • Behandlung empfohlen <u>SIGN 2012</u> • Empfehlung zum systematisches Screening • Urinkultur beim ersten Arztbesuch • Behandlung mit 7 Tage orale Antibiotika <u>Australien Health Minister 2012</u> • Empfehlung zum systematisches Screening • Urinkultur			

						in der 12.-16. Schwangerschaftswoche • Behandlung empfohlen			

5. Bewertungssysteme der ermittelten Leitlinien

5.1 Schema der Evidenzgraduierung nach NICE [2]

Der GRADE-Ansatz [3] für Fragen zu Interventionen wird seit 2009 bei der Entwicklung von klinischen Leitlinien des NICE verwendet. (Folgende Übersetzung erfolgte durch UroEvidence)

GRADE-Einstufungen [3]	**Eingeschlossene NICE-Leitlinien** • Urinary tract infection (catheter-associated): antimicrobial prescribing • Urinary tract infection (recurrent): antimicrobial prescribing • Pyelonephritis (acute): antimicrobial prescribing • Urinary tract infection (lower): antimicrobial prescribing guideline
Very low	Die tatsächliche Wirkung unterscheidet sich wahrscheinlich deutlich von der geschätzten Wirkung
Low	Die tatsächliche Wirkung kann sich deutlich von der geschätzten Wirkung unterscheiden
Moderate	Die Autoren sind der Meinung, dass die tatsächliche Wirkung wahrscheinlich nahe an der geschätzten Wirkung liegt
High	Die Autoren sind sehr zuversichtlich, dass der tatsächliche Effekt dem geschätzten Effekt ähnlich ist

5.2 Schema der Evidenzgraduierung nach EAU [4]

Für jede Empfehlung in den Leitlinien gibt es ein begleitendes Formular zur Bewertung der Leitungsstärke. Enthalten ist hierbei eine eine Bewertung des Verhältnisses zwischen Nutzen und Schaden sowie die Präferenzen der Patienten für jede Empfehlung.

Die Bewertungen der Stärke - 'strong' or 'weak' - orientieren sich an den Leitprinzipien der GRADE-Methodik, erheben aber nicht den Anspruch, GRADE zu sein [3]. Die Bewertung der Stärke beinhaltet folgende Schlüsselelementen:

1. Die in dem EAU-Leitlinien-Text verwendeten Referenzen werden nach dem Oxford Centre for Evidence-Based Medicine Levels of Evidence-Klassifizierungssystem [1] eingestuft;
2. das Ausmaß der Wirkung (individuelle oder kombinierte Wirkungen);
3. die Gewissheit der Ergebnisse (Präzision, Konsistenz, Heterogenität und andere statistische oder studienbezogene Faktoren);
4. das Gleichgewicht zwischen erwünschten und unerwünschten Wirkungen;
5. die Auswirkungen der Werte und Präferenzen der Patienten auf die Intervention;
6. die Gewissheit dieser Patientenwerte und –präferenzen.

5.3 Schema der Evidenzgraduierung nach SIGN 1999-2012 [5]

Evidenz-level	**Sign-160** Management of suspected bacterial lower urinary tract infection in adult women
1++	Qualitativ hochwertige Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall- Kontroll- oder Kohortenstudien oder

	Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance") und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance") und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance") und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserie
4	Expertenmeinung

SIGN-Empfehlungen (übersetzt durch UroEvidence)

R - Bei "starken" Empfehlungen zu Interventionen, die eingesetzt werden "sollten", ist die Leitlinienentwicklungsgruppe zuversichtlich, dass die Intervention(en) für die große Mehrheit der Menschen mehr Nutzen als Schaden bringen. Bei "starken" Empfehlungen zu Maßnahmen, die "nicht" eingesetzt werden sollten, ist die Gruppe für die Entwicklung der Leitlinie zuversichtlich, dass die Maßnahme(n) für die überwiegende Mehrheit der Menschen mehr Schaden als Nutzen bringen wird/werden.

R - Bei "bedingten" Empfehlungen zu Interventionen, die "in Betracht gezogen" werden sollten, ist die Leitlinienentwicklungsgruppe zuversichtlich, dass die Intervention für die meisten Patienten mehr Nutzen als Schaden bringen wird. Die Wahl der Intervention hängt daher eher von den Werten und Präferenzen einer Person ab, und die medizinische Fachkraft sollte sich mehr Zeit nehmen, um die Optionen mit dem Patienten zu besprechen.

Punkte für bewährte Praktiken:

✓ Empfohlene bewährte Verfahren auf der Grundlage der klinischen Erfahrung der Leitlinienentwicklungsgruppe.

5.4 Schema der Evidenzgraduierung nach DEGAM [6]

Die Bewertung des Evidenzlevels erfolgte nach den Oxford Centre for Evidence-based Medicine Kriterien von 2009. Wurden bei Empfehlungen und Statements mehrere Literaturstellen berücksichtigt, so wurde der jeweils höchste Evidenzgrad angegeben. Die Empfehlungsgrade (je nach Stärke der Empfehlung: soll, sollte, kann, soll nicht, sollte nicht) wurden von den Mitgliedern der Leitliniengruppe ausgesprochen.

5.5 Schema der Evidenzgraduierung nach der S3- Leitlinie Strategien zur Sicherung rationaler Antibiotika-Anwendung im Krankenhaus [7]

Das Klassifikationschema von Oxford Centre of Evidence Based Medicine 2009 wurde als Ausgangspunkt zur Ermittlung der Qualität der Evidenz herangezogen und modifiziert abgebildet:

Übersicht modifizierter Evidenzlevel nach Oxford 2009 [7] (Seite 24)

Level	Studientyp	Beurteilung der Studienqualität (modifiziert nach Oxford, 2009)
Ia	Systematische Reviews (SR) von RCTs (mit oder ohne Meta-Analyse)	• von RCTs
Ib	individuelle RCT	• mind. eine RCT • prospektive Kohortenstudie (bei diagnostischen Fragestellungen im Rahmen diagnostischer Testsysteme (ABS-Thema Mikrobiologie))
IIa	Systematische Reviews (SR) von CCTs (mit oder ohne Meta-Analyse)	• von Studien anderen Designs (Bsp.: Cochrane-Analyse von P. Davey et al.)
IIb	Individuelle Kohortenstudie	• individuelle CCT • prospektive CBA • gute prospektive (quasi-experimentelle) BA/ITS • bei diagnostischen Fragestellungen auch retrospektive Kohortenstudie
III	Fall-Kontroll-Studie (individuell or SR)	• retrospektive oder retrolektive BA/ITS • ITS mit weniger als 3 Messpunkten vor bzw. nach Einführung der Intervention • Fall-Kontroll-Studie
IV	Fallberichte oder -serien	• Expertenmeinung (narrative Reviews) • Berichte

RCT = randomisierte kontrollierte klinische Interventionstudie
CCT = kontrollierte klinische Interventionsstudie
CBA = kontrollierte vorher-nachher-Studie (before-after-study)
BA = vorher-nachher-Studie (before-after-study)
IST = Zeitreihenanalyse (interrupted-time-series)

6. Zuordnung internationaler Leitlinienempfehlungen zu den Schlüsselfragen

6.1 AG Diagnostik: Zuordnung internationaler Leitlinienempfehlungen zu den Schlüsselfragen

Frage	Leitlinie	Empfehlung / Statement (SM)
1.1 Welche Untersuchungen sind zur Diagnose einer **Harnwegsinfektion** (akute Zystitis, Pyelonephritis) oder der **asymptomatischen Bakteriurie** in den definierten Gruppen erforderlich?	**DEGAM (2018)** **Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**ANAMNESE** Bei Frauen, die an vaginalem Juckreiz oder Ausfluss leiden, sollten alternative Diagnosen und eine **gynäkologische Untersuchung** erwogen werden. (S. 17) (EG: B) (LoE: Ia)
		URINGEWINNUNG Für eine **orientierende Urinuntersuchung** (z. B. mittels Teststreifen) kann bei entsprechender Fragestellung auf eine Gewinnung von Mittelstrahlurin (zugunsten von Spontanurin) sowie auf eine Reinigung des Introitus vaginae bzw. der Glans penis verzichtet werden. (S.18) (EG: -) (LoE: IV)
		Weiterführende laborchemische und/oder mikrobiologische Untersuchungen erfordern jedoch eine exakte Gewinnung und Verarbeitung des Urins, in der Regel von Mittelstrahlurin. Kontaminationen durch Urethral- und/oder Umgebungsflora sind hierbei gering zu halten. (S. 18) (EG: -) (LoE: IV)
		URINMIKROSKOPIE Mit der **Urinmikroskopie** kann bei entsprechender Erfahrung eine Harnwegsinfektion weitgehend ausgeschlossen werden. (S. 21) (EG: -) (LoE: Ia)
		BILDGEBENDE DIAGNOSTIK Bei Patientinnen mit rezidivierenden Harnwegsinfektionen sollten eine **Urinkultur** und einmalig eine **Sonographie** erfolgen. Eine weitere invasive Diagnostik sollte nicht erfolgen (S. 22) (EG: B) (LoE: Ib)
		KOMPLIZIERTE HARNWEGSINFEKTIONEN **Harnwegsinfektionen in der Schwangerschaft**

		Die **Diagnostik** der akuten unkomplizierten Zystitis bei Schwangeren ohne sonstige relevante Begleiterkrankungen erfolgt bezüglich der Anamnese genauso wie bei nicht schwangeren Patientinnen. Allerdings soll in jedem Fall eine **körperliche Untersuchung** und eine **Urinuntersuchung einschließlich Kultur** erfolgen. (S. 37) (EG: A) (LoE: V)
		Nach der Antibiotikatherapie einer akuten unkomplizierten Zystitis soll in der Schwangerschaft die **Erregereradikation durch Urinkultur verifiziert** werden. Expertenkonsens basierend (S. 37) (EG: A) (LoE: V)
		Harnwegsinfektionen bei Männern **Diagnostik** Bei Männern mit rezidivierenden Harnwegsinfektionen sollten **weitere urologische Untersuchungen** erfolgen. Expertenkonsens basierend(S. 40) (EG: B) (LoE: IV)
		Therapie Wenn bei Männern mit einer Harnwegsinfektion eine Indikation zur Antibiotikatherapie gestellt wird, sollte **vor Therapiebeginn eine Urinkultur** durchgeführt werden und entsprechend resistenzgerecht behandelt werden. Expertenkonsens basierend(S. 40) (EG: B) (LoE: IV)
		Harnwegsinfektionen bei geriatrischen Patienten **Urinkatheter** Bei geriatrischen Patienten (mit/ohne Urinkatheter) soll **kein Screening** auf das Vorhandensein einer Bakteriurie erfolgen. Leitliniensynopse (S. 56) (EG: A) (LoE: -)
		Bei Verdacht auf einen Harnwegsinfekt bei Patienten mit liegendem Harnwegskatheter sollte eine **Urinkultur aus einem neugelegten Urinkatheter** gewonnen werden. Leitliniensynopse. (S.56) (EG: B) (LoE:-)
		PYELONEPHRITIS **Diagnostik** Bei der Diagnostik der akuten unkomplizierten Pyelonephritis bei nicht schwangeren Frauen ohne sonstige relevante Begleiterkrankungen sollen zum Ausschluss von komplizierenden Faktoren **weitergehende Untersuchungen (z. B. Sonographie)** erfolgen. Expertenkonsens basierend(S. 57) (EG: A) (LoE: V)
		Nach der Antibiotikatherapie einer Pyelonephritis soll in der Schwangerschaft die Erregereradikation durch **Urinkultur verifiziert** werden. Expertenkonsens basierend (S. 58) (EG: A) (LoE: V)
	EAU (2023) [4] **Urological infections** AGREE II (0,82/1,0)	**Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated cystitis** An accurate diagnosis of uncomplicated cystitis can be based on a **focused history of lower urinary tract symptoms** and **the absence of vaginal**

		discharge or irritation. (S.13) (LoE: 2b)
		Use urine **dipstick testing for diagnosis** of acute uncomplicated cystitis. (S.14) (2b) (weak)
		Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within four weeks after completion of treatment; • women who present with atypical symptoms; • pregnant women. (S.14) (LoE: 2b) (strong)
		Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis **Urine culture** and **antimicrobial susceptibility testing** should be performed in all cases of pyelonephritis in addition to **urinalysis**.☐(S. 19) (LoE: 4)
		A prospective observational cohort study found that radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule. (S. 19) (LoE: 2b)
		Additional **imaging** investigations, such as a contrast enhanced CT scan should be done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis. (S. 20) (LoE: 4)
		Perform **urinalysis** (e.g. using the dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis. (S. 20) (LoE: 2b to 4) (Strong)
		Perform **urine culture** and antimicrobial susceptibility testing in patients with pyelonephritis. (S. 20) (LoE: 2b) (Strong)
		Perform **imaging of the urinary tract** to exclude urgent urological disorders. (S. 20) (LoE: 2b to 4) (Strong)
		Complicated UTI **Summary of evidence table and recommendations for diagnostic evaluation of CA-UTI (S.25) Recommendations for diagnostic evaluation of CA-UTI**
		Do not carry out routine urine culture in asymptomatic catheterised patients. (LoE: 1a to 3) (Strong)
		Recommendations for disease management and prevention of CA-UTI (S.27) Take a **urine culture** prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed. (LoE: 1a to 1b) (Strong)
	SIGN 160 (2020) [5] Management of suspected bacterial lower urinary tract	**Lower urinary tract infection in women aged under 65 years** **Urinary symptoms (S.9)** **Dipstick testing**

	infection in adult women AGREE II (0,95/1,0)	R - Do not diagnose a UTI in the presence of a combination of new onset vaginal discharge or irritation and urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia). ✓ - In making a differential diagnosis it is important to investigate for urethritis and other causes of symptoms to rule out conditions that present in similar ways to uncomplicated UTI. R - Do not confirm the diagnosis of a UTI in the presence of a single urinary symptom (dysuria, frequency, urgency, visible haematuria or nocturia). ✓ - Advise the patient that a UTI cannot be confirmed based on a single urinary symptom and to return if the symptom fails to improve or worsens. R - Diagnose a UTI in the presence of two or more urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia) and a positive dipstick test result for nitrite. ✓ - Before carrying out a dipstick test urine should be retained in the bladder for at least four hours to allow conversion of urinary nitrates to nitrite by pathogens. Shorter incubation times may lead to false negative results. ✓ - On diagnosis of UTI in the presence of two or more urinary symptoms and a positive dipstick test result for nitrite, a urine specimen should only be sent for culture if the patient has a history of resistant urinary isolates, has taken any antibiotics in the past six months or fails to respond to empirical antibiotics. ✓ - Consider sending a urine specimen for culture to inform the diagnosis in patients who present with suspected UTI and two or more urinary symptoms and a negative dipstick test result for nitrite (S. 10) (LoE: 1+ to 1++)
		Choice of agent ✓ - **Local guidance** should take local resistance patterns and risk stratification into account. (S. 17) (LoE: 1+)
		Lower urinary tract infection in women aged 65 years and over **Urinary symptoms** ✓ - Where incontinence is a feature, causes other than UTI should be considered, for example prolapse, voiding dysfunction or functional impairment (S. 23) (LoE: 2++)
		Clinical assessment R: • **Be aware that women aged 65 years and over, especially those in long-term care facilities, may not display the usual symptoms and signs of UTI that are seen in younger women.** • Be aware that functional deterioration and/or changes to performance of activities of daily living may be indicators of infection in frail older people.

		✓ **- A holistic assessment is needed in the frail elderly to rule out other causes with both classical and non-classical signs of UTI. Signs and symptoms which may lead to functional decline include dehydration, constipation, electrolyte abnormality, polypharmacy, pain and urinary retention.** ✓ - Consider sepsis, non-urinary infections and other causes of delirium in an unwell older adult with abnormal vital signs (for example, fever, tachycardia, hypotension, respiratory rate and saturations). 2++ 4 R (S. S.24) (LoE: 2++ to 4)
		Urinalysis and dipstick testing R - Use of **dipsticks for diagnosis of UTI** in women aged 65 years and above in long-term care facilities or in frail elderly people requiring assisted living services is not recommended. ✓ - In women aged 65 years and over with symptoms suggestive of UTI a positive **test for nitrite in the urine** is a marker for bacteriuria, and this should be assessed in the context of the background incidence of asymptomatic bacteriuria. Insufficient evidence was identified to support a recommendation for or against use of urinary dipsticks for the prediction of UTI in non-frail women aged over 65 years. **Urine cultures will lead to false positives if used to diagnose UTI in the context of diffuse symptoms in elderly patients in residential homes and will lead to overdiagnosis.** ✓ **- Send a urine specimen for culture to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above prior to starting antibiotics for a UTI** (S.25) (LoE: 2+ to 3)
		Catheter-associated lower urinary tract infection in women **Diagnosis – Clinical assessment** R - **Clinical signs and symptoms** compatible with CA-UTI should be used to diagnose infection in catheterised patients with **urine culture and sensitivity testing** employed to confirm the diagnosis and pathogen. (S.35) (LoE: 4)
		Dipstick testing ✓ - **Urinary dipsticks should not be used** as part of the diagnostic assessment for UTI in patients with indwelling catheters (S. 35) (LoE: No evidence was identified for or against use of dipstick testing in patients with indwelling catheters and symptoms suggestive of CA-UTI.)
	NICE – Pyelonephritis (2018)* [9] AGREE II (0,88/1,0)	**Managing acute pyelonephritis** **Treatment** In people aged 16 years and over with acute pyelonephritis, obtain a **midstream**

		urine sample before antibiotics are taken and **send for culture and susceptibility** testing (S. 5) (LoE: *)
		Offer an antibiotic (see the recommendations on choice of antibiotic) to people with acute pyelonephritis. Take account of: • the severity of symptoms • the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract or immunosuppression • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria(S. 5) (LoE: *)
		When results of **urine cultures** are available: • review the choice of antibiotic and • change the antibiotic according to susceptibility results if the bacteria are resistant, using a narrow spectrum antibiotic wherever possible. (S. 5-6) (LoE: *)
		Reassessment **Reassess** if symptoms worsen at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as sepsis • previous antibiotic use, which may have led to resistant bacteria(S. 6) (LoE: *)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing lower urinary tract infection** **Treatment for women with lower UTI who are not pregnant** Consider a back-up antibiotic prescription (to use if symptoms do not start to improve within 48 hours or worsen at any time) or an immediate antibiotic prescription (see the recommendations on choice of antibiotic) for women with lower UTI who are not pregnant. Take account of: • the severity of symptoms • the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract or immunosuppression • the evidence for back-up antibiotic prescriptions, which was only in non-pregnant women with lower UTI where immediate antibiotic treatment was not considered necessary
		• **previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria • preferences of the woman for antibiotic use. (S. 5) (LoE: *)
		If a **urine sample has been sent for culture and susceptibility testing** and an antibiotic prescription has been given: • review the choice of antibiotic when microbiological results are available, and

		• change the antibiotic according to susceptibility results if bacteria are resistant and symptoms are not already improving, using a narrow-spectrum antibiotic wherever possible. (S. 5) (LoE: *)
		Managing lower urinary tract infection **Treatment for pregnant women and men with lower UTI** Offer an immediate antibiotic prescription (see the recommendations on choice of antibiotic) to pregnant women and men with lower UTI. Take account of: • **previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria. (S. 6) (LoE: *)
		Obtain a **midstream urine sample** from pregnant women and men before antibiotics are taken, and send for culture and susceptibility testing. (S. 6) (LoE: *)
		Reassessment **Reassess** if symptoms worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis • previous antibiotic use, which may have led to resistant bacteria. Send a **urine sample for culture and susceptibility testing** if this has not already been done and review treatment when results are available (see recommendations 1.1.4, 1.1.7, 1.1.8 and 1.1.12). (S. 8) (LoE: *)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)* [11] AGREE II (0,86/1,0) INDIREKTE EVIDENZ (rUTI hier nicht wirklich gefragt)	**Preventing recurrent urinary tract infections** **Antibiotic prophylaxis** For women with recurrent UTI who are not pregnant, ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable trigger (see the recommendations on choice of antibiotic prophylaxis). Take account of: • the severity and frequency of previous symptoms • the risk of developing complications • **previous urine culture and susceptibility** results • previous antibiotic use, which may have led to resistant bacteria • the woman's preferences for antibiotic use. (S. 7) (LoE: *)
		For women with recurrent UTI who are not pregnant and have had **no improvement after single-dose antibiotic** prophylaxis or have no identifiable triggers, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis). Take account of: • **any further investigations (for example, ultrasound) that may be needed to identify an underlying cause**

		• the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the woman's preferences for antibiotic use. (S. 8) (LoE: *)
		Treatment for men and pregnant women with recurrent UTI For men and pregnant women with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. Take account of: • **any further investigations (for example, ultrasound) that may be needed to identify an underlying cause** • the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications • previous **urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the person's preferences for antibiotic use. (S. 9) (LoE: *)
	NICE-Urinary tract infection (catheter-associated): antimicrobial prescribing (2018)* [12] AGREE II (0,86/1,0)	**Managing catheter-associated urinary tract infection** Be aware that: • a catheter-associated urinary tract infection (UTI) is a symptomatic infection of the bladder or kidneys in a person with a urinary catheter • the longer a catheter is in place, the more **likely bacteria will be found in the urine**; after 1 month nearly all people have bacteriuria • antibiotic treatment is not routinely needed for asymptomatic bacteriuria in people with a catheter. (S.5) (LoE: *)
		Treatment Obtain a **urine sample** before antibiotics are taken. Take the sample from the catheter, via a sampling port if provided, and use an aseptic technique (in line with the NICE guideline on healthcare-associated infections). • If the catheter has been changed, obtain the sample from the new catheter. • If the catheter has been removed, obtain a midstream specimen of urine. (S.5) (LoE: *)
		Send the **urine sample for culture and susceptibility testing**, noting a suspected catheter-associated infection and any antibiotic prescribed. (S.5) (LoE: *)
		Offer an antibiotic (see the recommendations on choice of antibiotic) to people with catheter-associated UTI. Take account of:

		• the severity of symptoms • **the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract, or immunosuppression** • previous **urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria. (S.5-6) (LoE: *)
		Reassessment **Reassess** people with catheter-associated UTI if symptoms worsen at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other **possible diagnoses** • any symptoms or signs suggesting a more serious illness or condition, such as sepsis • previous antibiotic use, which may have led to resistant bacteria. (S.6) (LoE: *)
		Referral and seeking specialist advice Consider referring or seeking specialist advice for people with catheter-associated UTI if they: • are significantly dehydrated or unable to take oral fluids and medicines or • are pregnant or • have a higher risk of developing complications (for example, people with known or suspected structural or functional abnormality of the genitourinary tract, or underlying disease [such as diabetes or immunosuppression]) or • have recurrent catheter-associated UTIs or • have bacteria that are resistant to oral antibiotics. See the evidence and committee discussion on antibiotics for managing catheter-associated UTI. (S.7) (LoE: *)
1.2 …der **asymptomatischen Bakteriurie** in den definierten Gruppen erforderlich?	**DEGAM (2018)** **Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**Therapie der asymptomatischen Bakteriurie** Vor einer erwartungsgemäß Schleimhaut-traumatisierenden Intervention im Harntrakt erhöht eine asymptomatische Bakteriurie das Infektionsrisiko. Deshalb soll **vor einer solchen Intervention nach einer asymptomatischen Bakteriurie gesucht** und diese bei Nachweis behandelt werden. (S. 25) (EG: A) (LoE: Ib).
		Therapie der asymptomatischen Bakteriurie (ABU) Bei asymptomatischen Patienten mit oder ohne Urinkatheter **sollte keine routinemäßige Urinkultur** durchgeführt werden. (S. 26) (EG: B) (LoE: IIIa)
		Für folgende Personengruppen hat eine asymptomatische Bakteriurie offenbar keine nachteiligen Folgen. Deshalb wird **weder ein Screening noch eine Therapie** der asymptomatischen Bakteriurie empfohlen. • nicht schwangere Frauen in der Prämenopause

		• Frauen mit Diabetes mellitus und stabiler Stoffwechsellage • ältere Personen, die zu Hause leben • ältere Personen, die in Heimen leben • Patienten nach Rückenmarksverletzungen • Patienten mit Dauerkatheter in situ • Patienten vor orthopädischen Eingriffen (S. 26) (EG: A) (LoE: Ia-IIb)
	EAU (2023) [4] **Urological infections** AGREE II (0,82/1,0)	**Do not screen** or treat asymptomatic bacteriuria in the following conditions: • women without risk factors (3b); • patients with well-regulated diabetes mellitus (1b); • post-menopausal women (1a); • elderly institutionalised patients (1a); • patients with dysfunctional and/or reconstructed lower urinary tracts (2b); • patients with renal transplants (1a); • patients prior to arthroplasty surgeries (1b); • patients with recurrent urinary tract infections (1b). (S.12-13) (All: EG: Strong)
		Screen for and treat **asymptomatic bacteriuria** prior to urological procedures **breaching the mucosa**. (S.13) (LoE: 1a) (strong)
		Screen for and treat **asymptomatic bacteriuria** in pregnant women with standard short course treatment. (S.13) (LoE: 1a) (Weak)
	SIGN 160 (2020) [5] **Management of suspected bacterial lower urinary tract infection in adult women** AGREE II (0,95/1,0)	**Lower urinary tract infection in women aged 65 years and over** **Urinalysis and dipstick testing** R - **Use of dipsticks** for diagnosis of UTI in women aged 65 years and above in long-term care facilities or in frail elderly people requiring assisted living services is not recommended. ✓ **- In women aged 65 years and over with symptoms suggestive of UTI a positive test for nitrite in the urine is a marker for bacteriuria, and this should be assessed in the context of the background incidence of asymptomatic bacteriuria.** Insufficient evidence was identified to support a recommendation for or against use of urinary dipsticks for the prediction of UTI in non-frail women aged over 65 years. Urine cultures will lead to false positives if used to diagnose UTI in the context of diffuse symptoms in elderly patients in residential homes and will lead to overdiagnosis.

		✓ - **Send a urine specimen for culture** to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above prior to starting antibiotics for a UTI (S.25) (LoE: 2+ to 3)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)*[10] AGREE II (0,88/1,0)	**Managing asymptomatic bacteriuria** Be aware that asymptomatic bacteriuria: • is significant levels of bacteria (greater than 105 colony forming units/ml) in the urine with no symptoms of UTI • **is not routinely screened** for, or treated, in **women who are not pregnant, men, young people and children** • **is routinely screened** for, and treated with **antibiotics, in pregnant women** because it is a risk factor for pyelonephritis and premature delivery (see the recommendations on choice of antibiotic). (S.8-9) (LoE: *)
		Offer an immediate antibiotic prescription to pregnant women with asymptomatic bacteriuria, taking account of: • recent **urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria. (S.8-9) (LoE: *)
2. Welchen Stellenwert hat die Urinuntersuchung mittels Teststreifen für die Diagnose einer Harnwegsinfektion (akute Zystitis, Pyelonephritis) oder der asymptomatischen Bakteriurie?	**DEGAM (2018) Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**URINGEWINNUNG** - Für eine **orientierende Urinuntersuchung (z. B. mittels Teststreifen)** kann bei entsprechender Fragestellung auf eine Gewinnung von Mittelstrahlurin (zugunsten von Spontanurin) sowie auf eine Reinigung des Introitus vaginae bzw. der Glans penis verzichtet werden. (S. 18) (EG: -) (LoE: IV)
		KOMPLIZIERTE HWI: HWI IN DER SCHWANGERSCHAFT Die Diagnostik der akuten unkomplizierten Zystitis bei Schwangeren ohne sonstige relevante Begleiterkrankungen erfolgt bezüglich der Anamnese genauso wie bei nicht schwangeren Patientinnen. Allerdings soll in jedem Fall eine **körperliche Untersuchung** und eine **Urinuntersuchung** einschließlich **Kultur** erfolgen (S. 37) (EG: A) (LoE: V)
	EAU (2023) [4] Urological infections AGREE II (0,82/1,0)	**Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated cystitis** Use urine **dipstick testing** for diagnosis of acute uncomplicated cystitis. (S.14) (LoE: 2b) (strong)
		Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis Perform urinalysis (e.g. using the **dipstick method**), including the assessment of

		white and red blood cells and nitrite, for routine diagnosis. (S. 20) (LoE: 2b to 4) (strong)
		Complicated UTIs **Summary of evidence table and recommendations for diagnostic evaluation of CA-UTI** **Recommendations for diagnostic evaluation of CA-UTI** Do not carry out routine urine culture in asymptomatic catheterised patients. (S.25) (LoE: 1a to 3) (Strong)
	SIGN 160 (2020) [5] **Management of suspected bacterial lower urinary tract infection in adult women** AGREE II (0,95/1,0)	**Lower urinary tract infection in women aged under 65 years** **Urinary symptoms** **Dipstick-Testing** R - Diagnose a UTI in the presence of two or more urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia) and a **positive dipstick test** result for nitrite. ✓ - Before carrying out a dipstick test urine should be retained in the bladder for at least four hours to allow conversion of urinary nitrates to nitrite by pathogens. Shorter incubation times may lead to false negative results. ✓ - On diagnosis of UTI in the presence of two or more urinary symptoms and a positive dipstick test result for nitrite, a urine specimen should only be sent for culture if the patient has a history of resistant urinary isolates, has taken any antibiotics in the past six months or fails to respond to empirical antibiotics. ✓ - Consider sending a urine specimen for culture to inform the diagnosis in patients who present with suspected UTI and two or more urinary symptoms and a negative dipstick test result for nitrite (S.9) (LoE: 1++ to 1+)
		Urinalysis and dipstick testing **R - Use of dipsticks for diagnosis of UTI in women aged 65 years and above in long-term care facilities or in frail elderly people requiring assisted living services is not recommended.** ✓ - In women aged 65 years and over with symptoms **suggestive of UTI a positive test for nitrite in the urine is a marker for bacteriuria, and this should be assessed in the context of the background incidence of asymptomatic bacteriuria.** **Insufficient evidence was identified to support a recommendation for or against use of urinary dipsticks for the prediction of UTI in non-frail women aged over 65 years.** Urine cultures will lead to false positives if used to diagnose UTI in the context of diffuse symptoms in elderly patients in residential homes and will lead to overdiagnosis. ✓ - Send a urine specimen for culture to confirm the pathogen and antibiotic

		susceptibility in women aged 65 years and above prior to starting antibiotics for a UTI. (S.25) (LoE: 2+ to 3)
		Catheter-associated lower urinary tract infection in women R - Clinical signs and symptoms compatible with CA-UTI should be used to diagnose infection in catheterised patients with **urine culture** and sensitivity testing employed to confirm the diagnosis and pathogen (S.35) (LoE: 4)
		Dipstick testing ✓ - **Urinary dipsticks should not be used** as part of the diagnostic assessment for UTI in patients with indwelling catheters (S. 35) (LoE: No evidence was identified for or against use of dipstick testing in patients with indwelling catheters and symptoms suggestive of CA-UTI.)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing lower urinary tract infection** **Treatment for pregnant women and men with lower UTI** Obtain a **midstream urine sample** from pregnant women and men before antibiotics are taken, and send for culture and susceptibility testing. (S.6) (LoE: *)
		Reassessment Reassess if symptoms worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis • previous antibiotic use, which may have led to resistant bacteria. Send a **urine sample for culture and susceptibility testing** if this has not already been done and review treatment when results are available (see recommendations 1.1.4, 1.1.7, 1.1.8 and 1.1.12). (S.8) (LoE: *)
		Managing asymptomatic bacteriuria Offer an immediate antibiotic prescription to pregnant women with asymptomatic bacteriuria, taking account of: • recent **urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria. (S.9) (LoE: *)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)*[11] AGREE II (0,86/1,0)	**Preventing recurrent urinary tract infections** **Antibiotic prophylaxis** For **women with recurrent UTI who are not pregnant**, ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable trigger (see the recommendations on choice of antibiotic prophylaxis). Take account of: • the severity and frequency of previous symptoms

		• the risk of developing complications • **previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria • the woman's preferences for antibiotic use. (S.7) (LoE: *)
		For women with recurrent UTI who are not pregnant and have had no improvement after single-dose antibiotic prophylaxis or have no identifiable triggers, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis). Take account of: • any further investigations (for example, ultrasound) that may be needed to identify an underlying cause • the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the woman's preferences for antibiotic use. (S.8) (LoE: *)
		Treatment for men and pregnant women with recurrent UTI For men and pregnant women with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. Take account of: • any further investigations (for example, ultrasound) that may be needed to identify an underlying cause • the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the person's preferences for antibiotic use. (S.9) (LoE: *)
3. Welchen Stellenwert hat die mikroskopische Urinuntersuchung für die Diagnose einer Harnwegsinfektion?	**DEGAM (2018)** **Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**URINGEWINNUNG** **Weiterführende laborchemische und/oder mikrobiologische Untersuchungen** erfordern jedoch eine exakte Gewinnung und Verarbeitung des Urins, in der Regel von Mittelstrahlurin. Kontaminationen durch Urethral- und/oder Umgebungsflora sind hierbei gering zu halten (S. 18) (EG: -) (LoE: IV).
		URINMIKROSKOPIE Mit der **Urinmikroskopie** kann bei entsprechender Erfahrung eine Harnwegsinfektion weitgehend ausgeschlossen werden. Literatur: [266] (S. 21) (EG:-) (LoE: Ia).

		BILDGEBENDE DIAGNOSTIK Bei Patientinnen mit rezidivierenden Harnwegsinfektionen sollten eine **Urinkultur** und einmalig eine Sonographie erfolgen. Eine weitere invasive Diagnostik sollte nicht erfolgen(S. 22) (EG:B) (LoE: Ib).
		Komplizierte HWI **Harnwegsinfektionen in der Schwangerschaft** Die **Diagnostik** der akuten unkomplizierten Zystitis bei Schwangeren ohne sonstige relevante Begleiterkrankungen erfolgt bezüglich der Anamnese genauso wie bei nicht schwangeren Patientinnen. Allerdings soll in jedem Fall eine körperliche Untersuchung und eine **Urinuntersuchung einschließlich Kultur** erfolgen. (S. 37) (EG:A) (LoE: V).
		Nach der Antibiotikatherapie einer akuten unkomplizierten Zystitis soll in der Schwangerschaft die Erregereradikation durch **Urinkultur** verifiziert werden. Expertenkonsens basierend. (S. 37) (EG:A) (LoE: V).
		Harnwegsinfektionen bei Männern **Therapie** Wenn bei Männern mit einer Harnwegsinfektion eine Indikation zur Antibiotikatherapie gestellt wird, sollte vor Therapiebeginn eine **Urinkultur** durchgeführt werden und entsprechend resistenzgerecht behandelt werden. Expertenkonsens basierend(S. 40) (EG:B) (LoE: IV).
		Harnwegsinfektionen bei geriatrischen Patienten **URINKATHETER** Bei Verdacht auf einen Harnwegsinfekt bei Patienten mit liegendem Harnwegskatheter sollte eine **Urinkultur aus einem neugelegten Urinkatheter** gewonnen werden. Leitliniensynopse(S. 56) (EG:B) (LoE: -).
		PYELONEPHRITIS Nach der Antibiotikatherapie einer Pyelonephritis soll in der Schwangerschaft die **Erregereradikation durch Urinkultur** verifiziert werden. Expertenkonsens basierend (S. 58) (EG:A) (LoE: V).
	EAU (2023) [4] **Urological infections** AGREE II (0,82/1,0)	**Recommendations for the diagnostic evaluation of uncomplicated cystitis** - **Urine cultures** should be done in the following situations: • suspected acute pyelonephritis; • symptoms that do not resolve or recur within four weeks after completion of treatment; • women who present with atypical symptoms; • pregnant women. (S. 14) (LoE: 2b) (Strong)
		Recommendations for the diagnostic evaluation and treatment of recurrent UTIs Diagnose recurrent UTI by **urine culture** (S.19) (LoE: 1a to 3) (strong).

		Do not perform an extensive routine workup (e.g cystoscopy, full abdominal ultrasound) in women younger than 40 years of age with recurrent UTI and no risk factors.(S.19) (LoE: 3) (weak)
		Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis **Urine culture and antimicrobial** susceptibility testing should be performed in all cases of pyelonephritis in addition to urinalysis. (S. 20) (LoE: 4)
		Perform **urinalysis** (e.g. using the dipstick method), including the assessment of white and red blood cells and nitrite, for routine diagnosis. (S.20) (LoE: 2b to 4) (strong)
		Perform **urine culture and antimicrobial** susceptibility testing in patients with pyelonephritis. (S.20) (LoE: 2b to 4) (strong)
		Complicated UTIs **Summary of evidence table and recommendations for diagnostic evaluation of CA-UTI** **Recommendations for diagnostic evaluation of CA-UTI** In the catheterised patient, the presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ABU from CA-UTI. (S.25) (2)
		Do not carry out routine urine culture in asymptomatic catheterised patients. (S.25) (LoE: 1a to 3) (strong)
		Recommendations for disease management and prevention of CA-UTI Take a **urine culture prior** to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed. (S.27) (LoE: 1a to 1b) (Strong)
		Recommendations for disease management and prevention of CA-UTI (S.27) Take a **urine culture prior to initiating antimicrobial therapy** in catheterised patients in whom the catheter has been removed. (LoE: 1a to 1b) (Strong)
		Urethritis **Recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis** A Gram stain of urethral discharge or a urethral smear that shows > 5 PMNL/HPF and gonococci located intracellularly as Gram-negative diplococci, indicates gonococcal urethritis. (S.33) (LoE: 3b)
		Validated NAATs of first-void urine samples have better sensitivity and specificity than any of the other tests available for the diagnosis of chlamydial and gonococcal infections. (S. 33) (LoE: 2a)
		Perform a Gram stain of urethral discharge or a urethral smear to preliminarily diagnose gonococcal urethritis.(S.34) (LoE: 3b) (Strong)
		Perform a validated **nucleic acid amplification test (NAAT)** on a first-void urine

		sample or urethral smear prior to empirical treatment to diagnose chlamydial and gonococcal infections. (S.34) (LoE: 2a) (strong)
		Perform a **urethral swab culture**, prior to initiation of treatment, in patients with a positive NAAT for gonorrhoea to assess the antimicrobial resistance profile of the infective strain. (S.34) (LoE: 1a to 3b) (Strong)
	SIGN 160 (2020) [5] Management of suspected bacterial lower urinary tract infection in adult women AGREE II (0,95/1,0)	**Lower urinary tract infection in women aged under 65 years** **Urinary symptoms (S.9)** **Dipstick testing** ✓ - On diagnosis of UTI in the presence of two or more urinary symptoms and a positive dipstick test result for nitrite, a **urine specimen** should only be sent for **culture if the patient has a history of resistant urinary isolates**, has taken any antibiotics in the past six months or fails to respond to empirical antibiotics. ✓ - Consider **sending a urine specimen for culture** to inform the diagnosis in patients who present with suspected UTI and two or more urinary symptoms and a negative dipstick test result for nitrite (S.10) (LoE: 1+ to 1++)
		Choice of agent ✓ - The choice of agent for an individual patient should be based on **available microbiological results**, tolerability and balance of risk versus benefit. (S.17) (LoE: 1+)
		Urinalysis and dipstick testing ✓ - In women aged 65 years and over with symptoms suggestive of UTI a positive test for nitrite in the urine is a marker for bacteriuria, and this should be assessed in the context of the background incidence of asymptomatic bacteriuria. Insufficient evidence was identified to support a recommendation for or against use of urinary dipsticks for the prediction of UTI in non-frail women aged over 65 years. **Urine cultures will lead to false positives if used to diagnose UTI in the context of diffuse symptoms in elderly patients in residential homes and will lead to overdiagnosis.** **✓ - Send a urine specimen for culture to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above prior to starting antibiotics for a UTI.** (S.25) (LoE: 2+ to 3)
		Catheter-associated lower urinary tract infection in women **Diagnosis – Clinical assessment** R - Clinical signs and symptoms compatible with CA-UTI should be used to diagnose infection in catheterised patients with **urine culture and sensitivity testing** employed to confirm the diagnosis and pathogen. (S.35) (LoE: 4)
	NICE – Pyelonephritis	**Managing acute pyelonephritis**

	(2018)* [9] AGREE II (0,88/1,0)	**Treatment** In people aged 16 years and over with acute pyelonephritis, obtain a midstream urine sample before antibiotics are taken and **send for culture and susceptibility testing**. (S.5) (LoE: *)
		When results of **urine cultures** are available: • review the choice of antibiotic and • change the antibiotic according to susceptibility results if the bacteria are resistant, using a narrow spectrum antibiotic wherever possible. (S.5) (LoE: *)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing lower urinary tract infection** **Treatment for women with lower UTI who are not pregnant** Consider a back-up antibiotic prescription (to use if symptoms do not start to improve within 48 hours or worsen at any time) or an immediate antibiotic prescription (see the recommendations on choice of antibiotic) for women with lower UTI who are not pregnant. Take account of: • the severity of symptoms • the risk of developing complications, which is higher in people with known or suspected structural or
		functional abnormality of the genitourinary tract or immunosuppression • the evidence for back-up antibiotic prescriptions, which was only in non-pregnant women with lower UTI where immediate antibiotic treatment was not considered necessary • **previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria • preferences of the woman for antibiotic use. (S. 5) (LoE: *)
		If a **urine sample has been sent** for culture and susceptibility testing and an antibiotic prescription has been given: • review the **choice of antibiotic when microbiological** results are available, and • change the antibiotic according to susceptibility results if bacteria are resistant and symptoms are not already improving, using a narrow-spectrum antibiotic wherever possible. (S.5-6) (LoE: *)
		Treatment for pregnant women and men with lower UTI Offer an immediate antibiotic prescription (see the recommendations on choice of antibiotic) to pregnant women and men with lower UTI. Take account of: • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria. (S.6) (LoE: *)
		Obtain a **midstream urine sample** from pregnant women and men before antibiotics are taken, and send for **culture and susceptibility testing**. (S.6) (LoE: *)
		For pregnant women with lower UTI:

		• review the choice of antibiotic when **microbiological results are available**, and • change the antibiotic according to susceptibility results if the bacteria are resistant, using a narrow-spectrum antibiotic wherever possible. (S.6) (LoE: *)
		Reassessment Reassess if symptoms worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis • previous antibiotic use, which may have led to resistant bacteria. Send a **urine sample for culture and susceptibility testing** if this has not already been done and review treatment when results are available (see recommendations 1.1.4, 1.1.7, 1.1.8 and 1.1.12). (S.6) (LoE: *)
	Ist keine unkompl. HWI	**Managing asymptomatic bacteriuria** Be aware that asymptomatic bacteriuria: • **is significant levels of bacteria** (greater than 105 colony forming units/ml) in the urine with no symptoms of UTI • is not routinely screened for, or treated, in women who are not pregnant, men, young people and children • is routinely screened for, and treated with antibiotics, in pregnant women because it is a risk factor for pyelonephritis and premature delivery (see the recommendations on choice of antibiotic). (S.8-9) (LoE: *)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)* [11] AGREE II (0,86/1,0)	**Preventing recurrent urinary tract infections** **Antibiotic prophylaxis** For **women with recurrent UTI who are not pregnant**, ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable trigger (see the recommendations on choice of antibiotic prophylaxis). Take account of: • the severity and frequency of previous symptoms • the risk of developing complications • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the woman's preferences for antibiotic use. (S.7) (LoE: *)
		For **women with recurrent UTI who are not pregnant and have had no improvement after single-dose antibiotic** prophylaxis or have no identifiable triggers, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis). Take account of: • any further investigations (for example, ultrasound) that may be needed to

		identify an underlying cause • the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the woman's preferences for antibiotic use. (S.8) (LoE: *)
		Treatment for men and pregnant women with recurrent UTI For men and pregnant women with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. Take account of: • any further investigations (for example, ultrasound) that may be needed to identify an underlying cause • the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications • previous **urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the person's preferences for antibiotic use. (S.9) (LoE: *)
	NICE-Urinary tract infection (catheter-associated): antimicrobial prescribing (2018)* [12] AGREE II (0,86/1,0)	**Managing catheter-associated urinary tract infection** Be aware that: • a catheter-associated urinary tract infection (UTI) is a symptomatic infection of the bladder or kidneys in a person with a urinary catheter • the longer a catheter is in place, the more **likely bacteria will be found in the urine**; after 1 month nearly all people have bacteriuria • antibiotic treatment is not routinely needed for asymptomatic bacteriuria in people with a catheter. (S.5) (LoE: *)
		Treatment Send the urine sample for culture and susceptibility testing, noting a suspected catheter-associated infection and any antibiotic prescribed. (S.5) (LoE: *)
		Offer an antibiotic (see the recommendations on choice of antibiotic) to people with catheter-associated UTI. Take account of: • the severity of symptoms • the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract, or immunosuppression • previous **urine culture and susceptibility** results

		• previous antibiotic use, which may have led to resistant bacteria. (S.5-6) (LoE: *)
		When **urine culture and susceptibility results are available**: • review the choice of antibiotic and • change the antibiotic according to susceptibility results if the bacteria are resistant, using narrow-spectrum antibiotics wherever possible. (S.6) (LoE: *)
		Referral and seeking specialist advice Consider referring or seeking specialist advice for people with catheter-associated UTI if they: • are significantly dehydrated or unable to take oral fluids and medicines or • are pregnant or • have a higher risk of developing complications (for example, people with known or suspected structural or functional abnormality of the genitourinary tract, or underlying disease [such as diabetes or immunosuppression]) or • have recurrent catheter-associated UTIs or • have **bacteria that are resistant to oral antibiotics**. See the evidence and committee discussion on antibiotics for managing catheter-associated UTI. (S.7) (LoE: *)
4. Wie können Symptome einer Harnwegsinfektion zur Diagnostik und Therapieverlauf am besten erfasst werden? ZUSATZ: Symptome werden immer wichtiger; auch im primären Outcome.	**DEGAM (2018)** **Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad) Indirekte Evidenz (es wird nicht direkt auf das WIE des Erfassens von Symptomen eingegangen)	**Klassifikation der Harnwegsinfektionen** Eine untere Harnwegsinfektion (Zystitis) wird angenommen, **wenn sich die akuten Symptome nur auf den unteren Harntrakt beziehen**, z. B. neu aufgetretene Schmerzen beim Wasserlassen (Algurie), imperativer Harndrang, Pollakisurie, Schmerzen oberhalb der Symphyse. (S. 10) (EG:-) (LoE: V).
		Eine obere Harnwegsinfektion (Pyelonephritis) sollte dann angenommen werden, wenn sich bei den **akuten Symptomen z. B. auch ein Flankenschmerz, ein klopfschmerzhaftes Nierenlager und/ oder Fieber (>38°C) finden.** (S. 10) (EG: B) (LoE: V).
		ANAMNESE Frauen mit Verdacht auf eine unkomplizierte Harnwegsinfektion sollen **gefragt** werden, ob sie 1. relevante Schmerzen beim Wasserlassen, häufige Miktionen und imperativen Harndrang haben 2. eine Harnwegsinfektion als Ursache vermuten 3. vaginale Beschwerden haben. Wenn 1. und/oder 2. bejaht werden, ist eine Harnwegsinfektion sehr wahrscheinlich. Bei vaginalen Beschwerden sollen auch **Differenzialdiagnosen** in Betracht gezogen werden. (S. 16) (EG: A) (LoE: Ia).
		Bei Frauen, die an vaginalem Juckreiz oder Ausfluss leiden, sollten alternative Diagnosen und eine **gynäkologische Untersuchung** erwogen werden. (S. 17)

		(EG: B) (LoE: Ia).
		Mit der **Urinmikroskopie** kann bei entsprechender Erfahrung eine Harnwegsinfektion weitgehend ausgeschlossen werden. (S. 21) (EG: -) (LoE: Ia).
		BILDGEBENDE DIAGNOSTIK Bei Patientinnen mit rezidivierenden Harnwegsinfektionen sollten eine **Urinkultur** und **einmalig eine Sonographie** erfolgen. Eine **weitere invasive Diagnostik** sollte nicht erfolgen(S. 22) (EG: B) (LoE: Ib).
		Bei der Diagnostik der akuten unkomplizierten Pyelonephritis bei nicht schwangeren Frauen ohne sonstige relevante Begleiterkrankungen sollen **zum Ausschluss** von komplizierenden Faktoren **weitergehende Untersuchungen (z. B. Sonographie)** erfolgen. Expertenkonsens basierend(S. 22) (EG: A) (LoE: V).
		Komplizierte Harnwegsinfektionen **Harnwegsinfektionen in der Schwangerschaft** Die Diagnostik der akuten unkomplizierten Zystitis bei Schwangeren ohne sonstige relevante Begleiterkrankungen erfolgt bezüglich der Anamnese genauso wie bei nicht schwangeren Patientinnen. Allerdings soll in jedem Fall eine **körperliche Untersuchung** und eine **Urinuntersuchung** einschließlich Kultur erfolgen. (S. 37) (EG: A) (LoE: V).
		Nach der Antibiotikatherapie einer akuten unkomplizierten Zystitis soll in der Schwangerschaft die **Erregereradikation durch Urinkultur** verifiziert werden. Expertenkonsens basierend(S. 37) (EG: A) (LoE: V).
		Harnwegsinfektionen bei Männern **DIAGNOSTIK** Bei Männern mit rezidivierenden Harnwegsinfektionen sollten **weitere urologische Untersuchungen** erfolgen. Expertenkonsens basierend (S. 40) (EG: B) (LoE: IV).
		THERAPIE Wenn bei Männern mit einer Harnwegsinfektion eine Indikation zur Antibiotikatherapie gestellt wird, sollte **vor Therapiebeginn eine Urinkultur** durchgeführt werden und entsprechend resistenzgerecht behandelt werden. Expertenkonsens basierend(S. 40) (EG: B) (LoE: IV).
		Für die empirische orale Therapie der akuten unkomplizierten Zystitis bei jüngeren Männern sollten Pivmecillinam und Nitrofurantoin* eingesetzt werden. *Voraussetzung: **keine Beteiligung der Prostata** (S. 41) (EG: B) (LoE: V).
		Harnwegsinfektionen bei geriatrischen Patienten **URINKATHETER** Bei geriatrischen Patienten (mit/ohne Urinkatheter) soll **kein Screening** auf das Vorhandensein einer Bakteriurie erfolgen. Leitliniensynopse(S. 56) (EG: A) (LoE: -).

		Bei Verdacht auf einen Harnwegsinfekt bei Patienten mit liegendem Harnwegskatheter sollte eine **Urinkultur aus einem neugelegten Urinkatheter** gewonnen werden. Leitliniensynopse(S. 56) (EG: B) (LoE: -).
		PYELONEPHRITIS **DIAGNOSTIK** Bei der Diagnostik der akuten unkomplizierten Pyelonephritis bei nicht schwangeren Frauen ohne sonstige relevante Begleiterkrankungen sollen zum Ausschluss von komplizierenden Faktoren **weitergehende Untersuchungen (z. B. Sonographie)** erfolgen. Expertenkonsens basierend(S. 57) (EG: A) (LoE: V).
	EAU (2023) [4] **Urological infections** AGREE II (0,82/1,0)	**Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated cystitis** An accurate diagnosis of uncomplicated cystitis can be based on a focused history of lower urinary tract symptoms and the absence of vaginal discharge or irritation. (S.13) (2b)
		Diagnose uncomplicated cystitis in women who have no other risk factors for complicated urinary tract infections based on: • a **focused history** of lower urinary tract symptoms (dysuria, frequency and urgency); • the **absence of vaginal discharge** (S. 14) (LoE: 2b) (all: strong)
		Use urine dipstick testing for diagnosis of acute uncomplicated cystitis. (S. 14) (LoE: 2b) (weak)
		Urine cultures should be done in the following situations: • suspected acute pyelonephritis; • **symptoms that do not resolve or recur within four weeks after completion of treatment**; • women who present with atypical symptoms; • pregnant women. (S. 14) (LoE: 2b) (strong)
		Recommendations for the diagnostic evaluation and treatment of recurrent UTIs Diagnose recurrent UTI by urine culture. (S.19) (LoE: 1a to 3) (strong)
		Do not perform an extensive routine workup (e.g cystoscopy, full abdominal ultrasound) in women younger than 40 years of age with recurrent UTI and no risk factors. (S.19) (LoE: 1a to 3) (weak)
		Summary of evidence and recommendations for the diagnostic evaluation of uncomplicated pyelonephritis A prospective observational cohort study found that radiologic imaging can selectively be applied in adults with febrile UTI without loss of clinically relevant information by using a simple clinical prediction rule. (S. 20) (2b)
		Additional imaging investigations, such as a contrast enhanced CT scan should be

		done if the patient remains febrile after 72 hours of treatment or in patients with suspected complications e.g. sepsis. (S. 20) (LoE: 4)
		Perform urine culture and **antimicrobial susceptibility** testing in patients with pyelonephritis. (S. 20) (LoE: 2b to 4) (Strong).
		Perform imaging of the urinary tract to exclude urgent urological disorders. (S. 20) (LoE: 2b) (Strong)
		Recommendations for diagnostic evaluation of CA-UTI **Do not carry out routine urine culture** in asymptomatic catheterised patients. (S.25) (LoE: 1a to 3) (strong)
		Do not use pyuria as sole indicator for catheter-associated UTI. (S.25) (LoE: 1a to 3) (Strong)
		Do not use the presence or absence of odorous or cloudy urine alone to differentiate catheter-associated asymptomatic bacteriuria from catheter-associated UTI. (LoE: 2) (Strong)
		Recommendations for disease management and prevention of CA-UTI Take a urine culture prior to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed. (S.27) (LoE: 1a to 1b) (Strong)
		Recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis A Gram stain of urethral discharge or a urethral smear that shows > 5 PMNL/HPF and gonococci located intracellularly as Gram-negative diplococci, indicates gonococcal urethritis. (S.33) (3b)
		Validated NAATs of first-void urine samples have better sensitivity and specificity than any of the other tests available for the diagnosis of chlamydial and gonococcal infections. (S.33) (2a)
		Perform a Gram stain of urethral discharge or a urethral smear to preliminarily diagnose gonococcal urethritis. (S.34) (LoE: 3b) (strong)
		Perform a validated nucleic acid amplification test (NAAT) on a first-void urine sample or urethral smear prior to empirical treatment to diagnose chlamydial and gonococcal infections. (S.34) (LoE: 2a) (strong)
		Perform a urethral swab culture, prior to initiation of treatment, in patients with a positive NAAT for gonorrhoea to assess the antimicrobial resistance profile of the infective strain. (S.34) (LoE: 1a to 3b) (strong)
	SIGN 160 (2020) [5] **Management of suspected bacterial lower urinary tract infection in adult women** AGREE II (0,95/1,0)	**Lower urinary tract infection in women aged under 65 years** **Urinary symptoms (S.9)** **Dipstick testing** R - Do not diagnose a UTI in the presence of a combination of new onset vaginal discharge or irritation and urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia).

		✓ - In making a differential diagnosis it is important to investigate for urethritis and other causes of symptoms to rule out conditions that present in similar ways to uncomplicated UTI. **R - Do not confirm the diagnosis of a UTI in the presence of a single urinary symptom (dysuria, frequency, urgency, visible haematuria or nocturia).** **✓ - Advise the patient that a UTI cannot be confirmed based on a single urinary symptom and to return if the symptom fails to improve or worsens.** **R - Diagnose a UTI in the presence of two or more urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia) and a positive dipstick test result for nitrite.** **✓ - Before carrying out a dipstick test urine should be retained in the bladder for at least four hours to allow conversion of urinary nitrates to nitrite by pathogens. Shorter incubation times may lead to false negative results.** **✓ - On diagnosis of UTI in the presence of two or more urinary symptoms and a positive dipstick test result for nitrite, a urine specimen should only be sent for culture if the patient has a history of resistant urinary isolates, has taken any antibiotics in the past six months or fails to respond to empirical antibiotics.** **✓ - Consider sending a urine specimen for culture to inform the diagnosis in patients who present with suspected UTI and two or more urinary symptoms and a negative dipstick test result for nitrite** (S. 10) (LoE: 1++ to 1+)
		Lower urinary tract infection in women aged 65 years and over **Urinary symptoms** ✓ - Where incontinence is a feature, causes other than UTI should be considered, for example prolapse, voiding dysfunction or functional impairment (S. 23) (LoE: 2++)
		Clinical assessment • R: Be aware that women aged 65 years and over, especially those in long-term care facilities, may not display the usual symptoms and signs of UTI that are seen in younger women. • R: Be aware that functional deterioration and/or changes to performance of activities of daily living may be indicators of infection in frail older people. ✓ - A holistic assessment is needed in the frail elderly to rule out other causes with both classical and non-classical signs of UTI. Signs and symptoms which may lead

		to functional decline include dehydration, constipation, electrolyte abnormality, polypharmacy, pain and urinary retention. ✓ - Consider sepsis, non-urinary infections and other causes of delirium in an unwell older adult with abnormal vital signs (for example, fever, tachycardia, hypotension, respiratory rate and saturations). 2++ 4 Rz (S. 24) (LoE: 2++ to 4)
		Urinalysis and dipstick testing R - **Use of dipsticks for diagnosis** of UTI in women aged 65 years and above in long-term care facilities or in frail elderly people requiring assisted living services is not recommended. ✓ - In women aged 65 years and over with symptoms suggestive of UTI a positive test for nitrite in the urine is a marker for bacteriuria, and this should be assessed in the context of the background incidence of asymptomatic bacteriuria. Insufficient evidence was identified to support a recommendation for or against use of urinary dipsticks for the prediction of UTI in non-frail women aged over 65 years. **Urine cultures will lead to false positives if used to diagnose UTI** in the context of diffuse symptoms in elderly patients in residential homes and will lead to overdiagnosis. ✓ - **Send a urine specimen** for culture to confirm the pathogen and antibiotic susceptibility in women aged 65 years and above prior to starting antibiotics for a UTI (S.25) (LoE: 2+ to 4)
		Catheter-associated lower urinary tract infection in women **Diagnosis – Clinical assessment** R - **Clinical signs and symptoms compatible with CA-UTI should be used to diagnose infection in catheterised patients with urine culture and sensitivity testing employed to confirm the diagnosis and pathogen.** ✓ - **Clinical scoring tools and decision aids may be considered to aid assessment of clinical signs and symptoms** (S.34) (LoE: 4)
	NICE – Pyelonephritis (2018)* [9] AGREE II (0,88/1,0)	**Managing acute pyelonephritis** **Treatment** In people aged 16 years and over with acute pyelonephritis, obtain a midstream urine sample before antibiotics are taken and **send for culture and susceptibility testing**. (S.5) (LoE: *)
		Offer an antibiotic (see the recommendations on choice of antibiotic) to people with acute pyelonephritis. Take account of: • the severity of symptoms • the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract or

		immunosuppression **• previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria (S.5) (LoE: *)
		Managing acute pyelonephritis **Reassessment** Reassess **if symptoms worsen at any time**, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as sepsis • previous antibiotic use, which may have led to resistant bacteria. (S.6) (LoE: *)
		Referral and seeking specialist advice Refer people aged 16 years and over with acute pyelonephritis to hospital if they have any symptoms or signs suggesting a more serious illness or condition (for example, sepsis). (S.6) (LoE: *)
		Consider **referring or seeking specialist advice** for people aged 16 years and over with acute pyelonephritis if they: • are significantly dehydrated or unable to take oral fluids and medicines or • are pregnant or • have a higher risk of developing complications (for example, people with known or suspected structural or functional abnormality of the genitourinary tract or underlying disease [such as diabetes or immunosuppression]). (S.6-7) (LoE: *)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing lower urinary tract infection** **Treatment for women with lower UTI who are not pregnant** Consider a back-up antibiotic prescription (to use if symptoms do not start to improve within 48 hours or worsen at any time) or an immediate antibiotic prescription (see the recommendations on choice of antibiotic) for women with lower UTI who are not pregnant. Take account of: **• the severity of symptoms** **• the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract or immunosuppression** **• the evidence for back-up antibiotic prescriptions, which was only in non-pregnant women with lower UTI where immediate antibiotic treatment was not considered necessary** **• previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria • preferences of the woman for antibiotic use. (S.5) (LoE: *)
		If a **urine sample has been sent** for culture and susceptibility testing and an antibiotic prescription has been given:

		• review the choice of antibiotic when microbiological results are available, and • change the antibiotic according to susceptibility results if bacteria are resistant and symptoms are not already improving, using a narrow-spectrum antibiotic wherever possible. (S.5-6) (LoE: *)
		Treatment for pregnant women and men with lower UTI Offer an immediate antibiotic prescription (see the recommendations on choice of antibiotic) to pregnant women and men with lower UTI. Take account of: • **previous urine culture** and susceptibility results • previous antibiotic use, which may have led to resistant bacteria. (S.6) (LoE: *)
		Reassessment **Reassess** if symptoms worsen rapidly or significantly at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as pyelonephritis • previous antibiotic use, which may have led to resistant bacteria. Send a **urine sample for culture and susceptibility testing** if this has not already been done and review treatment when results are available (see recommendations 1.1.4, 1.1.7, 1.1.8 and 1.1.12). (S.8) (LoE: *)
		Referral Refer people aged 16 years and over with lower UTI to hospital if they have any symptoms or signs suggesting a **more serious illness or condition** (for example, sepsis). (S.8) (LoE: *)
		Managing asymptomatic bacteriuria Be aware that asymptomatic bacteriuria: • is significant levels of bacteria (greater than 105 colony forming units/ml) in the urine with no symptoms of UTI **• is not routinely screened for, or treated, in women who are not pregnant, men, young people and children** **• is routinely screened for, and treated with antibiotics, in pregnant women because it is a risk factor for pyelonephritis and premature delivery (see the recommendations on choice of antibiotic).** (S.8-9) (LoE: *)
		Offer an immediate antibiotic prescription to pregnant women with **asymptomatic bacteriuria**, taking account of: • recent **urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria. (S.9) (LoE: *)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing-	**Preventing recurrent urinary tract infections** **Antibiotic prophylaxis** For **women with recurrent UTI who are not pregnant**, ensure that any

	(2018)* [11] AGREE II (0,86/1,0)	current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable trigger (see the recommendations on choice of antibiotic prophylaxis). **Take account of:** **• the severity and frequency of previous symptoms** **• the risk of developing complications** **• previous urine culture and susceptibility results** **• previous antibiotic use, which may have led to resistant bacteria** **• the woman's preferences for antibiotic use**(S.7) (LoE: *)
		For **women with recurrent UTI who are not pregnant and have had no improvement after single-dose antibiotic** prophylaxis or have no identifiable triggers, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis). Take account of: **• any further investigations (for example, ultrasound) that may be needed to identify an underlying cause**
		• the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications **• previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria • the woman's preferences for antibiotic use. (S.8) (LoE: *)
		Treatment for men and pregnant women with recurrent UTI For men and pregnant women with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. **Take account of:** **• any further investigations (for example, ultrasound) that may be needed to identify an underlying cause** **• the severity and frequency of previous symptoms** • the risks of long-term antibiotic use • the risk of developing complications **• previous urine culture and susceptibility results** • previous antibiotic use, which may have led to resistant bacteria • the person's preferences for antibiotic use. (S.9) (LoE: *)
	NICE-Urinary tract infection (catheter-associated): antimicrobial prescribing (2018)* [12] AGREE II (0,86/1,0)	**Treatment** Obtain a urine sample before antibiotics are taken. Take **the sample from the catheter,** via a sampling port if provided, and use an aseptic technique (in line with the NICE guideline on healthcare-associated infections). • If the catheter has been changed, obtain the sample from the new catheter.

		• If the catheter has been removed, obtain a midstream specimen of urine(S.5) (LoE: *)
		Send the urine sample for culture and susceptibility testing, noting a suspected catheter-associated infection and any antibiotic prescribed(S.5) (LoE: *)
		Offer an antibiotic (see the recommendations on choice of antibiotic) to people with catheter-associated UTI. Take account of: • **the severity of symptoms** ● the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract, or immunosuppression ● **previous urine culture and susceptibility results** ● previous antibiotic use, which may have led to resistant bacteria. (S.5-6) (LoE: *)
		Reassessment **Reassess** people with catheter-associated UTI if symptoms worsen at any time, or do not start to improve within 48 hours of taking the antibiotic, taking account of: • other possible diagnoses • any symptoms or signs suggesting a more serious illness or condition, such as sepsis • previous antibiotic use, which may have led to resistant bacteria. (S.6) (LoE: *)
		Referral and seeking specialist advice Refer people with catheter-associated UTI to hospital if they have **any symptoms or signs suggesting** a more serious illness or condition (for example, sepsis). (S.7) (LoE:*)
5. Wie sollte die Uringewinnung für die Diagnose einer Harnwegsinfektion erfolgen?	**DEGAM (2018)** **Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**URINGEWINNUNG** Für Patienten und Patientinnen, die nicht zur Standardgruppe gehören, sind die gängigen Empfehlungen mit dem Ziel der Reduktion von Kontaminationen • das Spreizen der Labien • die sorgfältige Reinigung des Meatus urethrae der Frau bzw. der Glans penis des Mannes mit Wasser • die Gewinnung von Mittelstrahlurin Expertenkonsens basierend auf: • das Spreizen der Labien: [14, 169] • die sorgfältige Reinigung des Meatus urethrae der Frau bzw. der Glans penis des Mannes mit Wasser: [192, 205] • die Gewinnung von Mittelstrahlurin: [170, 171, 192] (S. 18) (EG: B) (LoE: IV).
		Für eine orientierende Urinuntersuchung (z. B. mittels Teststreifen) kann bei entsprechender Fragestellung auf eine Gewinnung von Mittelstrahlurin (**zugunsten von Spontanurin**) sowie auf eine Reinigung des Introitus vaginae bzw. der Glans penis verzichtet werden. (S. 18) (EG: -) (LoE: IV).

		Weiterführende laborchemische und/oder mikrobiologische Untersuchungen erfordern jedoch eine **exakte Gewinnung** und Verarbeitung des Urins, in der **Regel von Mittelstrahlurin**. **Kontaminationen** durch Urethral- und/oder Umgebungsflora sind hierbei gering zu halten. (S. 18) (EG: -) (LoE: IV).
	EAU (2023) [4] **Urological infections** AGREE II (0,82/1,0)	**Recommendations for disease management and prevention of CA-UTI** Take a urine culture **prior** to initiating antimicrobial therapy in catheterised patients in whom the catheter has been removed. (S.27) (LoE: 1a to 1b) (strong)
		Urethritis **Recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis** A Gram stain of **urethral discharge or a urethral smear** that shows > 5 PMNL/HPF and gonococci located intracellularly as Gram-negative diplococci, indicates gonococcal urethritis (S.33) (LoE: 3b)
		Validated NAATs **of first-void urine samples** have better sensitivity and specificity than any of the other tests available for the diagnosis of chlamydial and gonococcal infections. (S.33) (LoE: 2a)
		Perform a Gram stain of **urethral discharge or a urethral smear** to preliminarily diagnose gonococcal urethritis. (S.34) (LoE: 3b) (strong)
		Perform a validated nucleic acid amplification test (NAAT) on a **first-void urine sample** or urethral smear prior to empirical treatment to diagnose chlamydial and gonococcal infections. (S.34) (LoE: 2a) (strong)
	SIGN 160 (2020) [5] **Management of suspected bacterial lower urinary tract infection in adult women** AGREE II (0,95/1,0)	**Lower urinary tract infection in women aged under 65 years** **Urinary symptoms** **Dipstick testing** R - Diagnose a UTI in the presence of two or more urinary symptoms (dysuria, frequency, urgency, visible haematuria or nocturia) and a positive dipstick test result for nitrite. ✓ **- Before carrying out a dipstick test urine should be retained in the bladder for at least four hours to allow conversion of urinary nitrates to nitrite by pathogens. Shorter incubation times may lead to false negative results.** ✓ - On diagnosis of UTI in the presence of two or more urinary symptoms and a positive dipstick test result for nitrite, a urine specimen should only be sent for culture if the patient has a history of resistant urinary isolates, has taken any antibiotics in the past six months or fails to respond to empirical antibiotics. ✓ - Consider sending a urine specimen for culture to inform the diagnosis in patients who present with suspected UTI and two or more urinary symptoms and a negative dipstick test result for nitrite (S. 9) (LoE: 1++ to 1+)
	NICE – Pyelonephritis	**Managing acute pyelonephritis**

	(2018)* [9] AGREE II (0,88/1,0)	**Treatment** In people aged 16 years and over with acute pyelonephritis, obtain **a midstream urine sample** before antibiotics are taken and send for culture and susceptibility testing. (S.5) (LoE: *)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing lower Urinary Tract Infections** **Treatment for pregnant women and men with lower UTI** Obtain a **midstream urine sample** from pregnant women and men before antibiotics are taken, and send for culture and susceptibility testing. (S.6) (LoE: *)
6. Welche weiteren diagnostischen Methoden/ Untersuchungen sollten bei rezidivierenden HWI in den definierten Gruppen angewendet werden?	**DEGAM (2018)** **Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**BILDGEBENDE DIAGNOSTIK** Bei Patientinnen mit rezidivierenden Harnwegsinfektionen sollten eine **Urinkultur** und einmalig eine **Sonographie** erfolgen. Eine **weitere invasive Diagnostik sollte nicht erfolgen**. (S. 22) (EG: B), (LoE: Ib)
		Behandlung rezidivierender unkomplizierte HWI Bei Frauen ohne sonstige relevante Begleiterkrankungen mit rezidivierenden Harnwegsinfektionen sollte **keine routinemäßige Zystoskopie** erfolgen. (S.34) (EG: B), (LoE: IIb)
		Harnwegsinfektionen bei Männern **Diagnostik** Bei Männern mit rezidivierenden Harnwegsinfektionen sollten **weitere urologische Untersuchungen** erfolgen. Expertenkonsens basierend auf (S.40) (EG: B); (LoE: IV)
	EAU (2023) [4] **Urological infections** AGREE II (0,82/1,0)	**Summary of evidence and recommendations for the diagnostic evaluation and treatment of Recurrent UTIs (rUTIs)** Extensive routine workup including cystoscopy, imaging, etc., has a low diagnostic yield for the diagnosis of rUTI. (S.19) (LoE: 3)
		Recommendations for the diagnostic evaluation and treatment of recurrent UTIs Diagnose recurrent UTI by **urine culture**. (S.19) (LoE: 1a to 3) (Strong)
		Do not perform an extensive routine workup (e.g cystoscopy, full abdominal ultrasound) in women younger than 40 years of age with recurrent UTI and no risk factors. (S.19) (LoE: 3) (weak)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)* [11] AGREE II (0,86/1,0)	**Preventing recurrent urinary tract infections** **Antibiotic prophylaxis** For **women with recurrent UTI who are not pregnant**, ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable trigger (see the

		recommendations on choice of antibiotic prophylaxis). **Take account of:** **• the severity and frequency of previous symptoms** **• the risk of developing complications** **• previous urine culture and susceptibility results** **• previous antibiotic use, which may have led to resistant bacteria** **• the woman's preferences for antibiotic use** (S.7) (LoE: *)
		For **women with recurrent UTI who are not pregnant and have had no improvement after single-dose antibiotic** prophylaxis or have no identifiable triggers, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis). Take account of: **• any further investigations (for example, ultrasound) that may be needed to identify an underlying cause** **• the severity and frequency of previous symptoms** **• the risks of long-term antibiotic use** **• the risk of developing complications** **• previous urine culture and susceptibility results** **• previous antibiotic use, which may have led to resistant bacteria** **• the woman's preferences for antibiotic use.** (S.8) (LoE: *)
		Treatment for men and pregnant women with recurrent UTI For men and pregnant women with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. Take account of: **• any further investigations (for example, ultrasound) that may be needed to identify an underlying cause** **• the severity and frequency of previous symptoms** **• the risks of long-term antibiotic use** **• the risk of developing complications** **• previous urine culture and susceptibility results** **• previous antibiotic use, which may have led to resistant bacteria** **• the person's preferences for antibiotic use.** (S.8) (LoE: *)
	NICE-Urinary tract infection (catheter-associated): antimicrobial prescribing (2018)* [12] AGREE II (0,86/1,0)	**Managing catheter-associated urinary tract infection** **Referral and seeking specialist advice** Consider referring or **seeking specialist advice for people with catheter-associated UTI if they**: • are significantly dehydrated or unable to take oral fluids and medicines or • are pregnant or • have a higher risk of developing complications (for example, people with known

		or suspected structural or functional abnormality of the genitourinary tract, or underlying disease [such as diabetes or immunosuppression]) or • **have recurrent catheter-associated UTIs or** • have bacteria that are resistant to oral antibiotics. See the evidence and committee discussion on antibiotics for managing catheter-associated UTI. (S.7) (LoE:*)
7. Welchen Stellenwert hat eine Behandlung einer Harnwegsinfektion (in Bezug auf die Therapiesicherheit) ohne Arzt-Patienten-Kontakt? ZUSATZ: Arzt-Patienten-Kontakt ist mehr geworden (spez. während COVID: tel. Patientensprechstunde)	**DEGAM (2018)** **Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**Medikamentöse Behandlung akuter Infektionen** **Nichtantibiotische Behandlungsmöglichkeiten** Bei häufig rezidivierender Zystitis der Frau kann Mannose empfohlen werden. Alternativ können verschiedene Phytotherapeutika (z. B. Präparate aus Bärentraubenblättern (max 1 Monat), Kapuzinerkressekraut, Meerrettichwurzel, erwogen werden. (S. 27) (EG: C) (LoE: Ib).
		Symptomatische Behandlung mit Ibuprofen Bei der akuten unkomplizierten Zystitis sollte eine antibiotische Therapie empfohlen werden. Bei Patientinnen mit leichten/mittelgradigen Beschwerden kann die alleinige symptomatische Therapie als Alternative zur antibiotischen Behandlung erwogen werden. **Eine partizipative Entscheidungsfindung mit den Patienten ist notwendig**. (S. 28) (EG: B) (LoE: Ia).
	EAU (2023) [4] **Urological infections** AGREE II (0,82/1,0) Indirekte Evidenz (präventiver Ansatz)	**Summary of evidence and recommendations for the diagnostic evaluation and treatment of Recurrent UTIs (rUTIs)** Increased water intake is an effective antimicrobial-sparing strategy to prevent rUTI in pre-menopausal women at high risk for recurrence who drink low volumes (< 1.5 L) of fluid daily (S.19) (LoE: 3)
	Indirekte Evidenz: Arzt-Kontakt zumindest einmal erforderlich	Vaginal oestrogen replacement has shown a trend towards preventing rUTI in post-menopausal women. (S.19) (1b)
		Immunoactive prophylaxis has been shown to be more effective than placebo in female patients with rUTIs in several RCTs with a good safety profile. (S.19) (1a)
		Probiotics containing L. rhamnosus GR-1, L. reuteri B-54 and RC-14, L. casei shirota, or L. crispatus CTV-05 are effective for vaginal flora restoration and prevention of rUTIs. (S.19) (1b)
		Current scientific evidence regarding the efficacy of cranberry products in the prevention of UTIs is divided. (S.19) **(1a)**
		Based on limited evidence, D-mannose can significantly reduce the number of UTI episodes and can be an effective agent for UTI prevention in selected patients. (S.19) **(2)**
		Both continuous low-dose antimicrobial prophylaxis and post-coital antimicrobial prophylaxis, have been shown to reduce the rate of rUTI.

		(S.19) **(1b)**
		A prospective cohort study showed that **intermittent self-start therapy is effective, safe and economical in women with rUTIs. (S.19) (2b)**
	Indirekte Evidenz (präventiver Ansatz)	**Recommendations for the diagnostic evaluation and treatment of recurrent UTIs** Advise pre-menopausal women regarding **increased fluid intake** as it might reduce the risk of recurrent UTI. (S.19) (LoE: 3) (weak)
	Indirekte Evidenz (präventiver Ansatz)	Use **vaginal oestrogen replacement** in post-menopausal women to prevent recurrent UTI (S.18) (1b) (strong)
		Use **immunoactive prophylaxis** to reduce recurrent UTI in all age groups. (S.19) (1a) (weak)
		Advise patients on the use of **local or oral probiotics** containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs. (S.19) (1b) (weak)
		Advise patients on the use of **cranberry products** to reduce recurrent UTI episodes; however, patients should be informed that the quality of evidence underpinning this is low with contradictory findings. (S.19) (1a)(weak)
		Use **D-mannose** to reduce recurrent UTI episodes, but patients should be informed that further studies are needed to confirm the results of initial trials. (S.19) (2) (weak)
		Use **endovesical instillations of hyaluronic acid** or a combination of hyaluronic acid and chondroitin sulphate to prevent recurrent UTIs in patients where less invasive preventive approaches have been unsuccessful. Patients should be informed that further studies are needed to confirm the results of initial trials. (S.19) (LoE: 1a to 3) (Weak)
		Use continuous or **post-coital antimicrobial prophylaxis** to prevent recurrent UTI when nonantimicrobial interventions have failed. Counsel patients regarding possible side effects. (S.19) (1b) (strong)
	Indirekte Evidenz - setzt Arzt-Kontakt voraus, um Antibiotika zu erhalten (Zumindest in Deutschland)	For patients with **good compliance self-administered short-term antimicrobial therapy** should be considered. (S.19) (2b) (strong)
	SIGN 160 (2020) [5] Management of suspected bacterial lower urinary tract infection in adult women AGREE II (0,95/1,0)	**Recurrent lower urinary tract infection in women** **Management – self care** R - Women with a history of recurrent UTI should be **advised to aim for a fluid intake** of around 2.5 L a day of which at least 1.5 L is water. To help achieve a **fluid intake** of around 2.5 L a day, it may be useful to express total fluid intake as 6 to 8 mugs a day (with a mug expected to hold around 350 ml) (S.28) (LoE: 1+ to 2+)
	Indirekte Evidenz - setzt Arzt-Kontakt voraus, um Antibiotika zu erhalten (Zumindest in Deutschland)	**Pharmacological treatment: antimicrobials** **Voiding behaviours and hygiene** R - Consider **prophylactic antimicrobials** for women experiencing recurrent UTI

		after discussion of self-care approaches and the risks and benefits of antimicrobial treatment involved. R - Long-term prophylactic antimicrobials for prevention of recurrent UTI should be used with caution in women aged 65 years and over, and careful consideration given to the risks and benefits involved (S.28) (LoE: 1++)
	Indirekte Evidenz - setzt Arzt-Kontakt voraus, um Antibiotika zu erhalten (Zumindest in Deutschland)	**Choice of agent for long-term prophylaxis of recurrent UTI** ✓ - To minimise the development of resistance antimicrobial prophylaxis should be used as a fixed course of three to six months in women with recurrent UTI. (S.29) (LoE: 1++ to 1+)
	NICE – Pyelonephritis (2018)*[9] AGREE II (0,88/1,0) Indirekte Evidenz - Patienten zumindest zuvor darüber informiert werden	**Managing acute pyelonephritis** **Advice when an antibiotic prescription is given** When an antibiotic is given, as well as the general advice on self-care, give advice about: • possible adverse effects of the antibiotic, particularly diarrhoea and nausea • nausea with vomiting also being a possible indication of worsening pyelonephritis • seeking medical help if: — symptoms worsen at any time oror — symptoms do not start to improve within 48 hours of taking the antibiotic or — the person becomes systemically very unwell. (S.6) (LoE: *)
	Indirekte Evidenz - Erfordert zumindest einmal Arzt-Kontakt	**Self-care** Advise people with acute pyelonephritis about using **paracetamol for pain, with the possible addition of a low-dose weak opioid** such as codeine for people over 12 years. (S. 7) (LoE: „No systematic reviews or randomised controlled trials (RCTs) of any non-antimicrobial treatments were identified that met the inclusion criteria.“)
		Advise people with acute pyelonephritis **about drinking enough fluids to avoid dehydration**. (S.7) (LoE: „No systematic reviews or randomised controlled trials (RCTs) of any non-antimicrobial treatments were identified that met the inclusion criteria.“)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing lower urinary tract infection** Give advice **about managing symptoms with self-care** (see the recommendations on self-care) to all people with lower UTI. (S.5) (LoE: *)
	Indirekte Evidenz - setzt Arzt-Kontakt voraus, um Antibiotika zu erhalten (Zumindest in Deutschland)	**Advice for all people with lower UTI when an antibiotic prescription is given** When a back-up antibiotic prescription is given, as well as the general advice on self-care, give advice about:

		• an antibiotic not being needed immediately • using the back-up prescription if symptoms do not start to improve within 48 hours or if they worsen at any time • possible adverse effects of antibiotics, particularly diarrhoea and nausea • seeking medical help if antibiotics are taken and: – symptoms worsen rapidly or significantly at any time, oror – symptoms do not start to improve within 48 hours of taking the antibiotic, or – the person becomes systemically very unwell. (S.7) (LoE: *)
	Indirekte Evidenz - Erfordert zumindest einmal Arzt-Kontakt	**Self-care** Advise people with lower UTI about using **paracetamol for pain**, or if preferred and suitable **ibuprofen** (S.9) (LoE: very low to moderate quality) **(Paracetamol: kein LoE)**
		Advise people with lower UTI about drinking enough **fluids to avoid dehydration** (S.9) (LoE: *)
		Be aware that no evidence was found on **cranberry products** or **urine alkalinising agents** to treat lower UTI (S.9) (LoE: no evidence)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)* [11] AGREE II (0,86/1,0)	**Preventing recurrent urinary tract infections** Give advice to people with recurrent UTI about **behavioural and personal hygiene measures and self-care treatments** (see the recommendations on self-care) that may help to reduce the risk of UTI. (S.5) (LoE: *)
		Self-care Be aware that: • Some women with recurrent UTI may wish to try **D-mannose** if they are not pregnant (the evidence for D-mannose was based on a study in which it was taken as 200 ml of 1% solution once daily in the evening). D-mannose is a sugar that is available to buy as powder or tablets; it is not a medicine. (S.11) (LoE: low to high quality evidence). • Some women with recurrent UTI may wish to try **cranberry products** if they are not pregnant (evidence of benefit is uncertain and there is no evidence of benefit for older women). (S.11) (LoE: very low to moderate quality of evidence).
		Advise people taking **cranberry products or D-mannose** about the sugar content of these products, which should be considered as part of the person's daily sugar intake. (S.11) (LoE: s. cranberry & D-Mannose)
		Be aware that evidence is inconclusive about whether **probiotics (lactobacillus)** reduce the risk of UTI in people with recurrent UTI. (S.11) (LoE: low to moderate quality evidence)
	NICE-Urinary tract infection (catheter-associated):	**Managing catheter-associated urinary tract infection** Give advice about **managing symptoms with self-care** (see the

	antimicrobial prescribing (2018)* [12] AGREE II (0,86/1,0)	recommendations on self-care) to all people with catheter-associated UTI. (S.5) (LoE:*)
		Self-care Advise people with catheter-associated UTI about using paracetamol for pain. (S.7) (LoE: No systematic reviews or RCTs of any other non-antimicrobial treatments were identified that met the inclusion criteria.)
		Advise people with catheter-associated UTI about drinking enough fluids to avoid dehydration. (S.7) (LoE: No systematic reviews or RCTs of any other non-antimicrobial treatments were identified that met the inclusion criteria.)

6.2 AG Therapie: Zuordnung internationaler Leitlinienempfehlungen zu den Schlüsselfragen

Frage	Leitlinie	Empfehlung / Statement (SM)
(SF1) Ist eine antibiotische Behandlung einer Harnwegsinfektion oder einer asymptomatischen Bakteriurie in den definierten Gruppen erforderlich?	**DEGAM (2018) Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**Nichtantibiotische Behandlungsmöglichkeiten** **Symptomatische Behandlung mit Ibuprofen** Bei der akuten unkomplizierten Zystitis sollte eine antibiotische Therapie empfohlen werden. Bei Patientinnen mit leichten/mittelgradigen Beschwerden kann die alleinige symptomatische Therapie als Alternative zur antibiotischen Behandlung erwogen werden. Eine partizipative Entscheidungsfindung mit den Patienten ist notwendig. (S. 28) (EG= B) (LoE= Ia)
		Pyelonephritis Bei Frauen in der Prämenopause mit einer milden oder mittelschweren Pyelonephritis und klinisch unauffälligem Verlauf sollte die antibiotische Therapie über 5 bis 10 Tage erfolgen. (S. 58) (EG: B) (LoE: Ib)
		Harnwegsinfektionen bei geriatrischen Patienten **Urinkatheter** Ein Harnwegsinfekt bei Patienten mit einem liegenden Harnwegskatheter sollte 7 Tage antibiotisch behandelt werden. Leitliniensynopse (S. 56) (EG= A) (LoE= -)
	EAU (2023) [4] Urological infections* AGREE II (0,82/1,0)	**Summary of evidence and recommendations for the management of ABU** Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment. (S. 13) (LoE: 1a) (weak)
		Summary of evidence and recommendations for the treatment of uncomplicated

		pyelonephritis (S.20) Treat patients with uncomplicated pyelonephritis requiring hospitalisation with an intravenous antimicrobial regimen initially (S. 21) (LoE: 1b) (strong)
		Switch patients initially treated with parenteral therapy, who improve clinically and can tolerate oral fluids, to oral antimicrobial therapy. (S. 21) (LoE: 1b) (strong)
		Recommendations for the diagnostic evaluation and antimicrobial treatment of urethritis Use a pathogen directed treatment based on local resistance data. (S.33) (LoE: 1a to 3b) (strong)
		Sexual partners should be treated maintaining patient confidentiality. (S.33) (LoE: *) (strong)
	Sofern CA-UTI-Anstätze auf geriatrische Patienten übertragbar sind	**Recommendations for disease management [and prevention] of CA-UTI (S.27)** Treat symptomatic catheter-associated-UTI according to the recommendations for complicated UTI (see section 3.7.5 ⇩). (S. 27) (LoE:1a to 1b) (strong)
		Do not treat catheter-associated asymptomatic bacteriuria in general. (S. 27) (LoE: *) (strong)
		[Do not use prophylactic antimicrobials to prevent catheter-associated UTIs (S.28) (LoE:*) (strong).]
		[Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal. (S.28) (LoE:*) (weak).]
		[Do not routinely use antibiotic prophylaxis to prevent clinical UTI after urethral catheter removal or in patients performing intermittent self-catheterisation (S.28) (LoE:*) (weak).]
	Sofern auf geriatrische Patienten übertragbar	**[Complicated UTIs]** **Summary of evidence** Use the combination of: • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms. (S. 24) (LoE: *) (strong)]
		[Only use ciprofloxacin provided that the local resistance percentages are < 10% when: • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials. (S. 24) (LoE: 1b to 2) (strong)]
		Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from urology departments or when patients have used fluoroquinolones in the last six months. (S. 24) (LoE: *) (strong)
	SIGN 160 (2020) [5] Management of suspected bacterial lower urinary tract infection in adult	**Lower urinary tract infection in women aged under 65 years** **Urinary symptoms** **Management** R - Consider NSAIDs as first-line treatment in women aged <65 years with suspected uncomplicated lower UTI who describe their symptoms as mild. ✓ - Consider **NSAIDs as an alternative to an antibiotic** following a discussion of risks and benefits in women aged <65 years with suspected uncomplicated lower UTI when symptoms are

	women AGREE II (0,95/1,0)	moderate to severe. ✓ - The decision to use an **NSAID or antibiotic** should be shared between patient and prescriber and risks and benefits should be fully discussed and considered. This is particularly important in women with comorbidities that increase renal impairment. ✓ - Duration of NSAIDs should be limited to three days to minimise adverse effects. ✓ - Patients receiving NSAIDs should be informed to contact their prescriber if UTI symptoms do not resolve within three days or worsen. All: (S. 13-15) (LoE: 1++ to 2+)
		Treatment of asymptomatic bacteriuria in non-pregnant women R - Do not treat asymptomatic bacteriuria in non-pregnant women of any age. (S. 21 und 27) (LoE: 1++)
		Delayed prescription of antimicrobials **Non-pharmacological treatment** ✓ - Decision making should be shared between patient and prescriber and risks and benefits should be fully discussed and considered. (S. 21) (LoE: 1++ to 1+)
		Lower urinary tract infection in women aged 65 years and over **Self-Care** ✓ - Exercise caution in women who are on fluid restriction for medical reasons (for example, those with chronic heart failure or on renal dialysis). ✓ - The Care Inspectorate document Eating and Drinking Well in Care provides best practice guidance on older people's dietary needs and related food and fluid requirements. (S.26) (1+ to 3)
		Pharmacological treatment: antimicrobials - Choice of agent (S.26) R - Consider use of a narrow-spectrum antimicrobial with activity against common uropathogens for treatment of LUTI in women aged 65 years and over. Consider individual patient factors such as impaired renal function, polypharmacy and adverse effects, such as CDI and antimicrobial resistance (see Table 4; s. Frage 7).
	NICE – Pyelonephritis (2018)* [9] AGREE II (0,88/1,0)	**Managing acute pyelonephritis** **Treatment** Offer an antibiotic (see the recommendations on choice of antibiotic) to people with acute pyelonephritis. (s. Frage 8)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing lower urinary tract infection** Consider a back-up antibiotic prescription (to use if symptoms do not start to improve within 48 hours or worsen at any time) or an immediate antibiotic prescription (see the recommendations on choice of antibiotic → s. Frage 7) for women with lower UTI who are not pregnant (S.5).
		Managing asymptomatic bacteriuria

		Offer an immediate antibiotic prescription to pregnant women with asymptomatic bacteriuria, taking account of: • recent urine culture and susceptibility results • previous antibiotic use, which may have led to resistant bacteria. All: (S. 9) s. Frage 7)
Sofern CA-UTI-Anstätze auf geriatrische Patienten übertragbar sind	**NICE-Urinary tract infection (catheter-associated): antimicrobial prescribing (2018)* [12]** AGREE II (0,86/1,0)	**Managing catheter-associated urinary tract infection** antibiotic treatment is not routinely needed for asymptomatic bacteriuria in people with a catheter (S.5).
		Treatment • […] Do not allow catheter removal or change to delay antibiotic treatment. […] (S.5) • […] Offer an antibiotic (see the recommendations on choice of antibiotic) to people with catheter-associated UTI (S.5). Recommendations for: - non-pregnant women and men aged 16 years and over - pregnant women aged 12 years and over (S. 7-8)
(SF 2) Welche weiteren Behandlungsalternativen zur Therapie einer Harnwegsinfektion in den definierten Gruppen können empfohlen werden?	**DEGAM (2018) Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**Nicht-medikamentöse Behandlung** Für nichtmedikamentöse Maßnahmen liegt kaum eine hochwertige Evidenz vor, es handelt sich daher zumeist um Expertenempfehlungen ▪ Ausreichende Trinkmenge (mind. 2 Liter/d) (Kontraindikationen beachten, z. B. Herzinsuffizinz) ▪ Ggf. Behandlung einer Obstipation ▪ Wärmeapplikation bei Schmerzen (S. 26)
	SIGN 160 (2020) [5] Management of suspected bacterial lower urinary tract infection in adult women AGREE II (0,95/1,0)	**Lower urinary tract infection in women aged under 65 years** **Urinary symptoms** **Management** R - Consider **NSAIDs as first-line treatment in women aged <65 years** with suspected uncomplicated lower UTI who describe their symptoms as mild. ✓ - Consider **NSAIDs as an alternative to an antibiotic following a discussion of risks and benefits in women aged <65 years** with suspected uncomplicated lower UTI when symptoms are moderate to severe. ✓ - The decision to use an NSAID or antibiotic should be shared between patient and prescriber and risks and benefits should be fully discussed and considered. This is particularly important in women with comorbidities that increase renal impairment. ✓ - Duration of NSAIDs should be limited to three days to minimise adverse effects. ✓ - Patients receiving NSAIDs should be informed to contact their prescriber if UTI symptoms do not resolve within three days or worsen.

		All: (S. 12-14) (LoE: 1++ to 2+)
		Delayed prescription of antimicrobials **Non-pharmacological treatment** ✓ - Decision making should be shared between patient and prescriber and risks and benefits should be fully discussed and considered. (S. 21) (LoE: 1++ to 1+)
		Lower urinary tract infection in women aged 65 years and over ✓ - Exercise caution in women who are on fluid restriction for medical reasons (for example, those with chronic heart failure or on renal dialysis) (S. 26) (LoE: 1+ to 3). ✓ - The Care Inspectorate document Eating and Drinking Well in Care provides best practice guidance on older people's dietary needs and related food and fluid requirements (S. 26) (LoE: 1+ to 3).
		Treatment of asymptomatic bacteriuria in non-pregnant women R - Do not treat asymptomatic bacteriuria in non-pregnant women of any age. (S. 21 und 27) (LoE: 1++)
	NICE – Pyelonephritis (2018)*[9] AGREE II (0,88/1,0)	**Managing acute pyelonephritis** **Treatment** Offer an *antibiotic* (see the recommendations on choice of antibiotic) to people with acute pyelonephritis. (s. Frage 1 und 8)
	NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10] AGREE II (0,88/1,0)	**Managing asymptomatic bacteriuria** **Self-Care** - Advise people with lower UTI about using paracetamol for pain, or if preferred and suitable ibuprofen. - Advise people with lower UTI about drinking enough fluids to avoid dehydration. - Be aware that no evidence was found on cranberry products or urine alkalinising agents to treat lower UTI. (S.9)
Sofern CA-UTI-Anstätze auf geriatrische Patienten übertragbar sind	**NICE-Urinary tract infection (catheter-associated): antimicrobial prescribing (2018)* [12]** AGREE II (0,86/1,0)	**Managing catheter-associated urinary tract infection** **Self-Care** • Advise people with catheter-associated UTI about using paracetamol for pain (S.7). • Advise people with catheter-associated UTI about drinking enough fluids to avoid dehydration. (S.7)
(SF 7) Welche Antibiotika kommen für die Therapie der unkomplizierten Zystitis in Frage?	**DEGAM (2018) Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**Medikamentöse Behandlung akuter Infektionen** **Antibiotische Behandlung** Bei der antibiotischen Therapie der akuten unkomplizierten Zystitis (nicht Pyelonephritis) sollte wenn möglich eine Kurzzeittherapie (1 bis 3 Tage) durchgeführt werden. **Antibiotische Behandlungsmöglichkeiten** Bei unkomplizierter Zystitis soll vorzugsweise eines der folgenden Antibiotika eingesetzt werden:

		Fosfomycin-Trometamol, Nitrofurantoin, Nitroxolin, Pivmecillinam, Trimethoprim* (in alphabetischer Reihenfolge). *bei Resistenzraten < 20 %. (S. 30) (EG: A) (LoE: Ia)
		Fluorchinolone und Cephalosporine sollen nicht als Antibiotika der ersten Wahl bei der unkomplizierten Zystitis eingesetzt werden. Basierend auf Expertenkonsens. (S. 30) (EG: A) (LoE: V)
		Harnwegsinfektionen in der Schwangerschaft Bei akuten unkomplizierten Harnwegsinfektionen bei Schwangeren ohne sonstige relevante Begleiterkrankungen sollten primär Penicillinderivate, Cephalosporine, oder Fosfomycin-Trometamol eingesetzt werden. (S. 37) (EG: B) (LoE: V)
		Harnwegsinfektionen bei Männern Für die empirische orale Therapie der akuten unkomplizierten Zystitis bei jüngeren Männern sollten Pivmecillinam und Nitrofurantoin* eingesetzt werden. *Voraussetzung: keine Beteiligung der Prostata (S. 41) (EG: B) (LoE: V)
	ABS (2018) [7] **AGREE II (0,78/1,0)** (EG= Empfehlungsgrad)	**Orale Bioverfügbarkeit** Bei ausreichend oral bioverfügbaren Substanzen und unter Berücksichtigung der klinischen Situation des Patienten soll von einer parenteralen auf eine perorale Antibiotikagabe umgestellt werden. S. 39 (EG: I) (Evidenzgrad: I)
		C. difficile ABS-Maßnahmen zur Reduktion bestimmter Substanzen/-klassen sollen verwendet werden, um die Häufigkeit von C. difficile-Infektionen zu senken. S. 48 (EG: A) (Evidenzgrad: I) (Erläuterung S. 49)
		Resistente gramnegative Bakterien, MRSA und VRE ABS-Maßnahmen zur Reduktion bestimmter Substanzen/-klassen sollten verwendet werden, um die Häufigkeit von Infektionen mit mehrfach resistenten gramnegativen Bakterien, insbesondere ESBL-Bildnern sowie MRSA und VRE zu senken. S. 48 (EG: B; LOE: I-II) (Erläuterung S. 49)
		Freigaberegelungen Das ABS-Team soll über die Verwendung von Freigaberegelungen entscheiden, wenn der angemessene Einsatz von Antibiotika nicht über ABS-Visiten oder Fortbildungsmaßnahmen gesichert werden kann. Dabei sollen Restriktionsmaßnahmen einer kontinuierlichen Verbrauchssurveillance unterliegen, um frühzeitig unerwünschte Auswirkungen der Maßnahme zu erkennen. S. 22 (EG: A) (Evidenzgrad: I)
		Qualitätssicherung, Struktur-/Prozessqualität ABS-Programme sollen in die einrichtungsspezifische Qualitätssicherung integriert werden. Auf bereits vorhandene Daten der externen Qualitätssicherung, der Surveillance resistenter Erreger oder des Antibiotikaverbrauches soll zurückgegriffen werden. In jedem ABS-Programm sollen

<table>
<tr><td></td><td></td><td>geeignete Qualitätsindikatoren zur Ausstattung (Strukturindikatoren), zur Behandlung bzw. zum Verordnungsverhalten (Prozessindikatoren) bestimmt werden.
S. 15 (EG: A) (Evidenzgrad: I)</td></tr>
<tr><td></td><td>EAU (2023) [4] Urological infections*
AGREE II (0,82/1,0)</td><td>Summary of evidence and recommendations for antimicrobial therapy for uncomplicated cystitis
Prescribe fosfomycin trometamol, pivmecillinam or nitrofurantoin as first-line treatment for uncomplicated cystitis in women. (S. 15) (LoE: *) (strong)</td></tr>
<tr><td></td><td></td><td>Do not use aminopenicillins or fluoroquinolones to treat uncomplicated cystitis. (S. 15) (LoE: *) (strong)</td></tr>
<tr><td></td><td></td><td>S.15 Table 1: Suggested regimens for antimicrobial therapy in uncomplicated cystitis
<table>
<tr><th>Antimicrobial</th><th>Daily dose</th><th>Duration of therapy</th><th>Comments</th></tr>
<tr><td colspan="4">First-line women</td></tr>
<tr><td>Fosfomycin trometamol</td><td>3 g SD</td><td>1 day</td><td rowspan="5">Recommended only in women with uncomplicated cystitis</td></tr>
<tr><td>Nitrofurantoin macrocrystal</td><td>50-100 mg four times a day</td><td>5 days</td></tr>
<tr><td>Nitrofurantoin monohydrate/ macrocrystals</td><td>100 mg b.i.d</td><td>5 days</td></tr>
<tr><td>Nitrofurantoin macrocrystal prolonged release</td><td>100 mg b.i.d</td><td>5 days</td></tr>
<tr><td>Pivmecillinam</td><td>400 mg t.i.d</td><td>3-5 days</td></tr>
<tr><td colspan="4">Alternatives</td></tr>
<tr><td>Cephalosporins (e.g. cefadroxil)</td><td>500 mg b.i.d</td><td>3 days</td><td>Or comparable</td></tr>
<tr><td colspan="4">If the local resistance pattern for E. coli is < 20%</td></tr>
<tr><td>Trimethoprim</td><td>200 mg b.i.d</td><td>5 days</td><td>Not in the first trimenon of pregnancy</td></tr>
<tr><td>Trimethoprimsulphamethoxazole</td><td>160/800 mg b.i.d</td><td>3 days</td><td>Not in the last trimenon of</td></tr>
</table></td></tr>
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<table>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td></td><td></td><td>pregnancy</td></tr>
<tr><td colspan="4">Treatment in men</td></tr>
<tr><td>Trimethoprimsulphamethoxazole</td><td>160/800 mg b.i.d</td><td>7 days</td><td>Restricted to men, fluoroquinolones can also be prescribed in accordance with local susceptibility testing.</td></tr>
</table>
SD = single dose; b.i.d = twice daily; t.i.d = three times daily.
</td></tr>
<tr><td></td><td>SIGN 160 (2020) [5]
Management of suspected bacterial lower urinary tract infection in adult women
AGREE II (0,95/1,0)</td><td>
Lower urinary tract infection in women aged under 65 years
Urinary symptoms
Management
R - Use a narrow-spectrum antimicrobial with activity against common uropathogens (see Table 4, p.25) for empirical treatment of LUTI in suitable patients.
R - Do not use fluroroquinolones or co-amoxiclav empirically for LUTI unless other narrow-spectrum agents are contraindicated due to comorbidity, toxicity or resistance.
✓ - Advise women with LUTI, who are prescribed nitrofurantoin, not to take alkalinising agents (such as potassium citrate, sodium citrate, or sodium bicarbonate)
All: (S. 17-18) (LoE: 1++ to 4)
Increasing resistance in urinary gram-negative isolates has recently led to a revival of the antimicrobial fosfomycin, which is given as a single oral dose of 3 g for acute uncomplicated UTI, but evidence for the effectiveness of this agent is conflicting (S.18).
</td></tr>
<tr><td></td><td></td><td>
Lower urinary tract infection in women aged under 65 years
Choice of agents
(S.25) Table 4: Comparison of selected antimicrobial agents for treatment of LUTI
<table>
<tr><th>First-line / empirical agents</th><th>Comments</th></tr>
<tr><td>Nitrofurantoin</td><td>First-line treatment option. Narrow-spectrum agent with low rate of resistance.
Not suitable for patients with eGFR <45 ml/min/1.73 m. Efficacy reduced when taken concurrently with over-the-counter urinary alkalinising remedies containing citrate.</td></tr>
<tr><td>Trimethoprim</td><td>First-line treatment option. Narrow-spectrum agent.
Dose adjustments required in patients with renal impairment.</td></tr>
</table>
</td></tr>
</table>

			Resistance rate for E. coli 33.6% in Scotland.
		Alternative agents	Comments
		Amoxicillin	Second-line treatment option but high rate of resistance in E. coli (52.8% in 2018) so only suitable for targeted treatment.
		Pivmecillinam	Second-line treatment option which is useful for targeted treatment (against organisms sensitive to pivmecillinam). Narrow-spectrum agent.
		Fosfomycin	Second-line treatment option which is useful for targeted treatment (against organisms sensitive to fosfomycin). Broad-spectrum agent. Single-dose treatment.
		Restricted agents	Comments
		Cefalexin	Broad-spectrum agent. 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. If a cephalosporin is essential in patients with a history of immediate hypersensitivity to penicillin, because a suitable alternative antibacterial is not available, then cefixime, cefotaxime,ceftazidime, ceftriaxone, or cefuroxime can be used with caution; cefaclor, cefadroxil, cefalexin, cefradine, and ceftaroline fosamil should be avoided. Cephalosporins are associated with an increased risk of CDI.
		Ciprofloxacin	Use only where other antibiotic choices are unsuitable. Adverse safety profile - MHRA warning; do not use for LUTI unless all other agents unsuitable. Fluoroquinolones are associated with an increased risk of CDI.
		Co-amoxiclav	Restricted treatment option. Less effective in achieving cure than other classes. Broad-spectrum agent. Contraindicated in patients with history of co-amoxiclav-associated jaundice or hepatic

<table>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>dysfunction and those with history of penicillinassociated
jaundice or hepatic dysfunction.
Resistance rates for E. coli around 25% in Scotland.
Co-amoxiclav is associated with an increased risk of CDI.</td></tr>
</table>
Local formularies will determine the dose and duration of individual antimicrobials used for treatment of UTI
</td></tr>
<tr><td></td><td></td><td>✓ - The choice of agent for an individual patient should be based on available microbiological results, tolerability and balance of risk versus benefit.
✓ - Local guidance should take local resistance patterns and risk stratification into account.
All: (S. 19) (LoE: 1++)</td></tr>
<tr><td></td><td></td><td>Duration of treatment
R - Use short (3-day) courses of antimicrobials for treatment for LUTI, as this is clinically effective and minimises the risk of adverse events (S. 19) (LoE: 1++).</td></tr>
<tr><td></td><td></td><td>Lower urinary tract infection in women aged 65 years and over
Pharmacological treatment: antimicrobials - Choice of agent
R - Consider use of a narrow-spectrum antimicrobial with activity against common uropathogens for treatment of LUTI in women aged 65 years and over. Consider individual patient factors such as impaired renal function, polypharmacy and adverse effects, such as CDI and antimicrobial resistance (S.26) (see Table 4 ⇧).</td></tr>
<tr><td></td><td>NICE - Urinary tract infection (lower): antimicrobial prescribing guideline (2018)* [10]
AGREE II (0,88/1,0)</td><td>Managing lower urinary tract infection
Consider a back-up antibiotic prescription (to use if symptoms do not start to improve within 48 hours or worsen at any time) or an immediate antibiotic prescription (see the recommendations on choice of antibiotic) for women with lower UTI who are not pregnant. (S.5)
Offer an immediate antibiotic prescription (see the recommendations on choice of antibiotic) to pregnant women and men with lower UTI. (S.6)
Antibiotics for non-pregnant women aged 16 years and overyear (S. 10-11)
<table>
<tr><th>Treatment</th><th>Antibiotic, dosage and course length</th></tr>
<tr><td>First choices
If there are symptoms of pyelonephritis (such as fever) or a complicated urinary tract infection (UTI), see the NICE guideline on acute pyelonephritis for antibiotic choices.</td><td>Nitrofurantoin (if estimated glomerular filtration rate [eGFR] is 45 ml/minute or more): 100 mg modified-release twice a day (or, if unavailable, 50 mg four times a day) for 3 days
Trimethoprim (if there is a low risk of resistance): 200 mg twice a day for 3 days</td></tr>
<tr><td>Second choices</td><td>Nitrofurantoin (if eGFR is 45 ml/minute or</td></tr>
</table>
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<table>
<tr><td></td><td></td><td>(if no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice is not suitable). If there are symptoms of pyelonephritis (such as fever) or a complicated UTI, see the NICE guideline on acute pyelonephritis for antibiotic choices.</td><td>more, and it was not used as first-choice): 100 mg modified-release twice a day (or, if unavailable, 50 mg
four times a day) for 3 days.
Pivmecillinam (a penicillin):
400 mg initial dose, then 200 mg three times a day for a total of 3 days.
Fosfomycin: 3 g single dose sachet</td></tr>
<tr><td></td><td></td><td colspan="2">Antibiotics for pregnant women aged 12 years and over (S.12)<table><tr><th>Treatment</th><th>Antibiotic, dosage and course length</th></tr><tr><td>First choice
If there are symptoms of pyelonephritis (such as fever) or a complicated urinary tract infection (UTI), see the NICE guideline on acute pyelonephritis for antibiotic choices.</td><td>Nitrofurantoin (if estimated glomerular filtration rate [eGFR] is 45 ml/minute or more):
100 mg modified-release twice a day (or, if unavailable, 50 mg four times a day) for 7 days
Avoid at term because it may produce neonatal haemolysis (BNF, August 2018)</td></tr><tr><td>Second choices (if no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice is not suitable). If there are symptoms of pyelonephritis (such as fever) or a complicated UTI, see the NICE guideline on acute pyelonephritis for antibiotic choices.</td><td>Amoxicillin (only if culture results are available and susceptible):
500 mg three times a day for 7 days
Cefalexin:
500 mg twice a day for 7 days</td></tr><tr><td>Alternative second choices</td><td>Consult local microbiologist, and choose antibiotics based on culture and susceptibility results</td></tr><tr><td>Treatment of asymptomatic bacteriuria</td><td>Choose from nitrofurantoin, amoxicillin or cefalexin based on recent culture and susceptibility results</td></tr></table></td></tr>
<tr><td></td><td></td><td colspan="2">Antibiotics for men aged 16 years and over (S.13)<table><tr><th>Treatment</th><th>Antibiotic, dosage and course length</th></tr><tr><td>First choices
If there are symptoms of pyelonephritis (such as fever) or a complicated urinary tract infection
(UTI), see the NICE guideline on acute pyelonephritis for antibiotic choices.</td><td>Trimethoprim:
200 mg twice a day for 7 days.
Nitrofurantoin (if estimated glomerular filtration rate [eGFR] is 45 ml/minute or more):
100 mg modified-release twice a day (or, if unavailable, 50 mg four times a day) for 7 days.</td></tr></table></td></tr>
</table>

			Nitrofurantoin is not recommended for men with suspected prostate involvement because it is unlikely to reach therapeutic levels in the prostate.
		Second choices (if no improvement in lower UTI symptoms on first choice taken for at least 48 hours, or when first choice is not suitable). If there are symptoms of pyelonephritis (such as fever) or a complicated UTI, see the NICE guideline on acute pyelonephritis for antibiotic choices.	Consider alternative diagnoses and follow recommendations in the NICE guideline on pyelonephritis (acute): antimicrobial prescribing or the NICE guideline on prostatitis (acute): antimicrobial prescribing, basing antibiotic choice on recent culture and susceptibility results.
(SF8) Welche Antibiotika kommen für die Therapie der unkomplizierten Pyelonephritis in Frage?	**DEGAM (2018) Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**Komplizierte Harnwegsinfektionen** **Harnwegsinfektionen in der Schwangerschaft** Bei akuten unkomplizierten Harnwegsinfektionen bei Schwangeren ohne sonstige relevante Begleiterkrankungen sollten primär Penicillinderivate, Cephalosporine, oder Fosfomycin-Trometamol eingesetzt werden. (S. 37) (EG: B) (LoE: V)	
		Pyelonephritis **Therapie** Bei einer unkomplizierten Pyelonephritis mit leichten bis moderaten Verlaufsformen soll vorzugsweise eines der folgenden oralen Antibiotika eingesetzt werden: Cefpodoxim, Ceftibuten*, Ciprofloxacin, Levofloxacin (in alphabetischer Reihenfolge). *in Deutschland nicht mehr im Handel (S. 58) (EG: A) (LoE: Ib)	
	EAU (2022) [4] Urological infections* AGREE II (0,82/1,0)	**Summary of evidence and recommendations for the treatment of uncomplicated pyelonephritis** Treat patients with uncomplicated pyelonephritis not requiring hospitalisation with short course fluoroquinolones as first-line treatment. (S. 21) (LoE: 1b) (strong)	
		Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis. (p. 21 LoE: 1b → Catrell 2018)	
		Intravenous antimicrobial regimens for uncomplicated pyelonephritis may include a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin. (S.21; LoE: 1b)→s. EAU Tab. 4 S. 22 Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis 2nd line treatment: Cefepime, Piperacillin/Tazobactam, Gentamicin, Amikacin)	
		Carbapenems should only be considered in patients with early culture results indicating the presence of multi-drug resistant organisms (S. 21; LoE: 4). [Last line: Imipenem/Cilastatin, Meropenem, Ceftolozane/tazobactam, Ceftazidime/avibactam, Cefiderocol, Meropenem-	

vaborbactam, Plazomicin → Consider only in patients with early culture results indicating the presence of multi-drug resistant organisms.]

Treat patients with uncomplicated pyelonephritis requiring hospitalisation with an intravenous antimicrobial regimen initially. (S. 21) (LoE: 1b) (strong)

Do not use nitrofurantoin, oral fosfomycin, and pivmecillinam to treat uncomplicated pyelonephritis. (S. 21) (LoE: *) (strong)

S.21: Table 3:
Suggested regimens for empirical oral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobial	Daily	Daily dose of therapy	Comments
Ciprofloxacin	500-750 mg b.i.d	7 days	Fluoroquinolone resistance should be less than 10%.
Levofloxacin	750 mg q.d	5 days	
Trimethoprim sulphamethoxazol	160/800 mg b.i.d	14 days	If such agents are used empirically, an initial intravenous dose of a longacting parenteral antimicrobial (e.g. ceftriaxone) should be administered.
Cefpodoxime	200 mg b.i.d	10 days	
Ceftibuten	400 mg q.d	10 days	

b.i.d = twice daily; q.d = every day.

S.21 Table 4:
Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis

Antimicrobial	Daily dose	Comments
First-line treatment		
Ciprofloxacin	400 mg b.i.d	
Levofloxacin	750 mg q.d	
Cefotaxime	2 g t.i.d	Not studied as monotherapy in acute uncomplicated pyelonephritis.
Ceftriaxone	1-2 g q.d	Lower dose studied, but higher dose recommended.
Second-line treatment		
Cefepime	1-2 g b.i.d	Lower dose studied, but higher dose recommended.
Piperacillin/ tazobactam	2.5-4.5 g t.i.d	

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<table>
<tr><td></td><td></td><td></td></tr>
<tr><td>Gentamicin</td><td>5 mg/kg q.d</td><td rowspan="2">Not studied as monotherapy in acute uncomplicated pyelonephritis.</td></tr>
<tr><td>Amikacin</td><td>15 mg/kg q.d</td></tr>
<tr><td>Last-line alternatives</td><td></td><td></td></tr>
<tr><td>Imipenem/ cilastatin</td><td>0.5 g t.i.d</td><td rowspan="7">Consider only in patients with early culture results indicating the presence of multidrug-resistant organisms.</td></tr>
<tr><td>Meropenem</td><td>1 g t.i.d</td></tr>
<tr><td>Ceftolozane/tazobactam</td><td>1.5 g t.i.d</td></tr>
<tr><td>Ceftazidime/ avibactam</td><td>2.5 g t.i.d</td></tr>
<tr><td>Cefiderocol</td><td>2 g t.i.d</td></tr>
<tr><td>Meropenemvaborbactam</td><td>2 g t.i.d</td></tr>
<tr><td>Plazomicin</td><td>15 mg/kg o.d</td></tr>
</table>
b.i.d = twice daily; t.i.d = three times daily; q.d = every day; o.d = once daily.
</td></tr>
<tr><td></td><td>NICE – Pyelonephritis (2018)* [9]
AGREE II (0,88/1,0)</td><td>Managing acute pyelonephritis
Treatment
Offer an antibiotic (see the recommendations on choice of antibiotic ⇩) to people with acute pyelonephritis. (S.5)</td></tr>
<tr><td></td><td></td><td>1.3 Choice of antibiotic
table 1 for non-pregnant women and men aged 16 years and over
table 2 for pregnant women aged 12 years and over (S.8)</td></tr>
<tr><td></td><td></td><td>Give oral antibiotics first line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics (S.8).</td></tr>
<tr><td></td><td></td><td>Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible (S.8).</td></tr>
<tr><td></td><td></td><td>
<table>
<tr><th colspan="2">Table 1: Antibiotics for non-pregnant women and men aged 16 years and over(S. 8):</th></tr>
<tr><th>Antibiotic, dosage and course length</th><th>Treatment</th></tr>
<tr><td>Cefalexin:
500 mg twice or three times a day (up to 1 to 1.5 g three or four times a day for severe infections) for 7 to 10 days
Co-amoxiclav (only if culture results available and susceptible):
500/125 mg three times a day for 7 to 10 days
Trimethoprim (only if culture results available and susceptible):</td><td>First-choice oral antibiotics</td></tr>
</table>
</td></tr>
</table>

		200 mg twice a day for 14 days **Ciprofloxacin**(consider safety issues): 500 mg twice a day for 7 days	
		Co-amoxiclav (only in combination or if culture results available and susceptible): 1.2 g three times a day **Cefuroxime**: 750 mg to 1.5 g three or four times a day **Ceftriaxone**: 1 g to 2 g once a day **Ciprofloxacin** (consider safety issues): 400 mg twice or three times a day **Gentamicin**: Initially 5 mg/kg to 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration Therapeutic drug monitoring and assessment of renal function is required (BNF information on gentamicin) **Amikacin**: Initially 15 mg/kg once a day (maximum per dose 1.5 g once a day), subsequent doses adjusted according to serum amikacin concentration (maximum 15 g per course) Therapeutic drug monitoring and assessment of renal function is required (BNF information on amikacin)	First-choice intravenous antibiotics (if vomiting, unable to take oral antibiotics, or severely unwell). Antibiotics may be combined if susceptibility or sepsis a concern.
		Consult a local microbiologist	Second-choice intravenous antibiotics
		Table 2: Antibiotics for pregnant women aged 12 years and over	
		Antibiotic, dosage and course length	**Treatment**
		Cefalexin: 500 mg twice or three times a day (up to 1 g to 1.5 g three or four times a day for severe infections) for 7 to 10 days	First-choice oral antibiotic
		Cefuroxime: 750 mg to 1.5 g three or four times a day	First-choice intravenous antibiotic (if vomiting, unable to take oral antibiotics, or severely unwell)
		Consult local microbiologist	Second-choice antibiotics or when combining

			antibiotics if susceptibility or sepsis a concern.

* Evidenzlevel ist nicht immer zuzuordnen bzw. nicht vorhanden. Bei der AGREE II-Bewertung wurde dieser Tatbestand entsprechend berücksichtigt.

6.3 AG Prävention: Zuordnung internationaler Leitlinienempfehlungen zu den Schlüsselfragen

Frage	Leitlinie	Empfehlung / Statement (SM)
SF 1: Welche nicht-medikamentösen Maßnahmen verringern die Häufigkeit rezidivierender HWIen?	**DEGAM (2018) Brennen beim Wasserlassen [8]** AGREE II (0,92/1,0) (EG= Empfehlungsgrad)	**Nichtantibiotische Behandlungsmöglichkeiten** Bei häufig rezidivierender Zystitis der Frau kann Mannose empfohlen werden. Alternativ können verschiedene Phytotherapeutika (z. B. Präparate aus Bärentraubenblättern (max 1 Monat), Kapuzinerkressekraut, Meerrettichwurzel, erwogen werden. (S. 27) (EG= C) (LoE= 1b)
	EAU (2023) [4] Urological infections* AGREE II (0,82/1,0)	**Recommendations for the diagnostic evaluation and treatment of recurrent UTIs** Advise pre-menopausal women regarding increased fluid intake as it might reduce the risk of recurrent UTI.(S.19) (LoE: 3) (weak)
		Increased water intake is an effective antimicrobial-sparing strategy to prevent rUTI in premenopausal women at high risk for recurrence who drink low volumes (< 1.5 L) of fluid daily Seite 19 (LoE: 3)
		Advise patients on the use of local or oral probiotics containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs (S.19) (LoE: 1b) (weak).
		Advise patients on the use of cranberry products to reduce recurrent UTI episodes; however, patients should be informed that the quality of evidence underpinning this is low with contradictory findings. (S. 19) (LoE: 1a) (weak)
	SIGN 160 (2020) [5] Management of suspected bacterial lower urinary tract infection in adult women AGREE II (0,95/1,0)	**Recurrent lower urinary tract infection in women** **Management – self care** R - Women with a history of recurrent UTI should be advised to aim for a fluid intake of around 2.5 L a day of which at least 1.5 L is water. To help achieve a fluid intake of around 2.5 L a day, it may be useful to express total fluid intake as 6 to 8 mugs a day (with a mug expected to hold around 350 ml). ✓ - Materials to support public awareness of the importance of hydration are available from Health Protection Scotland. ✓ - Exercise caution in women who are on fluid restriction for medical reasons (for example, those with chronic heart failure or on renal dialysis). All: (S.28) (LoE: 1+ to 2+)

		Spermicidal contraception R - Consider offering women who are experiencing recurrent UTI an alternative to spermicide- containing contraceptives. (S.28) (LoE: 2+ to 4)
		Non-pharmacological treatment - Cranberry (S.31-33) (LoE: 1++ to 1+) - Herbal products (S.33) (LoE: 1++) - Probiotics (S.33) (LoE: 1++ to 1+) - Acupuncture (S.33) (LoE: 4)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)*[11] AGREE II (0,86/1,0)	**Antibiotic prophylaxis** For women with recurrent UTI who are not pregnant, consider a trial of antibiotic prophylaxis only if **behavioural and personal hygiene measures**, and vaginal oestrogen (in postmenopausal women) are not effective or not appropriate (S.7).
		Self-care Be aware that: • Some women with recurrent UTI may wish to try D-mannose if they are not pregnant (the evidence for D-mannose was based on a study in which it was taken as 200 ml of 1% solution once daily in the evening). D-mannose is a sugar that is available to buy as powder or tablets; it is not a medicine. • Some women with recurrent UTI may wish to try cranberry products if they are not pregnant (evidence of benefit is uncertain and there is no evidence of benefit for older women). • Some children and young people under 16 years with recurrent UTI may wish to try cranberry products with the advice of a paediatric specialist (evidence of benefit is uncertain). All: (S.11)
		Advise people taking cranberry products or D-mannose about the sugar content of these products, which should be considered as part of the person's daily sugar intake. All: (S.11)
		Be aware that evidence is inconclusive about whether probiotics (lactobacillus) reduce the risk of UTI in people with recurrent UTI. All: (S.11)
SF 2: Welche medikamentösen Maßnahmen verringern die Häufigkeit rezidivierender HWIen?	**EAU (2023) [4] Urological infections*** AGREE II (0,82/1,0)	**[Summary of evidence and recommendations for the management of ABU** Do not screen or treat asymptomatic bacteriuria in the following conditions: • women without risk factors; • patients with well-regulated diabetes mellitus; • post-menopausal women; • elderly institutionalised patients; • patients with dysfunctional and/or reconstructed lower urinary tracts; • patients with renal transplants; • patients prior to arthroplasty surgeries; • patients with **recurrent urinary tract infections.** (S. 12-13) (LoE: 1b) (strong)]
		[Screen for and treat asymptomatic bacteriuria in pregnant women with standard short course treatment (S. 13) (LoE: 1a) (weak)]

		Recommendations for the diagnostic evaluation and treatment of recurrent UTIs Use vaginal oestrogen replacement in post-menopausal women to prevent recurrent UTI. (S.19) (LoE: 1b) (strong).
		Use immunoactive prophylaxis to reduce recurrent UTI in all age groups. (S. 19) (LoE: 1a) (strong)
		Use D-mannose to reduce recurrent UTI episodes, but patients should be informed that further studies are needed to confirm the results of initial trials. (S. 19) (LoE: 2) (weak)
		Use endovesical instillations of hyaluronic acid or a combination of hyaluronic acid and chondroitin sulphate to prevent recurrent UTIs in patients where less invasive preventive approaches have been unsuccessful. Patients should be informed that further studies are needed to confirm the results of initial trials. (S. 19) (LoE: 2) (weak)
		Use continuous or post-coital antimicrobial prophylaxis to prevent recurrent UTI when nonantimicrobial interventions have failed. Counsel patients regarding possible side effects. (S. 19) (LoE: 1b) (strong)
		For patients with good compliance self-administered short-term antimicrobial therapy should be considered. (S.19) (LoE: 2b) (strong)
	Sofern CA-UTI-Anstätze auf geriatrische Patienten übertragbar sind	**Recommendations for disease management and prevention of CA-UTI (S.27)** Treat symptomatic catheter-associated-UTI according to the recommendations for complicated UTI (see section 3.7.5 ⇩). (S. 27) (LoE: *) (strong)
		Do not use **prophylactic antimicrobials to prevent catheter-associated** UTIs (S. 28) (LoE:*) (strong).
		Do not routinely use **antibiotic prophylaxis to prevent** clinical UTI after urethral catheter removal or in patients performing intermittent self-catheterisation (S. 28) (LoE: *) (weak)
	Sofern auf geriatrische Patienten übertragbar	**Summary of evidence and recommendations for the treatment of complicated UTIs** Use the combination of: • amoxicillin plus an aminoglycoside; • a second generation cephalosporin plus an aminoglycoside; • a third generation cephalosporin intravenously as empirical treatment of complicated UTI with systemic symptoms. (S. 24) All: (LoE:2) (strong)
		Only use ciprofloxacin provided that the local resistance percentages are < 10% when: • the entire treatment is given orally; • patients do not require hospitalisation; • patient has an anaphylaxis for beta-lactam antimicrobials. (S. 24) All: (LoE:2) (strong)
		Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated UTI in patients from urology departments or when patients have used fluoroquinolones in the last six months. (S.24) All: (LoE: 1b-2) (strong)
	SIGN 160 (2020) [5] Management of suspected bacterial lower	**Recurrent lower urinary tract infection in women** **Pharmacological treatment: antimicrobials** R - Consider prophylactic antimicrobials for women experiencing recurrent UTI after discussion of self-care approaches and the risks and benefits of antimicrobial treatment involved. (S. 29) (LoE: 1++)

	urinary tract infection in adult women AGREE II (0,95/1,0)	
		Choice of agent for long-term prophylaxis of recurrent UTI **Duration of antimicrobial prophylaxis for prevention of recurrent UTI** ✓ - To minimise the development of resistance antimicrobial prophylaxis should be used as a fixed course of three to six months in women with recurrent UTI. (S.30) (LoE: 1++)
		Catheter-associated lower urinary tract infection in women **Prevention of recurrent UTI (S. 36)** R - Do not routinely prescribe antibiotics to prevent UTI in patients using intermittent self catheterisation for bladder emptying. Consider only after full discussion of the benefits and harms likely to apply to the individual. (S. 37) (LoE: 1+ to 4)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)* [11] AGREE II (0,86/1,0)	**Preventing recurrent urinary tract infections** Manage an acute UTI as outlined in the NICE guidelines on urinary tract infection (lower): antimicrobial prescribing or pyelonephritis (acute): antimicrobial prescribing (S.5).
		Treatment for women with recurrent UTI who are not pregnant **Oestrogen** Consider the lowest effective dose of vaginal oestrogen (for example, estriol cream) for postmenopausal women with recurrent UTI if behavioural and personal hygiene measures alone are not effective or not appropriate. Discuss the following with the woman to ensure shared decision-making: • the severity and frequency of previous symptoms • the risk of developing complications from recurrent UTIs • the possible benefits of treatment, including for other related symptoms, such as vaginal dryness • the possible adverse effects such as breast tenderness and vaginal bleeding (which should be reported because it may require investigation) • the uncertainty of endometrial safety with long-term or repeated use • preferences of the woman for treatment with vaginal oestrogen. Review treatment within 12 months, or earlier if agreed with the woman. In October 2018, this was an off-label use of vaginal oestrogen products. See NICE's information on prescribing medicines. All: (S.6)
		Do not offer oral oestrogens (hormone replacement therapy) specifically to reduce the risk of recurrent UTI in postmenopausal women (S.6).

		Antibiotic prophylaxis For women with recurrent UTI who are not pregnant, consider a trial of **antibiotic prophylaxis** only if behavioural and personal hygiene measures, and vaginal oestrogen (in postmenopausal women) are not effective or not appropriate. (S.7)
		For **women with recurrent UTI who are not pregnant**, ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable trigger (see the recommendations on choice of antibiotic prophylaxis). Take account of: • the severity and frequency of previous symptoms • the risk of developing complications • previous urine culture and susceptibility results • **previous antibiotic use, which may have led to resistant bacteria** • **the woman's preferences for antibiotic use. (S.7)**
		Choice of antibiotic prophylaxis When prescribing antibiotic prophylaxis for recurrent UTI, take account of local antimicrobial resistance (AMR) data from Public Health England and: • follow the recommendations in table 1 for people aged 16 years and over (s. Frage 5)
SF 5: Welche Antibiotika sind zur Langzeitprävention geeignet?	**SIGN 160 (2020) [5] Management of suspected bacterial lower urinary tract infection in adult women** AGREE II (0,95/1,0)	**Recurrent lower urinary tract infection in women** **Pharmacological treatment: antimicrobials (S. 29)** R - Long-term prophylactic antimicrobials for prevention of recurrent UTI should be used with caution in women aged 65 years and over, and careful consideration given to the risks and benefits involved. (S.29) (LoE: 1++)
	NICE - Urinary tract infection (recurrent): antimicrobial prescribing (2018)* [11] AGREE II (0,86/1,0)	**Preventing recurrent urinary tract infections** **Antibiotic prophylaxis** For **women with recurrent UTI who are not pregnant and have had no improvement after single-dose antibiotic** prophylaxis or have no identifiable triggers, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis ⇩). Take account of: • any further investigations (for example, ultrasound) that may be needed to identify an underlying cause • the severity and frequency of previous symptoms • the risks of long-term antibiotic use • the risk of developing complications • previous urine culture and susceptibility results • **previous antibiotic use, which may have led to resistant bacteria**

<table>
<tr><td></td><td></td><td>• the woman's preferences for antibiotic use (S.8)</td></tr>
<tr><td></td><td></td><td>Choice of antibiotic prophylaxis
When prescribing antibiotic prophylaxis for recurrent UTI, take account of local antimicrobial resistance (AMR) data from Public Health England and:
• follow the recommendations in table 1 for people aged 16 years and over (s. Frage 5)
People aged 16 years and over (S.12)
<table>
<tr><th>Treatment</th><th>Antibiotic prophylaxis and dosage</th></tr>
<tr><td>First-choice oral antibiotics</td><td>Trimethoprim:
200 mg as a single dose when exposed to a trigger, or 100 mg at night
There is a teratogenic risk in first trimester of pregnancy (folate antagonist; BNF
information on trimpethoprim). The companies advise that it is contraindicated in
pregnancy (trimethoprim summary of product characteristics)
Nitrofurantoin (if estimated glomerular filtration rate is 45 ml/minute or more):
100 mg as a single dose when exposed to a trigger, or 50 mg to 100 mg at night
Avoid at term in pregnancy; may produce neonatal haemolysis (BNF information on
nitrofurantoin)</td></tr>
<tr><td>Second-choice oral antibiotics</td><td>Amoxicillin (off-label use):
500 mg as a single dose when exposed to a trigger, or 250 mg at night
Cefalexin:
500 mg as a single dose when exposed to a trigger, or 125 mg at night</td></tr>
</table></td></tr>
<tr><td></td><td></td><td>Preventing recurrent urinary tract infections
Antibiotic prophylaxis
When a trial of daily antibiotic prophylaxis is given, give advice about:
• the risk of resistance with long-term antibiotics, which means they may be less effective in the future
• possible adverse effects of long-term antibiotics
• returning for review within 6 months
• seeking medical help if there are symptoms of an acute UTI (S.7).</td></tr>
<tr><td></td><td></td><td>Treatment for men and pregnant women with recurrent UTI
For men and pregnant women with recurrent UTI, ensure that any current UTI has been adequately treated then consider a trial of daily antibiotic prophylaxis (see the recommendations on choice of antibiotic prophylaxis) if behavioural and personal hygiene measures alone are not effective or not appropriate, with specialist advice. Take account of:
• any further investigations (for example, ultrasound) that may be needed to identify an underlying cause
• the severity and frequency of previous symptoms</td></tr>
</table>

		• the risks of long-term antibiotic use • the risk of developing complications • previous urine culture and susceptibility results • previous antibiotic use, which may have led to resistant bacteria • the person's preferences for antibiotic use. When a trial of daily antibiotic prophylaxis is given, give advice as in recommendation 1.1.11. All: (S. 9)
* Evidenzlevel ist nicht immer zuzuordnen. Bei der AGREE II-Bewertung wurde dieser Tatbestand entsprechend berücksichtigt. ** kein LoE angegeben		

7. Evidenztabellen

7.1 Epidemiologie

Schlüsselfrage

Welche Erreger sind für die Harnwegsinfektionen (akute Zystitis, Pyelonephritis) oder der asymptomatischen Bakteriurie im Geltungsbereich der Leitlinie verantwortlich?

Referenz	Studien-charakteristika	Studien-ziel	Patientenmerkmale	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
HWI (Germany/Austria/Switzerland)							
Collin, 2019 [13] 31028879	A systematic review and meta-analysis Total: n=74 studies and data sources Studies on UTI: n=42 of these n=1 study from Switzerland	The aim of this study was to quantify the role of Group B Streptococcus as a cause of surgical site and non-	All types of surgical site infection were included, namely superficial, deep, and organ/space, along with catheter-associated UTI and ventilator-associated pneumonia infections where GBS was detected in urine were included because UTIs are relatively common in	*In the following only data within the geographical scope of the guideline is presented.* **Switzerland** Kronenberg 2011 (n=1018 ambulatory-care patients (>15 years of age) presenting with acute uncomplicated urinary tract infections) • Recruiting period: Sep 2008 to Feb 2009 • Region: Canton of Bern • Study aim: comparison of the resistance results of samples that would not have been sent for analysis outside the study (solicited	Kronenberg 2011 Therefore, in the outpatient setting, susceptibility rates for E. coli isolates differ by indication for urinary culture and age. Surveillance based on samples taken during standard care may underestimate susceptibility rates for uncomplicated	Collin 2019 (SR) The search was restricted to publication dates from Jan 2000 to Jul 2017. Data extraction was mainly conducted by only 1 reviewer. Only a randomly selected sample (10%) was checked by a second independent reviewer Quality assessment was mainly conducted by only 1 reviewer. Only a randomly	3a - RoB: high

	Search period: Jan 2000 to Jul 2017	invasive infections at all ages.	the population and the overall proportion attributable to GBS is unquantified.	samples) with those of routine samples **The estimated annual incidence rate of lower UTI** • 1.6 episodes per 100 population The higher incidence observed in our study is probably a consequence of soliciting samples from non-complicated UTIs during the active surveillance study. The following information were extracted from the original paper Kronenberg 2011 (PMID: 21880098) • Routine samples Group B Streptococcus: n=6; Isolates: n=357; • Prevalence of Streptococcus agalactiae in isolates from community urinary tract infections: 1.55 (95 % CI: 0.57-3.34) • Solicited samples Group B Streptococcus: n=6; Isolates: n=388; • Prevalence of Streptococcus agalactiae in isolates from community urinary tract infections: 1.68 (95 % CI: 0.62- 3.62) **Bacteriology** <u>Bacteriuria</u> • Solicited samples: n=305 (71.3%) • Routine samples: n=348 (66.3%) p>0.05 <u>Single microorganism</u> • Solicited samples: n=248 (81.3 %) • Routine samples: n=323 (87.9%) p<0.001 <u>Escherichia coli</u> • Solicited samples: n=231 (75.7%) • Routine samples n=232 (66.7%) p=0.01 <u>Klebsiella spp.</u> • Solicited sample: n=13 (4.3%)	infections, especially among the elderly. Reports of resistance data should include age stratification. <u>Collin 2019 (SR)</u> No conclusion for the specific region of interest.	selected sample (10%) was checked by a second independent reviewer. Data were not extracted from sources/studies that were rated 'poor' No sensitivity analyses or funnel plots was conducted *The types of infection were not pre-specified, but the search strategy aimed to capture epidemiological studies and surveillance sources of surgical site, healthcare-associated, skin/soft tissue/wound, urinary tract, and respiratory tract infections.* <u>Funding</u> This work was supported by Pfizer Inc. The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data in the study and final responsibility for the decision to submit this paper <u>Conflict of interest</u> The authors declare no competing interests.	

				• Routine samples: n=22 (6.3%) p>0.05 <u>Proteus mirabilis</u> • solicited samples: n=10 (3.3%) • routine samples: n=14 (4.0%) p>0.05 <u>Other Enterobacteriaceae</u> • solicited samples: n=16 (5.2%) • routine samples: n=17 (4.9%) p>0.04 <u>Pseudomonas aeruginosa</u> • Solicited samples: n=2 (0.7%) • Routine samples: n=6 (1.7%) p>0.05 <u>Enterococcus spp.</u> • Solicited samples: n=61 (20.0%) • routine samples: n=52 (14.9%) p>0.05 <u>Staphylococcus aureus</u> • solicited samples: n=3 (1.0%) • routine samples: n=5 (1.4%) • p>0.05 <u>Staphylococcus saprophyticus</u> • solicited samples: n=10 (3.3%) • routine samples: n=17 (4.9%) p>0.05 <u>Streptococcus agalactiae</u> • solicited samples: n=6 (2.0%) • routine samples: n=6 (1.7%) p>0.05 <u>Other</u> • solicited samples: n=5 (1.6%) • routine samples: n=17 (4.9%) p=0.04 **Susceptibility rates for Escherichia coli** **<u>Age 15–45 years</u>**			

				Ampicillin • Solicited samples: n=107 (67.3 %) • Routine samples: n= 78 (57.7%) p>0.05 Amoxicillin–clavulanic acid • Solicited samples: n=107 (85%) • Routine samples: n=78 (69.2%) p=0.016 Cefuroxime axetil • Solicited samples: n=107 (76.6%) • routine samples: n=78 (73.1%) p>0.05 Fosfomycin • solicited samples: n=16 (100.0%) • routine samples: n=11 (100.0%) p>0.05 Nitrofurantoin • solicited samples: n=21 (95.2%) • routine samples: n=15 (93.3%) p>0.05 Norfloxacin • solicited samples: n=107 (98.1%) • routine samples: n=78 (92.3%) p>0.05 TMP-SMX • solicited samples: n=107 (79.4%) • routine samples: n=78 (75.6%) p>0.05 Dual resistance • solicited samples: n=107 (1.9%) • routine samples: n=78 (5.1%) p>0.05 Multiresistance • solicited samples: n=107 (6.5%) • routine samples: n=78 (10.3%) p>0.05			

				Susceptibility rates for Escherichia coli **<u>Age >45 years</u>** <u>Ampicillin</u> • solicited samples: n=112 (66.1%) • routine samples: n=133 (51.1%) p=0.026 <u>Amoxicillin–clavulanic acid</u> • solicited samples: n=112 (80.4%) • routine samples: n=133 (68.4%) p=0.049 <u>Cefuroxime axetil</u> • solicited samples: n=112 (81.3%) • routine samples: n=133 (64.7%) p=0.006 <u>Fosfomycin</u> • solicited samples: n=14 (100%) • routine samples: n=19 (100.0%) p>0.05 <u>Nitrofurantoin</u> • solicited samples: n=18 (100%) • routine samples: n=32 (84.4%) p>0.05 <u>Norfloxacin</u> • solicited samples: n=112 (90.2%) • routine samples: n=133 (76.7%) p=0.009 <u>TMP-SMX</u> • solicited samples: n=112 (79.5%) • routine samples: n=133 (71.4%) p>0.05 <u>Dual resistance</u> • solicited samples: n=112 (5.4%) • routine samples: n=133 (12.8%) p>0.05 <u>Multiresistance</u>		

				• solicited samples: n=112 (8.9%) • routine samples: n=133 (20.3%) p=0.022 **Prior antimicrobial treatment** (Antimicrobial treatment in the last 3 months) <u>Ampicillin</u> • Yes: n=110 (46.4%) • No: n=316 (66.5%) p<0.001 <u>Amoxycillin–clavulanic acid</u> • Yes: n=110 (61.8%) • No: n=316 (81.6%) p<0.001 <u>Cefuroxime axetil</u> • yes: n=110 (60.9%) • no: n=316 (78.5%) p<0.001 <u>Fosfomycin</u> • Yes: n=16 (100.0%) • No: n=40 (100.0%) p>0.05 <u>Nitrofurantoin</u> • Yes: n=24 (79.2%) • No: n=55 (98.2%) p=0.009 <u>Norfloxacin</u> • Yes: n=110 (70.9%) • No: n=316 (94.6%) p<0.001 <u>TMP-SMX</u> • Yes: n=110 (57.3%) • No: n=316 (83.9%) p<0.001			

Schlüsselfrage

Wie ist die Resistenzsituation der Erreger für die Harnwegsinfektionen (akute Zystitis, Pyelonephritis) oder der asymptomatischen Bakteriurie im Geltungsbereich der Leitlinie?

Referenz	Studien-charakteristika	Studienziel	Patienten-merkmale	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
HWI (Germany/Austria/Switzerland)							
Stapleton, 2020 [14] 32747356	Systematic review n=38 observational studies <u>Regions</u> Europe (n=16 of these: n=1 Austria; n=2 Germany; n=1 Switzerland); Asia (n=12); North America (n=6); South America (n=2); Saudi Arabia (n=1); Australia (n=1) Search period: Jan 2009-Dec 2019	The aim of this systematic review was to provide insights into the evolving epidemiology of antimicrobial resistance to fluoroquinolones in women with community-acquired uUTI caused by E. coli, with respect to variations over time, geography, and age.	women (aged 12 years or above) with community-acquired uUTI	*In the following only data within the geographical scope of the guideline is presented.* **I) E. coli isolate susceptibility to listed fluoroquinolones** **II) E. coli isolate resistance to listed fluoroquinolones** **Germany** <u>Schmiemann 2012</u> (already included in the last version of the guideline) (Age group: ≥18 y; primary care setting) Reporting period: Fall 2011 I) susceptibility rate • Ciprofloxacin: 91.3% II) resistance rate • Ciprofloxacin: 8.7% <u>Seitz 2017</u> (Age group: ≥18 y; outpatients department) Reporting period: Jan 2015–Jan 2017 I) susceptibility: • Ciprofloxacin: 84.9%, • Levofloxacin: 86.3%, • Mox: 86.0% II) resistance rate:	<u>Stapleton, 2020</u> Within Europe, ciprofloxacin resistance in E. coli isolates varied between countries and increased in some from 2006 to 2008 and 2014 to 2016, specifically in the United Kingdom (0.5% to 15.3%), Germany (8.7% to 15.1%), and Spain (22.9% to 30.8%), although methodologies and settings were often not comparable.	<u>Stapleton, 2020</u> Inclusion of articles published between Jan 2009 and Dec 2019; Data extraction was mainly conducted by only 1 reviewer, only a randomly selected sample (10%) was checked by a second independent reviewer; no detailed information on the quality assessment process of the included studies <u>Funding</u> This work was supported by GlaxoSmithKline, including editorial support. Editorial support was provided by Michelle Preston, MSc, of Livewire Editorial Communications, which was funded by GlaxoSmithKline. <u>Conflict of interest</u> Personal fees from GlaxoSmithKline (outside the submitted work). A.E.S. has the following disclosure: personal fees from GlaxoSmith-Kline (outside the submitted work). A.M. and M.T. are employees of GlaxoSmithKline.	3a - RoB: high

				• Not reported. **Austria** Kahlmeter 2012 (Age group: 18–65 y; primary care & outpatients department) Reporting period: Jun 2007–Nov 2008 I) susceptibility • Not reported. II) resistance • Ciprofloxacin: 4.1% **Switzerland** Plate 2019 (Age group: ≥18 y; primary care setting) Reporting period: Jun 2017–Aug 2018 I) susceptibility • Ciprofloxacin: 89.1% • Levofloxacin: 86.5% II) resistance: • Not reported.			

7.2 Diagnostik

Schlüsselfrage (nicht-geriatrische Patienten)

Welche Untersuchungen sind zur Diagnose einer Harnwegsinfektion (akute Zystitis, Pyelonephritis) oder der asymptomatischen Bakteriurie in den definierten Gruppen erforderlich?

*Piontek et al. 2023 wurde nachträglich bewertet, da das Paper außerhalb des Suchzeitraums lag. Aufgrund der Bedeutsamkeit wurde es allerdings mit einbezogen.

** Schmiemann et al. 2023 wurde wegen Relevanz nachträglich mit aufgenommen. Die Bewertung war nicht mehr möglich, da die Studie final zu spät erschienen ist.

Referenz	Studien-charakt-eristika	Studienziel	Patienten-merkmale	Untersuchungs-methoden	Referenz-standard	Ergebnisse	Schlussfolger-ungen des Autors	Methodische Bemerkungen	LoE/ RoB
Beyer, A. K. (2019) [15] 31304845	Systematic review N=8 (included in qualitative synthesis) diagnostic studies published in 1975 or later Search date: August 2017 Studies were conducted in: South Africa (n=1), Great Britain (n=2), Denmark (n=1), Sweden (n=2), Netherlands (n=1), Thailand (n=1)	To investigate the validity of microscopy as a diagnostic tool for urinary tract infection in general practice.	N= 4582 patients with symptoms of UTI	Midstream clean-catch (MSCC) was used by two of the studies, midstream urine (MSU) was used by three of the studies and the rest did not specify which method they used for urine sampling. Five studies used light microscopy, one study used phase-contrast microscopy and two studies did not specify which type of microscopy they used	using urine culture as a reference standard	Validity of POC microscopy Dornfest (1979) using MSCC and light microscopy • Prevalence =28% • PPV =85% • NPV =97% • SEN =93,5% • SPE =93,6% Wilks (1979) Using MSCC and light microscopy • Prevalence =68;33% • PPV =100;55% • NPV =48;88% • SEN =48,5;81,8% • SPE =100;67,5% Ditchburn (1990) Using MSU and light microscopy • Prevalence =41% • PPV =74% • NPV =95% • SEN =94,9% • SPE =76,3% Balslev (1980) Without any specific urine sampling method, type of microscopy is not available • Prevalence =48% • PPV =75% • NPV =85% • SEN =85,7% • SPE =73,7% Hallander (1986) Without any specific urine sampling	This review did not find solid evidence to determine the clinical validity of microscopy performed in general practice on urine samples from patients with symptoms of UTI. The lack of evidence is due to few available studies, wide variation of the cut-offs for the index test, the level of magnification and the method of microscopy.	Conflict of interest Not reported Risk of bias: Four of the studies were judged to have moderate risk of bias. Four studies were considered having low risk of bias. The most common error was in the process of patient selection (not a consecutive sample). The quality of the included studies is summarized in. No Prospero→ no a priori analysis; just one database was used; no robust results (no Funnel-plot, nos sensitivity-analysis); risk of bias 50:50 (moderate to low-risk)	1a- high The risk of bias of included studies was assessed by using the QUADAS-2 tool - a revised tool for the quality assessment of diagnostic accuracy studies

						method, using a Phase-contrast Microscopy • Prevalence =17;17% • PPV =87;65% • NPV =95;92% • SEN =74;60% • SPE =97;93% Winkens (1995) Without any specific urine sampling method, type of microscopy is not available • Prevalence =69% • PPV =73;85% • NPV =58;41% • SEN =91,9;47% • SPE =27;81% Ferry (1990) Using MSU and light microscopy • Prevalence = 82% • PPV =88% • NPV =74% • SEN =97% • SPE =38,9% Chalmers (2015) Using MSU and light microscopy • Prevalence =42% • PPV =79% • NPV =74% • SEN =57,1% • SPE =88,9%			
Piontek, K. et al. (2023) [16] 36795285	Systematic review N=23 PROM development and/or validation studies	To conduct a systematic review of the quality of existing patient-reported outcome	Women with uncomplicated UTIs including studies on recurrent UTIs	Patient-reported outcome measures	Evaluation of content validity Evaluation of internal structure including	According to COSMIN criteria, the ACSS and the UTISIQ-8 were placed into category A, (PROMs with evidence for sufficient content validity (any level) and at least low-quality	The ACSS and the UTI-SIQ-8 have the potential to be recommended for use in women with uncomplicated UTIs in future clinical trials. For all included	No information whether additional methods to database searching were used to identify relevant	3a low

	Last update search : 09/16/2022 Studies were conducted in: Uzbekistan/ Russia (n=5), Germany (n=3), UK (n=1), USA (n=3), Switzerland (n=1), France (n=2), Korea (n=1), Italy (n=1), Hungary (n=1), Greece (n=2), Thailand (n=1), Denmark (n=1), Taiwan (n=1)	measures (PROMs) for use in women with uncomplicated urinary tract infections (UTIs) applying the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) methodology, and to derive recommendations for their use in future research			structural validity, internal consistency, and cross-cultural validity/measurement invariance Evaluation of the remaining measurement properties including reliability, measurement error, criterion validity, hypotheses testing for construct validity, and responsiveness.	evidence for sufficient internal consistency.) and all other PROMs were placed into category B (PROMs of category B have the potential to be recommended for use, but require further validation).	PROMs, further validation studies are indicated.	reports. No information on efforts made to minimise error in data collection Solely at least 50% of the study sample needed to consist of women with uncomplicated UTIs. <u>Funding</u> Open Access funding enabled and organized by Projekt DEAL. This work was funded by Bionorica SE, Germany. The study sponsor had no role in the design of the study, data collection, data management, data analysis, data interpretation, and issues regarding the publication of results. <u>Conflict of interest</u> CA receives consultancy fees	

								from Bionorica SE, Dr Wolff Group, RHEACELL, and Sanofi for services related to patient-reported outcome measures. All other authors declare that they have no conflict of interest.	
Henderson 2019 [17]	Systematic review 19 studies (n = 8443) → 16 RCTs; 2 comparative cohort studies (n = 5289); 1 non-randomized CCT GB US Ireland Spain NL Jamaica Turkey Wales Greece Canada	To systematically review benefits and harms of asymptomatic bacteriuria screening and treatment in adults, including during pregnancy, to inform the US Preventive Services Task Force. **[Key questions:** -Does screening for asymptomatic bacteriuria improve health outcomes among adults, including pregnant	N = 8443 -Pregnant women (N= 7666) -Women till 65 (N= 94) -Women older 65 (N= 482) -Women with diabetes (N= 105) -Older adults; 83,9% women >65y.(N= 96)	screening and treatment of screen-detected asymptomatic bacteriuria	No screening and treatment of ABU	**Effectiveness of Screening** I) Pregnant Populations n=2 cohort studies (n = 5289): Prevalence of ABU Gratacós (1994) 4.7% of the screened participants were diagnosed with ABU Uncu (2020) 9.3% of the screened participants were diagnosed with ABU Prevalence of pyelonephritis *Screened cohort vs. an unscreened historical comparison group* Gratacós (1994) 0.5% vs. 1.8% rr = 0.30 (95% CI, 0.15-0.60) Uncu (2020) 0.54% vs. 2.2%	Screening and treatment for asymptomatic bacteriuria during pregnancy was associated with reduced rates of pyelonephritis and low birth weights, but the available evidence was not current, with only 1 study conducted in the past 30 years. Benefits of asymptomatic bacteriuria treatment in nonpregnant adult populations were not found. Trial evidence on harms of asymptomatic bacteriuria antibiotic treatment was limited.	Conflict of Interest Disclosures: None reported. Funding: Funding/Support: This research was funded under contract HHSA-290-2015-00007-I, Task Order 3, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF). The current evidence	1a - RoB: high

		women? -What are the harms of screening for asymptomatic bacteriuria? -Does treatment of screen-detected asymptomatic bacteriuria improve health outcomes? -What harms are associated with treatment of screen-detected asymptomatic bacteriuria?]				II) Nonpregnant adult populations n = 0 studies **Harms of Screening for ABU** I) Pregnant Populations Uncu (2020) No evidence of harms associated with the screening program were found II.) Nonpregnant adult populations n = 0 studies **Treatment effectiveness of screen-detected ABU and harms of treatment** I) Pregnant Populations n = 12 trails (n = 2377; 1 conducted within past 30 years) Pooled effects of ABU treatment <u>Pyelonephritis rates (n = 2068):</u> • intervention group: 0%-16.5%; • control group: 2.2%-36.4%; pooled RR= 0.24 [95% CI, 0.14-0.40]; I^2= 56.9%; 12 trials <u>Low birth weight (n = 1522):</u> • intervention group: 2.5%-14.8%; • control group: 6.7%-21.4%;		suggests that screening and treatment for asymptomatic bacteriuria during pregnancy is associated with reduced rates of pyelonephritis and low birth weight. However, findings of this review should be interpreted with caution as there were important **methodological limitations**.	

						pooled RR = 0.64 [95% CI, 0.46-0.90]; I^2= 15.8%; 7 trails <u>Perinatal mortality</u> (n = 6 studies, n = 1103) • intervention group: 0%-6.6% • control group: 0%-7.3% pooled RR, 0.98 [95% CI, 0.29-3.26]; I^2= 52.3%; 6 trails <u>Congenital malformation</u> (n = 5 studies, n = 961) • intervention group: 0%-1.6%; • control group: 1.4%-4.2% pooled RR, 0.44 [95% CI, 0.16-1.22]; I^2= 0 • Evidence related to other infant and maternal harms of ABU treatment in pregnancy was sparsely and inconsistently reported, and there was a lack of evidence on long-term neonatal outcomes after antibiotic treatment of ABU in pregnancy II.) Nonpregnant adult populations (n = 5 RCTs; n = 777)			

						• no report of any significant differences in risk of infection, mobility, or mortality. Limited evidence on harms of screening or treatment was available; no statistically significant differences were identified.			
Santoni, N. et al. (2018) [18] 30016804	Systematic review N=12 studies (n=6 retro-spective cohort; n=3 pro-spective cohort; n=2 cohort; n=1 Pro-spective case-control) Search date: 06/11/2018 Studies were conducted in: USA (n=3), Germany (n=1), UK (n=1), Australia (n=1), Netherlands n=2), Israel (n=1), Canada	We aimed to conduct a literature search to evaluate the evidence for investigation of recurrent UTIs in women with cystoscopy, imaging and urodynamics.	Women with recurrent UTI	**Urodynamics** Two reliable papers were identified for the use of urodynamics in investigating recurrent UTIs. **Cystoscopy** Seven studies were identified from which data on women who had cystoscopy purely for recurrent UTIs could be Extracted. **Imaging** Eight papers reliably reported imaging findings for women with recurrent UTIs, some for more than one imaging modality. Six papers reported IVU findings, 2 reported abdominal X-ray findings and 2 reported ultrasound.	**Primary outcomes** Percentage of abnormal findings; categorised by cystoscopy, urodynamics and imaging **Cystoscopy (n=7 studies))** • All ages, normal vs. abnormal: 505/151 (23%) • <50y normal vs. abnormal: • 88/20 (20%) **Urodynamics, total (abnormal in %) (n=2 studies)** • Flow ≥15 mL/s vs. <15 mL/s: Totals: 101 vs. 102 Abnormal: 50% • Post-void residual yes vs. no Totals: 70 vs. 133 Abnormal: 35% • Detrusor abnormality yes vs. no: Totals: 27 vs. 27 Abnormal: 50 % Overactive bladder yes vs. no: Totals: 15 vs. 39 Abnormal: 28 % • Stress incontinence yes vs. no: Totals: 21 vs. 393 Abnormal: 39 % **Imaging, total abnormal (n=8 studies) (abnormal in %)** • IVU normal vs. abnormal: 481 vs. 43 (8.2%) • AXR normal vs. abnormal: 191 vs. 2 (0.4%)	Women presenting with simple recurrent UTIs should have a flow rate and post-void residual measured. Cystoscopy is not warranted in these patients and imaging is unlikely to be of value in the absence of symptoms of upper tract disease or gynaecological problems.	No risk of bias assessment; no study protocol; only studies in English were included; no detailed information on the data extraction process Conflict of interest None Funding No information on funding.	2b- high

	(n=1), Ireland (n=1), Denmark (n=1)				• USS normal vs. abnormal: 164 vs. 20 (10.9%) • All imagining normal vs. abnormal: 714 vs. 71 (10.5%) **<u>Secondary outcome</u>** Serious, consequential or incidental findings **Serious abnormalities**: n detected/*n* imaged Totals: n= 10; Total imaging: 1,4% • IVU: 2/7; AXR: 0,5; USS: 5/6 **Consequential abnormalities** n detected/*n* imaged Totals: n= 30; Total imaging: 4,2% • IVU: 15/15; AXR: 2/5; USS: 6/6 **Incidental abnormalities** n detected/*n* imaged Totals: n= 33; Total imaging: 4,6% • IVU: 23/24; AXR: 0/5; USS: 8/8			

Schlüsselfrage

Wie sollte die Uringewinnung für die Diagnose einer HWI erfolgen? (nicht-geritarische Männer)

Refer-enz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Techniken zur Uringewinnung entsprechend der Einschlusskriterien**	**Referenz-standard**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Metho-dische Bemerkungen**	**LoE/ RoB**
Llor, 2022 [19] 35652481	Systematic review n=6 studies (n=2 RCTs, n=1 Pseudo-RCT, n=3 paired studies) Search period: up to Apr 2022 Recruitment	To assess the most adequate non-invasive method to collect a urine specimen for diagnosing UTI in symptomatic non-pregnant women.	n=1,010 self-helped nonpregnant adult women (aged 14 y or more) with symptoms of acute UTI in any healthcare setting <u>Cut-off point</u> <u>Morris 1979,</u>	MSCC with water and soap, MSCC with only water, MSU, and random samples or home-voided urine samples	We assumed an increasing contamination rate in the order of: 1) MSCC with water and soap, 2) MSCC with only water, 3) MSU 4) random samples or home-voided urine samples.	**<u>(a) MSCC vs. MSU samples</u>** (n=2 studies; n=338 patients). **Diagnostic accuracy** <u>Morris 1979 (n=180)</u> Definitive infection MSCC with sterile water at home and supervised by nurses: 92%	Overall, we did not find consistent evidence to suggest important differences in diagnostic accuracy or the percentage of contaminated samples among the different sampling collection techniques in the studies included. Despite being widely	*The least contaminated was used as the reference and the most contaminated as the index test. For example, if a study investigated both MSU*	2a RoB: low

	countries: UK, Norway, US, Australia, Denmark		Bradbury 1988 ≥ 10^5 CFU/ml Bærheim, 1990, Lifshitz, 2000 ≥ 10^4 CFU/ml Hølmkjær 2018 ≥ 10^3 CFU/ml Eley 2016 10 or more epithelial cells per high power feld		The least contaminated was used as the reference and the most contaminated as the index test.	• MSU collected in surgeries: 91% Bradbury 1988 (n=158 aged 16-75 y) Definitive infection MSCC after cleansing with water and soup: 23/93 (24.7%) • MSU: 16/65 (24.6%) **Contamination** Morris 1979 (n=180) • MSCC with sterile water at home and supervised by nurses: 8% • MSU collected in surgeries: 9% Bradbury 1988 (n=158 aged 16-75 y) • MSCC after cleansing with water and soup: 8/93 (8.6%) • MSU: 6/65 (9.2%) SEN: 0.75 (95% CI: 0.48–0.93) SPE: 0.92 (95% CI: 0.87–0.96) PPV: 0.52 (95% CI: 0.37–0.67) NPV: 0.97 (95% CI: 0.37–0.67) **(b) Home voided urine samples vs.**	recommended, our review did not find consistent evidence that asking women to provide midstream samples with or without cleansing is better. The overall strength of evidence was low, as multivariate modelling could not be performed, and thus, no recommendation for or against can yet be made.	*and random urine sampling in a paired design, MSU was used as the reference standard and random samples as the index test.* Funding None. Conflict of interest CL declares having reported funds for research from Abbott Diagnostics. The other authors declared no conflicts of interest.	

						<u>MSCC after cleansing with water</u> <u>Bærheim, 1990</u> (Paired samples; n=73 aged 18-60 y) **Diagnostic accuracy** Observed bacteriuria • Home voided urine samples: 52/73 (71.2%) • MSCC after cleansing with water: 54/73 (73.9%) Overall agreement rates: • Home voided urine samples: K=0.70 with a cut-off point of 10^4 CFU/ml • MSCC after cleansing with water: K=0.74 with a cut-off point of 10^5 CFU/ml SEN: 0.92 (95% CI: 0.81–0.98) SPE: 0.71 (95% CI: 0.48–0.89) PPV: 0.89 (95% CI: 0.80–0.94) NPV: 0.79 (95% CI: 0.58–0.91 **Contamination** • Home voided urine samples:			

						3/73 (4.1%) • MSCC after cleansing with water: 7/73 (9.6%) **(c) random voiding samples vs. MCCC with different cleansing techniques** Lifshitz, 2000 (3-arm RCT; n=242 aged 17–50 y) Group I: Urine into a clean container (no cleansing, no midstream) Group II: MSCC after cleansing with water and bactericidal wipe Group III: MSCC after cleansing with bactericidal wipe and insertion of a vaginal tampon prior to urine collection **Diagnostic accuracy** Definitive infection • Group I: 44/77 (57.1%) • Group II: 42/84 (50%) • Group III:46/81 (56.8%) **Contamination** • Group I: 44/77 (57.1%)			

						• Group II: 42/84 (50%) • Group III:46/81 (56.8%) No statistical significance. **(d) <u>MSCC samples after cleansing with water and a towelette after: verbal instructions vs. illustrated instructions</u>** <u>Eley 2016</u> (Pseudo-RCT; n=240 aged 18 over) **Diagnostic accuracy** Definitive infection: • Verbal instructions: 11/120 (9.2%) • Illustrated instructions 15/120 (12.5%) **Contamination** • Verbal instructions: 47/120 (39.2%) • Illustrated instructions 30/120 (25%) **<u>(e) FVU vs MSU</u>** <u>Hølmkjær 2018</u> (Paired samples; n=117 aged 18 or older)			

						Diagnostic accuracy Definitive infection • FVU: 90/117 (76.9%) • MSU: 98/117 (83.8%) SEN: 0.99 (95% CI: 0.94–1.00) SPE: 0.67 (95% CI: 0.46–0.83) PPV: 0.91 (95% CI: 0.85–0.94) NPV: 0.95 (95% CI: 0.72–0.99) **Contamination** No data.			
Holm 2016 [20]	Systematic review n=7 studies (n=2 RCTs; n=5 paired studies) Search period: up to May 2015	The aim of this study was to determine the accuracy of urine culture from different sampling-techniques in symptomatic non-pregnant women in primary care.	n=1062 symptomatic adult, self-helped, non-pregnant (and not post-partum) women with symptoms of UTI in primary care (general practice, outpatients clinics or comparable settings). No discrimination between complicated and uncomplicated cases of UTI. Cut-off point	Suprapubic puncture, urethral catheterization samples, MSCC, MSU, random samples, home-voided urine	Assuming an increasing contamination rate in the order of: 1) Suprapubic puncture, 2) urethral catheterization samples 3) MSCC 4) MSU 5) Random samples 6) Home-voided urine, the least contaminated was used as reference and the most contaminated as index test.	Lifshitz 2000; Bradbury 1988; Bærheim, 1990 as presented above in Llor, 2022 **MSCC vs. Urethral Catheterization** (2 studies with paired samples) Hooton 2013 (202 samples) SEN: 0.99 (95% CI: 0.96-1.00) SPE: 0.73 (95% CI: 0.60-0.84) PPV: 0.90 (95% CI: 0.84-0.94) NPV: 0.98 (95% CI: 0.86-1.00) Walter 1989 (105 patients) SEN: 0.98 (95%	At present, no evidence suggests that sampling technique affects the accuracy of the microbiological diagnosis in non-pregnant women with symptoms of urinary tract infection in primary care. However, the evidence presented is in-direct and the difference between mid-stream-clean-catch, mid-stream-urine and random samples remains to be investigated in a paired design to verify the present findings	No study protocol, study selection was conducted only by one author, data extraction mistakes (Lifshitz, 2000 cut-off point is ≥ 10^4 cfu/m in the original paper) *The studies were judged to be of moderate to high risk of bias.* Already	2a - RoB: high

			Hooton 2013, Stamm 1982, ≥10 cfu/ml Walter 1989 ≥ 10^5 cfu/ml Bradbury 1988 > 10^5 cfu/ml Bærheim, 1990, Lifshitz, 2000 ≥ 10^4 cfu/ml Mabeck 1969 Reporting absolute numbers, ≥ 10^4 cfu/ml			CI: 0.86–1.00) SPE: 0.97 (95% CI: 0.88–0.99) PPV: 0.95 (95% CI: 0.83–0.99) NPV: 0.98 (95% CI: 0.90–1.00) **MSCC vs. Urethral Catheterization/suprapubic puncture** Stamm 1982 (Paired samples, 187 patients) SEN: 1.00 (95% CI: 0.95-1.00) SPE: 0.71 (95% CI: 0.60-0.80) PPV: 0.79 (95% CI: 0.71-0.86) NPV: 1.00 (95% CI: 0-93-1.00) **MSCC vs. Suprapubic puncture** Mabeck 1969 (95 patients SEN: 1.00 (95% CI: 0.89-1.00) SPE: 0.93 (95% CI: 0.82-0.98) PPV: 0.91 (95% CI: 0.77–0.97) NPV: 1.00 (95% CI: 0.91-1.00)		included in the previous version of the guideline. Funding This study was funded by UC CARE, University of Copenhagen. Conflict of interest None.	

7.3 Therapie

Schlüsselfrage Ist eine antibiotische Behandlung einer HWI oder einer asymptomatischen Bakteriurie in den definierten Gruppen erforderlich?									
Refer-enz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Metho-dische Bemerkung-en**	**LoE/ RoB**
Cai et al. 2020 [21] 31651226	Systematic Review and Meta-Analysis N= 15 RCTs Studies conducted in: ? Search date: probably inception - Oct 2018	Comparing the effectiveness and safety profile of fosfomycin vs comparator antibiotics in women with acute uncomplicated cystitis.	n= 2.295 adult female patients older than 18 years old with microbio-logically confirmed and/or clinically suspected acute un-complicated cystitis who were rando-mized to receive treatment with FT or a com-parator antibiotic agent used to treat UTIs.	fosfomycin (3 gm single-dose)	comparator antibiotics (fluoroquinolones, Norfloxacin, cipro-floxacin, Trimethoprim, cotri-moxazole, nitrofurantoin, b-lactams (cephalexin, amoxicillin), ofloxacin/ cotrimoxazole, trimetho-prim)	**Primary ends: clinical resolution** (11 RCTs; 1.976 patients) women with cystitis (fosfomycin vs. other antibiotic agents): • RR 1.04 (95% CI 0.89-1.21, I^2= 33%); p= 0.62 Total: • OR 1.16, (95% CI 0.91-1.49); p=0.13 **microbiological eradication** (n= 14 RCTs; 2,052 patients) women with cystitis (fosfomycin vs. other antibiotic agents) • RR 0.99 (95% CI 0.81-1.20, I^2=35%); p= 0.88 Total: • OR 1.03, (95% CI 0.83-1.30); p=0.09 **Safety outcome**/ a**dverse effects** (= any adverse event	Single dose oral fosfomycin trometamol is equal to comparator regimens in terms of **clinical** and **microbiological** effectiveness and safety in women with microbiologically confirmed and/or clinically suspected, acute uncomplicated cystitis. It is associated with high patient compliance. **No significant difference** in reported adverse effects **between fosfomycin and comparator antibiotics**. →Most adverse effects (gastrointes-tinal type) reported for fosfomycin were transient and single	Financial interest and/or other relationship with Zambon, MSD, Pfizer and Astellas Fund ? NO pregnant women nut including **postmenopa usal** women! We considered only women with uncomplicated UTI to avoid study population heterogeneity and provide a more valid recommendati on for everyday clinical practice.	1a - RoB: high

						reported at any time during the study period.) (11 RCTs; 1.816 patients →does not fit to figure 4) <u>women with cystitis treated with fosfomycin vs other antibiotic agents (n= 15; ??? patients):</u> • RR 0.98 (95% CI 0.72-1.33, I^2= 5%); p= 0.91 <u>Total</u>: OR 1.17, (95% CI 0.86-1.58); p=0.33	dose therapy seems to have resulted in better patient compliance. No study withdrawals due to adverse events in any compared treatment groups in the 3 trials providing relevant data. Fosfomycin treatment was associated with only limited and transient adverse events, underlining high clinical efficacy with a tolerable safety profile. It is worth highlighting that **single dose fosfo-mycin achieved the same clinical efficacy as comparator antibiotics with longer treatment schedules (single dose vs several days).**	Slightly different numbers (RR declared wrongly (→OR)) in the forest plots and text for clinical resolution and microbiological eradication. →Unclear calculation of adverse events.	
Carey 2020 [22] 32270403	Systematic Review N= 5 RCTs -Germany, - Pakistan, - Switzerland, - Norway/ Denmark/	Comparing NSAIDs with antibiotics for treatment of uncomplicated UTIs in adult women.	N= 1309 adult women with uncomplicated UTI	NSAID (Ibuprofen, placebo Granules, Potassium Citrate, Flurbiprofen, Diclofenac) →partly plus placebo	Antibiotics (Ciprofloxacin, Fosfomycintrome-tamol, Norfloxa-cin, Pivmecillinam) →partly plus placebo	**<u>Primary Outcome:</u>** **Symptom Resolution** <u>Symptom resolution by day 3 or 4 (post-randomization) in %:</u> **Bleidorn** 2010: day 4 • NSAIS (n= 21 (58%) vs.	For the outcomes of symptom resolution and complications in adult women with UTI, evidence favors antibiotics over NSAIDs. In sum: The use of antibiotics as first-line treatment for	Four studies included adult women over the age of 18 while one study included women over the age of 15. Age range: 15-70	1a RoB: low

	Sweden inception until January 2020					Antibiotics (n= 17 (52%) • RD*: 9 (95% CI – 13 to 31) • p = 0.744 for difference **Gágyor** 2015: day 4; **Kronenberg** 2017: day 3; **Vik** 2018: day 4 • NSAIS (n= 233) vs. Antibiotics (n= 356) • RD*: (95% CI) 17 to 35 % points higher in the antibiotic group compared with the NSAID group. <u>Symptom resolution at the end of the trial (day 5 post-randomization)</u> **Jamil** 2016 • NSAIS: 1.4 vs. Antibiotics: 1.9; • p = 0.13 <u>Number Needed to Treat</u> *Antibiotics vs. NSAIDs to achieve symptom resolution in one additional*	uncomplicated UTI for both symptom resolution and prevention of pyelonephritis.	**Conflict of Interest**: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Department of Veterans Affairs. **Fund**:? Three studies were at low risk of bias, one had an unclear risk of bias, and one was at high risk of bias. *Positive numbers= higher rates of symptom resolution among patients receiving antibiotics vs. NSAIDS **Positive numbers= higher rates of antibiotic use in the NSAID	

						patient by days 3 to 4 post-randomization (3 RCTs)*:* **range: 3.0 to 6.4.** **Secondary Outcomes:** Women receiving antibiotics for any reason during study period: **Gágyor** 2015 • NSAID n= 85 (35%); antibiotics n= 243 (100%) • RD**: − 65 (95% CI − 71 to − 59) **Kronenberg** 2017 • NSAID n= 82 (62%); antibiotics n= 118 (98%) • RD**: − 37 (95% CI − 46 to − 28) Rates of pyelonephritis: Gágyor 2015 • NSAID n= 5 (2%); antibiotics n= 1 (0.4%) • RD***: 1.7 (95% CI − 0.3 to 3.6) Kronenberg 2017 • NSAID n= 6 (5%); antibiotics n= 0 (0%)		group *** Positive numbers = higher rates of pyelonephritis in the NSAID group	

						• RD***: 5 (95% Cl 1 to 8) Vik 2018 • NSAID n= 7 (4%); antibiotics n=0 (0%) • RD***: 4 (95% CI 1 to 8) Number Needed to Treat: *Antibiotics vs. NSAIDs to prevent one additional case of Pyelonephritis by Day 28 to 30* (3 RCTs): **range: 22.2 to 62.1** →2 RCTs: patients who received antibiotics had lower rates of pyelonephritis compared with those who received NSAIDs.			
Gonzalez - Garay, A., et al. (2021) [23] 32095956	Network meta-analysis n= 18 RCTs (n= 9 of these trials compared three arms) Mexico, Colombia, Ecuador, Venezuela, Salvador, Guatemala, Spain, USA,	The aim was to compare and hierarchize quinolones according to their efficacy and safety and to identify the best treatment for uncomplicated urinary tract infection in women through a systematic	n=8765 (pre- and postmeno-pausal) women. Age range: 18-80 [n= 6 studies (2445 participants) involved a treatment duration < 3 days and 4 trials (742 participants) involved a	Ciprofloxacin, Ofloxacin, Fleroxacin, Gatifloxacin, Levofloxacin	other types of quinolones	**Premenopausal women** **Treatment duration < 3 days** **ciprofloxacin, norfloxacin, ofloxacin** Clinical remission (n= 6 RCTs): • inconsistency factor (IF): p = 0.84 most likely - ciprofloxacin 250 mg and ofloxacin 200 mg: 58.5% and	Premenopausal: No significant differences for any type of quinolone compared with TMP/SMX. →Ofloxacin: 57% probability of achieving **remission** but an 83% frequency of **adverse events** Postmenopausal: ciprofloxacin: 82% more effective for	**Conflict of interest**: None. **Funding**: None. Limitations: - great **diversity of interventions** in the trials included in this review, **age** of the participants, **different**	1a RoB: Low

	Switzerland, Germany, Israel Search date: 2010-2015 (mentioned in Prospero)	review with network meta-analysis	treatment duration > 3 days]			57.5%, <u>Bacteriological remission (n= 6 RCTs):</u> • IF: p = 0.95 Most likely - ciprofloxacin 100 mg and ofloxacin 200mg: 65.5% and 63.2% <u>Safety - Adverse events (n= 6 RCTs)</u> (diarrhea, nausea and vomiting), dizziness, headache, rash and genital itching) quinolones and TMP/SMX: • IF: p = 0.25 lower risk - ciprofloxacin (100 and 250 mg): 26.4% to 29.5% and 35.1%. <u>Relapse (n= 6 RCTs)</u>: • IF: p = 0.74 highest risk - ciprofloxacin (250 and 500 mg): 77.7% to 80.4%. <u>Resistance</u>: Too high heterogeneity - no analysis Quinolone, **200 mg ofloxacin once daily**, has better probability of <u>clinical & bacteriological remission</u> and a <u>low frequency of relapse</u>	**remission**, with a 49% frequency of **adverse events**, compared with other types of quinolones Additional trials are needed to confirm findings, especially if treatment duration exceeds 3 days.	**doses** and **administration times**. RoB low though there was no complete search strategy presented but the other aspects were comprehensible.	

						rate but with the highest frequency of adverse events compared with the other types of quinolones **Postmenopausal Women** **Treatment duration < 3 days: ofloxacin ciprofloxacin, levofloxacin, norfloxacin** Clinical remission (n= 7 RCTs) • IF: p= 0.50 Ofloxacin 200 mg: • RR=1.16 (95%CI 1.02-1.32); • p=0.023 most likely - Ciprofloxacin 500 mg and ofloxacin 200 mg: 82.6% and 75.3%. Bacteriological remission Network plot IF: p =0.68 Significant: Ciprofloxacin 250 mg versus TMP/SMX: • RR=1.10 (95% CI 1.0-1.21); • p= 0.04, • cumul. probability: 79.6% Safety - Adverse events (AE) (n= 7 RCTs)			

						• IF: p= 0.76 lower risk: Ofloxacin 200 mg vs. TMP/SMX: • RR 0.56; (95% CI 0.36-0.88); • p=0.013 Levofloxacin 250 mg vs. TMP/SMX: • RR=0.52 (95% CI 0.31-0.87); • p = 0.013; • 28.6% (quinolone with smallest area for devel. AE) <u>Resistance & relapse (n= 5 RCTs)</u> High study heterogeneity: analysis of relapse and resistance wasn't possible <u>Resistance (n= 5 RCTs</u> • IF: p= 0,44 Lower risk: Ofloxacin 200 mg: 0.8%. Quinolone, **Ciprofloxacin 500 mg**, has the <u>best probabilities of clinical remission</u> but a <u>high frequency of adverse events</u> compared with the other types of quinolones.			

Konwar et al. 2022 [24] 34151754	systematic review and meta-analysis n= 4 RCTs Studies were conducted in: Belgium, NL, USA, CH-PL-Israel Search date: from inception until November 2020	Evaluation of efficacy and safety of fosfomycin versus nitrofurantoin for the treatment of uncomplicated lower urinary tract infection (UTI) in women	N= unclear women with lower uncomplicated UTI and asymptomatic bacteria (ABU) in pregnancy	Oral fosfomycin (Single-dose FOM 3 g) for lower uncom-plicated UTI	Oral nitrofurantoin for lower uncomplicated UTI	**Efficacy - Microbiological cure:** **Within 4 weeks post treatment:** UNCOMPLICATED UTI Fosfomycin (n=445) vs. nitrofurantoin (n=435): (N= 3 studies; 880 patients) • RR 0.95 (95% CI 0.84–1.08, I^2 = 76%); p=0.47 **after 4 weeks post treatment** fosfomycin (n=379) vs. nitrofurantoin (n=381) (N= 3 studies; 760 patients) • RR 1.00 (95% CI 0.88–1.14, I^2 = 82%); p=0.99 **Efficacy – Clinical cure**: LOWER UNCOMPLICATED UTI **within 4 weeks post treatment** fosfomycin (n=476) vs. nitrofurantoin (n=464) (N=2; 940 patients). • RR 0.95 (95% CI 0.81–1.12, I^2 = 83%); p=0.55 **after 4 weeks post treatment** fosfomycin (n= 535) vs. nitrofurantoin (n= 523) (N=3 studies; 1058 patients)	Single-dose (3 gram) oral fosfomycin treatment was equivalent to the various regimens of nitrofurantoin in terms of clinical efficacy in female patients with uncomplicated UTI as also safety in women with uncomplicated cystitis. A similar finding was noted regarding the microbiological cure for the above-mentioned populations.	Conflict of interest None Fund ? Limitation by the **significant heterogeneity** regarding the patient populations. Only 1 study involving pregnant patients reported that no difference was observed between the compared treatment groups. Majority of the included trials were from the **nineties**. Considerable number of the included **trials did not have blinding.** Information regarding allocation concealment was also inadequately reported. Our findings are thus **susceptible to selection**	1a RoB: low

						• RR 0.95 (95% CI 0.83–1.09, I^2= 80%); p=0.48 **Safety: Adverse events (AE)**: **uncomplicated UTI and pregnant** <u>females with ABU - fosfomycin (n= 750) vs. nitrofurantoin (n= 747)</u> (N= 4 studies; 1497 patients RR 1.05 (95% CI 0.59–1.87, I^2= 64%); p=0.86 **Quality of evidence for the safety** outcome measures → **very low** as in addition to wide point estimates, heterogeneity, different doses and duration of nitrofurantoin, the overall result (95% CI) fails to exclude the important benefit or harm.		**bias and need to be viewed in context**. All 4 RCTs: low RoB **Pregnant women**	
Porreca 2021 [25] 33535221	Systematic review n=9 RCTs search date: up to May 6, 2020	The aim of the current paper is to provide an updated systematic review of RCTs to investigate the clinical and microbiological efficacy of nitrofurantoin compared to	N=3154 (calculated!) women with uncomplicated UTI	Nitrofurantoin	Antibiotic (n=5) • Trimethoprim-sulfamethoxazole (n=4) • fosfomycin (n=3) • Oral ciprofloxacin (n=1) • Trimethoprim (n=1) • Cefadroxil (n=1)	**Symptomatic/Clinical Cure** • clinical cure rates in nitrofurantoin ranged from 51 to 94% • significantly higher clinical cure rate in patients treated with nitrofurantoin (n=1, placebo)	Although no firm conclusions can be made based on the current base of evidence, the studies generally suggest that nitrofurantoin is at least comparable to other common uncomplicated UTI treatments in terms of clinical and	no additional hand search, complete search strategy and number of patients of the included studies not reported, unclear, if younger women are	1a - RoB: high

		other antibiotics or placebo.			• Amoxicillin (n=1) • Ofloxacin (n=1) Placebo (n=1)	<u>Nitrofurantoin vs fosfomycin</u> (n=3) • significantly higher with nitrofurantoin (n=2) • no differences (n=1) <u>Nitrofurantoin vs trimethoprim-sulfamethoxazole</u> (n=2) • no significant difference <u>Nitrofurantoin vs oral ciprofloxacin</u> (n=1) • no significant difference <u>Ofloxacin vs nitrofurantoin</u> (n=1) • ofloxacin was superior (no statistical test was performed) • many nitrofurantoin patients discontinued because of side effects **Bacteriological Cure** • bacteriological cure rates ranged from 61 to 92% <u>Placebo</u> (n=1) • significantly higher bacteriological cure rate in patients treated with nitrofurantoin	bacteriological cure. Furthermore, recent fluoroquinolone warning on side effects represents another reason to prefer other molecules to treat uncomplicated UTI.	also included in the data synthesis (see inclusion criteria from included studies Christiaens, Stein and van Pienbroek) although the inclusion criteria only considered aged over 18, no funnel plot <u>Conflict of interest</u> None. <u>Funding</u> None.	

						Nitrofurantoin vs fosfomycin (n=3) • significantly higher bacteriological cure rate in patients treated with nitrofurantoin (n=1) • no significant difference (n=2) Nitrofurantoin vs trimethoprim-sulfamethoxazole (n=3) • no significant difference Nitrofurantoin vs oral ciprofloxacin (n=1) • ciprofloxacin had statistically significantly higher eradication rates than nitrofurantoin Nitrofurantoin vs cefadroxil (n=1) • no difference Nitrofurantoin vs amoxicillin (n=1) • no difference Nitrofurantoin vs trimethoprim (n=1) • no difference **Adverse events** • higher side effects in patients taking nitrofurantoin compared to cefadroxil,			

						amoxicillin, and trimethoprim-sulfamethoxazole (n=1) • nitrofurantoin fewer side effects than trimethoprim (n=1), co-trimoxazole (n=1), or fosfomycin (n=1) • no differences vs placebo (n=1), trimethoprim-sulfamethoxazole (n=2), ofloxacin (n=1), ciprofloxacin (n=1), fosfomycin (n=2) most commonly reported side effects in patients taking nitrofurantoin were gastrointestinal (e.g., nausea or diarrhea) and central nervous system (e.g., headache) symptoms			
Wang 2020 [26] 32417205	systematic review and meta-analysis n= 21 RCTs search: inception to 01 December 2019 countries:?	Efficacy and safety of **single-dose** fosfomycin tromethamine (FT) versus other antibiotic agents in women suffering from lower uncomplicated urinary tract infection (uUTI) and	N= 4589* women suffering from lower uncomplicated urinary tract infection (uUTI) and pregnant women with uUTI or asymptomatic bacteriuria (ASB) and being treated with FT and other antibiotic agents	N=2533 Fosfomycin (3g single dose)	N=2056 other antibiotic agents (Nitrofurantoin, Trimethoprim, Cephalexin, Norfloxacin, Amoxicillin, Ofloxacin, Cotrimoxazole, Pipemidic acid, Ceftibuten, Cefuroxime axetil, Amoxicillin/ clavulanate, Cefuroxime	**Clinical resolution of uUTI**: single-dose FT vs. other antibiotic agents Total (n= 9; 2122 women): • OR 0.89 (95% CI 0.71–1.10, I^2= 22%); p= 0.28 non-pregnant (n= 8; 2010 w): • OR 0.89 (95% CL	Single-dose fosfomycin tromethamine produces equivalent clinical outcomes to comparator antibiotics in terms of **clinical** efficacy and **microbiological** efficacy. It is therefore clinically effective and safe for women with uUTI and pregnant women with uUTI	Competing Interests None. Funding This work was supported by grants from the National Natural Science Foundation of China (No. 81870525, 81801429), Taishan	1a - RoB: high

		pregnant women with uUTI or asymptomatic bacteriuria (ASB).			axetyl)	0,71-1.11, I^2=35%); P = 0.32 pregnant women (n=1; 112 participants): • OR 0.80 (95% CI 0.31-2.04, I^2= 0%); p = 0.64. **Subgroup analysis based on drug classification:** Fosfomycin vs. ß-lact./cephalo. (n=2; 224 participants) • OR 1.18 (95% CI 0.60-2.32, I^2= 0%); p= 0.64 Fosfomycin vs. quinol. (n= 4; 592 participants) • OR 0.83 (95% CI 0.53-1.31, I^2= 0%); p = 0.43 Fosfomycin vs. sulfon. (n= 1; 190 participants) • OR 1.69 (95% CI 0.87-3.29, I^2= not applicable); p = 0.12 Fosfomycin vs. nitrofur. (n=3; 1116 participants) • OR 0.87 (95% CI	or ASB, and has higher patient compliance. No serious fosfomycin-related AE. Most frequent AE were mainly gastrointestinal.	Scholars Program of Shandong Province (No. tsqn201909199). →n=10 of all in- cluded studies: multicentre RCTs! One included study involved non-pregnant women >12 years old No complete search strategy presented, search terms far too narrow; unclear whether 2 independent reviewers assisted in risk of bias error assessment, no funnel plot or sensitivity analysis. *N= 3103 pooled patients (to determine microbiological resolution between uUTI	

						0.52-1.48, I^2= 62%); p = 0.61. <u>Total (n=9; 2122 participants):</u> Fosfomycin vs. other antib. • OR 0.94 (95% CI 0.72-1.23, I^2= 22%); p = 0.68. **Microbiological resolution**: <u>Total (n= 21; 3103 patients)</u> • OR 1.11 (95% CI 0.92–1.34, I^2= 0%); p = 0.29 <u>Non-pregnant women with uUTI</u> (n=13; 2249 participants) • OR 1.08 (95% CI 0.87–1.34, I^2= 18%); p= 0.48) <u>pregnant women with uUTI</u> (n= 3; 277 participants) • OR 1.11 (95% CI 0.48–2.56, I^2= 0%); p = 0.81 <u>pregnant women with ASB</u> (n= 5; 577 participants) • OR 1.32 (95% CI 0.78–2.22, I^2= 0%); p		or ASB)	

						= 0.30. **Subgroup analysis based on drug classification** <u>Fosfomycin vs. ß-lact./cephalo. (n=7; 686 participants)</u> • OR 1.46 (95% CI 0.96-2.19, I^2= 0%); p =0.07 <u>Fosfomycin vs. quinol</u>. (n= 7; 1146 participants) • OR 0.98 (95% CI 0.70-1.38, I^2= 0%); p = 0.92. <u>Fosfomycin vs. sulfon</u>. (n= 3; 270 participants) • OR 1.58 (95% CI 0.86-2.90, I^2= 0%); p = 0.14 <u>Fosfomycin vs. nitrofurantoin (n=5; 1001 participants)</u> • OR 0.95 (95% CI 0.69-1.31, I^2= 48%); p =0.76 <u>Total (n= 21; n= 3103 participants):</u> • OR 1.11 (95% CI 0.92-1.34, I^2= 0%); p =0.29			

						Safety/Adverse events: single- dose FT and comparator antibiotics: Total: (n= 15; n= 3201 participants) • OR 0.95 (95% CI 0.66-1.37, I^2= 41%); p = 0.78 Non-pregnant patients (n= 10 RCTs; n= 2624 patients) • OR 1.03 (95% CI 0.78-1.36, I^2= 0%); p = 0.83 Pregnant patients (n= 5; n= 577 participants) OR 0.65 (95% CI 0.11-3.96, I^2= 78%); p = 0.64			
Wingert 2019 [27] 30872538	N= 19 (Screening effective.: -4 Non-concurrent cohort Treatment effectiven.: - RCT (11) - CCT (4)) France, Spain, Turkey, USA, Australia, Denmark, Ireland,	Screening and treatment effectiveness and patient preferences on screening for asymptomatic bacteriuria in pregnancy.	N=10480 Pregnant women with ASB (Screening effectiveness: 7611 women Treatment effectiveness: 2869 women)	(n= 4 studies) Before the intro-duction of a screening programme (n=15 studies) antibiotic treatment	(n= 4 studies) after the intro-duction of a screening programme (n=15 studies) no treat-ment or placebo	**Screening versus no screening**: (no numbers for "Risk with screening) Pyelonephritis (n= 3 studies; 5659 ♀ ♀) • RR 0.28; (95% CI 0.15 to 0.54) • I^2=0%; ARR 1.3%; NNS 77, 95% CI 65 to 121 • Risk with no screening: 18 perinatal mort. (n=2	Antibiotic treatment for women having significant bacteriuria likely reduces the incidence of pyelonephritis and low birth weight, but we are uncertain about the magnitude of the effect and about the extent to which we can apply these results to asymptomatic populations and	**Funding** for the Evidence Review is provided by the Public Health Agency of Canada. **Competing interests:** All of the authors report grants from the Public Health Agency of Canada during the conduct of the study.	1a RoB. low

	Jamaica, Netherlands, UK. search date: inception until October 2016; update in October 2017					studies; 724 ♀ ♀) • RR 1.21, (95% CI 0.01 to 102.93), • I^2=84% • Risk with no screening: 19 Spontaneous abortion at ≤28 weeks of gestation(n= 1 study; 370 ♀ ♀) • RR 0.96, (95% CI 0.41 to 2.27) • Risk with no screening: 55 preterm delivery (n= 2 studies; 722 ♀ ♀) • RR 8.70, 95% CI 0.32 to 240.07; • I^2=80% • Risk with no screening: 13 Neonatal serious harm: fetal abnormalities (n=1 study; 372 ♀ ♀) • RR 1.50 (95% CI 0.25 to 8.87) • Risk with no screening: 11 **Frequent screening versus one-time screening** (no numbers for "Risk with frequent screening) pyelonephritis (n= 1	screening programmes. High-quality RCTs of the effectiveness of screening programmes should be undertaken.	PICOTS are made **Wrong**: "A total of 25 unique studies were included in the review." Majority of studies were published in the 1960s to 1980s, predating current obstetric practices having, for example, better recognition of risk factors for UTIs and other pregnancy complications, prompt treatment of symptoms, a broader range of antibiotic options and improved ascertainment of maternal and neonatal outcomes. GRADE: low to (mostly) very low.	

						studies; 1952 ♀ ♀): • RR 1.09; (95% CI 0.27 to 4.35) • Risk with 1 screening: 4 Perinatal mortality(n= 1; n= 1952 ♀ ♀) • RR 1.57; (95% CI 1.11 to 2.23) • Risk with no screening: 49 **Treatment versus no treatment/ placebo:** Pyelonephritis (n= 12; 2017 ♀ ♀): • RR 0.24; (95% CI 0.13 to 0.41) • I^2=60%; ARR 17.6%; NNT 6, 95% CI 5 to 7 • Risk with no treatment: 232 • Risk with treatment: 176 fewer (from 137 fewer to 202 fewer) Perinatal mortality (n= 6; n=1104 ♀ ♀): • RR 0.96 (95% Cl 0.27 to 3.39) • I^2=56%			

						• Risk with no treatment: 40 • Risk with treatment: no data <u>Spontaneous abortion (n= 2; 379 ♀ ♀)</u> • 0.60 (95% CI 0.11 to 3.10) • I^2=17% • Risk with no treatment: 33 • Risk with treatment: no data <u>Neonatal sepsis (n= 2 studies; 154 ♀ ♀)</u> • RR 0.22 (95% CI 0.01 to 4.54) • Risk with no treatment: 22 • Risk with treatment: no data <u>Preterm delivery (n= 4; n=533 studies)</u> • RR 0.22 (95% CI 0.21 to 1.56) • I^2=70% • Risk with no treatment: 158 • Risk with treatment: no data <u>Low birth weight 1522 (n=7; 1522 ♀ ♀):</u>			

						• RR 0.63 (95% CI 0.45 to 0.90) • I^2=20%; ARR 4.4%; NNT 23, 95% CI 15 to 85 • Risk with no treatment: 118 • Risk with treatment: 44 fewer (from 12 fewer to 65 fewer) **Neonatal serious harm:** <u>fetal abnormalities (n= 4; 821 ♀ ♀)</u> • RR 0.49 (95% CI 0.17 to 1.43) • I^2=0% • Risk with no treatment: 19 • Risk with treatment: no data <u>haemolytic anaemia (n= 1; 265 ♀ ♀)</u> • RR not estimable • Risk with no treatment: 0 Risk with treatment: no data			
Angelescu et al. 2016 [28] 27806709	Systematic Review N= 4 RCTs Publikationsz	Information on the benefits and harms of antibiotic treatment for	n= 454 pregnant women with ASB	**For 1. & 2.:** Any ASB screening strategy followed by treatment, if necessary	**For 1. & 2.:** • No ASB screening, but treatment if symptoms of UTI occur (question 1)	No eligible studies that investigated the benefits and harms of screening for ASB versus no screening or that compared	The available data did not allow conclusions to be drawn on adverse events, as in one study the **event**	**Fund**: ? **Interest**: ? Total number of randomised	1a RoB: low

	eitraum: inception until 2015 USA, GB, NL	women with ASB: 1. Assess the patient-relevant benefits and harms of screening for ASB versus no screening; 2. Compare the benefits and harms of different screening strategies; 3. in case no reliable evidence on the overarching screening question was identified, to determine the benefits and harms of treatment of ASB.		**For 3.:** Any treatment for ASB (Antibiotics)	• Any other ASB screening strategy followed by treatment, if necessary (question 2) **For 3.:** No treatment or placebo	different screening strategies. **Antibiotics with no treatment/placebo** pyelonephritis (1 RCT →study from 1969!; n= 163 analyzed patients) - 6 % vs. 23 %; - OR = 0.21, (95 % CI 0.07–0.59) - p = 0.002 pyelonephritis (n= 1→study from 2015; n= 85) - 0 % vs. 2.2 %; - OR = 0.37, (CI 0.01–9.25), - p = 0.515 lower UTI (1 RCT →study from 1960!; n= 100 patients) - 6 % vs. 40 %; - OR = 0.10, (95 % CI 0.03–0.35) - p < 0.001 lower UTI during pregnancy (n= 1→study from 2015; n= 85) -10 % vs. 18 %; - POR = 0.53, (CI 0.16–1.79), - p = 0.357. Preterm birth (<37 weeks of gestation) (n= 1 study; n= 85 patients→study from 2015): - 5.0 % vs. 4.4 %, - POR= 1.13, (CI 0.15–8.35), - p = 0.975	**rate** in the control group was not clearly stated, while no events (1 RCT) **or very few** (1 RCT) occurred in the other two studies (see Table 4). We therefore could not determine the **risk of adverse events under antibiotic treatment, placebo or no treatment.** The available evidence is limited to four treatment trials (problems: 3 methodological shortcomings and questionable ,,current medical-applicability'; 1 low-risk-ofbias trial). Consequently, no conclusions can be drawn on whether the benefits of screening for ASB outweigh the potential harms. → **No reliable evidence supports routine screening for ASB in pregnant women.**	participants is unknown →lack of data in one study. Data were insufficient to determine the risk of harms. As three of the four studies were conducted several decades ago and have serious methodological shortcomings, the applicability of their findings to current health care settings is likely to be low. The recent high-quality RCT was stopped early due to a very low number of primary outcome events, a composite of preterm delivery and pyelonephritis. Therefore, the results did not show a benefit of treating	

						(1 preterm birth event considered patient-relevant, i.e. preterm birth < 32 weeks in the interventional arm). <u>Infant morbidity</u> (n= 1 study; n= 85 patients→study from 2015): Event rates, in general, were low & did not reveal any statistically significant difference between study groups. <u>Perinatal mortality</u> (n= 1 study; n= 85 patients→study from 2015): difference was not statistically significant: only one case in the interventional arm. **<u>Adverse Events</u>**: N=0 →zero further predefined patient-relevant outcomes such as symptoms linked directly or indirectly to **UTI**, **birth weight** < 1500 g, **health-related quality of life**, and **psychosocial functioning**. <u>pre-eclampsia</u> (n= 1 study; n= 85 patients→study from 2015): - 5 % vs. 2.2 %,		ASB.	

						- POR = 2.24, - CI 0.23–22.22, - p = 0.596).			
Smail et al. 2019 (update) [29] 31765489	Systematic Review N= 15 RCTs (over 2000 women with urinary infections, but no symptoms) Just details about country of the setting: North Ameria, UK, Ireland, Australia, Netherlands (same as conducted??) Studies from inception till November 2018 (oldest from 1960)	Can giving antibiotics to pregnant women who have a urinary infection but no symptoms improve the outcomes for women and their babies?	N= over 2000 Pregnant women with asymptomatic bacteriuria found on antenatal screening.	antibiotic treatment	placebo or no treatment	Antibiotic treatment vs. placebo or no treatment: **Development of pyelonephritis:** (12 RCTs, 2017 women)→Grade: low • RR: 0.24, (95% CI: 0.13 to 0.41); • I^2= 60%; Risk with no treatment (95% CI): • Study pop. (SP)): 199 per 1000 Risk with antibiotics (95% CI): • 48 per 1000 (26 to 82) **preterm birth less than 37 weeks**: (3 RCTs, 327 women) GRADE: low • RR 0.34, (95% CI 0.13 to 0.88); • I^2= 32%; Risk with no treatment: • Study pop.: 174 per 1000 Risk with antibiotics: • 59 per 1000 (23 to 153) **low birthweight babies** less than 2500 g (6 RCTs, 1437 babies) GRADE:	Antibiotic treatment may prevent pyelonephritis, preterm birth, and birthweight less than 2500 g but confidence in the effect estimate is limited given the low certainty of the evidence (Quality of the evidence: low-certainty) Research implications identified in this review include the need for an up-to-date cost-effectiveness evaluation of diagnostic algorithms, and more evidence to learn whether there is a low-risk group of women who are unlikely to benefit from treatment of asymptomatic bacteriuria.	**Declaration of interests**: unclear regarding this study. Declared are all used studies ("Only 1 RCT reported any potential conflicts of interest"). **Funding**: This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. Only one trial at low risk of bias; other 14 RCTs were assessed as high or unclear risk of bias. Significant heterogeneity among studies.	1a RoB: low

						low • RR 0.64 (95% CI 0.45 to 0.93); • I^2= 28%; Risk with no treatment: • Study pop.: 136 per 1000 Risk with antibiotics: • 87 per 1000 (61 to 126) ***Secondary outcomes*** <u>Antibiotic treatment</u> **Persistent bacteriuria**: (4 RCTs, 596 women) • RR 0.30, (95% CI 0.18 to 0.539; • I^2 = 76%; Without treatment bacteriuria was present at the time of delivery in 66% of women. **Neonatal mortality/ or other serious adverse neonatal outcome**: (3 RCTs, 549 babies) • RR 0.64, (95% CI 0.23 to 1.79) **Birthweight** (2 RCTs, 495 babies): • MD 21.03, (95% CI -83.65 to		May be explained by study design or quality, type of antibiotic used, and the changes in obstetrical practice in the past five decades between the earliest and the latest study. Duration of antibiotic treatment did not appear to explain any heterogeneity.	

						125.70); **gestational age** (1 study, 203 babies): • MD 1.00, (95% CI 0.01 to 1.99) **Maternal side effects**: Costs and Women's satisfaction, as measured by trial authors are mentioned/defined by trial authors.			
Köves et al. (2017) [30] 28754533	Systematic review and meta-analysis n= 50 study-design in general not clear; **used studies here are RCTs** Search date: January 2000 to November 2016 Studies were conducted in: ? (not even mentioned in Suppl.)	to synthesise evidence about benefits and harms of treating ABU in relevant patient groups	n=7088 patients diabetes mellitus, postmenopausal women, elderly institutionalised patients, recurrent urinary tract infection (UTI), [irrelevant: renal transplants, prior to joint replacement]	Antibiotics (*→metho-dische Bemerkung)	No treatment or placebo	**<u>Antibiotic treatment vs. no treatment or placebo of ABU in:</u>** <u>pregnant women</u> • symptomatic UTI, (n=11 RCTs): RR = 0.22 (95% CI: 0.12–0.40), I^2=72%; p<0.00001 • resolving ABU, (n=6 RCTs): RR = 2.99 (95% CI: 1.65–5.39), I^2=84%; p= 0.0003 • risk of low-birth-weight (n= 8 RCTs) (RR = 0.58, 95% CI 0.36–0.94); I^2= 47%; p= 0,03	**Antibiotics**: No evidence of benefit for patients with no risk factors, patients with diabetes mellitus, postmenopausal women, elderly institutionalised patients and treatment was harmful for patients with recurrent urinary tract infection (UTI). <u>Pregnant women</u>: evidence that treatment of ABU decreased risk of symptomatic UTI, low birthweight, and preterm delivery. In addition, current evidence also suggests that ABU treatment is required in pregnant women,	Conflict of interest: None Funding: None Citation mistake in women with rUTI Single-dose versus short-term just in pregnant women Forrest Plot of low birth weight is missing Lot of low evidence in the studies. No Funnel Plot or Sensitivity-analysis. many included	1a - RoB: high

						• preterm delivery (n= 4 RCTs) (RR = 0.34, 95% CI 0.18–0.66); I^2= 11%; p= 0,001 Postmenopausal • symptomatic UTI (n=3 RCTs) RR = 0.71 (95% CI: 0.49–1.05, I^2=16%); p=0.09 • resolving ABU (n=3 RCTs): RR = 1.28 (95% CI: 0.50–3.24), I^2=82%; p=0.61 Women with rUTI (n=1 RCT, Cai 2012; data extracted from the original paper) • antibiotic treatment vs. no treatment: 169/361 (73.1%) vs. 41/312 (14.7%) diabetes mellitus • eradicating ABU did not reduce the risk of symptomatic UTI (n=1	although the results of a recent trial have challenged this view. The demonstration of lack of benefit in most clinical situations shown by this thorough and methodologically robust systematic review and meta-analysis supports our recommendation of not to treat ABU.	studies were conducted in previous decades, the methods used in the trials were often unclear. This resulted in an overall high RoB and confounding across studies.	

						RCT): RR = 1.05 (95% CI: 0.66–1.66) elderly patients • symptomatic UTI (n=3 RCTs): RR = 0.68, (95% CI: 0.46–1.00, I^2=0%); p=0.05 • resolution of ABU (n=6 RCTs): RR = 1.33 (95% CI: 0.63–2.79, I^2=69%); p=0.45 Single-dose versus short-term (2–7 d) antibiotic treatment of ABU in pregnant women • symptomatic UTI (n= 1 MA with 3 RCTs) (RR = 1.07, 95% CI 0.47–2.47); I^2= 41%, p= 0,87 • ABU resolution (n= 9 RCTs) (RR = 0.97, 95% CI			

						0.89–1.07); I^2= 50%; p= 0,58 • preterm delivery (n= 3 RCTs) (RR = 1.16, 95% CI 0.75–1.78); I^2=0%, p= 0,51 • low birthweights (n= 1 RCT) (RR = 1.65, 95% CI 1.06–2.57); I^2=?; p=? • side effects (n= 1 MA with 6 RCTs) (RR = 0.40, 95% CI 0.22–0.72); I^2=0%, p= 0,002			
Xue 2021 [31] 34628902	systematic review and Meta Analysis N= 5 RCTs Countries:? Search date: between 2000 and the present	The different efficacy of levofloxacin and ciprofloxacin in the treatment of urinary tract infection (UTI).	N= 2877 patients (all aged ≥18 years) who were diagnosed with one or more of acute cystitis, bacterial prostatitis, acute pyelone-phritis, epididymitis, and gonococcal urethritis.	Ciprofloxacin (partly intravenous injection)	Levo-floxacin, Ofloxacin	**Treatment response of levofloxacin vs. ciprofloxacin:** (n= 5 studies; 2877 patients) • OR= 1.18, (95% CI 0.94 to 1.46) • I^2= 0 • P=0.15 **Adverse reactions between levofloxacin vs. ciprofloxacin**:	Levofloxacin was more effective than ciprofloxacin (not statistically significant) in the treatment of UTI. If bacterial resistance is discovered after the treatment of one of the drugs, the other drug might become an alternative. Levofloxacin has more therapeutic	**Age Range:** 39.4±5.3 - 51.4±4.5 **Funding**: None **Conflicts of Interest:** None All patients involved were diagnosed with complicated	1a - RoB: high

						(n= 5 studies; 2877 patients) • OR= 0.91, (95% CI 0.78 to 1.07, • I^2= 0 • P=0.27 Specific data on uncomplicated cystitis or pyelonephritis were not collected	advantages due to the small number of daily doses and shorter total medication time, but this was not thoroughly explored in this study. Treatment methods: intravenous drip, orally administered drugs were not studied comprehend-sively, and its efficacy and safety still need to be further verified in larger sample & higher quality literatures.	symptoms. No Prospero, so unclear whether a priori planned analyses were performed; likely no other sources searched in addition to electronic search; inadequate search strategy; unclear whether 2 unaffiliated reviewers minimized errors in study selection.	
Zhang 2021 [32] 34339776	systematic review / Meta Analysis USA/Korea/Turkey/Singapore/India N= 3 RCTs, n= 7 cohort studies Search date: January 1979 to December 2020.	Efficacy of non-carbapenem β-lactam/ β-lactamase inhibitors (BLBLIs) versus carbapenems for the treatment of urinary tract infections (UTIs) caused by extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE)	N= 1612 adult patients (> 18 years old) with a diagnosis of UTI, cUTI, cystitis or pyelonephritis due to ESBL-PE	BLB- LIs	carbapenems	**efficacy outcomes** non-carbapenem BLBLIs versus carbapenems (TOTAL) **-Clinical success** (N= 7 studies) - Total: • RR = 0.99; (95% CI 0.96–1.03) • I^2= 18%, P = 0.71; **-Microbiological success** (6 studies) Total: • RR = 1.06; (95% CI 1.01–1.11) • P = 0.01,	BLBLIs were not inferior to carbapenems, with higher microbiological success, indicating an effective alternative non-carbapenem option for the treatment of UTIs caused by ESBL-PE. More high-quality and large-scale RCTs are required to further validate these findings. Slightly higher rate of microbiological success in BLBLI	**Funding**: This work was supported by the National Natural Science Foundation of China [81770 0 04 and 82073894] and the Cultivation Project of PLA General Hospital for Distinguished Young Scientists [2020-JQPY-004].	2a RoB: low

						(n=1RCT→ slightly higher in BLBL) • RR = 1.32, (95% CI 1.13–1.55) • P = 0.0 0 06. **- Clinical and microbiological success** <u>(N= 4 studies) - Total:</u> • RR = 0.97; (95% CI 0.90-1.05) • I^2 = 0%, P = 0.46 **-mortality** <u>(n= 6 studies) Total</u>: • RR = 0.63; (95% CI 0.30–1.32) • I^2 = 31%, P = 0.22. **Subgroup**: <u>Clinical success</u> (n= 3 articles) **PTZ** + carbapenems**,** • RR = 1.01 (95% CI 0.96–1.06) • I^2 = 0%, P = 0.76; (n= 2 articles) **CAZ-AVI** + carbapenems**,** • RR = 1.01, (95% CI 0.95–1.07) • I^2 = 0%, P = 0.79); (n= 2 articles) **other BLBLIs** + carbapenems, • RR = 0.94, (95% CI	group was mainly attributed to the efficacy of ceftazidime/avibactam based **on a single RCT**.	**Competing interests**: None declared.	

						0.80–1.10), P = 0.43 (n= 2) Heterogeneity in the other BLBLIs group (P = 0.03, I^2 = 79%). <u>Microbiological success</u> (n= 4 studies) for **PTZ**+ carbapenems • RR = 0.99, (95% CI 0.96–1.02) • P = 0.55; I^2 = 0% (n= 1 study) **CAZ-AVI** + carbapenems: • RR = 1.32, (95% CI 1.13–1.55) • P = 0.0006 Heterogeneity: not applicable (n=1 study) for **other BLBLIs** + carbapenems, • RR = 0.83 (95% CI 0.46–1.51) • P = 0.55. Heterogeneity: not applicable <u>Clinical and microbiological success</u> (n= 4 studies) PTZ+ carbapenems • RR =0,97 (95% 0.90-1.05) • I^2=0%, P = 0.46 <u>Mortality</u>:			

						(n= 4) **PTZ**+ carbapenems • RR =0.63 (95% 0.30-1.32) • I^2 = 31%, P = 0.22 **CAZ-AVI** + carbapenems (n= 1 study) • RR & 95% not estimable heterogeneity not applictable for **other BLBLIs** + carbapenems (n= 1 study) • RR & 95% not estimable heterogeneity not applictable			
Farrell 2021 [33] 33234514	Systematic Review N= 3 RCTs US, NL Search date: ?inception? till 2019	To evaluate the outcomes of randomised controlled trials (RCTs) comparing the effectiveness of different antimicrobial treatments and durations for uncomplicated UTIs in adult males in outpatient settings.	N= 101 adult men (≥18 y.) with uncomplicated UTI who were treated in primary care, were extracted and shared.	Antimicrobials (TMP-SMX, Lomefloxacin/ norfloxacin, Ciprofloxacin). Partly in addition with placebo		**Bacteriological cure** Gleckman et al 1979 (overall median age of 60 years) – recurrence: **TMP-SMX+Placebo(160/800 mg BD)** 14 days; n= 21 • N= 6 (29%) **TMP-SMX (160/800 mg BD)** 42 days; n= 21 • N= 13 (62%) Iravani 1992 (median age of 53 years and 45 years in each arm of the RCT) - Uncomplicated UTI:	Only outcome with sufficient data to allow comparison between RCTs was bacterial cure at the end of therapy: For 75% males with a UTI (76/101) bacteriological cure was reported at the end of the study. Of the 59 patients receiving a **fluoroquinolone**, 57 (97%) reported bacteriological and clinical cure within 2 weeks after treatment. Duration of symptoms is not	**Funding**: none **Competing interest**: none Comorbidities reported in Gleckman (n= 10 diabetes) and van Nieuwkoop (diabetes (9) and heart conditins) No Prospero, so it is unclear whether a priori planned analyses were	1a - RoB: high

					Lomefloxacin (400 mg QD) 7-10 days; n=10 • N= 10 (100%) **Norfloxacin (400 mg BD)** 7-10 days; n=11 • N= 10 (91%) <u>Van Nieuwkoop et al 2017 (overall median 64 years) - Febrile UTI:</u> **Ciprofloxacin 500 mg BD** 7 days; n= 19 • N= 19 (100%) **Ciprofloxacin 500 mg BD** 14 days; n= 19 • N= 18 (1 missing urine sample) (100%) **<u>Recurrence of symptoms</u>** (6 weeks, 5–9 days and 30 days after end of treatm.) <u>Gleckman et al 1979 (overall median age of 60 years) – recurrent UTI:</u> **TMP-SMX + Placebo (160/800 mg BD)** 14 days; n= 21 • n= 13 (62%)	reported across groups and RCTs. No inference about duration until clinical or bacteriological cure could be made. Recommendations in relation to **type** and **duration of antimicrobial treatment** for male UTIs are insufficient. Sufficiently powered RCTs are needed to identify best treatment type and duration for male UTIs in primary care.	performed	

					TMP-SMX (160/800 mg BD) 42 days; n= 21 • n= 6 (29%) Van Nieuwkoop et al 2017 (overall median 64 years) - Febrile UTI: **Ciprofloxacin 500 mg BD** 7 days; n= 19 • N= 2 (11%) **Ciprofloxacin 500 mg BD** 14 days; n= 19 • N= 2 (11%) **Clinical Cure** Iravani 1992 (median age of 53 years and 45 years in each arm of the RCT) - Uncomplicated UTI: **Lomefloxacin (400 mg QD)** 7-10 days; n=10 • N= 10 (100%) **Norfloxacin (400 mg BD)** 7-10 days; n=11 • N= 11 (100%) Van Nieuwkoop et al 2017 (overall median 64 years) - Febrile UTI: **Ciprofloxacin 500 mg BD** 7 days; n= 19 • N= 17 (90%) **Ciprofloxacin 500 mg BD** 14 days; n= 19			

					• N= 19 (100%) **Adverse events (n= 3 RCTs)** Iravani: no gender specific reported AE. Gleckman et al: n=2 patients; 14-day course: **trimethoprim):** chills, sweats and flushing, transient rash and pruritus. N= 4 patients; 42 days **trimethoprim**): diffuse urticarial, nausea, vomiting, elevated serums creatinine. Van Nieuwkoop et: N=2 patients; 7 days – ciprofloxacin): pyelonephritis. 14-day ciprofloxacin: No adverse events			

Schlüsselfrage

Welche weiteren Behandlungsalternativen zur Therapie einer Harnwegsinfektion in den definierten Gruppen können empfohlen werden?

Referenz	Studien-charakteristika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
Cai, T., et al. (2021) [34] 35052890	Systematic review and meta-analysis	to compare the effectiveness and safety profile of a medical	n=178 female patients aged >19 years with	xyloglucan, (or an equivalent mucopr	Placebo or other comparator	**Primary endpoint**: **Clinical Success/Cure (n= 3; 178 patients)** women with cystitis - Medical device compared	A medical device containing xyloglucan, hibiscus and propolis is superior to comparator regimens in terms of clinical effectiveness in adult women with microbiologically	Conflict of interest None. Funding None.	1a - RoB: high

	n=3 RCTs Search date: until April 2021	device containing xyloglucan, hibiscus and propolis (XHP) in women with uncomplicated cystitis	microbiologically confirmed or clinical suspicion of uncom-plicated cystitis who were rando-mized to receive treatment with a medical device containing xyloglucan (or an equivalent mucoprotectant substance), hibiscus and propolis or placebo or other comparator	otectant substance), hibiscus and propolis or placebo or other compara-tor		<u>to other antibiotic agents</u>: medical device compared to other antibiotic agents: • OR=0.13 (95% CI: 0.05-0.33, I^2=0%); p < 0.0001 **<u>Secondary endpoints</u>: Safety outcomes/Adverse Events (n= 3; 178 patients)** <u>women with cystitis – effects of the medical device:</u> adverse effects • OR 0.14 (95% CI 0.03–0.67, I^2= 31%); p = 0.001 →most common reported adverse effects were of the gastrointestinal type (abdominal pain, diarrhea)	confirmed or clinical suspicion of uncomplicated cystitis and is associated with a high patient compliance. No clinically significant adverse effects have been reported.	Funnel plots analysis did not suggest the exclusion of any study. no prospero therefore compliance with the a priori analyses is not comprehensible; inadequate search strategy	
Carey 2020 [22] 32270403	Systematic Review N= 5 RCTs - Germany, - Pakistan, - Switzerland, - Norway/ Denmark / Sweden	Comparing NSAIDs with antibiotics for treatment of uncomplicated UTIs in adult women.	N= 1309 adult women with uncomplicated UTI	NSAID (Ibuprofen, placebo Granules, Potassium Citrate, Flurbiprofen, Diclofenac) →partly plus placebo	Antibiotics (Ciprofloxacin, Fosfomycintrome-tamol, Norfloxa-cin, Pivmecillinam) →partly plus placebo	**<u>Primary Outcome:</u> Symptom Resolution** <u>Symptom resolution by day 3 or 4 (post-randomization) in %:</u> **Bleidorn** 2010: day 4 • NSAIS (n= 21 (58%) vs. Antibiotics (n= 17 (52%) • RD*: 9 (95% CI − 13 to 31) • p = 0.744 for difference **Gágyor** 2015: day 4; **Kronenberg** 2017: day 3; **Vik** 2018: day 4	For the outcomes of symptom resolution and complications in adult women with UTI, evidence favors antibiotics over NSAIDs. In sum: The use of antibiotics as first-line treatment for uncomplicated UTI for both symptom resolution and prevention of pyelonephritis.	Four studies included adult women over the age of 18 while one study included women over the age of 15. Age range: 15-70 **Conflict of Interest**: The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Department of Veterans Affairs.	1a RoB: low

	inception until January 2020					• NSAIS (n= 233) vs. Antibiotics (n= 356) • RD*: (95% CI) 17 to 35 % points higher in the antibiotic group compared with the NSAID group. Symptom resolution at the end of the trial (day 5 post-randomization) **Jamil** 2016 • NSAIS: 1.4 vs. Antibiotics: 1.9; • p = 0.13 Number Needed to Treat *Antibiotics vs. NSAIDs to achieve symptom resolution in one additional patient by days 3 to 4 post-randomization* (3 RCTs)*:* **range: 3.0 to 6.4.** **Secondary Outcomes:** Women receiving antibiotics for any reason during study period: **Gágyor** 2015 • NSAID n= 85 (35%); antibiotics n= 243 (100%) • RD**: – 65 (95% CI – 71 to – 59) **Kronenberg** 2017 • NSAID n= 82 (62%); antibiotics n=		**Fund**:? Three studies were at low risk of bias, one had an unclear risk of bias, and one was at high risk of bias. *Positive numbers= higher rates of symptom resolution among patients receiving antibiotics vs. NSAIDS **Positive numbers= higher rates of antibiotic use in the NSAID group *** Positive numbers = higher rates of pyelonephritis in the NSAID group	

						118 (98%) • RD**: – 37 (95% CI – 46 to – 28) <u>Rates of pyelonephritis:</u> Gágyor 2015 • NSAID n= 5 (2%); antibiotics n= 1 (0.4%) • RD***: 1.7 (95% CI – 0.3 to 3.6) Kronenberg 2017 • NSAID n= 6 (5%); antibiotics n= 0 (0%) • RD***: 5 (95% CI 1 to 8) Vik 2018 • NSAID n= 7 (4%); antibiotics n=0 (0%) • RD***: 4 (95% CI 1 to 8) <u>Number Needed to Treat</u>: *Antibiotics vs. NSAIDs to prevent one additional case of Pyelonephritis by Day 28 to 30* (3 RCTs): **range: 22.2 to 62.1** →2 RCTs: patients who received antibiotics had lower rates of pyelonephritis compared with those who received NSAIDs.			
Qin, 2020 [35] 32406571	Systematic review and meta-	This systematic review of RCTs	Women aged ≥18 y with a diagnosis of	Manual acupuncture, moxi-	Antibiotics (n=85)	*In the following only the studies are considered that evaluated acupuncture as therapy*	Acupuncture appeared to be beneficial for treatment and prophylaxis of rUTIs, noting the limitations of the current	Confidence in these results is limited due to the lack of detail reported and high risk of	1a RoB: low

	analysis n=5 RCTs (n=2 studies evaluated acupuncture as prophylactic therapy, n=3 studies recruited women during the acute infection stage) Search date: up to 2019	assessed the effects and safety of acupuncture therapies for uncomplicated rUTI in women.	uncomplicated rUTI	bustion (n=85)		*for acute infection* **Composite cure** <u>Acupuncture vs. antibiotics</u> (n=3 RCTs, Hong 2013; Liu 2018; Yu 2010; n=170 participants) • Acupuncture: 48/85 • Antibiotics: 25/85 RR=1.84 (95% CI: 1.12–3.02, I2=38%); p=0.02 (low certainty evidence) **Symptom duration** <u>Moxibustion vs. antibiotics</u> (Liu 2018; n=40 participants) Mean symptom duration by days: • Moxibustion: 4.22 (SD=0.88) • Antibiotics: 6.25 (SD=1.24) MD=-2.03 (95% CI: -2.70- -1.36) p<0.00001 (very low certainty) **Adverse events** <u>Moxibustion</u> (n=1) Overall: 1/20 (temporary local skin redness) None of the other RCTs reported whether adverse events had occurred.	evidence.	bias due to lack of blinding Planned sensitivity and subgroup analyses could not be conducted due to the small number of included studies <u>Funding:</u> The study was supported by China-Australia International Research Centre for Chinese Medicine (CAIRCCM) (International Cooperation Project, Grant Number 2012DFA31760) and the National Natural Science Foundation of China (NSFC) (Grant Number 81873261). The funding source was not involved in the process of the study. <u>Conflict of interest:</u> The funding source was not involved in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication. Completed disclosure of interests forms are available to view online as supporting information.	

Kaußner et al. 2022 [36] 35788049	systematic review & individual participant data meta-analysis n= 9 RCTs Germany, Belgium, Sweden, Switzerland, UK Search date: 1st literature search in 2019 (1990-2019); updated search in May 2021 & February 2022	Reducing antibiotic use in uncomplicated urinary tract infections in adult women with symptoms suggestive of acute uUTI presenting to general practice	n= 3602* adult women with symptoms suggestive of acute uUTI presenting to general practice. *n= 3524 adult women from eight trials + aggregates data of 78 additional patients from one trial median age: 25 and 45 years.	women, where strategy to reduce antibiotic use was followed (Diclofenac, Ibuprofen, herbal formulation (Uva ursi, BNO 1045), placebo)	women with immediately prescribed antibiotics (ciprofloxacin, nitrofurantoin, pivmecillinam, fosfomycin, norfloxacin, trimethoprim, mecilinam)	**Strategies to reduce antibiotics vs. immediate prescribed antibiotics** **Subgroup analysis – analgesics (Ibuprofen, Dicolfenac)**: Incomplete recovery (n= 6) **OR** 4.5 (95% CrI, 2.4-8.0); **pB** = 0.0006; **Tau**: 0.40(95% CrI 0.0 to 0.9). subsequent antibiotic treatment (n= 6) **OR** 4.5 (95% CrI, 2.3-8.2); **pB**= 0.0008; **Tau**: 0.43 (95% CrI 0.0 to 0.9) number of antibiotic courses (n= 7) **OR**: 0.4 (95% CrI 0.2 to 0.6); **Tau:** 0.4 (95% CrI 0.1 to 0.8). pyelonephritis and febrile UTI (n= 8) (less frequent with immediate antibiotics) **OR** 9.1(95% CrI, 2.1 to 38.7); **pB** = 0.003; **Tau**: 0.3(95% CrI 0.0 to 0.9). symptomatic incomplete recovery (n=8) **OR**= 2.8 (95% CrI, 1.36-5.91) **Tau**: 0.36 (95% CrI 0.0 to 0.9) Symptom burden on day 2 (MD) (n= 6) (→Supplement) **MD** 11.2(95% CrI 6.7 to 15.8); **Tau**: 1.9(95% CrI 0.0 to 56.6) effect on the rates of relapses/ recurrent UTIs (n= 7) (→Supplement) **OR** 2.2 (95% CrI 0.7 to 5.6); **Tau**: 0.8(95% CrI	Investigated non-antibiotic strategies: threefold increase in the rate of **incomplete recovery** compared to immediate antibiotic treatment. Assuming a rate of 25% with immediate antibiotics, this would correspond to a number needed to harm (NNH) of five for non-antibiotic strategies. Similar effects were observed for the secondary and safety outcomes, specifically, occurrence of **pyelonephritis and febrile UTI, incomplete symptomatic recovery, and clinical recovery**. **Subsequent treatment** with antibiotics was **less likely** in the antibiotic groups; those who had already been treated with antibiotics had a lower risk of follow-up antibiotics than those who had not. On the other hand, strategies to reduce antibiotics lowered the overall use of antibiotics by 63% - a relevant finding from the perspective of antimicrobial stewardship. Presence of erythrocytes and tests to confirm bacteria in urine could be used to target antibiotic prescribing.	Interest:? Fund: None Prospero: new Title, less authors	1a RoB: Low

						0.4 to 1.3) Clinical recovery (n= 9) **OR** 0.5(95% CrI 0.3 to 0.9); **Tau**: 0.4(95% CrI 0.0 to 0.9) serious adverse events (n= 6) **OR** 2.3(95% CrI 0.6 to 9.3); **Tau**: 0.3(95% CrI 0.0 to 0.9) **All combined:** incomplete recovery (n= 6) **OR** 3.0; (95% CrI, 1.7-5.5); **pB**= 0.0017; **Tau**: 0.6 (95% CrI 0.3 to 1.0) subsequent antibiotic treatment (n=6) **OR**= 3.5; (95% CrI, 2.1-5.8); **pB**= 0.0003; **Tau**: 0.5(95% CrI 0.3 to 0.9) number of antibiotic courses (n= 7) → reduced by 63% **IRR**= 0.4(95% CrI, 0.2-0.6); **pB** = 0.00024; **Tau**: 0.5(95% CrI 0.3 to 0.9) pyelonephritis & febrile UTIs with immediate antibiotics (n= 8) **OR**= 5.6; (95% CrI, 2.3-13.9); **pB**= 0.0003; **Tau**: 0.3(95% CrI 0.0 to 0.8) symptomatic incomplete recovery (n= 8) **OR**= 2.2; 95%, (CrI, 1.3-3.8); pB = 0.0073; **Tau**: 0.6(95% CrI 0.3 to 1.0) Symptom burden on day 2 (MD) (n= 6) (→Supplement) **MD** 9.7 (95% CrI, 5.5-			

						13.1); **pB**= 0.0013; Tau: 2.7(95% CrI 0.0 to 7.2). relapses/ recurrent UTIs (n= 7) (→Supplement) **OR**= 1.7 (95% CrI, 0.9-3.2); **pB** = 0.1; Tau: 0.7(95% CrI 0.4 to 1.1) Clinical recovery (n= 9) **OR**= 0.5 (95% 0.35-0.72); **Tau**: 0.4(95% CrI 0.1 to 0.8) serious adverse events (n= 6) **OR**= 2.2(95% CrI, 0.7-6.2); **pB** = 0.16; **Tau**: 0.3(95% CrI 0.0 to 0.9) Moderator analyses (→Supple.) Incomplete recovery: - when either moderator was positive): (OR 4.7; 95% CrI, 2.1-10.8) - when both were negative (OR 0.8; 95% CrI, 0.3-2.0) **Prognostic indicators** (analgesics, herbal formulations, delayed prescription, placebo) as well as the subset of analgesic studies (→Suppl.1 Table 5): **for subsequent antibiotic treatment**: (OR 2.4; 95% CrI, 1.6-3.7; pB = 0.0014; positive urine culture results: OR 3.2; 95% CrI, 1.9-5.6; pB = 0.0008) **pyelonephritis:** (OR 5.2; 95% CrI, 1.6-20.7; pB = 0.018;			

						positive urine culture: OR 3.8; 95% CrI, 1.2-14.9; pB = 0.004) **Clinical recovery:** (OR: 0.991; Crl, (0.983 to 0.999) pB= 0.031)			
New 2022 [37] 35156175	Systematic review n=9 studies (n=7 RCTs, n=2 cohort studies) Search date: 1st Jan 1990-1st Apr 2021	We conducted a systematic review of literature to assess the role of probiotics in management of UTIs.	n=772 female adults with urinary tract infections Mean age 34.2 y (18-65 y)	Probio-tics	-placebo -antibiotics -cranberry supplements	**Reduction in UTI** demonstrated by 2 studies: <u>Koradia 2019</u> BKPro-Cyan (Lactobacillus acidophilus PXN 35, Lactobacillus plantarum PXN 47, cranberry extract) one capsule twice a day vs. placebo **Recurrent UTI:** • Probiotics: 4/44 (9.1%) • Placebo: 15/45 (33.3%) **Adverse events** • Probiotics: 1/44 abdominal distension; 2/44 diarrhoea • Placebo: None. <u>Stapleton 2011</u> Lactobacillus crispatus (Lactin-V; Vaginal suppositories once daily for 5 days followed by once weekly for 10 weeks) vs. placebo Development of UTI • Probiotics: 7/48	There exists only limited clinical evidence to support the role of probiotics in the management of rUTIs, and based on the current evidence, probiotics can be a potential measure to reduce rUTIs	Funding Not reported. Conflict of interest The authors declare no competing interests. no study protocol, MeSH terms named in the paper are not included in the example search strategy, no information if efforts were made to minimise error in the data extraction process and risk of bias assessment, unclear which RoB tool was used for the cohort studies, no funnel plot	1a - RoB: high

						(14.5%) • Placebo: 13/48 (27%) **Adverse events** Probiotics: Adverse events • Probiotics: 56% described AE which include vaginal discharge/ itch and mild abdominal discomfort • Placebo: 50% (25) described AE which include vaginal discharge/ itch and mild abdominal discomfort **Recurrent UTI**: n=7 studies showed no significant reduction in the risk of rUTI (Baerheim 1994; Kontiokari 2001; Reid 2003; Czaja 2007; Beerepoot 2011; Pugliese 2020; Wolff 2020) **Adverse events** (all studies) Vaginal discharge or irritation, abdominal discomfort and gastrointestinal symptoms were the most documented with similar rates across all the studies where AEs			

						occurred. Treatment withdrawal or exclusion due to adverse events (across all studies) • Probiotics: 16 Control: 9			
Ong Lopez 2021 [38] 34187385	meta-analysis and systematic review n= 4 RCT Germany, Switzerland, Norway-Denmark-Sweden search date: inception to April 2021	Can non-steroidal anti-inflammatory drugs serve as an effective and safe option in the treatment of uncomplicated lower UTI among non-pregnant women compared to antibiotics	N= 1165 non-pregnant women ≥18 years old with uncomplicated lower urinary tract infection	N= 584 Non-steroidal anti-inflammatory drugs (Ibuprofen, diclofenac) Mean-Age: 28.1-44.6	N= 560 in the antibiotic group (ciprofloxacin, fosfomycin, norfloxacin, pivmecillinam) Mean-Age: 28.5-43.7	**Primary outcomes**: a.) (n= 4 RCTs) symptom resolution of UTI by Day 3 or 4 of intervention - NSAID vs. antibiotic treatment: • RR: 0.69, • 95% CIs [0.55, 0.86], • p = 0.0008, I^2 = 73%, →moderate certainty of evidence b.) (n= 3 RCTs) Odds of developing upper UTI complications - NSAID vs. antibiotic treatment: • Peto OR: 6.49, • 95% CIs [3.02, 13.92], • p < 0.00001, I^2 = 0%, →moderate certainty of evidence **Secondary outcomes**: a.) (n= 3 RCTs) positive urine culture - NSAID versus antibiotic group • RR: 2.77, • 95% CIs [1.95, 3.94], • p < 0.00001, I^2 = 36%, →moderate certainty of evidence b.) (n= 4 RCTs) need for	Antibiotic treatment is more effective than use of non-steroidal anti-inflammatory drugs for acute uncomplicated lower urinary tract infection with an overall moderate certainty of evidence. **Primary outcome**: The probability of having a symptom resolution by Day 3 or 4 with NSAID [Ibu, Diclo] use is only less than three-fourths of that with antibiotic treatment. Developing upper UTI complications with use of NSAIDs: Odds are 6.49 to 1 for antibiotics. **Secondary Outcome**: NSAID [Ibu, Diclo] group is 2.77x more likely to have persistence of a positive microbiologic urine culture than the antibiotic group. Treatment with NSAIDs are three times more likely to use a secondary or rescue antibiotic due to persistent or worsening symptoms as compared to antibiotics	**Funding**: None **Competing interests**: None Due to some unexplained inconsistencies or heterogeneities in the study results, one may implement an individual participant data meta-analysis, or do more studies in relevant subgroups No major differences in the baseline characteristics between both groups in all the individual trials. Community based Prospero missing, so compliance with a priori analyses remains unclear; inadequate search strategy	1a - RoB: high

						<u>another rescue antibiotic - NSAID versus antibiotic group</u> • RR: 3.16, • 95% CIs [2.24, 4.44], • p < 0.00001, I^2 = 47%, →low certainty of evidence			
Parazzini, 2022 [39] 35815191	Systematic review N=7 (Cross-sectional, cohort, case–control studies, clinical trials) including n= 1 →neurogenic bladder and n= 1 →breast cancer **FINAL**: **→ 5 paper** (1x random. cross-over trial, 3x prospective uncontrolled, 1x RCT)	Effect of D-mannose, alone or in association with other compounds, on the typical symptoms of UTI/cystitis.--> PICO: Is D-mannose effective in the treatment of symptoms of UTI/cystitis	[N= 386 → Excl. 2 Paper:] n= 248 Women with symptoms of low urinary tract infection/cystitis Age-range: >18-65	D-mannose (sometimes given alongside with cranberry extract, Morinda citrifolia fruit extract, pomegranate extract, fructooligosaccharides, lactobacilli, and N-acetylcysteine.)	n= 2 no treatment, n= 3 antibiotic therapy TMP/SMX	**Outcome: Reduction of symptoms** <u>Porro et al.</u> (text mentioned n= 60 but table 2 presents n= 46 women, acute cystitis and rUTI-history, random. cross-over trial) <u>trimethoprim/sulfamethoxazole or oral D-mannose three times a day group, for 2 weeks:</u> **Before D-mannose vs. After D-Man →Mean score VAS:** • Suprapubic pain: 4.1 (1.1) vs. 2.2 (0.5) • Frequent voiding: 7.1 (1.1) vs. 4.7 (1.0) • Urgency: 4.6 (1.1) vs. 2.6 (0.7) → dysuria, hematuria, overall symptoms: no data • No adverse events <u>Vicariotto et al.</u> (n= 33 premeno-pausal, nonpregnant women with acute uncomplicated	In women with symptoms of UTI/ cystitis, treatment with D-mannose alone or in association with other compounds is useful for lowering the intensity of symptoms both in the short and middle-term for all typical symptoms, except hematuria. → D-mannose interacts with bacteria to promote UPEC excretion. May explain a **faster resolution of symptoms**. **Biological** and **clinical** explanations of the results are **not entirely clear**. Observational studies and clinical trials: → D-mannose may be useful in the treatment of UTI/cystitis symptoms. Its non-pharmacological, non-metabolic, non-bacteriostatic or bactericidal, but biomechanical mechanism of action, and the fact that it does not affect antibiotic resistance may support the use of D-mannose in **the treatment of UTI/cystitis**.	<u>Competing interests:</u> None. <u>Funding:</u> None. To evaluate the effect of D-mannose on the symptoms of UTI /cystitis, from the studies that presented data on long-term follow-up: only information obtained during the evaluation of first symptoms after study entry were considered. 1.limited data: no opportunity for detailed analysis of the role of different doses of D-mannose or the effect of D-mannose alone or in association with other compounds. 2. Most data were derived from uncontrolled studies. 3. These findings are based on an extremely limited number of studies with small sample sizes. 4. Heterogenious	1b - ROB: high

	Search Date: 1990 to January 2022 All 5 sudies from Italy					cystitis; prospective observational study) Compound (D-mannose, cranberry dry extract, exopolysaccharides produced by Streptococcus thermophilus ST10, tara gum, Lactobacillus plantarum, Lactobacillus paracasei, two doses per day for 1 month.) **Baseline vs. day 30 → mean score UTI-SAQ:** • Suprapubic pain: 1.39 vs. 0.97 • Dysuria: 2.03 vs. 1.36 • Frequent voiding: 2.18 vs. 1.70 • Urgency: 2.15 vs. 1.64 • Hematuria: 0.61 vs. 0.58 • Overall symptoms: no data Domenici et al (n= 43 women with acute cystitis were included; observational prospective study.) D-mannose: twice daily for 3 days and then once a day for 10 days **Baseline vs. Day 15 → mean score UTI-SAQ:** • Suprapubic pain: 1.47 (0.95) vs. 0.15 (0.36)		population 5. Methods concerning evaluation of the symptoms differed →comparison among studies of the magnitude of the effect of D-mannose is not feasible 6. Most studies conducted in Italy The two from 5 trials had a low risk of bias according to the Cochrane risk of bias tool → risk of bias has been assessed but reviewers have not incorporated it into findings/ conclusions	

						• Dysuria: 1.60 (±1.00) vs. 0.31 (0.47) • Frequent voiding: 2.16 (1.52) vs. 0.60 (0.63) • Urgency: 1.73 (0.92) vs. 0.23 (0.43) • Hematuria: 0.34 (0.90) vs. 0.10 (0.45) • Overall symptoms: no data Pugliese et al (n= 33 women (mean age 38.1±11.2 years) with urinary symptoms suggestive of an UTI; conducted study) D-mannose, pomegranate extract, prebiotics and probiotics twice daily for 5 days and then once a day for 10 days. Antibiotics: permitted on a clinical basis. No adverse events were reported. **Baseline vs. 15 days → mean score ACSS**: **→No data**: Suprapubic pain, dysuria, frequent voiding, urgency, Hematuria. • Overall symptoms: 11.5 (95% CI 10.5-12.6) vs. 4.9 (95% CI 4.0-5.9); p<0.0001 • Differential			

						symptoms (i.e., lower back pain, vaginal discharge, urethral discharge, fever, and chills: 3.1 (95% CI 2.6-3.6) vs. 0.6 (95% CI 0.3-0.9); p<0.0001 • QoL mean score: 7.2 (95% CI 6.7-7.7) vs. 4.0 (95% CI 3.3-4.6); P<0.0001 • No adverse events Rădulescu et al (n= 93 non-pregnant healthy women (mean age of 39.77±10.36 years) with uncomplicated lower UTI; randomized study) Antibiotics alone or in association with D-mannose plus cranberry extract for 7 days. **Baseline vs. 7 days → mean score 3 degrees questionnaire:** • Suprapubic pain: 72.9 (35/48) vs. 2.1 (1/48) • Dysuria: 60.4 (29/48) vs. 0% (0/48) • Frequent voiding: 85.4 (41/48) vs. 2.1% (1/48) • Urgency: 89.6% (43/48) vs. 0% (0/48) • Hematuria: 10.4% (5/48)			

						vs. 0% (0/48) • Overall symptoms: no data Co-administration of D-mannose plus cranberry extract: no statistically significant differences in symptoms, except for urinary urgency/pollakiuria (P=0.024).			
Gbinigie 2020 [40] 33375566	Systematic Review N= 3 RCTs Non-randomised studies Search: inception to 3rd February 2020 USA/India/UK	Is the use of cranberry extracts effective for symptoms of acute urinary tract infection (UTI) → Identification and critically appraisal of the supporting evidence	n = 688 Patients* aged 18 years and above with acute uncomplicated UTI - treated with cranberry extract with other treatment *(finally just women were involved)	n= 628 cranberry juice, n= 60 encapsulated cran-berry powder	N= 319 Placebo, n= 309 water, N= 60 no treatment	**Primary outcomes** <u>1 RCT (n = 319) Cranberry juice vs. Placebo</u> Presence of urinary and vaginal symptoms was similar between groups at 3 days and at 1–2 weeks <u>1 RCT (n=309) Cranberry juice vs. water</u> • IRR 1.18 (95% CI: 1.95 to 1.47), p = 0.13), frequency symptom severity (mean difference: • -0.01 (95% CI: -0.37 to 0.34), p = 0.94), severity of unwell symptoms: • MD 0.02 (95% CI: -0.36 to 0.39), p = 0.93), use of antibiotics: • OR 1.27 (95% CI:0.47 to 3.43) p = 0.64)	<u>Comsumption of cranberry juice versus water</u>: No evidence that cranberry juice improves: - urinary frequency - symptoms, - feeling unwell or - the duration of symptoms rated moderately bad or worse in women with acute UTIs. Advice to consume cranberry juice **did not reduce the use of antibiotics** compared with promoting the consumption of water or time to re-consultation. In women receiving immediate **antibiotics and cranberry** juice, urinary symptoms were not reduced compared with immediate antibiotics and placebo juice. Consuming encapsulated cranberry powder may reduce E. coli load and improve symptoms after 10 days of consumption compared with baseline. The studies did not report evidence of serious harm associated with cranberry consumption.	**Funding: YES! (**O.A.G.; E.A.S; NIHR) The views are those of the authors and not necessarily those of the Wellcome Trust, the NIHR or Department of Health and Social Care. **Conflicts of Interest:** partly Limited number of studies with a moderate risk of bias for the outcomes of interest in this review, which were not the primary objectives of the trials. → no clinical recommendations can be made at present Empirical data were not provided for all of the outcomes assessed in the review→cranberry extract as an acute UTI treatment was not the primary focus of the included RCTs.	1a RoB: low

						time to reconsultation • hazard ratio 0.74 (95% CI: 0.49 to 1.13), p = 0.17). <u>1 RCT (n = 60) encapsulated cranberry powder versus no treatent</u>: Significant within-*group improvement of symptoms* at day 10 compared to the baseline in both treatment (low+high) groups, but not in the untreated controls. Significant within-group *reduction in E. coli load* in both treatment groups after 10 days of treatment • low dose, p < 0.01; • high dose p < 0.0001; • level of 95%, but not in the untreated controls • p = 0.72. (2 RCT; n= 369) **No serious adverse effects**. (1 RCT; n= 319) **serious adverse events** occurred equally between groups → not related to treatment received in the trial		Further adequately powered, well-conducted randomised clinical trials are necessary outpatient settings	
Zhang 2021 [32] 34339776	systematic review / Meta Analysis	Efficacy of non-carbapenem β-lactam/ β-	N= 1612 adult patients (> 18 years	BLB-LIs	carbapenems	**<u>efficacy outcomes</u>** <u>non-carbapenem BLBLIs versus carbapenems (TOTAL)</u>	BLBLIs were not inferior to carbapenems, with higher microbiological success, indicating an effective	**Funding**: This work was supported by the National Natural Science Foun- dation of	2a RoB: low

	USA/Korea/Turkey/Singapore/India N= 3 RCTs, n= 7 cohort studies Search date: January 1979 to December 2020.	lactamase inhibitors (BLBLIs) versus carbapenems for the treatment of urinary tract infections (UTIs) caused by extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-PE)	old) with a diagnosis of UTI, cUTI, cystitis or pyelonephritis due to ESBL-PE			**-Clinical success** <u>(N= 7 studies) - Total</u>: • RR = 0.99; (95% CI 0.96–1.03) • I ^{2}= 18%, P = 0.71; **-Microbiological success** (6 studies) <u>Total</u>: • RR = 1.06; (95% CI 1.01–1.11) • P = 0.01, (n=1RCT→ slightly higher in BLBL) • RR = 1.32, (95% CI 1.13–1.55) • P = 0.0 0 06. **- Clinical and microbiological success** <u>(N= 4 studies) - Total:</u> • RR = 0.97; (95% CI 0.90-1.05) • I ^{2} = 0%, P = 0.46 **-mortality** <u>(n= 6 studies) Total</u>: • RR = 0.63; (95% CI 0.30–1.32) • I ^{2} = 31%, P = 0.22. **Subgroup**: <u>Clinical success</u> (n= 3 articles) **PTZ** + carbapenems**,** • RR = 1.01 (95% CI 0.96–1.06) • I ^{2} = 0%, P = 0.76; (n= 2 articles) **CAZ-AVI**	alternative non-carbapenem option for the treatment of UTIs caused by ESBL-PE. More high-quality and large-scale RCTs are required to further validate these findings. Slightly higher rate of microbiological success in BLBLI group was mainly attributed to the efficacy of ceftazidime/avibactam based **on a single RCT**.	China [81770 0 04 and 82073894] and the Cultivation Project of PLA General Hospital for Distinguished Young Scientists [2020-JQPY-004]. **Competing interests**: None declared.	

						+ carbapenems, • RR = 1.01, (95% CI 0.95–1.07) • I^2 = 0%, P = 0.79); (n= 2 articles) **other BLBLIs** + carbapenems, • RR = 0.94, (95% CI 0.80–1.10), P = 0.43 (n= 2) Heterogeneity in the other BLBLIs group (P = 0.03, I^2 = 79%). <u>Microbiological success</u> (n= 4 studies) for **PTZ**+ carbapenems • RR = 0.99, (95% CI 0.96–1.02) • P = 0.55; I^2 = 0% (n= 1 study) **CAZ-AVI** + carbapenems: • RR = 1.32, (95% CI 1.13–1.55) • P = 0.0006 Heterogeneity: not applicable (n=1 study) for **other BLBLIs** + carbapenems, • RR = 0.83 (95% CI 0.46–1.51) • P = 0.55. Heterogeneity: not applicable <u>Clinical and microbiological success</u> (n= 4 studies) PTZ+ carbapenems • RR =0,97 (95% 0.90-1.05)			

						• I^2=0%, P = 0.46 Mortality: (n= 4) **PTZ**+ carbapenems • RR =0.63 (95% 0.30-1.32) • I^2 = 31%, P = 0.22 **CAZ-AVI** + carbapenems (n= 1 study) • RR & 95% not estimable heterogeneity not applictable for **other BLBLIs** + carbapenems (n= 1 study) • RR & 95% not estimable • heterogeneity not applictable			

Schlüsselfrage

Welche weiteren Behandlungsalternativen zur Therapie einer Pyelonephritis in den definierten Gruppen können empfohlen werden?

Referenz	Studien-charakteristika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolger-ungen des Autors	Methodische Bemerkungen	LoE/ RoB
Allameh 2016 [41] 27162800	Systematic review n=22 interventional studies (n=8 human studies of these n=6 on children; n=14	Pyelonephritis is an inflammatory process, and oxidative stress plays a major role in it. Anti-inflammatory or antioxidant therapy given concomitantly with antibiotics should lower the risk of postpyelonephritic scarring. As the lack of review studies in the use of antioxidants in	Any type of subjects	Antioxidant drug	Not defined.	*In the following only the human studies are presented that included adults.* Gordiushina 2013 (Article in Russian; PMID: 21678656) • Antioxidant: Cytoflavin • Effective in reducing oxidative stress (following 2 remarks	Studies show that antioxidants are capable of reducing oxidative stress and can be used effectively along with antibiotics to reduce the scar formation.	No study protocol; no detailed information on the search strategy; the literature search is not reproducible; no additional methods to database search in order to	3a - RoB: high

	animal studies) Search period: not specifically stated presumably up to 2015	urinary tract infections was detected, this study was designed				correspond almost verbatim to those of the abstract!!!) • The antioxidant drug cytoflavin in combination with basic therapy reduces the intensity of lipid peroxidation processes with retention of the antioxidant status in patients with chronic pyelonephritis. • The proposed treatment normalizes the ratio of blood plasma phospholipid fractions and erythrocytes membranes. <u>Ushakova 2004</u> (Article in Russian; PMID: 15199807; n=67 subjects with acute obstructive pyelonephritis complicated by urosepsis) • Antioxidant: Perfluoran (following last review-comments are an exact copy of the abstract) • surgical manipulations aiming at recovery of urodynamics and normalization of hemodynamic indices of the kidney are accompanied by development of reperfusion syndrome of the affected and contralateral kidney. • Use of perfluoran in this situation promotes rapid compensation of gas transport disturbances, stabilization of the		identify relevant reports or grey literature; no detailed information on the study selection process and the data extraction process; no assessment of the study quality; for the 2 human studies considering adults only the information presented in the abstract of the original papers are reported <u>Funding</u> The research project was conducted and sponsored by Shahid Beheshti School of Pharmacy, Tehran, Iran. <u>Conflict of interest</u> There are no conflicts of interest reported.	

						equilibrium in the system prooxidants-antioxidants, regress of pyoinflammatory reactions, earlier recovery of functions of a more affected kidney and antiischemic protection of the contralateral organ. • Antiischemic and membrane-stabilizing actions of perfluoran make this drug adequate for use in patients with complicated renal infection.			

Schlüsselfrage 5

Welche Antibiotika kommen für die Therapie der unkomplizierten Zystitis in Frage?

Refer-enz	Studien-charak-teristika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolger-ungen des Autors	Methodische Bemerkungen	LoE/ RoB
Alfaresi et al. 2019 [42] DOI: 10.2174/1874285 8019130 10193	Systematic Review and Meta-Analysis N= 20 RCTs* Turkey, USA Spain, UK, Jerusalem, NL, Europe, France, Italy, Belgium Search date: up to	This current meta-analysis and systematic review evaluate the use of single-dose Fosfomycin-Trometamol (FMT) *versus* alternative antimicrobial regimens in the management of uncomplicated LUTI.	N=3779 patients with uncomplicated LUTIs (any age group or gender)	single-dose fosfomycin or FMT as mono-therapy	other anti-microbials. (Ciprofloxacin, Nitro-furantoin, TMP, Cepha-lexin, Norflo-xacin, Amoxycillin, Pipemidic acid, Amoxicillin/clavulanic (acid), Pefloxacin, Netilmicin, Trimethoprim, Cotri-moxazole)	**<u>Main outcome</u>:** **Clinical Outcome success rate** **Clinical Response:** <u>Single-dose Fosfomycin vs. Alternate Antibiotic Regimens</u> N= 2886 patients (8 studies) • OR, 0.957 (95% CI, 0.717-1.276); p=0.764 → sensitivity analysis: • OR, 1.53 (95% CI, 1.05–2.38); p=0.04 **Microbiological Eradication** <u>Single-dose Fosfomycin vs. Alternate Antibiotic</u>	**No significant difference between single-dose FMT and the commonly prescribed antibiotic** regimens in LUTI treatment outcomes such as clinical improvement and microbial eradication. →Single-dose fosfomycin is an effective treatment modality for (women age 18 years and older with acute) uncomplicated LUTI. Optimal antimicrobial **treatment duration** for uncomplicated LUTI	*Number and design of eligible studies is unclear. Text says N=19 but Table 1 presents n=20 eligible studies. Furthermore, no precise information about amount of observational or RCTs. <u>Funding</u> None <u>Conflict of interest</u>	1a - RoB: high

	June 2018.					Regimens N= 3779 (20 studies) • OR, 1.026 (95% CI, 1.250-0.798); p=0.798 → sensitivity analysis: • OR, 1.53 (significant) (95% CI, 1.05-2.38); p=0.04 **Overall Outcome** Single-dose Fosfomycin *Versus* Alternate Antibiotic Regimens for LUTI Treatment N= 3779 (n=20 studies) • OR 1.003 (95% CI, 0.853-1.181); p=0.967 → sensitivity analysis: OR 1.53 (95% CI, 1.05-2.38); p=0.04	depends on a host of factors. Short (1–3 days) therapy: most effective in young, non-pregnant women with symptoms less than 7 days and without a recent history of failed treatment. Short courses-therapy: associated with worse outcomes in uncomplicated LUTIs caused by Staphylococcus saprophyticus. **Single-dose regimens**: no standard of care as many antimicrobials, especially the beta-lactam group, have reduced efficacy when prescribed as a single dose, even in the case of supratherapeutic doses. UTI symptoms often persist beyond a single day of treatment, which may produce anxiety in patients who fear that their antimicrobial treatment course is inadequate. **Results of small clinical trials:** clinical cure and microbial eradication with FMT is equivalent to comparable antibiotic agents, such as norfloxacin and STX when administered for periods of 1, 3, 5 or 7 days.	None No prospero; inadequate search strategy; whether the a priori targets were met is unclear; Risk of bias has been assessed but reviewers have not incorporated it into findings/ conclusions. Setting: Hospital, multi center	
Hanretty 2018	Systematic review	To demonstrate that shorter	patients with community-	short course single-agent	long course single-agent	*Results presented for uncomplicated cystitis*	Optimal durations of therapy: dependent on	no study protocol, pre-	1a -

[43] 29679383	n=23 RCTs Search date: up to November 1, 2017	durations of antibiotic therapy are as efficacious as longer durations for many infections,	acquired pneumonia, ventilator-associated pneumonia, intraabdominal infections, skin and soft tissue infections, uncomplicated cystitis, and complicated cystitis or pyelonephritis n=1009 patients with complicated cystitis or pyelonephritis	antibiotics	antibiotics	**(Hooton 2005, n= 370 women with cystitis)** **Short-Course**: 3 day, amoxicillin/ clavulanate 500 mg/125 mg BID **Longer-Course**: 3 day, ciprofloxacin 250 mg BID **Clinical cure:** • 58% (amoxicillin/ clavulanate) vs 77% (ciprofloxacin) (p<0.001) **Microbiologic cure at 2 wks:** • 76% (amoxicillin/ clavulanate) vs 95% (ciprofloxacin) (p<0.001) **(Hootom 2012; N= 300 women with cystitis)** **Short Course**: 3 day, cefpodoxime-proxetil 100 mg BID // **Longer Course**: 3 day, ciprofloxacin 250 mg BID **Clinical cure at day 30:** • 82% (cefpodoxime) vs 93% (ciprofloxacin) [11%; 95% CI 3 to 18] **Clinical cure at first follow-up visit after treatment:** • 88% (cefpodoxime) vs 93%	antibiotic selection. Durations of therapy of 5 days for nitrofurantoin, 3 days for fluoroquinolones and trimethoprim/ sulfamethoxazole, and 1 day for fosfomycin are sufficient. Although IDSA guidelines recommend a range of 3–7 days when using a beta-lactam, 3-day regimens were found to be less efficacious than ciprofloxacin in two of the aforementioned studies and similar to trimethoprim/sulfamethoxazole in another. If using a beta-lactam in uncomplicated cystitis, the longer duration of 7 days may be warranted.	defined population was changed, only one database used, complete search strategy not reported, no additional hand search, no risk of bias assessment **Conflict of interest** JCG has received research grants from Merck; served as a consultant for Achaogen, Allergan, Astellas, Cempra, Cidara, CutisPharma, Merck, Paratek, Shionogi, Tetraphase, Theravance, and The Medicines Company; and serves on speakers' bureaus for Allergan, Astellas, Merck, and The Medicines Company **Funding** None.	RoB: high

						(ciprofloxacin) [5%; 95% CI _1 to 12] **(Gupta 2007, n= 338 women with cystitis)** **Short C.:** 3 day, trimethoprim/ sulfamethoxazole 800 mg/ 160 mg BID **Longer C.:** 5 day, nitrofurantoin 100 mg BID **Clinical cure at day 30:** • 79% (3 day) vs 84% (5 day) [_5%; 95% CI _13 to 4] **Early clinical cure:** • 90% (3 day) vs 90% (5 day) [_0.2%; 95% CI _7 to 7] **(Kavatha 2007, n= 163 women with cystitis)** **Short C.:** 3 day, cefpodoxime-proxetil 100 mg BID // **Longer C.**: 3 day, trimethoprim/ sulfamethoxazole 800 mg/ 160 mg BID **Clinical cure at end of treatment:** • 98.4% (cefpodoxime) vs 100% (trimethoprim/ sulfamethoxazole) **Microbiologic cure at end of treatment:** • 98.4%			

						(cefpodoxime) vs 100% (trimethoprim/ sulfamethoxazole) **Short-course therapy** in cystitis, the concentration-dependent nature of fluoroquinolones may give them a natural advantage over time-dependent beta-lactams in cystitis given the high concentrations achieved in the bladder.			
Lyu, 2020 [44] 31885707	Systematic review with meta-analysis n=8 RCTs Search date: December 2018	To determine the efficacy and safety of Sanjin tablets combined with antibiotics for the treatment of patients with acute lower urinary tract infections and to evaluate the quality of evidence.	n= 790 patients with acute lower urinary tract infections	Sanjin tablet combined with antibiotics (levofloxacin, gatifloxacin, oxyfluoxacin)	Sanjin tablet Placebo combined with antibiotics (levofloxacin, gatifloxacin, oxyfluoxacin)	**Cure rate** Total (n=7) • Sanjin+antibiotics: 297/365 • Antibiotics: 236/344 RR=1.17 (95% CI: 1.08-1.28, I^2=0%); p=0.0002 Sanjin+gatifloxacin vs. gatifloxacin (n=3) • Sanjin+gatifloxacin: 79/106 • gatifloxacin: 61/106 RR=1.30 (95% CI:1.07-1.57, I^2=0%); p=0.009 Sanjin+levofloxacin vs. levofloxacin (n=4) • Sanjin+levofloxacin: 218/259 • levofloxacin: 175/238 RR=1.13 (95% CI: 1.04-1.24, I^2=0%); p=0.006 **Total effective rate** (n=3) • Sanjin+levofloxacin: 177/187	Compared with the effects of antibiotics treatment, Sanjin tablets combined with antibiotics improved the cure rate, total effective rate and bacterial clearance rate, and decreased the recurrence rate. In addition, no serious adverse reactions were observed in patients with acute lower urinary tract infections.	unclear which languages be in accordance with the inclusion criteria: *The potential publication bias may be due to the high proportion of published positive results in China. All of the studies included in the present meta-analysis are written in Chinese, which may cause linguistic publication bias.* no additional hand search, complete search strategy not reported, no	1a - RoB: high

						• levofloxacin: 141/166 RR=1.11 (95% CI: 1.03-1.19, I^2=29%); p=0.005 **Recurrence rate** (n=3) • Sanjin+antibiotics: 4/115 • Antibiotics: 10/86 RR=0.35 (95% CI:0.13-0.97, I^2=0%); p=0.04 **Bacterial clearance rate** (n=2) • Sanjin+antibiotics: 40/50 • Antibiotics: 30/55 RR=1.41 (95% CI: 1.09-1.84, I^2= 0%); p=0.009 **Incidence of adverse reactions** (n=4 RCTs) mainly reported: nausea and stomach discomfort • Sanjin+antibiotics: 14/225 • Antibiotics: 21/205 RR=0.61 (95% CI: 0.32-1.17, I^2=11%); p=0.14)		information if efforts were made to minimise error in the risk of bias assessment Conflict of interests None. Funding supported by The National Key Research and Development Program of China (grant no. 2018YFC1707400).	
Pinart, 2017 [45] 28341436	Systematic review with meta-analysis n= 23 RCTs Search date: up to April 2016 Studies were conducted in: Denmark,	To compare the efficacy and safety of different pivmecillinam regimes for uncomplicated lower UTIs.	n=5637 patients with uncomplicated lower UTIs • men (n=93) • women (n=5544)	Pivmecillinam	• Cephalexin • Sulfamethizole • Sulfadiazine • Trimethoprim • Ampicillin • Nalidixic • Co-trimoxazole • Placebo • Different dosages of Pivmecillinam	**Clinical cure** Short-term • high vs. moderate total dosage (n=2 studies, 818 patients): RR=1.01 (95% CI: 0.90-1.14, I2= 0%); p = 0.813 • high vs. low total dosage (n=1 study, 125 patients): MD=0 (95% CI: -0.44-0.45); p = 1 • within-dosage groups comparisons (high vs. moderate): no statistically significant	There is insufficient evidence to support the use of an optimal combination of dosage, frequency, and duration of Pivmecillinam therapy for the treatment of uncomplicated lower UTI.	Conflict of interest None. Funding This work was supported by Leo Pharma, which assigned an unrestricted grant to the "Deutsche Gesellschaft für Urologie" to conduct this work. The sponsor had no	1a - RoB: low

	Finland, Germany, Japan, Netherlands, Sweden, United Kingdom					result • within-dosage groups comparisons (low): not possible due to a lack of data <u>Long-term</u> • high vs. moderate total dosage (n=1 study, 487 patients): RR=1.09 (95% CI: 0.96-1.23); p = 0.174 • within-dosage groups comparisons (high vs. moderate): no statistically significant result • within-dosage groups comparisons (low): not possible due to a lack of data **Bacteriological cure** <u>Short-term</u> • high vs. moderate total dosage (n=2 studies, 691 patients); RR=1.05 (95% CI: 0.99-1.10, I2= 0%); p = 0.056 • high vs. low total dosage (n=2 studies, 124 patients): RR=1.02 (95% CI: 0.89-1.18, I2= 35%); p = 0.759 • within-dosage groups comparisons (2800 vs 2400 mg): n=1, 530 patients; RR 1.12 (95% CI 1.04.1.2); p = 0.001 <u>Long-term</u> • high vs. moderate		role in the study design, data selection, or analysis and interpretation of the results, and the interaction rules have been documented in an official contract. Two studies included pregnant women.	

						total dosage (n=1, 523 patients; RR 1.05 (95% CI 0.98-1.13); p = 0.131 • high vs. low total dosage (n=1, 53 patients; RR 1.13, 95% CI 0.91-1.40); p = 0.247 • within-dosage groups comparisons (4200 vs 3600 mg): n=1, 240 patients; RR 1.08 (95% CI 1.00-1.18); p = 0.045 **Re-infection** • 4200 mg vs 8400 mg Pivmecillinam (n=2 studies, 129 patients): RR=0.62 (95% CI: 0.08-4.61, I2 = 0%); p = 0.639 • 4200 mg vs 3600 mg Pivmecillinam (n=1, 221 patients): RR=4.29 (95% CI: 0.20-88.31) p = 0.346 **Relapse** • high vs. moderate total dosages (n=1 study, 48 patients): RR=0.28 (95% CI: 0.06-1.26); p = 0.097 • high vs. low total dosage (two studies, 161 patients; RR=1.24 (95% CI: 0.57-2.70, I2= 37%); p = 0.579 **Clinical failure** • high vs. moderate Pivmecillinam (n=1 study, 657 patients):			

						RR=0.94 (95% CI: 0.76-1.16); p = 0.548; • high vs. low Pivmecillinam (n=1 study, 70 patients) RR=0.53 (95% CI 0.14-1.95), p = 0.339 • within-dosage groups comparisons (2800 vs 2400 mg): n=1, 440 patients; RR 0.80 (95% CI 0.63-1.02); p = 0.066 • within-dosage groups comparisons (8400 vs 4200 mg): n=2, 129 patients; RR 1.68 (95% CI 0.51-5.52, I^2= 0%); p = 0.395 • within-dosage groups comparisons (4200 vs 3600 mg): n=2, 281 patients; RR 1.31 (95% CI 0.59-2.90, I^2 = 0%); p = 0.508 **Adverse events** • main adverse event: gastrointestinal discomfort, mainly nausea, diarrhea, and abdominal pain (17/22 studies; 77.3%) • vaginitis/vaginal candidiasis (7/22 studies, 31.8%) • skin rash (7/22 studies, 31.8%) • headache (6/22 studies, 27.3%)			
Angelescu et al. 2016 [28]	Systematic Review N= 4 RCTs	Information on the benefits and harms of antibiotic	n= 454 pregnant women with ASB	**For 1. & 2.:** Any ASB screening strategy	**For 1. & 2.:** • No ASB screening, but treatment if	No eligible studies that investigated the benefits and harms of screening for ASB versus no	The available data did not allow conclusions to be drawn on adverse events, as in one study	**Fund**:? **Interest**:?	1a RoB: low

27806709	Publikationszeitraum: inception until 2015 USA, GB, NL	treatment for women with ASB: 1. Assess the patient-relevant benefits and harms of screening for ASB versus no screening; 2. Compare the benefits and harms of different screening strategies; 3. in case no reliable evidence on the overarching screening question was identified, to determine the benefits and harms of treatment of ASB.		followed by treatment, if necessary **For 3.:** Any treatment for ASB (Antibiotics)	symptoms of UTI occur (question 1) • Any other ASB screening strategy followed by treatment, if necessary (question 2) **For 3.:** No treatment or placebo	screening or that compared different screening strategies. **Antibiotics with no treatment/placebo** pyelonephritis (1 RCT →study from 1969!; n= 163 analyzed patients) - 6 % vs. 23 %; - OR = 0.21, (95 % CI 0.07–0.59) - p = 0.002 pyelonephritis (n= 1→study from 2015; n= 85) - 0 % vs. 2.2 %; - OR = 0.37, (CI 0.01–9.25), - p = 0.515 lower UTI (1 RCT →study from 1960!; n= 100 patients) - 6 % vs. 40 %; - OR = 0.10, (95 % CI 0.03–0.35) - p < 0.001 lower UTI during pregnancy (n= 1→study from 2015; n= 85) -10 % vs. 18 %; - POR = 0.53, (CI 0.16–1.79), - p = 0.357. Preterm birth (<37 weeks of gestation) (n= 1 study; n= 85 patients→study from 2015): - 5.0 % vs. 4.4 %, - POR= 1.13, (CI 0.15–8.35), - p = 0.975	the **event rate** in the control group was not clearly stated, while no events (1 RCT) **or very few** (1 RCT) occurred in the other two studies (see Table 4). We therefore could not determine the **risk of adverse events under antibiotic treatment, placebo or no treatment.** The available evidence is limited to four treatment trials (problems: 3 methodological shortcomings and questionable ,,current medical-applicability'; 1 low-risk-ofbias trial). Consequently, no conclusions can be drawn on whether the benefits of screening for ASB outweigh the potential harms. → **No reliable evidence supports routine screening for ASB in pregnant women.**	Total number of randomised participants is unknown →lack of data in one study. Data were insufficient to determine the risk of harms. As three of the four studies were conducted several decades ago and have serious methodological shortcomings, the applicability of their findings to current health care settings is likely to be low. The recent high-quality RCT was stopped early due to a very low number of primary outcome events, a composite of preterm delivery and pyelonephritis. Therefore, the results did not show a benefit of treating ASB.	

						(1 preterm birth event considered patient-relevant, i.e. preterm birth < 32 weeks in the interventional arm). Infant morbidity (n= 1 study; n= 85 patients→study from 2015): Event rates, in general, were low & did not reveal any statistically significant difference between study groups. Perinatal mortality (n= 1 study; n= 85 patients→study from 2015): difference was not statistically significant: only one case in the interventional arm. **Adverse Events**: N=0 →zero further predefined patient-relevant outcomes such as symptoms linked directly or indirectly to **UTI**, **birth weight** < 1500 g, **health-related quality of life**, and **psychosocial functioning**. pre-eclampsia (n= 1 study; n= 85 patients→study from 2015): - 5 % vs. 2.2 %, - POR = 2.24, - CI 0.23–22.22, - p = 0.596).			

Schulz, 2022 [46] 34995367	systematic review and meta-analysis n= 9 RCTs search date: until August 2021 NZL, USA, Austria, Italy, Slovakia, Turkey, Spain	To verify whether the use of antibiotic therapy in a single dose when compared with multiple doses in lower tract urinary infections during pregnancy is effective to obtain microbiologic cure.	n= 1063 pregnant women with micro-biologic confirmation /clinical suspicion of ABU or lower UTI with no complications	(n = 554) **antibiotic therapy in a single dose** (co-trimo-xazole, ampicillin plus pro-benecid, amoxicillin, fosfo-mycin trometamol)	(n = 509) **antibiotic therapy with multiple doses** (Co-trimoxazole, ampicillin, pipemidic acid, ceftibuten, cefuroxime axetil, amoxicillin clavulanate).	**Outcome measurements** **Primary outcome**: **microbiologic efficacy (n= 9 RCTs; 1063 patients)**: TOTAL: multiple-day (n= 509) use of antibiotics vs. single-dose (n= 554) treatment: statistically similar results in reaching culture cure. • OR 1.02 (95% CI 0.73–1.44, I^2= 1%); p= 0.43 **microbiologic efficacy (n= 5 RCTs; 637 pregnant women)** Fosfomycin (n= 327) vs. other antibiotics (n= 310) • OR 1.18 (95% CI 0.71–1.98, I^2 = 0%); p= 0.82 **Secondary outcomes:** recurrence rates of UTI **after 1 month** of microbiologic cure (2 RCT): no statistically significant difference. recurrence in the fosfomycin single-dose group versus 8 in the amoxicillin-clavulanate **7-day group** (1 RCT): • RR = 0.13 (95% CI 0.02–0.81); p=0.045	Use of **single-dose** treatment for **lower tract urinary infections during pregnancy** can be recommended, especially using **fosfomycin**. Giving consideration to the other outcomes of interest, the majority of the data reported found no statistically significant difference in the **recurrence of urinary infections** between single-dose antibiotic therapy and multiple-day courses, suggesting a similar acquired protection for at least a month. The studies selected **lack information regarding preterm birth** and development of **pyelonephritis**, outcomes that could provide further clinical efficacy measures.	Conflict of Interest None. Funding ? no prospero therefore compliance with the a priori analyses is not comprehensible Limitations The RCTs included assessed **different antibiotics at multiple doses** as intervention groups, and also different agents at **different doses and periods in the control groups**; therefore, the comparator group was very variable, although this does not indicate statistical heterogeneity. Besides, the period of follow up and detection of microbiologic cure varied among the	1a - RoB: high

						(1 RCT): higher **recurrence** rate in the single-dose treatment group (not reporting the association measure). (1 RCT): **preterm delivery** and **pyelonephritis**: no statistically significant difference between both treatment groups. **Most commonly reported adverse effect** <u>(n= 6 studies) diarrhea</u> single-dose fosfomycin group: 10.7% amoxicillin-clavulanate-group: 11.1% cefuroxime axetil-group: 6.9% (no statistically significant differences among the groups)		studies. The **variability of the mean gestational age** for the pregnant women included in the selected studies is a possible source of bias. No forest plots concerning secondary outcome.	
Cai et al. 2020 [21] 31651226	Systematic Review and Meta-Analysis N= 15 RCTs Studies conducted in: ? Search date: probably inception - Oct 2018	Comparing the effectiveness and safety profile of fosfomycin vs comparator antibiotics in women with acute uncomplicated cystitis.	n= 2.295 adult female patients older than 18 years old with microbio-logically confirmed and/or clinically suspected acute un-complicated cystitis who were rando-mized to receive treatment with FT or a com-parator	fosfomycin (3 gm single-dose)	comparator antibiotics (fluoroquinolones, Norfloxacin, cipro-floxacin, Trimethoprim, cotri-moxazole, nitrofurantoin, b-lactams (cephalexin, amoxicillin), ofloxacin/ cotrimoxazole, trimetho-prim)	**<u>Primary ends:</u>** **clinical resolution** (11 RCTs; 1.976 patients) <u>women with cystitis</u> (fosfomycin vs. other antibiotic agents): • RR 1.04 (95% CI 0.89-1.21, I^2= 33%); p= 0.62 <u>Total</u>: • OR 1.16, (95% CI 0.91-1.49); p=0.13 **microbiological eradication** (n= 14 RCTs; 2,052 patients) <u>women with cystitis</u> <u>(fosfomycin vs. other</u>	Single dose oral fosfomycin trometamol is equal to comparator regimens in terms of **clinical** and **microbiol.** effectiveness and safety in women with microbiologically confirmed and/or clinically suspected, acute uncomplicated cystitis. It is associated with high patient compliance. **No significant difference** in reported adverse effects **between fosfomycin and comparator antibiotics**.	<u>Financial interest</u> and/or other relationship with Zambon, MSD, Pfizer and Astellas <u>Fund</u> ? NO pregnant women nut including **postmeno-pausal** women! We considered only women with uncomplicated	1a - RoB: high

			antibiotic agent used to treat UTIs.			antibiotic agents) • RR 0.99 (95% CI 0.81-1.20, I^2=35%); p= 0.88 Total: • OR 1.03, (95% CI 0.83-1.30); p=0.09 **Safety outcome**/ a**dverse effects** (= any adverse event reported at any time during the study period.) (11 RCTs; 1.816 patients →does not fit to figure 4) women with cystitis treated with fosfomycin vs other antibiotic agents (n= 15; ??? patients): • RR 0.98 (95% CI 0.72-1.33, I^2= 5%); p= 0.91 Total: • OR 1.17, (95% CI 0.86-1.58); p=0.33	→Most adverse effects (gastrointestinal type) reported for fosfomycin were transient and single dose therapy seems to have resulted in better patient compliance. No study withdrawals due to adverse events in any compared treatment groups in the 3 trials providing relevant data. Fosfomycin was associated with only limited and transient adverse events, underlining high clinical efficacy with a tolerable safety profile. It is worth highlighting that **single dose fosfomycin achieved the same clinical efficacy as comparator antibiotics with longer treatment schedules (single dose vs several days).**	UTI to avoid study population heterogeneity and provide a more valid recommendation for everyday clinical practice. Slightly different numbers (RR declared wrongly (→OR)) in the forest plots and text for clinical resolution and microbiological eradication. →Unclear calculation of adverse events. Abstracts presented at scientific conferences were not considered. Search excluded non-English language studies. Embase database was not searched → other relevant information might missed. Search terms were provided but no full search strategy → could not be assessed as to how efficient it	

								was.	
Cai, T., et al. (2021) [34] 35052890	Systematic review and meta-analysis n=3 RCTs Search date: until April 2021	to compare the effectiveness and safety profile of a medical device containing xyloglucan, hibiscus and propolis (XHP) in women with uncomplicated cystitis	n=178 female patients aged >19 years with microbiologically confirmed or clinical suspicion of uncom-plicated cystitis who were rando-mized to receive treatment with a medical device containing xyloglucan (or an equivalent mucoprotectant substance), hibiscus and propolis or placebo or other comparator	xyloglucan, (or an equivalent mucoprotectant substance), hibiscus and propolis or placebo or other compara-tor	Placebo or other comparator	**Primary endpoint**: **Clinical Success/Cure (n= 3; 178 patients)** women with cystitis - Medical device compared to other antibiotic agents: medical device compared to other antibiotic agents: • OR=0.13 (95% CI: 0.05-0.33, I^2=0%); p < 0.0001 **Secondary endpoints**: **Safety outcomes/Adverse Events (n= 3; 178 patients)** women with cystitis – effects of the medical device: adverse effects • OR 0.14 (95% CI 0.03–0.67, I^2= 31%); p = 0.001 →most common reported adverse effects were of the gastrointestinal type (abdominal pain, diarrhea)	A medical device containing xyloglucan, hibiscus and propolis is superior to comparator regimens in terms of clinical effectiveness in adult women with microbiologically confirmed or clinical suspicion of uncomplicated cystitis and is associated with a high patient compliance. No clinically significant adverse effects have been reported.	Conflict of interest None. Funding None. Funnel plots analysis did not suggest the exclusion of any study. no prospero therefore compliance with the a priori analyses is not comprehensible; inadequate search strategy	1a - RoB: high
Konwar et al. 2022 [24] 34151754	systematic review and meta-analysis n= 4 RCTs Studies were conducted	Evaluation of efficacy and safety of fosfomycin versus nitrofurantoin for the treatment of uncomplicated lower urinary tract infection (UTI) in women	N= ? women with lower uncomplicated UTI and asymptomatic bacteria (ABU) in pregnancy	Oral fosfomycin (Single-dose FOM 3 g) for lower uncomplicated UTI	Oral nitrofurantoin for lower uncomplicated UTI	**Efficacy - Microbiological cure:** **Within 4 weeks post treatment:** UNCOMPLICATED UTI Fosfomycin (n=445) vs. nitrofurantoin (n=435): (N= 3 studies; 880 patients)	Single-dose (3 gram) oral fosfomycin treatment was equivalent to the various regimens of nitrofurantoin in terms of clinical efficacy in female patients with uncomplicated UTI as also safety in women	Conflict of interest None Fund ? Limitation by the **significant heterogeneity**	1a RoB: low

	in: Belgium, NL, USA, CH-PL-Israel Search date: from inception until November 2020					• RR 0.95 (95% CI 0.84–1.08, I^2 = 76%); p=0.47 **after 4 weeks post treatment** fosfomycin (n=379) vs. nitrofurantoin (n=381) (N= 3 studies; 760 patients) • RR 1.00 (95% CI 0.88–1.14, I^2 = 82%); p=0.99 **Efficacy – Clinical cure**: LOWER UNCOMPLICATED UTI **within 4 weeks post treatment** fosfomycin (n=476) vs. nitrofurantoin (n=464) (N=2; 940 patients). • RR 0.95 (95% CI 0.81–1.12, I^2 = 83%); p=0.55 **after 4 weeks post treatment** fosfomycin (n= 535) vs. nitrofurantoin (n= 523) (N=3 studies; 1058 patients) • RR 0.95 (95% CI 0.83–1.09, I^2= 80%); p=0.48 **Safety: Adverse events (AE)**: **uncomplicated UTI and pregnant** females with ABU - fosfomycin (n= 750) vs.	with uncomplicated cystitis. A similar finding was noted regarding the microbiological cure for the above-mentioned populations.	regarding the patient populations. Only 1 study involving pregnant patients reported that no difference was observed between the compared treatment groups. Majority of the included trials were from the **nineties**. Considerable number of the included **trials did not have blinding.** Information regarding allocation concealment was also inadequately reported. Our findings are thus **susceptible to selection bias and need to be viewed in context**. Insufficient search strategy but otherwise everything was well considered. **Pregnant women**	

						nitrofurantoin (n= 747) (N= 4 studies; 1497 patients • RR 1.05 (95% CI 0.59–1.87, I^2= 64%); p=0.86 Quality of evidence for the safety outcome measures → very low as in addition to wide point estimates, heterogeneity, different doses and duration of nitrofurantoin, the overall result (95% CI) fails to exclude the important benefit or harm.		All 4 RCTs: low RoB	
Parazzini, 2022 [39] 35815191	Systematic review N=7 (Cross-sectional, cohort, case–control studies, clinical trials) including n= 1 →neurogenic bladder and n= 1 →breast cancer **FINAL**: **→ 5 paper** (1x random.	Effect of D-mannose, alone or in association with other compounds, on the typical symptoms of UTI/cystitis.--> PICO: Is D-mannose effective in the treatment of symptoms of UTI/cystitis	[N= 386 → Excl. 2 Paper:] n= 248 Women with symptoms of low urinary tract infection/cystitis Age-range: >18-65	D-mannose (sometimes given alongside with cranberry extract, Morinda citrifolia fruit extract, pomegranate extract, fructooligosaccharides, lactobacilli, and N-acetylcysteine.)	n= 2 no treatment, n= 3 antibiotic therapy TMP/SMX	**Outcome: Reduction of symptoms** Porro et al. (text mentioned n= 60 but table 2 presents n= 46 women, acute cystitis and rUTI-history, random. cross-over trial) trimethoprim/sulfamethoxazole or oral D-mannose three times a day group, for 2 weeks: **Before D-mannose vs. After D-Man →Mean score VAS:** • Suprapubic pain: 4.1 (1.1) vs. 2.2 (0.5) • Frequent voiding: 7.1 (1.1) vs. 4.7 (1.0) • Urgency: 4.6 (1.1) vs. 2.6 (0.7)	In women with symptoms of UTI/ cystitis, treatment with D-mannose alone or in association with other compounds is useful for lowering the intensity of symptoms both in the short and middle-term for all typical symptoms, except hematuria. → D-mannose interacts with bacteria to promote UPEC excretion. May explain a **faster resolution of symptoms**. **Biological** and **clinical** explanations of the results are **not entirely clear**. Observational studies and clinical trials: → D-mannose may be	Competing interests: None. Funding: None. To evaluate the effect of D-mannose on the symptoms of UTI /cystitis, from the studies that presented data on long-term follow-up: only information obtained during the evaluation of first symptoms after study entry were considered.	1b - ROB: high

	cross-over trial, 3x prospective uncontrolled, 1x RCT) Search Date: 1990 to January 2022 All 5 sudies from Italy					→ dysuria, hematuria, overall symptoms: no data • No adverse events Vicariotto et al. (n= 33 premenopausal, nonpregnant women with acute uncomplicated cystitis; prospective observational study) Compound (D-mannose, cranberry dry extract, exopolysaccharides produced by Streptococcus thermophilus ST10, tara gum, Lactobacillus plantarum, Lactobacillus paracasei, two doses per day for 1 month.) **Baseline vs. day 30** **→ mean score UTI-SAQ:** • Suprapubic pain: 1.39 vs. 0.97 • Dysuria: 2.03 vs. 1.36 • Frequent voiding: 2.18 vs. 1.70 • Urgency: 2.15 vs. 1.64 • Hematuria: 0.61 vs. 0.58 • Overall symptoms: no data Domenici et al (n= 43 women with acute cystitis were included;	useful in the treatment of UTI/cystitis symptoms. Its non-pharmacological, non-metabolic, non-bacteriostatic or bactericidal, but biomechanical mechanism of action, and the fact that it does not affect antibiotic resistance may support the use of D-mannose in **the treatment of UTI/cystitis**..	1.limited data: no opportunity for detailed analysis of the role of different doses of D-mannose or the effect of D-mannose alone or in association with other compounds. 2. Most data were derived from uncontrolled studies. 3. These findings are based on an extremely limited number of studies with small sample sizes. 4. Heterogenious population 5. Methods concerning evaluation of the symptoms differed →comparison among studies of the magnitude of the effect of D-mannose is not feasible 6. Most studies conducted in Italy	

						observational prospective study.) <u>D-mannose: twice daily for 3 days and then once a day for 10 days</u> **Baseline vs. Day 15 → mean score UTI-SAQ:** • Suprapubic pain: 1.47 (0.95) vs. 0.15 (0.36) • Dysuria: 1.60 (±1.00) vs. 0.31 (0.47) • Frequent voiding: 2.16 (1.52) vs. 0.60 (0.63) • Urgency: 1.73 (0.92) vs. 0.23 (0.43) • Hematuria: 0.34 (0.90) vs. 0.10 (0.45) • Overall symptoms: no data <u>Pugliese et al</u> (n= 33 women (mean age 38.1±11.2 years) with urinary symptoms suggestive of an UTI; conducted study) <u>D-mannose, pomegranate extract, prebiotics and probiotics twice daily for 5 days and then once a day for 10 days. Antibiotics: permitted on a clinical basis.</u> No adverse events were reported. **Baseline vs. 15 days →**		The two from 5 trials had a low risk of bias according to the Cochrane risk of bias tool → risk of bias has been assessed but reviewers have not incorporated it into findings/ conclusions	

						mean score ACSS: →**No data**: Suprapubic pain, dysuria, frequent voiding, urgency, Hematuria. • Overall symptoms: 11.5 (95% CI 10.5-12.6) vs. 4.9 (95% CI 4.0-5.9); p<0.0001 • Differential symptoms (i.e., lower back pain, vaginal discharge, urethral discharge, fever, and chills: 3.1 (95% CI 2.6-3.6) vs. 0.6 (95% CI 0.3-0.9); p<0.0001 • QoL mean score: 7.2 (95% CI 6.7-7.7) vs. 4.0 (95% CI 3.3-4.6); P<0.0001 • No adverse events Rădulescu et al (n= 93 non-pregnant healthy women (mean age of 39.77±10.36 years) with uncomplicated lower UTI; randomized study) Antibiotics alone or in association with D-mannose plus cranberry extract for 7 days.			

						Baseline vs. 7 days → mean score 3 degrees questionnaire: • Suprapubic pain: 72.9 (35/48) vs. 2.1 (1/48) • Dysuria: 60.4 (29/48) vs. 0% (0/48) • Frequent voiding: 85.4 (41/48) vs. 2.1% (1/48) • Urgency: 89.6% (43/48) vs. 0% (0/48) • Hematuria: 10.4% (5/48) vs. 0% (0/48) • Overall symptoms: no data Co-administration of D-mannose plus cranberry extract: no statistically significant differences in symptoms, except for urinary urgency/pollakiuria (P=0.024).			
Porreca 2021 [25] 33535221	Systematic review n=9 RCTs search date: up to May 6, 2020	The aim of the current paper is to provide an updated systematic review of RCTs to investigate the clinical and microbiological efficacy of nitrofurantoin compared to other antibiotics	N=3154 (calculated!) women with uncomplicated UTI	Nitrofurantoin	Antibiotic (n=5) • Trimethoprim-sulfamethoxazole (n=4) • fosfomycin (n=3) • Oral ciprofloxacin (n=1) • Trimethoprim (n=1) • Cefadroxil (n=1)	**Symptomatic/Clinical Cure** • clinical cure rates in nitrofurantoin ranged from 51 to 94% • significantly higher clinical cure rate in patients treated with nitrofurantoin (n=1, placebo) <u>Nitrofurantoin vs fosfomycin</u> (n=3)	Although no firm conclusions can be made based on the current base of evidence, the studies generally suggest that nitrofurantoin is at least comparable to other common uncomplicated UTI treatments in terms of clinical and bacteriological cure. Furthermore, recent	no additional hand search, complete search strategy and number of patients of the included studies not reported, unclear, if younger women are also included in the data synthesis	1a - RoB: high

		or placebo.			• Amoxicillin (n=1) • Ofloxacin (n=1) Placebo (n=1)	• significantly higher with nitrofurantoin (n=2) • no differences (n=1) <u>Nitrofurantoin vs trimethoprim-sulfamethoxazole</u> (n=2) • no significant difference <u>Nitrofurantoin vs oral ciprofloxacin</u> (n=1) • no significant difference <u>Ofloxacin vs nitrofurantoin</u> (n=1) • ofloxacin was superior (no statistical test was performed) • many nitrofurantoin patients discontinued because of side effects **Bacteriological Cure** • bacteriological cure rates ranged from 61 to 92% <u>Placebo</u> (n=1) • significantly higher bacteriological cure rate in patients treated with nitrofurantoin <u>Nitrofurantoin vs fosfomycin</u> (n=3) • significantly higher bacteriological cure rate in patients treated with nitrofurantoin (n=1) • no significant difference (n=2)	fluoroquinolone warning on side effects represents another reason to prefer other molecules to treat uncomplicated UTI.	(see inclusion criteria from included studies Christiaens, Stein and van Pienbroek) although the inclusion criteria only considered aged over 18, no funnel plot <u>Conflict of interest</u> None. <u>Funding</u> None.	

						Nitrofurantoin vs trimethoprim-sulfamethoxazole (n=3) • no significant difference Nitrofurantoin vs oral ciprofloxacin (n=1) • ciprofloxacin had statistically significantly higher eradication rates than nitrofurantoin Nitrofurantoin vs cefadroxil (n=1) • no difference Nitrofurantoin vs amoxicillin (n=1) • no difference Nitrofurantoin vs trimethoprim (n=1) • no difference **Adverse events** • higher side effects in patients taking nitrofurantoin compared to cefadroxil, amoxicillin, and trimethoprim-sulfamethoxazole (n=1) • nitrofurantoin fewer side effects than trimethoprim (n=1), co-trimoxazole (n=1), or fosfomycin (n=1) • no differences vs placebo (n=1), trimethoprim-sulfamethoxazole			

						(n=2), ofloxacin (n=1), ciprofloxacin (n=1), fosfomycin (n=2) • most commonly reported side effects in patients taking nitrofurantoin were gastrointestinal (e.g., nausea or diarrhea) and central nervous system (e.g., headache) symptoms			
Kim, 2020 [47] 32446327	Systematic review with network meta-analysis n=61 RCTs search date: up to Dec 31, 2019	This study was done to reappraise the treatment duration of each antibiotic in current guidelines for acute uncomplicated cystitis to investigate whether the regimen lengths of guideline approved antibiotics could be reduced.	n=20780 women with acute uncomplicated cystitis	• Nitrofurantoin • Fosfomycin • Trometamol • Pivmecillinam • co-trimoxazole • trimethoprim • fluoroquinolone • cephalosporin • amoxicillin • clavulanate	• Antibiotic • Placebo	**Clinical response** • All antibiotic therapy regimens were significantly more effective than placebo <u>Nitrofurantoin: 5 days vs. 3 days</u> RR: 1.294 (95% CI 0.714-2.244) Quality of evidence: very low <u>Pivmecillinam: 5 days vs. 3 days</u> RR: 1.041 (95% CI 0.91-1.193) Quality of evidence: moderate <u>Pivmecillinam: 7 days vs. 3 days</u> RR: 1.095 (95% CI 0.999-1.203) Quality of evidence: moderate <u>Co-trimoxazole: 3 days vs single dose</u> RR: 1.147 (95% CI	Treatment duration of the third-generation and fourth-generation quinolones and pivmecillinam could be shorter than the currently recommended regimens for acute uncomplicated cystitis. For other antibiotics, shorter duration of regimens could be considered, but further research is needed because of the low quality of supporting evidence.	no additional hand search, no information if efforts were made to minimise error in the risk of bias assessment, no information about heterogeneity, no funnel plot, <u>Conflict of interest</u> None. <u>Funding</u> None. excluded: studies that investigated only women aged 65 years or older	1a - RoB: high

						1.008-1.309) Quality of evidence: low <u>Trimethoprim: 5 days vs. single dose</u> RR: 0.99 (95% CI 0.862-1.146) Quality of evidence: low <u>Fluoroquinolone: 3 days vs. single dose</u> • Second-generation: RR: 1.044 (95% CI 1.01-1.084) • Third-generation: RR: 0.944 (95% CI 0.939-1.052) • Fourth-generation: RR: 1.024 (95% CI 0.974-1.083) Quality of evidence: moderate <u>Third-generation cephalosporin: 3 days vs single dose</u> RR: 1.039 (95% CI 0.849-1.339) Quality of evidence: very low <u>Third-generation cephalosporin: 7 days vs single dose</u> RR: 1.019 (95% CI 0.754-1.385) Quality of evidence: very low <u>Amoxicillin and Clavulanic acid: 3 days vs. single dose</u> RR: 0.987 (95% CI 0.879-1.098) Quality of evidence: low			

						Microbial response • All antibiotic therapy regimens, except the single dose first-generation cephalosporin and nitrofurantoin 3-day regimens, were significantly more effective than placebo <u>Nitrofurantoin: 5 days vs. 3 days</u> RR: 1.745 (95% CI 0.96-3.658) Quality of evidence: very low <u>Pivmecillinam: 5 days vs. 3 days</u> RR: 1.021 (95% CI 0.903-1.153) Quality of evidence: moderate <u>Pivmecillinam: 7 days vs. 3 days</u> RR: 1.058 (95% CI 0.987-1.145) Quality of evidence: moderate <u>Co-trimoxazole: 3 days vs single dose</u> RR: 1.023 (95% CI 0.954-1.102) Quality of evidence: low <u>Trimethoprim: 5 days vs. single dose</u> RR: 1.086 (95% CI 0.939-1.265) Quality of evidence: low			

						Fluoroquinolone: 3 days vs. single dose • Second-generation: RR: 1.039 (95% CI 1.003-1.076) • Third-generation: RR: 1.028 (95% CI 0.957-1.108) • Fourth-generation: RR: 1.031 (95% CI 0.972-1.094) Quality of evidence: moderate Third-generation cephalosporin: 3 days vs single dose RR: 1.329 (95% CI 0.799-2.456) Quality of evidence: low Third-generation cephalosporin: 7 days vs single dose RR: 1.057 (95% CI 0.877-1.343) Quality of evidence: low Amoxicillin and Clavulanic acid: 3 days vs. single dose RR: 0.985 (95% CI 0.894-1.140) Quality of evidence: low			
Wang 2020 [26] 32417205	systematic review and meta-analysis n= 21 RCTs search: inception	Efficacy and safety of **single-dose** fosfomycin tromethamine (FT) versus other antibiotic agents in women suffering from lower uncomplicated urinary tract	N= 4589* women suffering from lower uncomplicated urinary tract infection (uUTI) and pregnant women with	N=2533 Fosfomycin (3g single dose)	N=2056 other antibiotic agents (Nitrofurantoin, Trimethoprim, Cephalexin, Norfloxacin, Amoxicillin, Ofloxacin, Cotrimoxazole	**Clinical resolution of uUTI**: single-dose FT vs. other antibiotic agents Total (n= 9; 2122 women): • OR 0.89 (95% CI 0.71–1.10, I^2= 22%); p= 0.28 non-pregnant (n= 8;	Single-dose fosfomycin tromethamine produces equivalent clinical outcomes to comparator antibiotics in terms of **clinical** efficacy and **microbiological** efficacy. It is therefore clinically effective and safe for women with uUTI and pregnant	Competing Interests None. Funding This work was supported by grants from the National Natural Science Foundation of	1a - RoB: high

	to 01 December 2019 countries:?	infection (uUTI) and pregnant women with uUTI or asymptomatic bacteriuria (ASB).	uUTI or asymptomatic bacteriuria (ASB) and being treated with FT and other antibiotic agents		, Pipemidic acid, Ceftibuten, Cefuroxime axetil, Amoxicillin/ clavulanate, Cefuroxime axetyl)	2010 w): • OR 0.89 (95% CL 0,71-1.11, I^2=35%); P = 0.32 pregnant women (n=1; 112 participants): • OR 0.80 (95% CI 0.31-2.04, I^2= 0%); p = 0.64. **Subgroup analysis based on drug classification:** Fosfomycin vs. ß-lact./cephalo. (n=2; 224 participants) • OR 1.18 (95% CI 0.60-2.32, I^2= 0%); p= 0.64 Fosfomycin vs. quinol. (n= 4; 592 participants) • OR 0.83 (95% CI 0.53-1.31, I^2= 0%); p = 0.43 Fosfomycin vs. sulfon. (n= 1; 190 participants) • OR 1.69 (95% CI 0.87-3.29, I^2= not applicable); p = 0.12 Fosfomycin vs. nitrofur. (n=3; 1116 participants) • OR 0.87 (95% CI 0.52-1.48, I^2= 62%); p = 0.61. Total (n=9; 2122 participants): Fosfomycin vs. other antib.	women with uUTI or ASB, and has higher patient compliance. No serious fosfomycin-related AE. Most frequent AE were mainly gastrointestinal.	China (No. 81870525, 81801429), Taishan Scholars Program of Shandong Province (No. tsqn201909199) . →n=10 of all in-cluded studies: multicentre RCTs! One included study involved non-pregnant women >12 years old No complete search strategy presented, search terms far too narrow; unclear whether 2 independent reviewers assisted in risk of bias error assessment, no funnel plot or sensitivity analysis. *N= 3103 pooled patients (to determine microbiological resolution between uUTI or ASB)	

						• OR 0.94 (95% CI 0.72-1.23, I^2= 22%); p = 0.68. **Microbiological resolution**: <u>Total (n= 21; 3103 patients)</u> • OR 1.11 (95% CI 0.92–1.34, I^2= 0%); p = 0.29 <u>Non-pregnant women with uUTI</u> (n=13; 2249 participants) • OR 1.08 (95% CI 0.87–1.34, I^2= 18%); p= 0.48) <u>pregnant women with uUTI</u> (n= 3; 277 participants) • OR 1.11 (95% CI 0.48–2.56, I^2= 0%); p = 0.81 <u>pregnant women with ASB</u> (n= 5; 577 participants) • OR 1.32 (95% CI 0.78–2.22, I^2= 0%); p = 0.30. **Subgroup analysis based on drug classification** <u>Fosfomycin vs. ß-lact./cephalo. (n=7; 686 participants)</u> • OR 1.46 (95% CI 0.96-2.19, I^2= 0%); p =0.07			

						Fosfomycin vs. quinol. (n= 7; 1146 participants) • OR 0.98 (95% CI 0.70-1.38, I^2= 0%); p = 0.92. Fosfomycin vs. sulfon. (n= 3; 270 participants) • OR 1.58 (95% CI 0.86-2.90, I^2= 0%); p = 0.14 Fosfomycin vs. nitrofurantoin (n=5; 1001 participants) • OR 0.95 (95% CI 0.69-1.31, I^2= 48%); p =0.76 Total (n= 21; n= 3103 participants): • OR 1.11 (95% CI 0.92-1.34, I^2= 0%); p =0.29 **Safety/Adverse events**: single- dose FT and comparator antibiotics: Total: (n= 15; n= 3201 participants) • OR 0.95 (95% CI 0.66-1.37, I^2= 41%); p = 0.78 Non-pregnant patients (n= 10 RCTs; n= 2624 patients) • OR 1.03 (95% CI 0.78-1.36, I^2= 0%); p = 0.83 Pregnant patients (n= 5;			

						n= 577 participants) • OR 0.65 (95% CI 0.11-3.96, I^2= 78%); p = 0.64			

Schlüsselfrage 6:

Welche Antibiotika kommen für die Therapie der unkomplizierten Pyelonephritis in Frage?

Referenz	Studien-charakteristika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
Cao 2021 [48] 33897441	Systematic review with meta-analysis n=5 RCTs search date: up to January 2021	Our objective was to compare the efficacy and safety of the two drugs in the treatment of UTIs, by performing a meta-analysis of high-quality RCTs that compared levofloxacin and ciprofloxacin.	n=2352 adults with chronic bacterial prostatitis, acute pyelonephritis or complicated urinary tract infections	Levofloxacin (once a day at 250~750 mg, orally or intravenously)	Ciprofloxacin (twice a day with a total dose of 900–1,000 mg orally or a single dose of 400 mg intravenously)	*Results presented for acute pyelonephritis studies (n=2)* **Clinical success rate** • End-of-Therapy: RR 1.16 (95% CI 0.93-1.46), p=0.19 • Posttherapy: RR 1.16 (95% CI 0.86-1.55), p=0.33 **Microbial eradication rate** • RR 1.12 (95% CI 0.86-1.46), p=0.41 **Adverse events** • RR 0.92 (95% CI 0.45-1.88), p=0.83 • no serious adverse event was reported	There is no significant difference between the 2 drugs in end-of-therapy or posttherapy clinical success rate, microbial eradication rate or adverse event rate.	no study protocol, no information if efforts were made to minimise error in data collection, no funnel plot/sensitivity analyses serious heterogeneity ($I^2 \geq 75\%$) in the clinical succes rate and microbial eradication rate analysis Conflict of interest None. Funding This work was funded by the National Natural Science Foundation of China (Grant no. 82000721), Post-Doctor Research Project, West China Hospital, Sichuan University (Grant no. 2019HXBH089), Health commission of	1a - RoB: high

								Sichuan province (20PJ036).	
Díaz-Brochero, 2021 [49] 35017105	Systematic review n=7 RCTs search date: up to January 2021 Canada, Japan, Switzerland, United States	To evaluate the efficacy and safety of first-generation cephalosporins for community-acquired complicated upper urinary tract infection in adults requiring hospital care.	n=731 adults with community-acquired complicated upper urinary tract infection n=279 patients with pyelonephritis	First-generation cephalosporin	• Second-generation cephalosporin • Third-generation cephalosporin • Fluoroquinolone	*Results presented for pyelonephritis studies (n=2)* **Sandberg 1990** *definition: acute pyelonephritis as the presence of flank pain and/or costovertebral angle tenderness and fever of 38.0 °C or chills* <u>Cefadroxil vs. nofloxacin</u> • Clinical cure: cefadroxil: 38% norfloxacin: 38% • Microbiological cure: lower probability of microbiological cure with norfloxacin (OR 0.21, 95% CI, 0.07, 0.61) • Relapse: greater probability of relapse with the use of cefadroxil com- pared with norfloxacin (OR 19.76, 95% CI, 1.12, 349.44) • Reinfection: OR 3.13 (95% CI, 0.13, 78.19) • Adverse events greater probability of non- serious adverse events with cefadroxil compared with norfloxacin with an estimated OR of 2.27 (95% CI, 1.20, 4.28)	In conclusion, considering that no differences were found in the outcomes of clinical cure, reinfection, and days of hospital stay with first-generation cephalosporins compared with other antibiotic regimens, and given its adequate safety profile and lesser impact in the development of bacterial resistance, this therapy could be postulated as an alternative option in this clinical set- ting. However, because of the risk of bias and imprecision for sev- eral of the analyzed outcomes, the benefits, and harms of using first-generation cephalosporins to treat complicated pyelonephritis should be regarded with caution.	disease inclusion criteria unclear described <u>Conflict of interest</u> Two authors have received research grants from Pfizer, through the International Society of Infectious Diseases. The other authors have no conflict of interests to declare. <u>Funding</u> None. not included: pregnant women *no clear differentiation between complicated and uncomplicated pyelonephritis*	1a - RoB: high

						Lea 1982 *definition: patients with a clinical diagnosis of acute pyelonephritis, without further details of the definition* <u>Cefazolin vs. moxalactam</u> • Microbiological cure: OR 1.05 (95% CI, 0.16, 6.92 • Relapse: OR of 0.95 (95% CI, 0.14, 6.28) • Reinfection: no re- infection events were reported in either of the groups • Adverse events: OR 0.50 (95% CI, 0.21, 1.21) • Days of hospital stay: 5.7 days of hospital stay for both treatment groups (cefazolin and moxalactam)			
Chen, 2020 [50] 32131414	Systematic review with meta-analysis n=5 RCTs Search date: up to August 13	This meta-analysis aimed to assess the efficacy and safety of sitafloxacin in treating acute bacterial infection.	n=756 patients with acute bacterial infection (pneumonia, complicated urinary tract infections or pyelonephritis)	sitafloxacin • oral (n=4) • intravenous (n=1)	• Imipenem (n=1) • Ertapenem (n=1) • Levofloxacin (n=1) • Garenoxacin (n=1) • eftriaxone/ cefdinir (n=1)	**Clinical response rate** *Result presented for acute pyelonephritis (n=3)* • OR 1.9 (95% CI, 0.46–7.83) **Microbiological response** *Result presented for acute pyelonephritis/complicated urinary tract*	Sitafloxacin is noninferior to other commonly used antibiotics with respect to both clinical and microbiological response rates in patients with an acute bacterial infection, including	no study protocol, complete search strategy not reported, no information if efforts were made to minimise error in study selection, data collection and risk of bias assessment <u>Conflict of interest</u> None.	1a - RoB: high

						infections (n=3) • OR 1.77 (95% CI, 0.57–5.56) **Adverse events** • treatment-emergent adverse event (n=4) OR 1.14 (95% CI, 0.64–2.01) • risk of drug-related treatment-emergent adverse event (n=3) OR 1.14 (95% CI, 0.48–2.69) • Mortality (n=3) OR, 0.93 (95% CI, 0.09–9.44)	complicated urinary tract infections/acute pyelonephritis and pneumonia.	<u>Funding</u> None.	
Ten Does-schate 2020 [51] 32795483	Systematic review n=16 RCTs Search date: up to 4 March 2020	The aim of this systematic review was to identify carbapenem-alternative antimicrobial strategies with comparable efficacy and safety as carbapenems that could be used for the empirical or pathogen-directed treatment of complicated urinary tract infections.	patients with complicated urinary tract infection or acute pyelonephritis	Non-carbapenem class antimicrobial agents with in vitro activity against ESBL-producing Enterobacteriaceae	Carbapenem-class antimicrobial agents	**Early clinical failure** <u>Empirical treatment</u> (n=11) • no differences (n=9) Favours carbapenem: • Naber 2009 (Levofloxacin iv vs doripenem): RR: 2.00 (95 % CI 1.07-3.74) • Tetraphase 2018 (Eravacyline vs. ertapenem): RR: 1.55 (95 % CI 1.04-2.32) <u>Pathogen-directed treatment</u> (n=5) • no differences (n=4) Favours carbapenem: • Seo 2017 (Cefepime vs. ertapenem): RR 22 (95% CI 2.94-164.4)	Ceftazidime–avibactam, plazomicin, cefiderocol and ceftriaxon–sulbactam disodium-EDTA for the empirical treatment and ceftazidime–avibactam for the pathogen-directed treatment for complicated urinary tract infections are potential alternatives to carbapenem. Results for empiric piperacillin–tazobactam, ceftaro- line fosamil-	no funnel plot/sensitivity analyses <u>Conflict of interest</u> None. <u>Funding</u> Not reported. *mixed patient population: complicated urinary tract infection or acute pyelonephritis*	1b RoB: low

						Early microbiological failure <u>Empirical treatment</u> (n=12) • no differences (n=8) Not favours carbapenem: • Portsmouth 2018 (Cefiderocol vs. imipenem–cilastatin): RR: 0.62 (95 % CI 0.46-0.82) • Wagenlehner 2016 (Ceftazidime–avibactam vs. doripenem): RR: 0.78 (95 % CI 0.62-0.99) • Wagenlener 2019 (Plazomicin vs. meropenem): RR: 0.45 (95 % CI 0.29-0.70) Favours carbapenem: • Tetraphase 2018 (Eravacyline vs. ertapenem): RR: 2.91 (95 % CI 1.82-4.68) <u>Pathogen-directed treatment</u> (n=5) • no differences (n=4) Favours carbapenem: • Seo 2017 (Cefepime vs. ertapenem): RR 22 (95% CI 2.94-164.4) **Adverse events** <u>Ceftazidime–avibactam vs. best available</u>	avibactam, eravacycline, cefuroxime-gentamicin, amoxicillin-clavulanic acid, ciprofloxacin and low dose levofloxacin and pathogen-directed piperacillin–tazobactam, sitafloxacin and cefepime were either inconclusive or suggested inferiority.		

						therapy • Less adverse events RR: 0.63, 95%CI: 0.44–0.91 (n=1) • no difference (n=1) Levofloxacin vs. doripenem • RR: 0.54, 95%CI: 0.29–1.00 Cefiderocol vs. high dose imipenem–cilastin • less serious adverse events RR: 0.79, 95%CI: 0.64–0.98 • More non-severe adverse events were found after using eravacycline than ertapenem (RR: 3.34 95%CI: 2.50-4.46) • In the other studies: no significant differences were reported regarding adverse or serious adverse events between the treatment arms.			
Suliman 2021 [52] *keine Pubmed-ID*	Systematic review n=11 RCTs Search period: 2010-2020	The objective of this review was to determine the efficacy and safety of antibiotics in complicated urinary tract infections and acute pyelonephritis,	n=4060 adult patients with complicated urinary tract infections and/or acute pyelonephritis	• Amino-glycosides • β-lactam/β-lactamase inhibitor combinations • fluoro-quinolones	traditional antibiotics: • imipenem–cilastatin • levofloxaci • doripenem • ertapenem • piperacillin–tazobactam • ciprofloxacin • ceftriaxone • cefdinir	**Overall treatment success** • study drugs were noninferior or equivalent to more conventional alternatives **Adverse events** • drugs were well-tolerated compared with conventional alternatives	The β-lactam/β-lactamase–inhibitor combinations (meropenem–vaborbactam, ceftazidime–avibactam, ceftolozane–tazobactam, and imipenem/cilastatin plus	some differences between protocol and paper (e. g. search period, used databases) no information if efforts were made to minimise error in the data collection and risk of bias assessment Conflict of interest	1a - RoB: high

		including relatively new aminoglycosides (plazomicin), β-lactam/β-lactamase inhibitor combinations (e.g., meropenem–vaborbactam, ceftolozane–tazobactam, ceftazidime–avibactam, and imipenem/cilastatin plus relebactam or plus sulbactam–durlobactam), and fluoroquinolones (finafloxacin, sitafloxacin) compared with traditional therapies.					relebactam or plus sulbactam–durlobactam), plazomicin, fluoroquinolones (finafloxacin and sitafloxacin), and fosfomycin may provide suitable alternatives to current therapy of complicated urinary tract infections and acute pyelonephritis with comparable efficacy and safety profiles.	None. Funding None. *mixed patient population: complicated urinary tract infection or acute pyelonephritis* not included: pregnant women	
Lai 2019 [53] 31269697	Systematic review with meta-analysis n=8 RCTs Search date: up to April 2019	We could conduct a comprehensive review and updated meta-analysis to assess the efficacy and safety of doripenem on treating patients with acute bacterial infections in comparison with other antibiotics,	n=3499 patients with acute bacterial infections	Doripenem	• Piperacillin/tazobactam (n=1) • Meropenem (n=2) • Imipenem/cilastatin (n=3) • Levofloxacin (n=1) • Ceftazidime-avibactam (n=1)	**Doripenem vs. Levofloxacin/ Ceftazidime-avibactam** *Results presented for acute pyelonephritis (n=2)* • Clinical success OR, 1.89, 95% CI, 1.13–3.17 [No adverse events extracted here because of different drug comparisons and different diseases]	The similar efficacy in terms of clinical response and microbiological eradication was found between dorpenem and other carbapenems. This results was not affected by the different types of infections.	no study protocol, no additional hand search, no information if efforts were made to minimise error in data collection and risk of bias assessment, Conflict of interest None. Funding Not reported.	1a - RoB: high

		especially imipenem and meropenem.							
Chen 2019 [54] 31190923	Systematic review with meta-analysis n=7 RCTs Search date: up to September 2018 China, USA	This meta-analysis aims to assess the efficacy and safety of high-dose, short-dose levofloxacin in comparison with conventional therapy on treating acute bacterial infection.	n=3731 patients with community-acquired pneumonia, sinusitis, acute pylonephritis or complicated urinary tract infection	Levofloxacin (750 mg per day for 5 days)	• Ciprofloxacin (400 mg IV or 500 mg oral, twice daily for 10 days) • Levofloxacin, (500 mg per day for 7-14 days)	**high-dose, short-course Levofloxacin vs. conventional regimen** *Results presented for acute pyelonephritis/complicated urinary tract infection studies (n=3)* • Clinical success RR: 1.04; 95%CI: 0.99–1.10 • Microbiologic eradication RR: 1.03; 95%CI: 0.97–1.10 **Adverse events** • Incidence of treatment-emergent adverse events (n=7) RR: 1.07; 95%CI: 0.99–1.17 • incidence of headache (n=5) RR: 1.45; 95%CI: 0.94–2.22 • drug-related adverse events (n=3) RR: 1.23; 95%CI: 0.70–2.15 • Serious adverse events (n=6) RR: 0.73; 95%CI: 0.49–1.07 • risk of discontinuing drug due to adverse	High-dose, short-course levofloxacin exhibits similar clinical success and microbiologic eradication rates with conventional regimen in the treatment of acute bacterial infection. Moreover, the high-dose, short-course levofloxacin regimen was well tolerated and had comparable safety profiles with the conventional regimen.	no study protocol, no information if efforts were made to minimise error in data collection and risk of bias assessment, serious heterogeneity ($I^2 \geq 75\%$) in drug-related adverse events analysis <u>Conflict of interest</u> None. <u>Funding</u> Was not reported.	1a - RoB: high

						effects (n=2) RR: 0.84; 95%CI: 0.44–1.60			
Hanretty 2018 [43] 29679383	Systematic review n=23 RCTs Search date: up to November 1, 2017	To demonstrate that shorter durations of antibiotic therapy are as efficacious as longer durations for many infections,	patients with community-acquired pneumonia, ventilator-associated pneumonia, intraabdominal infections, skin and soft tissue infections, uncomplicated cystitis, and complicated cystitis or pyelonephritis n=1009 patients with complicated cystitis or pyelonephritis	short course single-agent antibiotics	long course single-agent antibiotics	*Results presented for acute pyelonephritis/complicated urinary tract infection studies (n=3)* **Talan 2000** *(acute uncomplicated pyelonephritis, premenopausal women)* 7 day, ciprofloxacin 500 mg twice daily vs. 14 day, trimethoprimsulfamethoxazole 800 mg/160 mg twice daily <u>Bacteriologic cure rates</u> 99% vs 89% (14 day); p=0.004 (95% CI 0.04-0.16) <u>Clinical cure rates</u> 96% vs. 83%; p=0.002 (95% CI 0.06-0.22) **Peterson 2008** (*Complicated urinary tract infections or acute pyelonephritis)* 5 day, levofloxacin 750 mg daily vs. 10 day, ciprofloxacin 400/500 mg twice daily <u>Microbiologic eradication at end of treatment</u> 88.3% vs. 86.7% (1.6; 95% CI 8.8 to 4.1)	Studies of fluoroquinolones have demonstrated that short courses are very effective. Recent data on other classes of antibiotics such as beta-lactams are lacking, and more studies are needed before recommending short courses (7 days or less) of other antibiotic classes.	no study protocol, pre-defined population was changed, only one database used, complete search strategy not reported, no additional hand search, no risk of bias assessment <u>Conflict of interest</u> JCG has received research grants from Merck; served as a consultant for Achaogen, Allergan, Astellas, Cempra, Cidara, CutisPharma, Merck, Paratek, Shionogi, Tetraphase, Theravance, and The Medicines Company; and serves on speakers' bureaus for Allergan, Astellas, Merck, and The Medicines Company <u>Funding</u> None.	1a - RoB: high

						Clinical success at end of treatment 91.3% vs. 87.1% (4.2; 95% CI 9.6-1.2) **Sandberg 2012** *(acute pyelonephritis)* 7 day, ciprofloxacin 500 mg twice daily vs. 14 day, ciprofloxacin 500 mg twice daily Clinical cure: 97% vs 96% [-0.9%; 90% CI -6.5-4.8]			
Berti 2018 [55] *keine Pubmed-ID*	Systematic review and meta-analysis n=4 RCTs Search date: up to June 2016 Studies were conducted in: • Europe (n=3) • USA (n=1)	To compare effectiveness and tolerability of short- versus long-course treatment with the same antibiotic agent in patients with acute pyelonephritis.	n=439 patients, ≥ 18 and older with acute pyelonephritis	Short-term antibiotics • ampicillin • trimethoprim - sulfathoxazole • β-lactams • (pivampicillin/pivmecillinam) • fluoroquinolones • fleroxacin • ciprofloxacinin	Long-term antibiotics • ampicillin • trimethoprim - sulfathoxazole • β-lactams • (pivampicillin/pivmecillinam) • fluoroquinolones • fleroxacin • ciprofloxacinin	**Short vs. long antibiotic therapy** Clinical success • RR=1.01 (95% CI: 0.96-1.07, I2= 0%), p=0.67 Microbiological success RR=0.99 (95% CI: 0.92-1.07, I2=0%), p=0.80 Clinical relapse • RR=1.20 (95% CI: 0.43-3.30, I2=0%); p=0.73) Microbiological relapse • RR=2.39 (95% CI: 1.19-4.38, I2=0%); p=0.01) Microbiological recurrence or reinfection • RR=2.40 (95% CI: 0.68-8.49, I2=0%); p=0.18) Adverse event • RR=0.63 (95% CI: 0.39-1.02, I2=0%); p=0.06)	Short-term treatment for acute pyelonephritis seems to be equivalent to long-term treatment in terms of clinical and microbiological success at the end of treatment or tolerability. The only relevant difference is the frequency of recurrence of the same biological germ up to 4-6 weeks after the end of treatment, which is significantly higher with the short-term therapy.	Conflict of interest None. Funding Was not reported. *pregnant women and patients, both hospitalized and outpatients, with anatomical or functional abnormalities of the urinary tract, permanent bladder catheter, immunosuppressed, oncological and diabetic were also considered*	1a RoB: low

Cattrall 2018 [56] 30191339	Systematic review n=5 RCTs search date: October/November 2016 USA/Europe	Determine the clinical efficacy and safety of oral antibiotics for the treatment of pyelonephritis in adults.	n=1003 adults with pyelonephritis	Antibiotics (cefaclor, ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, loracarbef, norfloxacin, rufloxacin, trimethoprim-sulfamethoxazole)		**Clinical and microbiological cure** <u>Cefaclor, ciprofloxacin, levofloxacin, loracarbef and norfloxacin</u> • 5-9 days: 84 to 95% • 4-6 weeks: 83 to 95% <u>Beta-lactam antibiotics</u> • 5-9 days: 76 and 50% (cefaclor) • 4-6 weeks: 81 and 64% (loracarbef) <u>Ciprofloxacin and levofloxacin</u> • 5-9 days: 85 to 94% • 4-6 weeks: 72 to 87% **Adverse events** <u>Ciprofloxacin (n=3)</u> • overall: 0%, 8% and 24% • most commonly: gastrointestinal-related adverse events <u>Trimethoprim-sulfamethoxazole (n=1)</u> • overall: 33% • most commonly: headaches <u>Levofloxacin (n=1)</u> • overall: 2%	In summary, our review has identified clinical data in support of oral norfloxacin and cefaclor for the outpatient treatment of pyelonephritis. Further, high-quality RCTs are required to investigate the role of these antibiotics in the oral antibiotic management of pyelonephritis.	inclusion criteria unclear: "*We did not include being male*" vs. Table 1 with 13-43% males in 4 studies, unclear if efforts were made to minimise error in risk of bias assessment, no funnel plot *Significant heterogeneity between all aspects of the trial designs was identified, with all studies having a potential for bias.* <u>Conflict of interest</u> None. <u>Funding</u> Was not reported. not included: diabetic, pregnant women	1a - RoB: high
Carey 2020 [22] 32270403	Systematic Review N= 5 RCTs -Germany, - Pakistan, - Switzerland, - Norway/	Comparing NSAIDs with antibiotics for treatment of uncomplicated UTIs in adult women.	N= 1309 adult women with uncomplicated UTI	NSAID (Ibuprofen, placebo Granules, Potassium Citrate, Flurbiprofen, Diclofenac) →partly plus placebo	Antibiotics (Ciprofloxacin, Fosfomycintrome-tamol, Norfloxa-cin, Pivmecillinam) →partly plus placebo	**<u>Primary Outcome:</u> Symptom Resolution** <u>Symptom resolution by day 3 or 4 (post-randomization) in %:</u> **Bleidorn** 2010: day 4 • NSAIS (n= 21 (58%) vs. Antibiotics (n= 17 (52%)	For the outcomes of symptom resolution and complications in adult women with UTI, evidence favors antibiotics over NSAIDs.	Four studies included adult women over the age of 18 while one study included women over the age of 15. Age range: 15-70 **Conflict of Interest**: The findings and	1a RoB: low

	Denmark/ Sweden inception until January 2020					• RD*: 9 (95% CI − 13 to 31) • p = 0.744 for difference **Gágyor** 2015: day 4; **Kronenberg** 2017: day 3; **Vik** 2018: day 4 • NSAIS (n= 233) vs. Antibiotics (n= 356) • RD*: (95% CI) 17 to 35 % points higher in the antibiotic group compared with the NSAID group. <u>Symptom resolution at the end of the trial (day 5 post-randomization)</u> **Jamil** 2016 • NSAIS: 1.4 vs. Antibiotics: 1.9; • p = 0.13 <u>Number Needed to Treat</u> *Antibiotics vs. NSAIDs to achieve symptom resolution in one additional patient by days 3 to 4 post-randomization* <u>(3 RCTs)</u>*:* **range: 3.0 to 6.4.** **Secondary Outcomes:** <u>Women receiving antibiotics for any reason during study period:</u> **Gágyor** 2015 • NSAID n= 85 (35%); antibiotics n=	In sum: The use of antibiotics as first-line treatment for uncomplicated UTI for both symptom resolution and prevention of pyelonephritis.	conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Department of Veterans Affairs. **Fund**: ? Three studies were at low risk of bias, one had an unclear risk of bias, and one was at high risk of bias. *Positive numbers= higher rates of symptom resolution among patients receiving antibiotics vs. NSAIDS **Positive numbers= higher rates of antibiotic use in the NSAID group *** Positive numbers = higher rates of pyelonephritis in the NSAID group	

						243 (100%) • RD**: – 65 (95% CI – 71 to – 59) **Kronenberg** 2017 • NSAID n= 82 (62%); antibiotics n= 118 (98%) • RD**: – 37 (95% CI – 46 to – 28) <u>Rates of pyelonephritis:</u> Gágyor 2015 • NSAID n= 5 (2%); antibiotics n= 1 (0.4%) • RD***: 1.7 (95% CI – 0.3 to 3.6) Kronenberg 2017 • NSAID n= 6 (5%); antibiotics n= 0 (0%) • RD***: 5 (95% CI 1 to 8) Vik 2018 • NSAID n= 7 (4%); antibiotics n=0 (0%) • RD***: 4 (95% CI 1 to 8) <u>Number Needed to Treat</u>: *Antibiotics vs. NSAIDs to prevent one additional case of Pyelonephritis by Day 28 to 30* (3 RCTs): **range: 22.2 to 62.1** →2 RCTs: patients who			

						received antibiotics had lower rates of pyelonephritis compared with those who received NSAIDs.			

7.4 Prävention

Schlüsselfrage Welche nicht-medikamentösen Maßnahmen verringern die Häufigkeit rezidivierender Harnwegsinfektionen									
Referenz	**Studiencharakteristika**	**Studienziel**	**Patientenmerkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Ghouri 2018 [57] 29653573	Systematic review n=4 RCTs; n=4 observational studies Search date: up to July 2017	The aim of this study was to systematically review the literature to identify and evaluate potential measures to prevent UTIs in pregnant women.	Pregnant Women	Non-antibiotic prevention measures	Any	**Incidence of bacteriuria or UTI** Hygiene behaviour (n=2 studies: Amiri 2009; Elzayat 2017) • Both studies show that hygiene behaviours are associated with the incidence of UTIs. Amiri 2009 (observational case-control study, n=250 pregnant women): • Sexual activity > thrice a week (OR=5.62; 95% CI: 3.10–10.10)	All the approaches identified in this review are reported to be safe and effective. However apart from hygiene behaviours, the evidence behind these approaches is not robust enough to be recommended in practice.	No protocol, only one author screened the papers for eligibility for the systematic review, no information on the data extraction process, search terms were limited to prevention (terms such as prophylaxis were not used) Funding This work was supported by the University of Reading as a PhD studentship for F.G.	For the intervention: Hygiene behaviour: 3a - Cranberry juice: 1a - Immunisation: 2a -

						• Not voiding the bladder after intercourse (OR=8.62; 95% CI: 6.66–16.66) • Washing genital area from back to front (OR=-2.96; 95% CI: 1.66–5.28) Elzayat 2017 (observational study, n=170 pregnant women): • There was an association between sexual activity and incidence of ASB and 14% of women with ASB reported sexual activity > twice per week (p=0.01). • There was also an association between direction of wiping and 15% of women with ASB reported wiping their genitals from back to front (p=0.03). <u>Cranberry juice</u> (n=2 studies; Wing 2008, Essadi 2010) Wing 2008 (Pilot RCT, n=188 pregnant women): • Authors concluded that cranberries provide		<u>Conflict of interest</u> The authors declare that they have no competing interests.	Ascorbic acid: 1a - Canephron® N: 2a - RoB: high

						protection against ASB as well as symptomatic infections. • 57% reduction in bacteriuria compared to placebo • 41% reduction in all UTIs compared to placebo Essadi 2010 (RCT, n=760 pregnant women): • 70.5% of patients who drank cranberry juice showed a significant reduction ($p<0.05$) in frequency of UTI compared to 32.16% who drank water • Of women who developed symptomatic UTI, 4.12% delivered prematurely <u>Immunisation</u> (n=2 studies; Baertschi 2003, Grischke 1987) Baertschi 2003 (before and after study, n=62 pregnant women): • Bacterial extract (OM-8930) significantly reduced the recurrence of UTIs			

						from 52.5% to 19.4% (p=0.002) • Number of people needing antibiotic treatment reduced from 55.7% to 12.9% (p=0.0002) • Duration of antibiotic treatment reduced from a mean of 3.2 to 2 days (p= 0.0016) Grischke 1987 (comparative randomised trial, n=400 pregnant and non-pregnant women) Vaccine preparation Solco-Urovac® vs. nitrofurantoin or another appropriate antibiotic: • Solco-Urovac®: 28/200 infections • nitrofurantoin or another appropriate antibiotic: 84/198 infections (p≤0.001). <u>Ascorbic acid</u> (n=1 randomised trial, Ochoa-Brust 2007, n=110 pregnant women) Group A: ferrous sulphate (200 mg), folic acid (5 mg) and ascorbic acid (100 mg) daily for 3			

						mo vs. Group B: ferrous sulphate (200 mg) and folic acid (5 mg) daily for 3 months • group A: 12.7% infections • group B: 29.1% infections OR=0.35 (CI 95%: 0.13–0.91), p=0.03 • The number needed to treat was 6. • The authors concluded that pregnant women in areas with high rates of antimicrobial resistance should take ascorbic acid during gestation to prevent UTIs. <u>Canephron® N</u> (n=1 cohort study, Ordzhonikidze 2009, n=300 pregnant women) Group 1: n=160 women with an exacerbation of pyelonephritis received Canephron® N in combination with standard therapy (antibiotics). Group 2: n=140 women with chronic history of urinary tract disease			

						received Canphron®N alone for prevention. The dose of Canephron® N was two tablets three times a day Frequency of exacerbation of pyelonephritis: • Group 1: 10–6.25% • Group 2: 3–2.1% • The authors state that there was a 1.5-fold decrease in the frequency of infectious complications in the first group and a 1.3-fold decrease in the second group when comparing results to previous years.			
Special dietary & fluid intake									
Zaragoza-Martí 2022 [58] 35433794	Systematic review n=14 studies (of these 2 RCTs reported on UTIs) Search period:	The aim of this study was to conduct a systematic review of the literature to study the effects of Mediterranean diet during the gestational period.	<u>Assaf-Balut 2017</u> pregnant women at 8–12 gestational weeks <u>Assaf-Balut 2019</u> pregnant women at 12–14	<u>Assaf-Balut 2017 & 2019</u> Intervention group had two group sessions where they were instructed to increase their consumption of extra	<u>Assaf-Balut 2017 & 2019</u> Control group received basic dietary guidelines and was told to limit all types of fat consumption types of	<u>Assaf-Balut 2019</u> There was a linear association between high, moderate, and low adherence and UTIs OR=0.19 (95% CI: 0.07-0.52); p=0.001 <u>Assaf-Balut 2017</u> Frequency of UTIs OR=0.41 (95% CI: 0.26-	This result may be due to the relationship between Mediterranean diet, inflammation, and immunomodulation. This effect is possibly due to the presence of some food components, such as phenolic compounds and oleic acid.	no study protocol, only articles considered which were published between 2010 and 2020, no information if efforts were made to minimise error in the study selection process and data extraction, no funnel plot <u>Funding</u> Not reported.	1a - RoB: high

	2010-2020		gestational weeks	virgin olive oil and nuts and received 10 l of oil and 2 kg of pistachios in each session	fat consumption	0.64); p=0.001	<u>Assaf-Balut 2019</u> High adherence at the end of the first trimester to the six predefined dietary targets is associated with a reduction in the risk of UTIs. <u>Assaf-Balut 2017</u> Early nutritional intervention with supplemented Mediterranean diet improves several maternal outcomes.	<u>Conflict of interest</u> The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.	
Scott 2020 [59] 31988085	Systematic review and meta-analysis n=8 RCTs Search date: up to Jan 2019	To assess the impact of increased fluid intake in individuals at risk for UTIs, for impact on UTI recurrence (primary outcome), antimicrobial use, and UTI symptoms (secondary outcomes).	n=3979 individuals at risk for UTIs (as defined by each individual trial's inclusion criteria), of any age and sex, who were ambulatory, that is, non-catheterised	Increased fluid intake (e.g., water, D-mannose dissolved in fluid, or juice)	• No inter-vention • reduced fluid intake compared to the intervention group	**Number of participants with UTIs** <u>Increased fluid intake vs. control (at ≤6 or 12 mo)</u> (n=5 RCTs) • Increased fluid intake: 115/292 • Control: 156/242 OR=0.39 (95% CI: 0.15-1.03, I^2=77%), p=0.06 *Subgroup analyses* <u>Increased fluid intake vs. control at ≤6 mo</u> (n=2	Given the minimal potential for harm of increased fluid intake, this review suggests considering clinically adopting its results and advising patients with recurrent UTIs to drink more to reduce recurrent UTIs.	the protocol was changed and cranberry juice comparisons were additionally included, it remains unclear why the protocol changed <u>Funding</u> The present systematic review was conducted as part of the work of the Centre of Research Excellence in Minimising Antibiotic Resistance in the Community (CRE-MARC), funded by the National Health and Medical	1a RoB: low

						RCTs) •Increased fluid intake: 18/123 •Control: 70/122; OR=0.13 (95% CI: 0.07-0.25, I^2=7%), p<0.00001 <u>Increased fluid intake vs. control at 12 mo</u> (n=2 RCTs) Increased fluid intake: 97/169 • Control: 86/120; OR=0.72 (95% CI: 0.39-1.35, I^2=0%), p=0.31 <u>Increased fluid intake ≥200 ml</u> • Increased fluid intake: 90/243 • Control: 145/217; OR=0.25 (95% CI: 0.11-1.59, I^2=58%), p=0.001 **Number of participants with antimicrobial use** <u>Increased fluid intake vs. control</u>		Research Council (NHMRC), Australia (grant reference number: GNT1153299). The funder had no involvement in this systematic review. <u>Conflict of interest</u> The authors have declared no competing interests. *Nearly all trials included 100% females, with the exception of a crossover trial that took place in nursing homes that included 68% females* *Mean age of the participants in the included studies ranged from 7.5 y to 85 y*	

						(n=3 RCTs) • Increased fluid intake: 76/222 • Control: 78/148; OR=0.52 (95% CI: 0.25-1.07, I^2=0%), p=0.08			
Phytotherapy									
Kranz 2022 [60] 35101170	Systematic review n=12 RCTs (10 RCTs on prevention) Search date: Jan 2011-Aug 2021	In this review, we aim to pool the current evidence concerning phytotherapeutic agents in the treatment and prevention of recurrent uncomplicated cystitis in adults.	• healthy adults (>16 years) with a history of recurrent uncomplicated cystitis or • adults (+16 years) with an acute episode of recurrent cystitis n=1797 participants	phytotherapy as monotherapy or as combination therapy (any mode of administration)	• medication (e.g., antibiotics, analgesics) • non-pharmaceutical interventions (e.g., diet, lifestyle, acupuncture) • placebo no treatment	• No trial included men or pregnant women. **Cranberry products vs. placebo** (n=5 RCTs) <u>Maki 2016</u> Cranberry drink vs. placebo Reported symptomatic UTI episodes: • 0: 82% (152/185) vs. 73% (138/188) • 1: 15% (27/185) vs. 19% (36/188) • 2: 3% (6/185) vs. 6% (11/188) • 3: 0% (0/185) vs. 2% (3/188) • ≥1: 18% (33/185) vs. 27% (50/188) Total number of UTIs: 39	Phytotherapeutic agents are an option for the treatment and prevention of recurrent cystitis in women. Given the heterogeneous state of the evidence on phytotherapy, no dependable recommendations can now be made for the clinical management of these patients with respect to phytotherapeutic agents.	Only articles considered that were published between 2011-2021, no rational is given to support this restriction <u>Funding</u> Not reported. <u>Conflict of interest</u> PD Dr. med. habil. Kranz has served as a paid consultant for, and received lecture honoraria from, Bionorica. Prof. Dr. med. Wagenlehner has served as a paid consultant for, and received lecture honoraria and reimbursement of travel expense	1a RoB: low

						vs. 67 Total UTI with pyuria: 32 vs. 53 Incidence ratio: • UTI: 0.61 (95% CI: 0.41-0.91); p=0.016. • UTI with pyuria: 0.63 (95% CI:0.40-0.97); p=0.037 Adverse events: Serious adverse events were probably not related to the treatments. <u>Vostalova 2015</u> Cranberry capsules vs. placebo Within 6 mo: • ≥1 UTI: 11% (9/83) vs. 26% (24/93); p=0.04. • 2 UTI: 1% (1/83) vs. 6% (6/93) Relative risk reduction: 58% Cumulative incidence of UTI over 6 mo: 9% vs. 19% <u>Takahashi 2013</u>			

						rUTI • total: 27% (22/82) vs. 39% (34/88); p=0.1300 • <50 years: 22% (6/27) vs. 12% (3/25); p=0.3623 • ≥50 years: 29% (16/55) vs. 49% (31/63); p=0.0425 Multivariate analysis (≥=50 years): HR: 1.037 (95% CI; 1.002–1.073); p=0.038 Adverse events: No serious adverse events <u>Stapleton 2012</u> Cranberry juice vs. placebo UTI in follow-up: • total: 28% (33/120) vs. 30% (17/56); p=0.70 • >1 UTI: 8% (10/120) vs. 7% (4/56) Cumulative UTI rate at 6 mo: 0.29 (95% CI: 0.21–0.38) vs. 0.37 (95% CI: 0.25–0.54); p=0.82 Adjusted HR for UTI:			

						0.68 (95% CI:0.33–1.39); p=0.29 Adverse events: No serious adverse events <u>Sengupta 2011</u> Cranberry capsule vs. no treatment • Cranberry (total): 41% (18/44) complete resolution of urologic symptoms • Untreated: no improvement Use of the emergency drug • Cranberry (low dose): 10% (2/21) • Cranberry (high dose): 9% (2/23) • Untreated: 25 % (4/16) Adverse events: No serious adverse events **TMP-SMX vs. cranberry** <u>Beerepoot 2011</u> After 12 mo: Mean number of rUTIs: 1.8 (95% CI: 0.8–2.7) vs. 4.0 (95% CI: 2.3–5.6); p=0.02. After 15 mo Mean number of rUTIs:			

						0.5 (95% CI: 0.3–0.7) vs. 0.7 (95% CI: 0.4–0.9); p=0.30 Serious adverse events • TMP-SMX: 0.91% (1/110) Stevens-Johnson syndrome • Cranberry: none **Seidlitzia rosmarinus vs. placebo** <u>Kamalifard 2020</u> Cystitis incidence rate: • At 2 months: 19% (11/58) vs. 55% (32/58); OR: 0.19 (95% CI: 0.08-0.43); p<0.001. • At 4 months: 22% (13/58) vs. 57% (33/58); OR: 0.21 (95% CI:0.98-0.49); p<0.001 • At 6 months: 33% (19/58) vs. 73% (43/59); OR: 0.18 (95% CI: 0.08-0.40); p<0.001. Incidence of recurrent cystitis: 4% (8/58) vs. 66% (39/59); OR: 0.08 (95% CI: 0.03-0.20); p<0.001 Adverse events: No side effects were			

						observed in either group **Combined preparations** <u>Murina 2021</u> Cranberry, Lactobacillus paracasei LC11, D-mannose vs. no treatment No UTI • Cranberry group 1: 65.8% (12/19) • Cranberry group 2: 68.8% (13/19) • Control group: 36.9% (6/17); p=0.05 1 UTI • Cranberry group 1: 18.2% (4/19) • Cranberry group 2: 15.6% (3/19) • Control group: 10.2% (2/17) • Not significant ≥=2 UTI • Cranberry group 1: 16% (3/19) • Cranberry group 2: 15.6% (3/19) • Control group: 52.9% (9/17); p<0.01 Adverse events: No			

						adverse events <u>Bruyère 2019</u> 600 mg cranberry extract, 400 mg propolis, 5 mg zinc vs. placebo ≥1 cystitis: 2.3 ± 1.8 vs. 3.1 ± 1.8; p=0.09 No clinically relevant change in quality of life Adverse events Serious adverse events were probably not related to treatment			
Xia 2021 [61] 34473789	Systematic review and meta-analysis n=23 RCTs Search date: up to Jun 2021	This study aims to update and determine cranberry effects as adjuvant therapy on the recurrence rate of UTIs in susceptible groups.	n=3979 participants with recurrent UTIs, elderly men and women, pregnant women, children, participants with indwelling catheter, and participants with neuropathic bladder	cranberry-containing products n=1978 participants	placebo or non-placebo control group n=2001 participants	**UTI cumulative incidence** (n=23 RCTs) • Cranberry intervention: 427/1978 • Control: 574/2001 RR=0.70 (95% CI: 0.59-0.83; I^2=48%); p<0.01 *Subgroup analyses* <u><= 18 y</u> (n=19 RCTs) • Cranberry intervention: 393/1978 • Control: 515/1803 RR=0.72 (95% CI: 0.60-0.87; I^2=50.4%) <u>Women with rUTIs</u> (n=8	Our meta-analysis demonstrates that cranberry supplementation significantly reduced the risk of developing UTIs in susceptible populations. Cranberry can be considered as adjuvant therapy for preventing UTIs in susceptible populations.	no study protocol, no information if efforts were made to minimise error in the study selection process and risk of bias assessment <u>Funding</u> The author(s) received no specific funding for this work. <u>Conflict of interest</u> The authors have declared that no competing interests exist.	1a - RoB: high

						RCTs) • Cranberry intervention: 152/672 • Control: 204/671 RR=0.68 (95% CI: 0.56-0.81; I^2=56.60%) <u>Pregnant women</u> (n=2 RCTs) • Cranberry intervention: 11/125 • Control: 14/126 RR=0.79 (95% CI: 0.37-1.67; I^2=0%) <u>Elderly patients</u> (n=3 RCTs) • Cranberry intervention: 134/615 • Control: 190/659 RR=0.89 (95% CI: 0.75-1.05; I^2=60.5%)			
Tambunan 2019 [62] No PMID	Systematic review and meta-analysis n=9 RCTs	This meta-analysis was aimed to assess the effectiveness, safety, and adherence of cranberry as a prophylactic drug for treating rUTI.	n=1542 non-pregnant women aged ≥18 years with a history of UTI	cranberry derivatives (capsule or juice)	placebo and antibiotic prophylaxis	<u>Cranberry vs. placebo for rUTI treatment</u> (n=7 studies) • Cranberry: 174/792 • Placebo: 199/750 RR=0.81 (95% CI: 0.67–0.96, I^2=41%); p=0.02 <u>Cranberry juice vs. placebo for rUTI treatment</u> (n=5 studies)	Cranberry, especially cranberry capsule consumption, had a significant effect in reducing the incidence of rUTI compared with placebo, with good adherence rates, and minor adverse events. In contrast, although antibiotic use had a greater efficacy, it was associated with a	No study protocol, no search date reported, complete search strategy not reported, no information if efforts were made to minimise error in the data extraction and risk of bias assessment, no funnel plot <u>Funding</u> None.	1a - RoB: high

						• Cranberry: 141/617 • Placebo: 147/564 RR=0.85 (95% CI: 0.70–1.04, I^2=40%); p=0.12 <u>Cranberry capsule vs. placebo for rUTI treatment</u> (n=2 studies) • Cranberry: 33/175 • Placebo: 52/186 RR=0.67 (95% CI: 0.45–0.98, I^2=65%); p=0.004 <u>Cranberry vs. antibiotic for rUTI treatment</u> (n=2 studies) • Antibiotic: 82/163 • Cranberry capsule: 107/173 RR=0.83 (95% CI: 0.70–0.98, I^2=67%); p=0.03 <u>Adverse events</u> Overall • Most of the participants experienced minor adverse events **Stapleton 2012** • No serious adverse events in both study groups (cranberry juice vs. placebo juice) Rate of minor adverse	higher risk of severe adverse events.	<u>Conflict of interest</u> The authors affirm no conflict of interest in this study.	

						events: • Cranberry juice: 24.2% • placebo: 12.5% p=0.07 **McMurdo 2009** trimethoprim vs. cranberry capsule • itch/rash and loss to follow-up occurred more commonly in the trimethoprim group • gastrointestinal symptoms were equally common in both groups • Other adverse events were comparable between groups **Beerepoot 2013** trimethoprim-sulfamethoxazole vs. cranberry • minor adverse effects (rash and gastrointestinal symptoms) with no significant differences between both groups • trimethoprim-sulfamethoxazole group: one subject experienced a severe adverse event (Stevens-Johnson syndrome)_			

Fu 2017 [63] 29046404	Systematic review and meta-analysis n=7 RCTs Update search date: Jan 2010-Jul 2017 (Literature before 2011 was obtained from 2 published systematic reviews)	We undertook this systematic review and meta-analysis to evaluate the evidence of cranberry in the prevention of UTI among generally healthy women.	n=1498 generally healthy nonpregnant women aged ≥ 18 y with a history of UTI	Cranberry interventio n n=798	Placebo or nontreatm ent control n=702	**Pooled cumulative incidence of UTI & risk reduction of recurrence** ***Overall analysis:*** (n=7 RCTs) • Cranberry: 165/796 • Placebo/control: 186/702 Reduction of the risk of UTI recurrence: 26% RR=0.74 (95% CI: 0.55-0.98; I^2=54%), p=0.04 ***Subgroup analysis:*** <u>Culture-confirmed UTI:</u> (n=5 RCTs) • Cranberry: 100/504 • Placebo/control: 98/408 RR=0.71 (95% CI: 0.45-1.12; I^2=68%), p=0.01 <u>Form of cranberry:</u> <u>Juice</u> (n=6 RCTs) • Cranberry: 146/663 • Placebo/control: 162/609; RR=0.79 (95% CI: 0.59-1.06; I^2=50%), p=0.075 <u>Capsule or tablet</u> (n=2 RCTs) • Cranberry: 18/133 • Placebo/control:	In summary, our meta-analysis suggests that cranberry can be a potential nonpharmacologic approach for generally healthy women to prevent an uncomplicated recurrent UTI. However, studies were generally small, with only 2 having >300 participants, and further studies are needed to confirm these find	Literature published before January 2011 was obtained from 2 published systematic reviews with search dates of Nov 2011 and Jul 2012. The Inclusion/exclusion criteria of these systematic reviews were not reported. Studies with high risk of bias were not accounted for in sensitivity analyses. In some included studies women with an active UTI and unknown history were enrolled and the subsequent UTI was considered a recurrent UTI; other studies relied on a history of UTI in the preceding 6 or 12 mo, with a variable number of previous UTI episodes. <u>Funding</u> Supported by a grant from Ocean Spray Cranberries Inc. to DL. <u>Conflict of interest</u> Author disclosures: ZF, DT, and MC, no conflicts of	1a - RoB: high

						40/143; RR=0.48 (95% CI: 0.29-0.79; I^2=0%), p=0.57 <u>Follow-up duration 6 mo</u> (n=6 RCTs) • Cranberry: 146/696 • Placebo/control: 170/652; RR=0.76 (95% CI: 0.55-1.04; $I^{2=}$59%), p=0.03 <u>Follow-up duration 12 mo</u> (n=2 RCTs) • Cranberry: 31/146 • Placebo/control: 35/95; RR=0.61 (95% CI: 0.40-0.91; I^2=0%), p=0.92 <u>UTI status at baseline</u> <u>Free of UTI</u> (n=4 RCTs) • Cranberry: 94/488 • Placebo/control: 107/387; Reduction of the risk of UTI recurrence: 26% RR=0.65 (95% CI: 0.51, 0.84; I^2=10%), p=0.35 <u>Active UTI episode at baseline & then treated with antibiotics before UTI recurrence assessment</u> (n=3 studies)		interest. DL has received grant funding from Ocean Spray Cranberries. The funding source had no role in the study design, conduct, or interpretation and reporting	

						• Cranberry: 71/308 • Placebo/control: 79/315; RR: 0.84 (95% CI: 0.47-1.50; I^2=73%), p=0.025 **Adverse events/tolerance** • n=2 RCTs showed a higher number of participants reporting adverse events in the cranberry vs. placebo/control group • n=1 RCT showed similar numbers of participants reporting adverse events in both groups • gastrointestinal disturbances were the most commonly reported complaint • no serious adverse events occurred • overall interventions were considered to be well tolerated			
Luis 2017 [64] 28288837	Systematic review and meta-analysis n=25 studies (n=22 RCTs, n=1	We sought to clarify the association between cranberry intake and the prevention of urinary tract infections.	n=4947 patients at certain risk for repeated UTIs, *including children and elderly patients, long-term care facility residents, patients with*	Cranberry products	Placebo	**Incidence of repeated UTIs** <u>Cranberry treatment vs. placebo</u> *Overall* WRR=0.675 (95% CI: 0.552-0.797, I^2=58.17); p<0.0001 *Subgroup analyses*	The results of the current study could be used by physicians to recommend cranberry ingestion to decrease the incidence of urinary tract infections, particularly in individuals with recurrent urinary	no study protocol, no clear inclusion and exclusion criteria defined, complete search strategy not reported, no risk of bias assessment for three non-RCTs, no information if efforts were made to minimise error in the risk of bias assessment	1a - RoB: high

	observa-tional study, n=1 non-randomized , n=1 registry, supplement and pilot study) Search date: up to September 2016		*cancer or spinal cord injury, and patients on clean intermittent catheterization*			<u>rUTIs</u> (n=15 studies) WRR=0.645 (95% CI: 0.523-0.796 I^2=60.406%); p<0.0001 <u>Middle-aged adults (36-55y)</u> (n=10 studies) WRR=0.565 (95% CI: 0.449-0.711, I^2=44.10%); p<0.0001 <u>Older adults (>55 y)</u> (n=5 studies) WRR=0.883 (95% CI: 0.697-1.119, I^2=24.61%); p=0.304 <u>Elderly patients (≥60 y)</u> (n=1 study, McMurdo 2005) WRR=0.505 (95% CI: 0.209-1.224, I^2=not applicable); p=0.130 <u>Pregnant women</u> (n=1 study; Wing 2008) WRR=0.792 (95% CI: 0.371-1.687, I^2=not applicable); p=0.545 <u>Male</u> *(patients with prostatic adenocarcinoma or*	tract infections.	<u>Funding</u> Supported by Universidade da Beira Interior and bank Santander/Totta protocol post-doctoral research fellowship BIPD/ICI-FC-BST-UBI 2016 <u>Conflict of interest</u> No direct or indirect commercial incentive associated with publishing this article. *3 of the 25 included studies were divided into 2 trials for a total of 28 studies.*	

						spinal cord injury) (n=2) WRR=0.364 (95% CI: 0.232-0.571, I^2=0%); p<0.0001			
Acupuncture									
Qin 2020 [35] 32406571	Systematic review and meta-analysis n=5 RCTs (n=2 studies evaluated acupuncture as prophylactic therapy, n=3 studies recruited women during the acute infection stage) Search date: up to 2019	This systematic review of RCTs assessed the effects and safety of acupuncture therapies for uncomplicated rUTI in women.	Women aged ≥18 y with a diagnosis of uncomplicated rUTI	Manual acupuncture (8 sessions over 4 weeks) n=94	No treatment n=41 Sham acupuncture n=26	*In the following only the studies are considered that evaluated acupuncture as prophylactic therapy* **UTI recurrence** <u>Acupuncture vs. no treatment</u> (n=2 RCTs, Alraek 2002, Aune 1998) • Acupuncture: 25/94 • No treatment: 28/41; RR=0.39 (95% CI: 0.26–0.58; I^2=0%), p<0.00001; low certainty evidence) <u>Acupuncture vs. sham</u> (n=1 RCT, Aune 1998) • Acupuncture: 7/27 • Sham: 15/26 RR=0.45 (95% CI: 0.22–0.92, heterogeneity not applicable, p=0.03; moderate certainty evidence) **Adverse events**	Acupuncture appeared to be beneficial for treatment and prophylaxis of rUTIs, noting the limitations of the current evidence.	*Confidence in these results is limited due to the lack of detail reported and high risk of bias due to lack of blinding* *Planned sensitivity and subgroup analyses could not be conducted due to the small number of* *included studies* <u>Funding</u> The study was supported by China-Australia International Research Centre for Chinese Medicine (CAIRCCM) (International Cooperation Project, Grant Number 2012DFA31760) and the National Natural Science Foundation of China (NSFC) (Grant Number 81873261). The funding source was not involved in the process	1a RoB: low

						Acupuncture (1=RCT) Overall: 8 • 3/27: feeling warm in the legs • 2/27: gastrointestinal discomfort • 2/27: more frequent menstruation • 1/27: dizziness Sham (1=RCT) Overall: 7/26 • 2/26: sensation of warmth in the legs • 2/26: gastrointestinal discomfort • 1/26: pain • 1/26: less frequent menstruation • 1/26: less climacteric discomfort		of the study. Conflict of interest The funding source was not involved in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication. Completed disclosure of interests forms are available to view online as supporting information.	

Suchbegriffe Welche medikamentösen Maßnahmen verringern die Häufigkeit rezidivierender Harnwegsinfektionen?									
Referenz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Interven-tion**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Phytotherapy									
Kranz, 2022 [60] 35101170	Systematic review n=12 RCTs (10 RCTs on prevention) Search date: Jan 2011-Aug 2021	In this review, we aim to pool the current evidence concerning phytotherapeutic agents in the treatment and prevention of recurrent uncomplicated cystitis in adults.	• healthy adults (>16 y) with a history of recurrent uncomplicated cystitis or • adults (+16 y) with an acute episode of recurrent cystitis n=1797 participants	phytotherapy as monotherapy or as combination therapy (any mode of administration)	• medication (e.g. antibiotics, analgesics) • non-pharmaceutical interventions (e.g., diet, lifestyle, acupuncture) • placebo • no treatment	• No trial included men or pregnant women. **Cranberry products vs. placebo** (n=5 RCTs) <u>Maki 2016</u> Cranberry drink vs. placebo Reported symptomatic UTI episodes: • 0: 82% (152/185) vs. 73% (138/188) • 1: 15% (27/185) vs. 19% (36/188) • 2: 3% (6/185) vs. 6% (11/188) • 3: 0% (0/185) vs. 2% (3/188) • ≥1: 18% (33/185) vs. 27% (50/188) Total number of UTIs: 39 vs. 67 Total UTI with pyuria: 32	Phytotherapeutic agents are an option for the treatment and prevention of recurrent cystitis in women. Given the heterogeneous state of the evidence on phytotherapy, no dependable recommendations can now be made for the clinical management of these patients with respect to phytotherapeutic agents.	Only articles considered that were published between 2011-2021, no rational is given to support this restriction <u>Funding</u> Not reported. <u>Conflict of interest</u> PD Dr. med. habil. Kranz has served as a paid consultant for, and received lecture honoraria from, Bionorica. Prof. Dr. med. Wagenlehner has served as a paid consultant for, and received lecture honoraria and reimbursement of travel expense.	1a RoB: low

						vs. 53 **Incidence ratio**: • UTI: 0.61 (95% CI: 0.41-0.91); p=0.016. • UTI with pyuria: 0.63 (95% CI:0.40-0.97); p=0.037 **Adverse events:** Serious adverse events were probably not related to the treatments. <u>Vostalova 2015</u> Cranberry capsules vs. placebo Within 6 mo: • ≥1 UTI: 11% (9/83) vs. 26% (24/93); p=0.04. • 2 UTI: 1% (1/83) vs. 6% (6/93) Relative risk reduction: 58% Cumulative incidence of UTI over 6 mo: 9% vs. 19% <u>Takahashi 2013</u>			

						rUTI • total: 27% (22/82) vs. 39% (34/88); p=0.1300 • <50 years: 22% (6/27) vs. 12% (3/25); p=0.3623 • ≥50 years: 29% (16/55) vs. 49% (31/63); p=0.0425 Multivariate analysis (≥=50 y): HR: 1.037 (95% CI; 1.002–1.073); p=0.038 Adverse events: No serious adverse events <u>Stapleton 2012</u> Cranberry juice vs. placebo UTI in follow-up: • total: 28% (33/120) vs. 30% (17/56); p=0.70 • >1 UTI: 8% (10/120) vs. 7% (4/56) Cumulative UTI rate at 6 mo: 0.29 (95% CI: 0.21–0.38) vs. 0.37 (95% CI: 0.25–0.54); p=0.82			

						Adjusted HR for UTI: 0.68 (95% CI:0.33–1.39); p=0.29 **Adverse events**: No serious adverse events <u>Sengupta 2011</u> Cranberry capsule vs. no treatment • Cranberry (total): 41% (18/44) complete resolution of urologic symptoms • Untreated: no improvement Use of the emergency drug • Cranberry (low dose): 10% (2/21) • Cranberry (high dose): 9% (2/23) • Untreated: 25% (4/16) Adverse events: No serious adverse events **TMP-SMX vs. cranberry** <u>Beerepoot 2011</u>			

						After 12 mo: Mean number of rUTIs: 1.8 (95% CI: 0.8–2.7) vs. 4.0 (95% CI: 2.3–5.6); p=0.02. After 15 mo Mean number of rUTIs: 0.5 (95% CI: 0.3–0.7) vs. 0.7 (95% CI: 0.4–0.9); p=0.30 Serious adverse events • TMP-SMX: 0.91% (1/110) Stevens-Johnson syndrome • Cranberry: none **Seidlitzia rosmarinus vs. placebo** <u>Kamalifard 2020</u> Cystitis incidence rate: • At 2 mo: 19% (11/58) vs. 55% (32/58); OR=0.19 (95% CI: 0.08-0.43); p<0.001. • At 4 mo: 22% (13/58) vs. 57% (33/58); OR=0.21 (95% CI:0.98-0.49); p<0.001 • At 6 mo: 33% (19/58) vs. 73% (43/59); OR=0.18 (95% CI: 0.08-0.40);			

						p<0.001. Incidence of recurrent cystitis: 4% (8/58) vs. 66% (39/59); OR=0.08 (95% CI: 0.03-0.20); p<0.001 Adverse events No side effects were observed in either group **Combined preparations** <u>Murina 2021</u> Cranberry, Lactobacillus paracasei LC11, D-mannose vs. no treatment No UTI • Cranberry group 1: 65.8% (12/19) • Cranberry group 2: 68.8% (13/19) • Control group: 36.9% (6/17); p=0.05 1 UTI • Cranberry group 1: 18.2% (4/19) • Cranberry group 2: 15.6% (3/19) • Control group:			

						10.2% (2/17) Not significant ≥=2 UTI • Cranberry group 1: 16% (3/19) • Cranberry group 2: 15.6% (3/19) • Control group: 52.9% (9/17); p<0.01 Adverse events: No adverse events <u>Bruyère 2019</u> 600 mg cranberry extract, 400 mg propolis, 5 mg zinc vs. placebo ≥1 cystitis: 2.3 ± 1.8 vs. 3.1 ± 1.8; p=0.09 No clinically relevant change in quality of life **Adverse events** Serious adverse events were probably not related to treatment			
Probiotics									
New 2022 [37]	Systematic review n=9 studies	We conducted a systematic review of literature to assess the role of probiotics in	n=772 female adults with urinary tract infections	probiotics	• placebo • antibiotics • cranberry supple-ments	**Reduction in UTI** demonstrated by 2 studies:	There exists only limited clinical evidence to support the role of probiotics in the management	no study protocol, MeSH terms named in the paper are not included in the example search strategy, no information if efforts were made to minimise	1a - RoB: high

35156175	(n=7 RCTs, n=2 cohort studies) Search date: Jan 1990-Apr 2021	management of UTIs.	<u>Mean age</u> 34.2 y (18-65 y)			<u>Koradia 2019</u> BKPro-Cyan (Lactobacillus acidophilus PXN 35, Lactobacillus plantarum PXN 47, cranberry extract) one capsule twice a day vs. placebo Recurrent UTI: • Probiotics: 4/44 (9.1%) • Placebo: 15/45 (33.3%) Adverse events • Probiotics: 1/44 abdominal distension; 2/44 diarrhoea • Placebo: None. <u>Stapleton 2011</u> Lactobacillus crispatus (Lactin-V; Vaginal suppositories once daily for 5 days followed by once weekly for 10 weeks) vs. placebo Development of UTI • Probiotics: 7/48 (14.5%) • Placebo: 13/48	of rUTIs, and based on the current evidence, probiotics can be a potential measure to reduce rUTIs	error in the data extraction process and risk of bias assessment, unclear which RoB tool was used for the cohort studies, no funnel plot <u>Funding</u> Not reported. <u>Conflict of interest</u> The authors declare no competing interests.	

						(27%) Adverse events Probiotics: Adverse events • Probiotics: 56% described AE which include vaginal discharge/ itch and mild abdominal discomfort • Placebo: 50% (25) described AE which include vaginal discharge/ itch and mild abdominal discomfort **Recurrent UTI**: n=7 studies showed no significant reduction in the risk of rUTI (Baerheim 1994; Kontiokari 2001; Reid 2003; Czaja 2007; Beerepoot 2011; Pugliese 2020; Wolff 2020) **Adverse events** (all studies) Vaginal discharge or irritation, abdominal discomfort and gastrointestinal symptoms were the most documented with similar rates across all the			

						studies where AEs occurred. Treatment withdrawal or exclusion due to adverse events (across all studies) • Probiotics: 16 • Control: 9			
Abdullatif 2021 [65] 34671514	Systematic review and meta-analysis n=3 RCTs Search date: 2001-2021	The current systematic review and meta-analysis was conducted to evaluate the efficacy of probiotics for prophylaxis in UTIs in premenopausal women.	n=284 premenopausal adult women with a history of one or more UTI within the 12 mo before entering the study	probiotics (Supplements included oral gelatin capsules, beverages, or vaginal suppositories)	placebo	**UTI recurrence** (n=3 studies, n=284 patients) • treatment group: 21.3% (30/141) • placebo group: 32.2% (46/143) RR=0.59 (95% CI: 0.26-1.33, I^2=70%); p=0.20	Probiotics did not demonstrate a significant benefit in reducing UTI recurrence compared to placebo in premenopausal women	no study protocol <u>Funding</u> None. <u>Conflicts of interest</u> None.	1a RoB: low
D-mannose									
Kyriakides 2021 [66] 32972899	Systematic review n=8 studies (n=4 RCTs; n=2 prospective cohort studies; n=2 laboratory studies) Search date: up to Feb	We performed a systematic review to assess the effect of D-mannose in the prevention of rUTIs.	n=695 participants from 6 clinical studies <u>Mean age</u> 46 y (range 42–50)	D-mannose n=292	Control or antibiotic	**Results of the clinical trials (n=6)** **UTI-associated symptoms** n=5 studies (Kranjčec 2014, Porru 2014, Domenici 2016, Del Popolo 2018, Phé 2017) reported that D-mannose significantly decreased UTI-associated symptoms	D-mannose improved quality of life and significantly reduced recurrent UTIs in both catheter and non-catheter users. D-mannose was effective in reducing the incidence of recurrent UTIs and prolonging UTI-free periods, which consequently	no study protocol, inclusion and exclusion criteria not clearly defined, no additional hand search, complete search strategy not reported, no information if efforts were made to minimise error in the data extraction process, baseline characteristics for the 2 laboratory studies not reported, no risk of bias assessment, no funnel plot	1a - RoB: high

	2020					Palleschi 2017 Reported no difference between the nutraceutical (D-mannose, N-acetylcysteine and Morinda citrifolia fruit extract) vs. antibiotic groups **Time to recurrence** n=3 studies (Kranjčec 2014, Porru 2014, Domenici 2016) showed that the time to recurrence was significantly longer among patients who received D-mannose than for the comparative groups **Quality of life** Domenici 2016 • D-mannose was effective in reducing UTI incidence in a 6-mo period and consequently in increasing quality of life	increased quality of life. This review confirms the potential role of D-mannose as an alternative or supplementary strategy for rUTI treatment.	Funding Not reported Conflicts of interest The authors have nothing to disclose.	
Lenger 2020 [67] 32497610	Systematic review and meta-analysis n=8 studies	Our objective was to systematically review and combine data from published original literature	women (age of 18 y or older) receiving care in an outpatient setting for	D-mannose	Placebo, antibiotic, supplement or probiotic	**Recurrent UTI** *3 studies included in the meta-analysis* D-mannose vs. placebo/control (n=2 studies; Domenici 2016,	D-mannose appears protective for recurrent UTI (vs. placebo) with possibly similar effectiveness as antibiotics.	no information if efforts were made to minimise error in the data extraction process and the risk of bias assessment, high level of bias of the included studies was not	1a - RoB: high

	(n=2 RCTs, n=1 randomized cross-over trial, n=4 prospective cohort studies, n=1 retrospective cohort study) Search date: up to 15th Apr 2020	evaluating the effectiveness of D-mannose compared to other agents for rUTI prevention in adult women. Secondary objectives were to evaluate side effects and compliance with D-mannose use.	rUTI			Kranjčec 2014) • D-mannose: 16/125 • Placebo/control: 69/123 RR=0.23 (95% CI: 0.14-0.37; I^2=0%); p<0.0001 <u>D-mannose vs. antibiotic</u> (n=2 studies; Porru 2014, Kranjčec 2014) • D-mannose: 27/163 • Antibiotic: 76/163 RR=0.39 (95% CI: 0.12-1.25; I^2=88%): p=0.1126 **Adverse events** no significant side effects (n=3 studies, Porru 2014, Domenici 2016, Del Popolo 2018) <u>Kranjčec 2014</u> • D-mannose: 8/103 diarrhea (7.8%); no nausea, headache, skin rash, or vaginal burning • Nitrofurantoin: 27.2% reported adverse events: Diarrhea (n=10) Nausea (n=6), Headache (n=3), Skin rash (n=1), Vaginal burning (n=9) RR=0.276 (95% CI: 0.132–0.574); p<0.0001)	Overall, D-mannose appears well tolerated with minimal side effects - only a small percentage experiencing diarrhea.	sufficiently addressed <u>Del Popolo 2018</u> includes patients with neurogenic baldder patients with multiple sclerosis <u>Funding</u> Dr. Sutcliffe was supported by the Foundation for Barnes-Jewish Hospital, CTSA Grant UL1 TR002345, and the Alvin J. Siteman Cancer Center (P30 CA091842). Dr. Bertolet was supported through the National Institutes of Health Grant Number UL1TR001857. <u>Conflict of interest</u> The authors report no conflicts of interest.	

Estrogen									
Chen 2021 [68] 32564121	Systematic review and meta-analysis n=8 RCTs Search date: up to Dec 2019	The aim of this review was to evaluate current data and evidence to elucidate the efficacy of estrogen treatment as non-antimicrobial prophylaxis for rUTIs in postmenopausal women. Vaginal pH and hormone-associated adverse events were also analyzed to evaluate the safety of the treatment.	n=4702 postmenopausal women with rUTIs	Estrogen n=2367	Placebo n=2335	**rUTIs** <u>Vaginal estrogen vs. placebo</u> (n=5 RCTs, n=1936 patients) • Vaginal estrogen: 98/993 • Placebo: 227/934 RR=0.42 (95% CI: 0.30-0.59, I^2=64%); p<0.00001 <u>Oral estrogen vs. placebo</u> (n=3 RCTs; n=2766 patients) • Oral estrogen: 163/1374 • Placebo: 149/1392 RR=1.11 (95% CI: 0.92–1.35, I^2=0%); p=0.28 **Adverse events** • associated with vaginal estrogen therapy included vaginal discomfort, irritation, burning, and itching • Vaginal estrogen: 29/165 • Placebo: 7/159 RR=3.06 (95% CI: 0.79–11.90, I^2=55%); p=0.11	Compared with placebo, vaginal estrogen treatment could reduce the number of rUTIs and lower the vaginal pH in postmenopausal women.	no study protocol, complete search strategy not reported, no information if efforts were made to minimise error in the study selection process and risk of bias assessment, no funnel plot <u>Funding</u> None. <u>Conflict of interest</u> None.	1a - RoB: high

Dueñas-Garcia, 2016 [69]	Systematic review n=9 RCTs Search date: 1970-2015	The purpose of this systematic review was to evaluate and summarize pharmacological interventions evaluated in randomized clinical trials designed to prevent recurrent episodes of UTIs in postmenopausal women.	postmenopausal women with rUTI	pharmacological interventions	pharmacological interventions or placebo	**Topical Estrogen** (5 RCTs, n=596 patients) • Vaginal estrogen appeared to be inferior to continuous oral antibiotic suppression Adverse events • most common adverse effects involved local reactions with itching or burning with a range of 0% to 36% for treatment groups and placebo groups **Systemic Estrogen (estriol)** (2 RCTs, Cardozo 1998; Kirkengen 1992; n=112 patients) • Both studies showed no significant reduction in episodes of UTIs when compared with placebo Adverse events • Kirkengen 1992 reported no side effects • Cardozo 1998 reported breast tenderness and post-menopausal bleeding	This review supports the use of antibiotic suppression, vaginal estrogen, and oral lactobacillus for prevention of recurrent UTIs in postmenopausal women. However, the overall dearth of data suggests that this is an important but understudied population.	complete search strategy was not reported, no efforts were made to minimise error in: the study selection process, the data extraction and risk of bias assessment, no funnel plot <u>CAVE:</u> • the number of patients of the two estrogen studies amounts to 112 • some incorrectly assigned reference numbers <u>Funding</u> None. <u>Conflict of interest</u> None.	1a - RoB: high

						Antibiotics (n=3 RCTs, Zhong 2011; Raz 2003; Beerepoot 2012; n=491 patients) <u>Beerepoot 2012</u> No significant difference in outcome using sulfamethoxazole plus trimethoprim vs. vaginal lactobacilli (MD=2.9 vs. 3.3, p=0.42) <u>Zhong 2011</u> • continuous vs. intermittent dosing of various antibiotics • continuous group showed a higher number of UTIs over 1 year of follow-up (59.4% vs. 35.5%; p<0.05) • as well as a higher rate of side effects <u>Raz 2003</u> • nitrofurantoin vs. estriol pessary patients using nitrofurantoin suppression had fewer UTIs compared to estriol pessary users (48 vs. 124, p<0.0003).			

Vaccines									
Prattley, 2020 [70] 31806578	Systematic review n=17 studies (n=12 RCTs, n=2 prospective cohort studies, n=2 retrospective cohort studies, n=1 cross over trial) search date: up to Jul 2018	To systematically review the role of vaccines in the treatment of rUTIs, looking at efficacy, adverse events, and discontinuation from treatment.	n=3228 patients with rUTIs	Vaccine group (n=1970 participants) • Uromune • UroVaxom • Solco-Urovac • ExPEC4V	Comparison (n=1258 participants)	**Short term efficacy** (≤ 6 mo) Vaccince vs. placebo (n=12 studies) • Vaccine: 392/1048 • Placebo: 794/940; OR=0.17 (95% CI: 0.06–0.50, I^2=92%); p=0.001 **UroVaxom vs. placebo** OR=0.29 (95% CI 0.10–0.87) **Efficacy of Solco-Urovac with booster** • Vaccince: 37/75 • Placebo: 59/73; OR=0.23 (95% CI: 0.11-0.48, I^2=0%); p<0.0001 **Efficacy of Solco-Urovac without booster** • Vaccince: 54/72 • Placebo: 59/73; OR=0.71 (95% CI: 0.32-1.58, I^2=0%); p=0.41 **Long term efficacy** (>6	Vaccines seem to have a short-term role in the prevention of recurrent urinary tract infections with tolerable side effects.	no study protocol, complete search strategy not reported, no additional hand search, no information if efforts were made to minimise error in the study selection process and risk of bias assessment, no funnel plot, unclear if a risk of bias assessment for the cross-over trial was carried out <u>CAVE:</u> • Table 4 and 5 are the same • The tables with the risk of bias results of the cohort studies and the overall safety profile are missing *Solco-Urovac was the only vaccine to demonstrate a lack of heterogeneity* <u>Funding</u> None. <u>Conflict of interest</u>	1a - RoB: high

						mo) Vaccince vs. placebo (n=8 studies) • Vaccine: 343/1032 • Placebo: 759/1000; OR=0.20 (95% CI: 0.06–0.59, I^2=93%); p=0.004 **UroVaxom vs. placebo** (>6 mo) (n=7 studies) • Vaccince: 255/604 • Placebo: 338/582; OR=0.36 (95% CI: 0.14-0.92, I^2=91%); p=0.03 **Adverse events** the adverse effect profile for each individual vaccine is reportedly good with no severe adverse events being recorded for any vaccine <u>Withdrawal/exclusion due to adverse events</u> (n=11, n=2 Uromune, n=9 UroVaxon) • reasons unclear (n=7) • rash, incompatibility with lifestyle, gastrointestinal upset,		None.	

						and nausea and erythema (n=4)			
Nickel 2020 [71] 33626320	Systematic review n=5 (n=2 retrospective cohort studies; n= 3 prospective cohort studies) Literature search: Jan 2010-Mar 2020	We systemically reviewed the role of Uromune in the prevention of rUTI in an attempt to understand its potential role for Canadian women suffering from this condition.	n=1907 women with uncomplicated rUTI	Uromune (n=1408)	antibiotic prophylaxis (n=499)	**UTI-free rate % (n)** <u>Lorenzo-Gómez et al (2013)</u> Uromune (3 mo treatment) [n=159 subjects] vs. SMX/TMP (6 mo treatment) [n=160 subjects] At 3 mo study period, • Uromune: 63.5% (101) • SMX/TMP: 5.6% (9) p<0.0001 At 9 mo study period, • Uromune: 56.6% (90) • SMX/TMP: 2.5% (4) p<0.0001 15 mo study period, • Uromune: 34.6% (55) • SMX/TMP: 0 (0) p<0.0001 <u>Lorenzo-Gómez et al (2015)</u> Uromune (3 mo treatment) [n= 360 subjects] vs. SMX/TMP or nitrofurantoin (6 mo treatment) [n=339 subjects] 12 mo study period	Although these findings require confirmation in currently active, prospective clinical studies, including a randomized placebo-controlled trial, Uromune may be an alternative to antibiotics to prevent rUTI in Canadian women. The novel sublingual spray vaccine, Uromune, appears to be a safe and effective alternative to repeated or long-term dosing of antibiotics to prevent rUTI in Canadian women.	no protocol, no information about potential /inclusion exclusion criteria concerning the language of the publications, complete search strategy was not reported, no information if the data selection process was conducted independently by the two authors, no detailed information if two independent authors conducted the risk of bias assessment, included studies show a significant potential for reporting bias *One presented study included women with uncomplicated and complicated rUTI (53.6% of 166 participants was categorized as uncomplicated UTI)* <u>Funding</u> Not reported. <u>Conflict of interest</u> Dr. Nickel has been a	2a - RoB: high

						(Follow-up period begins after completion of vaccination) Uromune: 90.3% (325) SMX/TMP or nitrofurantoin: 0 (0) p<0.0001 <u>Yang et al (2018)</u> Uromune (3 mo treatment; n=75 subjects) 12 mo study period: 78.7% (59) <u>Ramírez-Sevilla et al (2019)</u> Uromune (3 mo treatment; n=648 subjects) 3 mo study period: 45.4 (294) 6 mo study period: 32.7 (212) <u>Carrión-López et al (2020)</u> Uromune (3 mo treatment; n=166 subjects) 3 mo study period: 74.4 (124) 6 mo study period:		consultant for Alivio, Farr Labs, Inmunotek, Kanglaite, MicroGenDx, Redleaf Medical, Seikagaku Corp, TEVA, Urogen Pharma, and Valensa Int; has participated in scientific studies/trials supported by CIHR, Inmunotek, MicroGenDx, NIH, and Redleaf Medical; and is the Editor of AUA Update Series. Dr. Saz-Leal is an employee of Inmunotek. Dr. Doiron reports no competing personal or financial interests related to this work.	

						68.1(113) 12 mo study period: 52.4 (87) 24 mo study period: 44.5 (43/96) Those with uncomplicated UTIs had fewer rUTI after vaccination compared to those with complicated UTIs: coefficient β 0.40 (95% CI: -0.8- -0.14) p=0.015 **Adverse events** The overall safety data from these five studies did not indicate any major safety concerns. <u>Lorenzo-Gómez et al (2013) & Lorenzo-Gómez et al (2015)</u> No adverse events reported <u>Yang et al (2018)</u> • one serious adverse event (allergic reaction) • seven minor adverse events (post-nasal drip, stinging around mouth, pruritus over old BCG scar, pruritus over abdomen, intermittent abdominal pain, mild nausea, and			

						exacerbation of underlying asthma) were reported <u>Ramírez-Sevilla et al (2019)</u> minor side effects: • dry mouth (8 subjects) • gastritis (4 subjects) • general illness (4 subjects) <u>Carrión-López et al (2020)</u> minor side effects glossitis (2 subjects) and one flareup of rheumatoid arthritis, which was not believed to be associated with treatment			
Aziminia 2019 [72] 30378242	Systematic review and meta-analysis n=10 RCTs search date: up to Jan 2018	To systematically review the evidence regarding the efficacy of vaccines or immunostimulants in reducing the recurrence rate UTIs.	n=1537 adult (>18 years) male and female participants with a history of recurrent UTIs, as defined by the study authors, were eligible.	vaccines or immunostimulants: • Urovac • ExPEC4V • Uro-Vaxom	Placebo	**UTI recurrence rate** (n=10 RCTs) Vaccine vs. control • Vaccine: 354/775 • Control: 440/720 RR=0.74 (95% CI: 0.67-0.81, I^2=84%); p<0.001 *low quality of evidence* **UTI recurrence rate at 3 mo, Uro-Vaxom vs. placebo** (n=4 RCTs) • Uro-Vaxom: 127/297	While there is evidence for the efficacy of vaccines in patients with recurrent UTIs, significant heterogeneity amongst these studies renders interpretation and recommendation for routine clinical use difficult at present.	no information if efforts were made to minimise error in the data collection process, no funnel plot *lack of subgroup analysis, including no differentiation between male and female participants* *pregnant women and patients with uncontrolled diabetes mellitus were*	1a RoB: low

						• Placebo: 187/294 RR=0.67 (95% CI: 0.57-0.78, I^2=92%); p<0.001 *low quality of evidence* **UTI recurrence rate at 6 mo, Uro-Vaxom vs. placebo** (n=6 RCTs) • Uro-Vaxom: 246/583 • Placebo: 305/565 RR=0.78 (95% CI: 0.69-0.88, I^2=86%); p<0.001 *low quality of evidence* **All UTI recurrence rate at 20 weeks, Urovac vs. placebo** (n=5 RCTs) • Urovac: 88/147 • Placebo: 92/116 RR=0.75 (95% CI: 0.63-0.89, I^2=0%); p<0.001 *low quality of evidence* **Incidence of AEs, vaccine vs. placebo** (n=5 RCTs) • Vaccine: 326/690 • Control: 323/688 RR=1.03 (95% CI: 0.95-1.13, I^2=4%); p=0.48 *low quality of evidence*		*excluded* <u>Funding</u> None. <u>Conflict of interest</u> None.	
Antibiotics									
Jent 2022	Systematic review and	The objective of this systematic	men or women aged	antibiotic prophylaxis	placebo or a comparator	**Antibiotic prophylaxis for rUTI**	For the time being, this meta-	no information if efforts were made to minimise	1a

[73] 35899289	meta-analysis n=23 RCTs Search date: October 13, 2020	review and meta-analysis was to systematically assess the efficacy and safety of antibiotic prophylaxis for the prevention of RUTI in adults.	≥12 y with either ≥2 episodes of lower UTI within the last 6 mo or ≥3 in the course of the past y		antibiotic	<u>Antibiotics vs. placebo</u> (n=11 studies; 746 patients) • Antibiotics: 33/400 (8%) • Placebo: 225/346 (65%) RR=0.15 (95% CI: 0.08–0.29, I^2=64%); p<.001 overall risk reduction: 55% NNT=1.81 (95% CI: 1.67– 2.17) <u>Antibiotics controlled excluding cinoxacin vs. placebo</u> (n=6 studies; 520 patients) RR=0.11 (95% CI: 0.07–0.17); p<.001 overall risk reduction: 61% NNT=1.64 <u>Nitrofurantoin vs. other antibiotic</u> (n=7 studies; 486 patients) RR=1.01 (95% CI: 0.74–1.37; I^2=64%); p=0.97 <u>TMP (± SMZ) vs. other antibiotic</u> (n=4 studies, 176 patients) RR=1.34 (95% CI: 0.89–2.03); p=0.16	analysis confirms that antibiotic prophylaxis is an effective prevention strategy for rUTIs and that a number of antimicrobial substances can be used with similar likelihood of success. The prophylactic effect seems, though, to be limited to the period of antibiotic intake, and the effectiveness of antibiotic prophylaxis should be weighed against concerns for resistance selection.	error in the data selection process, heterogeneity was not presented for all analyses <u>CAVE</u>: • Appendix figure 7 shows a different number of patients considered in the pooled analysis for Nitrofurantoin vs. another antibiotic than presented in table 1 *only two studies also allowed the inclusion of men* <u>Funding</u> This study had no external funding source; article access fees were covered by the department. <u>Conflict of interest</u> Dr. Trautner's work is supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and the Center for Innovations in Quality, Effectiveness and	RoB: low

						Norfloxacin vs. another antibiotic (n=3 studies, 239 patients) RR=1.17 (95% CI: 0.43–1.70); p=0.66 Continuous vs. intermittent (n=3 studies, 564 patients) RR=1.78 (95% CI: 0.62–5.09); p=0.28 Intermittent vs. placebo (n=1 study, 25 patients) RR=0.15 (95% CI: 0.04–0.55); p=0.004 **Adverse events** Non-severe adverse events with antibiotic prophylaxis RR=3.42 (95% CI: 2.16–5.43; NNH=7.89) Severe adverse events with antibiotic prophylaxis vs. placebo RR=3.22 (95% CI: 1.32–7.89; NNH=30.97) • most commonly reported adverse events with antibiotic prophylaxis:		Safety (CIN 13-413).	

						○ gastrointestinal complaints (including nausea) and oral or vaginal candidiasis Allergic reactions occurred with the following antibiotics: • norfloxacin (5 patients), cinoxacin (3) • nitrofurantoin (7) • trimethoprim-sulfamethoxazole/trimethoprim (2). Skin rashes were described with: • cinoxacin (4), • nitrofurantoin (2) • trimethoprim-sulfa-methoxazole/trimethoprim (1) • cephalexin (1) • fosfomycin (1) • a nonidentifiable antibiotic (5) • placebo (2) Neither renal insufficiency nor *C. difficile* enterocolitis was mentioned as a possible adverse event in the included studies, also suggesting underreporting of AEs.			

Ahmed 2017 [74] 28554926	Systematic review and meta-analysis n=3 RCTs Literature search: up to 2016 Recruitment countries: Croatia, Israel, Netherlands	To determine the clinical effectiveness and safety of long-term antibiotic therapy for preventing recurrent UTIs in older adults.	n= 534 postmenopausal women with rUTI	Long-term antibiotic therapy (defined as antibiotic dosing for at least 6 mo)	Non-antibiotic intervention • vaginal oestrogens (n=150) • oral lactobacilli (n=238) • D-mannose powder (n=94)	**Frequency of UTI recurrences during the prophylaxis period** *Pooled analysis* <u>Antibiotic vs. non-antibiotic</u> (n=3 RCTs) • Antibiotic: 97/228 • Non-antibiotic: 138/254 RR=0.76 (95% CI: 0.61-0.95; I^2=20%); p=0.29 *Narrative analyses* Beerepoot, 2012 <u>480 mg trimethoprim-sulfamethoxazole vs. capsule of lactobacilli for 12 mo (n=1)</u> Microbiologically-confirmed UTI episodes per patient-year • Trimethoprim-sulfamethoxazole:1.2 • Capsule of lactobacilli: 1.8 MD=0.6 episodes (95% CI: 0.0-1.4); p=0.02 Microbiologically confirmed UTI during prophylaxis • Trimethoprim-sulfamethoxazole: 49.4% • Capsule of lactobacilli: 62.9%	Findings from three small trials with relatively short follow-up periods suggest long-term antibiotic therapy reduces the risk of recurrence in postmenopausal women with recurrent UTI. We did not identify any evidence to inform several clinically important scenarios including, benefits and harms in older men or frail care home residents, optimal duration of prophylaxis, recurrence rates once prophylaxis stops and effects on urinary antibiotic resistance.	**KSR-Bewertung** (*https://ksrevidence.com/index.php?recordID=KSRA35758#recordpage*) Studies were restricted based on publication format and language, meaning relevant studies may have been missed. Only a single author was involved in study screening and data extraction, meaning that bias may have been introduced. Insufficient study characteristics were provided, making it challenging for the reader to interpret results. Study heterogeneity was high for adverse event outcomes. *Slightly differing information on the literature search period: abstract till August 2016 and in the method part it is stated March 2016* <u>Funding</u> This report is independent research arising from the National Institute of Health Research (NIHR) Doctoral Research Fellowship awarded to Haroon	1a - RoB: high

						RR=0.79 (95% CI: 0.63-1.0) Microbiologically confirmed UTI episodes 3 mo after cessation of prophylaxis • Trimethoprim-sulfamethoxazole:0.1 • Capsule of lactobacilli: 0.2 MD=0.0 (95% CI: -0.1-0.3); p=0.64 Raz, 2003 <u>nitrofurantoin (100g) for 9 mo vs. vaginal oestrogen pessaries</u> UTI during prophylaxis • Nitrofurantoin: 42.3% • Vaginal oestrogen pessaries: 64.6% RR 0.65 (95% CI: 0.8-0.90) Kranjčec, 2014 <u>Nitrofurantoin (50g) for 6 mo vs. D-mannose powder (2g)</u> UTI during prophylaxis • Nitrofurantoin: 24% • D-mannose: 19% RR=1.24 (95% CI: 0.57-		Ahmed, and supported by Health and Care Research Wales (HCRW). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS Wales, HCRW or the Welsh Government. The funders had no role in the design or preparation of this manuscript. <u>Conflict of interest</u> None declared.	

						2.69) **Adverse events** *Pooled analysis* Mild adverse events (n=3 RCTs) • Antibiotic: 118/242 • Non-antibiotic: 107/261 RR=1.52 (95% CI: 0.76- 3.03, I^2=86%); p=0.23 Serious adverse events resulting in treatment withdrawal (n=2 RCTs) • Antibiotic: 21/200 • Non-antibiotic: 22/209 RR=0.90 (95% CI: 0.31-2.66, I^2=67%); p=0.85 **Effect of long-term antibiotic therapy on bacterial resistance** <u>Beerepoot, 2012</u> % of urinary and faecal E coli isolates that were resistant to trimethoprim–sulfamethoxazole, trimethoprim and amoxicillin:			

						• baseline: 20%–40% • after 1 mo of treatment with trimethoprim–sulfamethoxazole: 80%–95%			
Köves 2017 [30] 28754533	Systematic review and meta-analysis n=50 studies (1 RCT on women with rUTI treated for asymptomatic bacteriuria) Search date: Jan 2000-Nov 2016	To synthesise evidence about benefits and harms of treating asymptomatic bacteriuria in relevant patient groups	*In the following one identified study encompassing patients with rUTIs treated for ABU is considered (Cai 2012)* n=673 women (between 18-40 y of age) with asymptomatic bacteriuria and rUTI	Antibiotic (n=361)	No treatment (n=312)	**Recurrence at 1 y follow-up** (n=1 RCT, Cai 2012; data extracted from the original paper) antibiotic treatment vs. no treatment • Antibiotic: 169/361 (73.1%) • No treatment: 41/312 (14.7%) RR=3.17 (95% CI, 2.55–3.90; p< .0001)	**Antibiotics**: No evidence of benefit for patients with recurrent urinary tract infection (UTI). Asymptomatic bacteriuria can play a protective role in preventing recurrent UTIs	CAVE: Köves et al 2017 made mistakes in the data extraction process. The values of Supplementary Table 1 and the original study of Cai 2012 are mixed up. Moreover, the reported RR=0.28 (95% CI: 0.21–0.38) does not correspond to the RR at 1 y in the original paper RR=3.17 (95% CI, 2.55–3.90; p< .0001) Funding None. Conflict of interest None.	*For the subgroup of patients with rUTI:* 1a - RoB: high
Muller 2017 [75] 27542332	Systematic review and meta-analysis	To assess the efficacy and safety of Nitrofurantoin in the prophylaxis of	n=3052 human patients of all ages and both genders in all	Oral nitrofurantoin at any dose and any	Placebo, no treatment, a different drug, Nitrofurantoin at a	*In the following only the results for adult patients with rUTI are presented* **Long-term prophylaxis**	When used for the prevention of UTI, nitrofurantoin's clinical efficacy appears	no study protocol, complete search strategy not reported, no additional hand search, no funnel plot	1a - RoB: high

	n=26 controlled clinical trials Literature search: 1946-2015 Recruitment countries: Australia, Belgium, Chile, Croatia, Denmark, Finland, Germany, India, Israel, United Kingdom, United States of America	UTI.	settings	duration for primary or secondary prophylaxis of UTI	different dose, frequency, or duration	(subgroup analyses) <u>Nitrofurantoin vs. quinolones</u> (n=3) • Nitrofurantoin: 25/84 • Quinolones: 15/102 RR=2.26 (95% CI: 0.73-7.00, I^2=61%); p=0.16 <u>Nitrofurantoin vs. methamine hippurate</u> (n=2) • Nitrofurantoin: 24/67 • Methamine hippurate: 66/129 RR=0.6 (95% CI: 0.43-0.85, I^2=0%); p=0.004 **Adverse events (long-term use)** <u>Nitrofurantoin vs. quinolones</u> (n=3) • Nitrofurantoin: 24/112 • Quinolones: 18/118 RR=1.37 (95% CI: 0.79-2.36, I^2=0%); p=0.26	equivalent to that of other antibiotics. Although its non-severe toxicity profile appears somewhat less favorable than those of comparators, severe toxicity is rare. Clinicians should be aware, however, that the risk of severe toxicity seems to increase with the duration of nitrofurantoin prophylaxis.	<u>Funding</u> This work was supported in part by the European Commission under the Life Science Health Priority of the 7th Framework Programme (AIDA grant agreement 278348). <u>Conflict of interest</u> The authors have no conflicts of interest to declare.	

						<u>Nitrofurantoin vs. methamine hippurate</u> (n=2) • Nitrofurantoin: 24/67 • Methamine hippurate: 9/129 RR=4.22 (95% CI: 2.06-8.67, I^2=0%); p<0.0001 <u>Nitrofurantoin vs. trimethoprim/sulfamethoxazole</u> (n=1) • Nitrofurantoin: 1/6 • Trimethoprim/ sulfamethoxazole: 1/13 RR=2.17 (95% CI: 0.16-19.10); p=0.56			
Dueñas-Garcia, 2016 [69]	Systematic review n=9 RCTs Search date: 1970-2015 Recruitment	The purpose of this systematic review was to evaluate and summarize pharmacological interventions evaluated in randomized clinical trials designed to prevent recurrent episodes of	postmenopausal women with rUTI	pharmacological interventions	pharmacological interventions or placebo	**Topical Estrogen** (5 RCTs, n=596 patients) • Vaginal estrogen appeared to be inferior to continuous oral antibiotic suppression Adverse events • most common adverse effects involved local reactions	This review supports the use of antibiotic suppression, vaginal estrogen, and oral lactobacillus for prevention of recurrent UTIs in postmenopausal women. However, the overall dearth of data suggests that this is an	complete search strategy was not reported, no efforts were made to minimise error in: the study selection process, the data extraction and risk of bias assessment, no funnel plot <u>CAVE:</u> • the number of patients of the two	1a - RoB: high

	countries: China, Israel, Netherlands, United Kingdom, Norway, Italy	UTIs in postmenopausal women.				with itching or burning with a range of 0% to 36% for treatment groups and placebo groups **Systemic Estrogen (estriol)** (2 RCTs, Cardozo 1998; Kirkengen 1992; n=112 patients) • Both studies showed no significant reduction in episodes of UTIs when compared with placebo Adverse events • Kirkengen 1992 reported no side effects • Cardozo 1998 reported breast tenderness and post-menopausal bleeding **Antibiotics** (n=3 RCTs, Zhong 2011; Raz 2003; Beerepoot 2012; n=491 patients) <u>Beerepoot 2012</u> No significant difference in outcome using sulfamethoxazole plus trimethoprim vs. vaginal	important but understudied population.	estrogen studies amounts to 112 • some incorrectly assigned reference numbers <u>Funding</u> None. <u>Conflict of interest</u> None.	

						lactobacilli (MD=2.9 vs. 3.3, p=0.42) <u>Zhong 2011</u> • continuous vs. intermittent dosing of various antibiotics • continuous group showed a higher number of UTIs over 1 y of follow-up (59.4% vs. 35.5%; p<0.05) • as well as a higher rate of side effects <u>Raz 2003</u> • nitrofurantoin vs. estriol pessary patients using nitrofurantoin suppression had fewer UTIs compared to estriol pessary users (48 vs. 124, p<0.0003).			
Price 2016 [76] 27457111	Systematic review and meta-analysis n=12 RCTs Search	The objective of this review was to provide current pooled estimates of randomized control trials comparing the effects of nitrofurantoin vs other agents	n=1063 women with recurrent UTI aged 18-85 y who are receiving care in an outpatient setting	Nitrofurantoin	Trimethoprim, cefaclor, sulfamethoxazole/trimethoprim, cefixime, vaginal estrogen, estrogen of all types, cranberry	**Clinical cure** <u>Nitrofurantoin vs. other agents</u> Pooled analysis (9 RCTs, n= 673 patients) RR=1.06 (95% CI: 0.89-1.27, I^2=65%)	Nitrofurantoin had similar efficacy but a greater risk of adverse events than other prophylactic treatments. Balancing the risks of adverse events, particularly	Forest plots were not presented for the separate analyses comparing nitrofurantoin with the different types of antibiotic agents *A large number of the included trials did not have a blinded design, and*	1a RoB: low

	period: up to Jan 31th, 2015 Recruitment countries: United States, England, Finland, Denmark, Germany, Peru, Poland, and Israel	in reducing recurrent urinary tract infections in adult, nonpregnant women and assess relative adverse side effects.			supplements, bladder instillations, or fosfomycin	**Microbiological cure** <u>Nitrofurantoin vs. other agents</u> Pooled analysis (12 RCTs, n=1063 patients) RR=1.06, 95% CI: 0.90-1.26, I^2=76%) • No significant difference was found regarding microbiological success between patients treated with nitrofurantoin vs. those treated with comparator(s) in the separate analysis comparing nitrofurantoin with each of the different types of antibiotic agents used <u>Short prophylaxis (daily 6 mo nitrofurantoin regimens)</u> Nitrofurantoin vs. other agents 5 RCTs, n=305 patients) RR=0.93 (95% CI: 0.76-1.14, I^2=56%) <u>Longer prophylaxis</u>	gastrointestinal symptoms, with potential benefits of decreasing collateral ecological damage should be considered if selecting nitrofurantoin.	*limited information regarding allocation concealment was reported. Therefore, selection bias might have influenced the findings.* <u>CAVE:</u> *The majority of the trials were old (published between 1977 and 2007).* *In an era of increasing antibiotic resistance, this may compromise the extrapolation of the meta-analysis findings in current outpatient practice.* *3 studies enrolled men in addition to women (less than 20% male) and 9 were undertaken exclusively in female patients.*	

						<u>(regimes greater than 6 mo)</u> Nitrofurantoin vs. other agents 7 RCTs, n=758 patients) RR=1.01 (95% CI: 0.90-1.13, I^2=84%) **Microbiological infection during prophylaxis** <u>Nitrofurantoin vs. comparator(s)</u> Pooled analysis (10 RCTs, n=897 patients) RR=1.08, 95% CI: 0.66-1.76, I^2=71%) • There was no significant difference found between patients treated with nitrofurantoin vs. those treated with comparator(s) in the separate analyses regarding microbiological infection during prophylaxis **Adverse events** <u>Nitrofurantoin vs.</u>			

						trimethoprim Pooled analysis (3 RCTs, n=265 patients) RR=2.03, 95% CI: 1.12-3.70, I^2=5%) Nitrofurantoin vs. methenamine hippurate Pooled analysis (2 RCTs, n=244 patients) RR=4.17, 95% CI: 2.11-8.25, I^2=0%) Nitrofurantoin vs. other agents Pooled analysis (10 RCTs, n=948 patients) RR=1.83, 95% CI: 1.18-2.84, I^2=54%) The majority of these adverse events were gastrointestinal symptoms **Study withdrawal because of adverse events** Nitrofurantoin vs. other agents Pooled analysis (10			

						RCTs, n=1002 patients) RR=2.14, 95% CI: 1.29-3.56, I^2=8%) • No significant difference was found in study withdrawals because of adverse events in the separate analyses			
Intravesical hyaluronic acid and chondroitin sulfate									
Reddy 2022 [77] 34982189	Systematic review n=13 studies (n=2 RCTs, n=4 prospective studies, n=6 retrospective studies, and n=1 study that used both retrospective and prospective analysis) Search date: to April 2021 Recruitment	The aim of this systematic review is to recapitulate all available data on the efficacy of IVAs in the management of uncomplicated RUTIs.	n=764 female and male patients over the age of 18 with uncomplicated rUTI <u>Median age</u> 53.1 y (27-80 y)	intravesical administration of antimicrobial treatment (HA+ chondroitin sulfate; gentamicin)		**Overall** • reduction in UTI frequency in 12/13 studies • 10/13 studies showing a statistically significant decrease **gentamicin IVA** (n=3 studies; Chernyak 2020; Stalenhoef 2019; Abrams 2017) • 3/3 gentamicin studies (87 participants) reported decreases in UTI recurrence after completion of the IVA instillations compared with before IVA <u>Chernyak 2020</u> Reduction mean UTI frequency:	The IVAs gentamicin and hyaluronic acid with chondroitin sulphate demonstrated efficacy in the management of uncomplicated rUTIs, mostly in women.	no study_protocol, no clear outcome definition: "to recapitulate all available data", complete search strategy not reported, no information if efforts were made to minimise error in the data selection process and risk of bias assessment, no funnel plot <u>Funding</u> No funds, grants, or other support was received. <u>Conflicts of interest</u> None. *Mostly women*	2a - RoB: high

	countries: Austria, Greece, Italy, Netherlands, United Kingdom					2.5 to 1.5 UTIs (p=0.025) <u>Stalenhoef 2019</u> Reduction mean UTI frequency: 4.8 to 1.2 (p<0.001) **hyaluronic acid (n=10 studies)** • 9/10 studies with IVA of HA and chondroitin sulfate,(674 participants) reported a decrease in UTI recurrence Eleven participants reported gentamicin-resistant infections after IVA treatment.			
Goddard 2018 [78] 29181550	Systematic review and meta-analysis n=8 studies • n=2 RCTs • n=6 nonrandomized studies	The objective was to assess the efficacy of intravesical hyaluronic acid and chondroitin sulfate, alone or in combination, for recurrent urinary tract infections in adult female patients using a systematic	n=800 adult female patients with documented history of rUTI and who received HA, CS or HA+CS	intravesical hyaluronic acid (HA), chondroitin sulfate (CS) or HA+CS	Placebo, standard of care prophylaxis, retrospective patient review	**mean UTI rate per patient-y** (n=7 RCTs) • HA/HA+CS vs. control MD=-2.56 (95% CI: -3.86-1.26, I^2=98.8%); p<0.001 **time to first UTI recurrence (in days)** (n=6 RCTs) • HA/HA+CS vs.	HA ± CS appears to reduce the rate of UTI and increase the time to recurrence in women with rUTI.	no information if efforts were made to minimise error in the data selection process and risk of bias assessment *The high heterogeneity among studies and the likelihood of publication bias are limitations that may lessen the validity and robustness of the*	2a - RoB: high

	Search date: up to November 2016	review and meta-analysis.				control MD=130.05 days (95% CI: 5.84-254.26, I^2=99.9%); p=0.04 **Percentage of patients with UTI recurrence during follow-up** (n=3 RCTs) • HA+CS vs. control RR=0.75 (95% CI: 0.57-0.99; I^2=75,2%); p=0.043 **Number of 3-day voids and SF-36 outcomes** did not show significant differences between the HA+CS and control groups		*results.* <u>Conflict of interest</u> None. <u>Funding</u> The funding for this study was provided by IBSA Institut Biochimique SA, Switzerland.	
Methenamine salts									
Bakhit 2021 [79] 34001538	systematic review and meta-analysis n=6 RCTs Search date: up to 2020	To systematically review RCTs of adult women in the community with a history of recurrent UTIs and who use methenamine hippurate prophylactically.	n=557 adult women (aged ≥18 y) with a history of recurrent or confirmed UTIs	methenamine hippurate	Placebo/ no treatment or any antibiotic	**Prevention of UTI** (n=6 studies, n=557 participants) *Patients remaining asymptomatic after 6 or 12 mo:* <u>Methenamine hippurate vs. antibiotics</u> (n=3 RCTs) • Methenamine Hippurate: 37/124 • Antibiotic: 49/106 RR=0.65 (95% CI: 0.40-	There is insufficient evidence to be certain of the benefits of methenamine hippurate to prevent UTI.	*The included studies also featured: considerable clinical and statistical heterogeneity; poor reporting of bacterial resistance as one of the harms of using antibiotics in trials with an antibiotic arm; and general unclear risk of bias.* <u>Funding</u> No funding or other material support was sought or received to	1a RoB: low

						1.07; I^2=49%); p=0.09 <u>Methenamine hippurate</u> <u>vs. control</u> (n=3 RCTs) (Placebo or antiseptic iodine perineal wash) • Methenamine Hippurate: 15/39 • Antibiotic: 14/33 RR=1.0 (95% CI: 0.27-3.66; I^2= 78%); p=1.00 *Patients remaining abacteriuric after 12 mo:* <u>Methenamine hippurate vs.</u> <u>any antibiotic</u> (n=2 RCTs) • Methenamine Hippurate: 53/81 • Antibiotic: 51/63 RR=0.80 (95% CI: 0.62-1.03, I^2=23%); p=0.08 *Number of symptomatic UTI episodes after 6 or 12 mo:* <u>Methenamine hippurate</u> <u>vs. any antibiotic</u> (n=2 RCTs) RR=1.95 (95% CI: 0.87-4.38. I^2=82%); p=0.10 <u>Methenamine hippurate</u> <u>vs. placebo or antiseptic</u>		perform this work specifically. <u>Conflict of interest</u> The authors have declared no competing interests.	

						iodine perineal wash) (n=2 RCTs) RR 0.56 (95% CI: 0.13-2.35, I^2=93%); p=0.42 *Number of bacteriuric episodes after 12 mo:* Methenamine hippurate vs. any antibiotic (n=2 RCTs) RR 2.09 (95% CI: 0.72-6.09, I^2=71%); p=0.18 **Adverse events** The most common adverse events reported in all studies were nausea, headache, and abdominal pain Methenamine hippurate vs. antibiotic (n=3 RCTs) • methenamine hippurate:19/128 • any antibiotic: 30/127 OR=0.77 (95% CI: 0.11-5.46; I^2=87%), p=0.79 Methenamine hippurate vs. placebo or antiseptic iodine perineal wash (n=2 RCTs) • methenamine hippurate:6/55 • any antibiotic: 2/27			

						OR=1.32 (95% CI: 0.23-7.77, I^2=0%); p=0.76 <u>Methenamine hippurate vs. any comparator (n=5 RCTs)</u> • methenamine hippurate: 25/183 • any antibiotic: 32/154 OR=0.89 (95% CI: 0.21-3.67, I^2=76%); p=0.87			
Escherichia coli									
Taha Neto 2016 [80] 26601727	systematic review with meta-analysis n=5 RCTs (double blinding studies) studies included published between 1985-2005	To evaluate the efficacy of Escherichia coli extract (OM-89) in the prophylaxis of recurrent uncomplicated urinary tract infection (UTI) through a contemporary systematic review and meta-analysis.	n=794 patients	OM-89 group n=396	control group n=392	<u>Bacteriuria at 3 mo (n=3 RCTs)</u> • OM-89 group: 18.4% (29/157) • control group: 45.7% (70/153) OR=0.28 (95% CI: 0.17, 0.46, I^2=78%); p<0.00001 <u>Bacteriuria at 6 mo (n=3 RCTs)</u> • OM-89 group: 13.2% (21/159) • control group: 29.4% (45/153) OR=0.36 (95% CI: 0.20-0.65, I^2=41%); p=0.0007 <u>Dysuria at 6 mo (n=5 RCTs)</u> • OM-89 group: 7.5% (29/385) • control group:	Current literature on prospective randomized controlled trials evaluating the use of oral OM-89 vaccine in the recurrent urinary tract infection prophylaxis is of low quality, limited to the first six mo only and with variable definition of bacteriuria and UTI. Although all studies show benefit in favor of vaccine, no robust trial was identified, resulting in a high heterogeneity in the data analyzed.	no study protocol, inclusion criteria for patients and search date not reported, complete search strategy not reported (noticeably few hits), no information if efforts were made to minimise error in the study selection process, data collection process and risk of bias assessment, study characteristic of the included studies not reported, 10 papers excluded because of poor quality (references and bias assessment not reported), results of sensitivity analysis not shown <u>Funding</u>	1a - RoB: high

						18.9% (73/385) OR=0.35 (95% CI: 0.22-0.55, I^2=0%); p<0.00001 <u>Acute cystitis at 6 mo (n=4 RCTs)</u> • OM-89 group: 45% (145/322) • control group: 65.4% (212/324) OR=0.43 (95% CI: 0.31-1.30, I^2=77%); p<0.00001		Not reported. <u>Conflict of interest</u> Not reported.	
Vitamin D									
Deng 2019 [81] 30814089	Systematic review and meta-analysis n=9 studies •1 RCT (n=1) •case control (n=6) •cross-control (n=2) Search date: up to march 2018	Whether or not Vitamin D deficiency is associated with UTI.	n=1921 participants •580 patients with UTI •1341 without UTI	insufficient Vitamin D	sufficient Vitamin D	**Relationship between insufficient Vitamin D and risk of UTI** (n=7 studies) SMD=-1.647 (95% CI: -2.692 -0.602); p<0.001 **Relationship between insufficient Vitamin D and risk of UTI** (n=8 studies) OR=3.01 (95% CI: 2.31–3.91); p<0.001 The reviewed studies showed limited evidence of heterogeneity (I^2=49.5%; P=0.054).	Our results showed that a deficiency in Vitamin D may increase the risk of UTI. More clinical trials and studies are needed to determine the effects of Vitamin D supplements on the prevention of UTIs. According to these findings, healthcare providers should encourage the public to follow the guidelines for the daily intake of Vitamin D.	no study protocol, the search strategy does not include MeSH-Terms, no risk of bias assessment *Four studies focused on the association of Vitamin D levels and UTI in children, while three studies investigated the* *association in adults.* <u>Funding</u> Not reported. <u>Conflict of interest</u> Not reported.	2b - RoB: high

	Asia, Europe								

Schlüsselfrage Welche Antibiotika sind zur Langzeitprävention geeignet?									
Referenz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Intervention**	**Kontrolle**	**Ergebnisse**	**Schlussfolger-ungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Jent 2022 [73] 35899289	Systematic review and meta-analysis n=23 RCTs Search date: October 13, 2020	The objective of this systematic review and meta-analysis was to systematically assess the efficacy and safety of antibiotic prophylaxis for the prevention of RUTI in adults.	men or women aged ≥12 y with either ≥2 episodes of lower UTI within the last 6 mo or ≥3 in the course of the past y	antibiotic prophy-laxis	placebo or a comparator antibiotic	**Antibiotic prophylaxis for rUTI** <u>Antibiotics vs. placebo</u> (n=11 studies; 746 patients) • Antibiotics: 33/400 (8%) • Placebo: 225/346 (65%) RR=0.15 (95% CI: 0.08–0.29, I^2=64%); p<.001 overall risk reduction: 55% NNT=1.81 (95% CI: 1.67– 2.17) <u>Antibiotics controlled excluding cinoxacin vs. placebo</u> (n=6 studies; 520 patients) RR=0.11 (95% CI: 0.07–0.17); p<.001 overall risk reduction: 61% NNT=1.64 <u>Nitrofurantoin vs. another antibiotic</u> (n=7 studies; 486 patients) RR=1.01 (95% CI: 0.74–1.37; I^2=64%); p=0.97	For the time being, this meta-analysis confirms that antibiotic prophylaxis is an effective prevention strategy for rUTIs and that a number of antimicrobial substances can be used with similar likelihood of success. The prophylactic effect seems, though, to be limited to the period of antibiotic intake, and the effectiveness of antibiotic prophylaxis should be weighed against concerns for resistance selection.	no information if efforts were made to minimise error in the data selection process, heterogeneity was not presented for all analyses CAVE: • Appendix figure 7 shows a different number of patients considered in the pooled analysis for Nitrofurantoin vs. another antibiotic than presented in table 1 *only two studies also allowed the inclusion of men* <u>Funding</u> This study had no external funding source; article access fees were covered by the department.	1a RoB: low

						<u>TMP (± SMZ) vs. another antibiotic</u> (n=4 studies, 176 patients) RR=1.34 (95% CI: 0.89–2.03); p=0.16 <u>Norfloxacin vs. another antibiotic</u> (n=3 studies, 239 patients) RR=1.17 (95% CI: 0.43–1.70); p=0.66 <u>Continuous vs. intermittent</u> (n=3 studies, 564 patients) RR=1.78 (95% CI: 0.62–5.09); p=0.28 <u>Intermittent vs. placebo</u> (n=1 study, 25 patients) RR=0.15 (95% CI: 0.04–0.55); p=0.004 **Adverse events** <u>Non-severe adverse events with antibiotic prophylaxis</u> RR=3.42 (95% CI: 2.16–5.43; NNH=7.89) <u>Severe adverse events with antibiotic prophylaxis vs. placebo</u> RR=3.22 (95% CI: 1.32–7.89; NNH=30.97) • most commonly reported adverse events with antibiotic prophylaxis: ○ gastrointestinal		<u>Conflict of interest</u> Dr. Trautner's work is supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, and the Center for Innovations in Quality, Effectiveness and Safety (CIN 13-413).	

						complaints (including nausea) and oral or vaginal candidiasis Allergic reactions occurred with the following antibiotics: • norfloxacin (5 patients), cinoxacin (3) • nitrofurantoin (7) • trimethoprim-sulfamethoxazole/trimethoprim (2). Skin rashes were described with: • cinoxacin (4), • nitrofurantoin (2) • trimethoprim-sulfa-methoxazole/trimethoprim (1) • cephalexin (1) • fosfomycin (1) • a nonidentifiable antibiotic (5) • placebo (2) Neither renal insufficiency nor *C. difficile* enterocolitis was mentioned as a possible adverse event in the included studies, also suggesting underreporting of AEs.			
Ahmed 2017 [74] 28554926	Systematic review and meta-analysis n=3 RCTs Literature search: up to 2016 Recruitment	To determine the clinical effectiveness and safety of long-term antibiotic therapy for preventing recurrent UTIs in	n=534 postmenopausal women with rUTI	Long-term antibiotic therapy (defined as antibiotic dosing for at least 6 mo).	Non-antibiotic intervention •vaginal oestrogens (n=150) •oral lactobacilli (n=238)	**Frequency of UTI recurrences during the prophylaxis period** *Narrative analyses* Beerepoot, 2012 480 mg trimethoprim-sulfamethoxazole vs. capsule of lactobacilli for	Findings from three small trials with relatively short follow-up periods suggest long-term antibiotic therapy reduces the risk of recurrence in postmenopausal	**KSR-Bewertung** (*https://ksrevidence.com/index.php?recordID=KSRA35758#recordpage*) Studies were restricted based on publication format	1a - RoB: high

	countries: Israel, the Netherlands, Croatia	older adults			•D-mannose powder (n=94)	<u>12 mo (n=1)</u> Microbiologically-confirmed UTI episodes per patient-year • trimethoprim-sulfamethoxazole:1.2 • capsule of lactobacilli: 1.8 MD=0.6 episodes (95% CI: 0.0-1.4); p=0.02 Microbiologically confirmed UTI during prophylaxis • trimethoprim-sulfamethoxazole: 49.4% • capsule of lactobacilli: 62.9% RR=0.79 (95% CI: 0.63-1.0) Microbiologically confirmed UTI episodes 3 mo after cessation of prophylaxis • trimethoprim-sulfamethoxazole:0.1 • capsule of lactobacilli: 0.2 MD=0.0 (95% CI: -0.1-0.3); p=0.64 Raz, 2003 <u>nitrofurantoin (100g) for 9 mo vs. vaginal oestrogen pessaries</u> UTI during prophylaxis • nitrofurantoin: 42.3% • vaginal oestrogen pessaries: 64.6% RR 0.65(95% CI: 0.8-0.90)	women with recurrent UTI. We did not identify any evidence to inform several clinically important scenarios including, benefits and harms in older men or frail care home residents, optimal duration of prophylaxis, recurrence rates once prophylaxis stops and effects on urinary antibiotic resistance.	and language, meaning relevant studies may have been missed. Only a single author was involved in study screening and data extraction, meaning that bias may have been introduced. Insufficient study characteristics were provided, making it challenging for the reader to interpret results. Study heterogeneity was high for adverse event outcomes. *Slightly differing information on the literature search period: abstract till August 2016 and in the method part it is stated March 2016* <u>Funding</u> This report is independent research arising from the National Institute of Health Research (NIHR) Doctoral Research Fellowship awarded to Haroon Ahmed, and supported by Health and Care Research Wales (HCRW). The views	

						Kranjčec, 2014 <u>Nitrofurantoin (50g) for 6 mo vs. D-mannose powder (2g)</u> UTI during prophylaxis • nitrofurantoin: 24% • d-mannose: 19% RR=1.24 (95% CI: 0.57-2.69) **Adverse events** *Pooled analysis* Mild adverse events (n=3 RCTs) • Antibiotic: 118/242 • Non-antibiotic: 107/261 RR=1.52 (95% CI: 0.76-3.03, I^2=86%); p=0.23 Serious adverse events resulting in treatment withdrawal (n=2 RCTs) • Antibiotic: 21/200 • Non-antibiotic: 22/209 RR=0.90 (95% CI: 0.31-2.66, I^2=67%); p=0.85 **Effect of long-term antibiotic therapy on bacterial resistance** <u>Beerepoot, 2012</u> % of urinary and faecal E coli isolates that were resistant to trimethoprim–sulfamethoxazole, trimethoprim and amoxicillin: • baseline: 20%–40% • after 1 mo of treatment with		expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS Wales, HCRW or the Welsh Government. The funders had no role in the design or preparation of this manuscript. <u>Conflict of interest</u> None declared.	

						trimethoprim–sulfamethoxazole: 80%–95%			
Muller 2017 [75] 27542332	Systematic review and meta-analysis n=26 controlled clinical trials Literature search: 1946-2015 Recruitment countries: Australia, Belgium, Chile, Croatia, Denmark, Finland, Germany, India, Israel, United Kingdom, United States of America	To assess the efficacy and safety of Nitrofurantoin in the prophylaxis of UTI.	n=3052 human patients of all ages and both genders in all settings	Oral nitrofurantoin at any dose and any duration for primary or secondary prophylaxis of UTI	Placebo, no treatment, a different drug, Nitrofurantoin at a different dose, frequency, or duration	*In the following only the results for adult patients with rUTI are presented* **Long-term prophylaxis** (subgroup analyses) <u>Nitrofurantoin vs. quinolones</u> (n=3) • Nitrofurantoin: 25/84 • Quinolones: 15/102 RR=2.26 (95% CI: 0.73-7.00, I^2=61%); p=0.16 <u>Nitrofurantoin vs. methamine hippurate</u> (n=2) • Nitrofurantoin: 24/67 • Methamine hippurate: 66/129 RR=0.6 (95% CI: 0.43-0.85, I^2=0%); p=0.004 **Adverse events (long-term use)** <u>Nitrofurantoin vs. quinolones</u> (n=3) • Nitrofurantoin: 24/112 • Quinolones: 18/118 RR=1.37 (95% CI: 0.79-2.36, I^2=0%); p=0.26 <u>Nitrofurantoin vs. methamine hippurate</u> (n=2) • Nitrofurantoin: 24/67 • Methamine hippurate: 9/129 RR=4.22 (95% CI: 2.06-8.67, I^2=0%); p<0.0001 <u>Nitrofurantoin vs.</u>	When used for the prevention of UTI, nitrofurantoin's clinical efficacy appears equivalent to that of other antibiotics. Although its non-severe toxicity profile appears somewhat less favourable than those of comparators, severe toxicity is rare. Clinicians should be aware, however, that the risk of severe toxicity seems to increase with the duration of nitrofurantoin prophylaxis.	no study protocol, complete search strategy not reported, no additional hand search, no funnel plot <u>Funding</u> This work was supported in part by the European Commission under the Life Science Health Priority of the 7th Framework Programme (AIDA grant agreement 278348). <u>Conflict of interest</u> The authors have no conflicts of interest to declare.	1a - RoB: high

						trimethoprim/sulfamethoxazole (n=1) • Nitrofurantoin: 1/6 • Trimethoprim/ sulfamethoxazole: 1/13 RR=2.17 (95% CI: 0.16-19.10); p=0.56			
Price 2016 [76] 27457111	Systematic review and meta-analysis n=12 RCTs (Secondary prevention was the goal of n=11 RCTs) Search period: up to Jan 31th, 2015 Recruitment countries: United States, England, Finland, Denmark, Germany, Peru, Poland, and Israel	The objective of this review was to provide current pooled estimates of randomized control trials comparing the effects of nitrofurantoin vs other agents in reducing recurrent urinary tract infections in adult, nonpregnant women and assess relative adverse side effects.	n=1063 women with recurrent UTI aged 18-85 y who are receiving care in an outpatient setting	Nitrofur-antoin	Trimethoprim, cefaclor, sulfamethoxazole/trimethoprim, cefixime, vaginal estrogen, estrogen of all types, cranberry supplements, bladder instillations, or fosfomycin	**Clinical cure** Nitrofurantoin vs. other agents Pooled analysis (9 RCTs, n= 673 patients) RR=1.06 (95% CI: 0.89-1.27, I^2=65%) **Microbiological cure** Nitrofurantoin vs. other agents Pooled analysis (12 RCTs, n=1063 patients) RR=1.06, 95% CI: 0.90-1.26, I^2=76%) • No significant difference was found regarding microbiological success between patients treated with nitrofurantoin vs. those treated with comparator(s) in the separate analysis comparing nitrofurantoin with each of the different types of antibiotic agents used Short prophylaxis (daily 6 mo nitrofurantoin regimens) Nitrofurantoin vs. other agents	Nitrofurantoin had similar efficacy but a greater risk of adverse events than other prophylactic treatments. Balancing the risks of adverse events, particularly gastrointestinal symptoms, with potential benefits of decreasing collateral ecological damage should be considered if selecting nitrofurantoin.		1a RoB: low

						5 RCTs, n=305 patients) RR=0.93 (95% CI: 0.76-1.14, I^2=56%) <u>Longer prophylaxis (regimes greater than 6 mo)</u> Nitrofurantoin vs. other agents 7 RCTs, n=758 patients) RR=1.01 (95% CI: 0.90-1.13, I^2=84%) **Microbiological infection during prophylaxis** <u>Nitrofurantoin vs. comparator(s)</u> Pooled analysis (10 RCTs, n=897 patients) RR=1.08, 95% CI: 0.66-1.76, I^2=71%) • There was no significant difference found between patients treated with nitrofurantoin vs. those treated with comparator(s) in the separate analyses regarding microbiological infection during prophylaxis **Adverse events** <u>Nitrofurantoin vs. trimethoprim</u> Pooled analysis (3 RCTs, n=265 patients) RR=2.03, 95% CI: 1.12-			

						3.70, I^2=5%) <u>Nitrofurantoin vs. methenamine hippurate</u> Pooled analysis (2 RCTs, n=244 patients) RR=4.17, 95% CI: 2.11-8.25, I^2=0%) <u>Nitrofurantoin vs. other agents</u> Pooled analysis (10 RCTs, n=948 patients) RR=1.83, 95% CI: 1.18-2.84, I^2=54%) The majority of these adverse events were gastrointestinal symptoms **Study withdrawal because of adverse events** <u>Nitrofurantoin vs. other agents</u> Pooled analysis (10 RCTs, n=1002 patients) RR=2.14, 95% CI: 1.29-3.56, I^2=8%) • No significant difference was found in study withdrawals because of adverse events in the separate analyses			

7.5 Geriatrie

Schlüsselfrage Geriatrie-Diagnostik: Welche Untersuchungen sind zur Diagnose einer Harnwegsinfektion (akute Zystitis, Pyelonephritis) oder der asymptomatischen Bakteriurie in den definierten Gruppen erforderlich?									
Referenz	**Studien-charakteristika**	**Studien-ziel**	**Patienten-Merkmale**	**Indextest**	**Referenztest**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Eriksen 2016 [82]	Systematic review n=6 studies (5 cross-sectional, 1 case-control study) Canada, England, Israel, Sweden, USA Search date: January 2015	Investigate whether or not urine dipstick is a reliable tool to diagnose urinary tract infection in the elderly patients in nursing homes and home care services.	1458 participants over 65 y	Urine dipstick	Urine culture	**Sensitivity** Sensitivity varied considerably in the included studies: • presence of nitrite or leukocytes or both, had a sensitivity of 72%-100% • Leukocytes alone: 69-98% • Nitrite alone: 54-83% **Specificity** The specificity varies in the various studies: • urine dipstick is positive for leukocytes and nitrite, or for either one: 20-70% • Leukocytes alone: 26-81% • Nitrite alone: 48-100% **Positive predictive value** • both leukocytes and nitrite are present, or when leukocytes or nitrite alone: 31-93% **Negative predictive value** both leukocytes and nitrite are present, or when leukocytes or nitrite alone: 49-100%	Urine dipstick does not seem to be an appropriate tool in the diagnosis of urinary tract infection among elderly patients. It has low reliability and it cannot differentiate between a urinary infection and asymptomatic bacteriuria.	no study protocol, search filter to find articles with persons aged over 65 y not reported, no efforts were made to minimise error in the study selection and data extraction, no risk of bias assessment, no funnel plot Funding Not reported. Conflict of interest Not reported. *patients with catheter not included*	3a - RoB: high
Gbinigie et al. (2018) [83]	Systematic review and meta-analysis	To critically appraise and evaluate	N=12039 patients over 65 years in	**Symptoms**: • Urinary tract	• laboratory-proven urinary tract	**ROC Plots - predictors of UTI: Urine incontinence (n= 6)** • Sensitivity: 0.41 (95% CI 0.15-0.72)	There is limited evidence of varying quality appraising the utility of a	Conflict of interest CJH has received expenses and payments for media work. He	3a - RoB: high

29964141	n= 15 studies n= 11 cross-sectional studies n=4 cohort-studies Search date: February 2016-September 2017 Studies were conducted in: Iceland (n=1), England (n=1), Netherlands (n=1), Sweden (n=2), Canada (n=1), Finland (n=2), Germany (n=1), USA (n=4), Sweden and Finland (n=2)	the diagnostic value of symptoms and signs in identifying UTI in older adult outpatients, using evidence from observational studies.	(nursing) homes/institutions	symptoms (incontinence, frequency, dysuria, urgency, character of urine, nocturia, difficulty passing urine) • Non-urinary tract specific symptoms (abdominal signs, chest signs) • Signs (fever, tachycardia, wounds and hypotension) • Markers of functional status • Cognitive status/ behavioural	infection or bacteriuria • Physician diagnosis • documented diagnosis	• Specificity: 0.79 (95% CI 0.52-0.93) • DOR: 2.26 (95% CI 1.98-3.49) • +ve LR: 1.96 (95% CI 1.48-2.60) • -ve: 0.75 (0.56-1.00) **Dysuria (n= 6)** • Sensitivity: 0.13 (95% CI 0.06-0.27) • Specificity: 0.92 (95% CI 0.86-0.96) • DOR: 1.80 (95% CI 1.11-2.92) • +ve LR: 1.70 (95% CI 1.12-2.57) • -ve: 0.94 (95% CI 0.87-1.02) **Urinary tract specific symptoms** Assessment of both sexes (together): **Incontinence** and a change in the **character of urine** were found to be predictors of UTI. 1/3 estimates for **dysuria** produced a significant result. Women: • Cloudy urine significant predictor of UTI in women, but not foul smelling urine or haematuria. • 1/4 estimates for urinary incontinence and urinary frequency predicted UTI • 1/6 estimates nocturia predicted UTI • none estimates for dysuria and urgency in women were significant Men (n=1 study): • **dysuria**, **cloudy urine**, **foul smelling urine, urine incontincence, frequency** and **haematuria** was helpful in diagnosing UTI • **Nocturia** was not a predictor of UTI	range of symptoms and signs in diagnosing UTI in older adult outpatients. A number of symptoms and signs traditionally associated with UTI such as urgency, nocturia and abnormal vital signs may be of limited diagnostic value in older adult outpatients. Less classical features, such as inability to perform a range of acts of daily living, might be better predictors of UTI.	has received expenses from the WHO and holds grant funding from the NIHR, the NIHR School of Primary Care Research, The Wellcome Trust and the WHO. On occasion, he receives expenses for teaching EBM and is an NHS GP in the out of hours service in Oxford. AP receives grant funding from the NIHR and occasionally receives expenses for teaching EBM. OAG has received grant funding from the Scientific foundation board of the RCGP, the NIHR SPCR and is currently funded by the Wellcome Trust. JMOM and TRF have received grant funding from the National Institute for Health Research (NIHR) Community Healthcare Medtech and In Vitro Diagnostics Cooperative (MIC), and JMOM has received funding from the NIHR Biomedical Research Centre, Oxford. Funding OAG was funded by the Scientific Foundation Board of the Royal College of General Practitioners (Grant number SFB 2016-01), the Wellcome Trust (Grant	

				change		**Non-urinary tract specific symptoms** • **unintentional loss of faeces** and **bowel incontinence** were predictors of UTI in all participants • **diarrhoea** or **abdominal pain** did not predict UTI **Signs**: • traditional signs associated with UTI (**fever, tachycardia, and hypotension**) were not predictors of UTI **Markers of functional status**: • Examples of **disability in performing a number of acts of daily living** was a predictor of UTI in all participants were all significant **Cognitive status, behavioural symptoms and other symptoms**: • Markers of cognitive status had limited use in predicting UTI • 1/5 estimates for **change in a behaviour** produced a significant result • **Patient or family request** to check for UTI did not help predict UTI Women: **delirium** was a predictor of UTI		number 203921/Z/16/Z) and the National Institute for Health Research School for Primary Care Research (NIHR SPCR). The work of JMOM and TRF was partly funded by the NIHR Community Healthcare Medtech and In Vitro Diagnostics Cooperative (MIC). CJH and AP are funded by the NIHR School of Primary Care Research Evidence Synthesis Working Group (Project number 390). The work of JMOM was also supported by the NIHR Biomedical Research Centre, Oxford. This research is independent of the funders: these funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. No Prospero, so no conclusions about compliance with planned analyses possible; no additional sources to the regular databases were	

								used; probably no robust results (no sensitivity analysis although more than 10 studies were included)	
Gbinigie et al. (2019) [84] 31315578	Systematic review N= 11 studies (n=8 prospective diagnostic accuracy, n=2 retrospective, n=1 prospective cohort study) Search date: up to January 2018 Studies were conducted in: USA, Turkey, Taiwan, Canada, Israel, UK,	The aim of this review is to critically appraise and evaluate biomarkers for diagnosing bacterial infections in older adults (aged 65 years and above)	N=11034 patients, aged 65 years and above	urine dipstick, blood analyses	urine culture, blood cultures, biochemical parameters, Mid-stream urine	**Results** **Bacteraemia** elevated Procalcitonin (≥ 0.2 ng/mL) may help diagnose bacteraemia in older adults • +ve LR range 1.50 to 2.60 • CRP ≥ 50 mg/L only raises the probability of bacteraemia by 5%. **Urinary tract infection (UTI)** Positive urine dipstick • +ve LR range 1.23 to 54.90 absence helps rule out UTI • −ve LR range 0.06 to 0.46 **Intra-abdominal infection** Elevated white blood cell count • WBC > 15.5 cells/mm3 leds to a +ve LR range 0.75 to 2.62 (95% CI 1.11–6.19) but only increased the probability of appendicitis by 3%. • may aid differentiation of bacterial infection from other acute illness (+ve LR range 2.14 to 7.12) **Tests used to diagnose UTI** Reagent strip positive • LR+= 2.49 (95% CI: 1.62-3.82) • LR-=0.37 (95% CI: 0.17-0.8) Nitrites/leucocytes positive on dipstick • LR+= 1.23 (95% CI: 1.08-1.4) • LR-=0.06 (95% CI: 0-1.03) Nitrites positive • LR+= 54.90 (95% CI: 3.5-861.29) • LR-=0.10 (95% CI: 0.03-0.38)	The review contradict Recommendations of SIGN (guidelines for UTI in older adults) and Public Health England, and suggest that a **positive urine dip-stick for nitrites and leucocytes** is helpful in diagnosing UTI in symptomatic **older adults**. The limited available evidence suggests that many diagnostic tests useful in younger patients, do not help to diagnose bacterial infections in older adults. Until then, symptoms and signs remain the mainstay of diagnosis in community based populations. Further studies in this area are required to corroborate or refute these findings.	Conflict of interest Authors are supported by: National Institute of Health Research NIHR, National Institute of Health Research School for Primary Care (NIHR SPCR), Wellcome Trust, NHS, the Naji Foundation, Rotary Foundation, Clarendon Scholarship, a Goodger and Schorstein Scholarship , WHO Funding Research and is currently funded by the Wellcome Trust. The results of our review were limited by many of the studies having small sample sizes apart from one, the moderate quality, and the limitation to mainly emer-gency departments. Limited evidence may suggest the diagnostic utility of an elevated PCT may be helpful for diagnosing bacteraemia, a positive urine dipstick man be helpful in diagnosing UTI. Studies written in non English	LoE: 2a - RoB: high

						Blood positive • LR+= 3.90 (95% CI: 1.65-9.24) • LR-=0.42 (95% CI: 0.23-0.78) Protein positive • LR+= 2.25 (95% CI: 0.73-6.98) • LR-=0.81 (95% CI: 0.59-1.11) Leucocytes positive • LR+= 4.50 (95% CI: 1.69-11.99) • LR-=0.46 (95% CI: 0.27-0.8) HNP1-3>1.42ng/mg • LR+= 2.49 (95% CI: 1.29-4.82) • LR-=0.11 (95% CI: 0.01-1.59) HD5>0.924 pg/mg • LR+= 2.13 (95% CI: 1.19-3.84) • LR-=0.12 (95% CI: 0.01-1.79) hBD-2>0.034 pg/mg • LR+= 4.98 (95% CI: 1.76-14.05) • LR-=0.08 (95% CI: 0.01-1.21)	The limited evidence of moderate quality suggests that an elevated PCT may be helpful for diagnosing **bacteraemia**, a positive urine dipstick may be helpful in **diagnosing UTI.** Although an elevated WBC count has limited utility in diagnosing **intra-abdominal** infections, it may have utility, along with elevated WBC differentials, in differentiating bacterial infections from other acute illness. Further studies of high quality are urgently needed in this area.	language were excluded which means relevant studies and their outcomes may have been missed in the synthesis.	
Shen & Cui (2021) [85] 34596149	Meta-analysis N=6 studies (n=1 Prospective cross-sectional study, n=1 Retrospective cohort study, n=1 Prospective and retrospective	to evaluate the diagnostic accuracy of an electronic surveillance tool for catheter-associated urinary tract infections (CAUTIs) in tertiary care	N= 16492 patients with urinary catheterization hospitalized in a tertiary care hospital	Electronic health record system for CAUTI surveillance	manual recording of CAUTI by healthcare professionals	**Results for HSU (2016), USA** Diagnostic modality: Augmented electronic surveillance, n= 175 patients, mean-age: 72.5 • TP=32 • FP=139 • FN=0 • TN=10557 • Sensitivity: 1.00 (95% CI: 0.89-1.00) • Specificity: 0.03 (95% CI: 0.01-0.07)	In all, we found that diagnostic electronic surveillance is highly useful for CAUTIs among hospitalized patients due to its high sensitivity and specificity. Our results suggest that this surveillance modality can be used for CAUTI screenings in	Conflict of interest None. Funding None. No subgroup-analyses for elderly population → **indirect evidence!** Due to the **limited number of eligible studies** authors were not able to explore the source of **heterogeneity**.	2 a - RoB: high

	surveillance, n=2 Prospective, n=1 Retrospective) Search date: up to November 2019 Studies were conducted in: USA (n=5 studies), China (n=1 study)	hospitals					tertiary care hospitals as it is efficient and time-saving.	**Publication bias** was not performed. No Prospero, so no information can be provided regarding a priori analyses; inadequate search strategy.	
Jameson 2019 [86] 34652709	Mapping/ umbrella review N= 26 describing 36 diagnostic tests	To describe the range of near-patient tests for UTI in older people and their predictive properties.	Older people with UTI	Urinalysis, Griess test for nitrites, Chlorhexidine reaction, Uriscreen catalase test, Novel biomarkers, Microscopy, Analytic tools, Biosensors for volatile organic compounds, Genome sequencing tools, Blood tests,	urine and blood cultures, biochemical parameters	17 out of 36 identified diagnostic tests were considered potentially useful in the urgent care context: **Urinalysis (nitrites and leucocytes)**: sensitivity 59–83%, specificity 79–94% • **Uriscreen catalase test**: sensitivity 50–78%, specificity 98–100% • **Lactoferrin**: no data • **Secretory immunoglobulin A**: no data • **Xanthine oxidase**: sensitivity 100%, specificity 100% • **Soluble triggering receptor expressed on myeloid cells**: no data • **A-1 microglobulin (a1 Mg) and a1 Mg/creatinine ratio** • **Cytokine IL-6**: specific to UTI • **RapidBac**: sensitivity 96%, specificity 94% • **MALDI-TOF**: sensitivity 67%,	A wide range of existing and novel tests might be useful in diagnosing UTI, but a more limited number are potentially feasible to apply in the urgent care setting. Clinicians should be vigilant about over-reliance on near-patient diagnostic tests when assessing older people with possible UTI. Further studies are required to define optimal approaches for diagnosing UTI in older people in urgent care settings.	**Conflict of interest**: none **Funding**: Not reported Authors refer to the article as a mapping review, methodologically this corresponds to an umbrella review. No study protocol, no information on additional method to database searching, grey literature was not searched therefore there is the risk of a lack of detail on emerging tests, only one author conducted the data extraction process without an independent check. The umbrella review just gave a presentation of the	1a - RoB: high

						specificity 100% • **Electronic noses**: sensitivity 95%, specificity 97% • **Colorimetric sensor arrays**: sensitivity 91%, specificity 99% • **Electro chemical biosensor:** sensitivity 92%, specificity 97% • **WBC count (blood)**: no data specific to UTI • **CRP**: sensitivity 85–97%, specificity 23–58% • **ESR**: sensitivity 77–93%, specificity 32–64% • **Prolactin**: 0.25 ng/mL—sensitivity 89–98%, specificity 46-55%; 0.5 ng/mL—sensitivity 71–93%, specificity 55–87%	Near-patient tests for UTI in older people in urgent care settings have been poorly evaluated and have limited predictive properties.	results of the individual included reviews. No further analyses made. To select out tests that could be used in the urgent care setting and with existing technologies (or technology that might be reasonably adapted to the urgent is context—characterised by the need for rapid results (<24 h) and high volumes), we used a consensus building approach. The microbiology team reviewed each of the different tests for their potential use in the urgent care context. Additional discussions were undertaken involving two chemical pathologists to advise upon the blood markers.	

Schlüsselfrage

Geriatrie-Therapie: Ist eine antibiotische Behandlung einer HWI oder einer asymptomatischen Bakteriurie in den definierten Gruppen erforderlich?

Referenz	**Studien-charakteristika**	**Studien-ziel**	**Patienten-merk-male**	**Inter-vention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Köves et al. (2017) [30] 28754533	Systematic review and meta-analysis	to synthesise evidence about benefits and harms	n=7088 patients diabetes mellitus, postmenopa	Antibiotics	No treatment or placebo	**Antibiotic treatment vs. no treatment or placebo of ABU in:** Elderly, institutionalised patients	**Antibiotics**: No evidence of benefit for patients with no risk factors, patients with diabetes mellitus, postmenopausal women, **elderly institutionalised**	Conflict of interest: None Funding: None Citation mistake in women with rUTI	1a - (here in general unclear) RoB:

	n= 50 study-design in general not clear; studies for elder population are RCTs Search date: January 2000 to November 2016 Studies were conducted in: ? (not even mentioned in Suppl.)	of treating ABU in relevant patient groups	usal women, elderly institutionalised patients, recurrent urinary tract infection (UTI), [irrelevant: renal transplants, prior to joint replacement]			• symptomatic UTI_(n=3 RCTs): RR = 0.68, (95% CI: 0.46–1.00, I^2=0%); p=0.05 • resolution of ABU (n=6 RCTs): RR = 1.33 (95% CI: 0.63–2.79, I^2=69%); p=0.45	**patients** and treatment was harmful for patients with recurrent urinary tract infection (UTI). The demonstration of lack of benefit in most clinical situations shown by this thorough and methodologically robust systematic review and meta-analysis supports our recommendation of not to treat ABU.	Single-dose versus short-term just in pregnant women Forrest Plot of low birth weight is missing Lot of low evidence in the studies. No Funnel Plot or Sensitivity-analysis. many included studies were conducted in previous decades, the methods used in the trials were often unclear. This resulted in an overall high RoB and confounding across studies.	high
Krzyzaninia k (2022) [87] 35940886	Systematic review and meta-analysis n= 9 RCTs Search date: from inception until November 2021 Studies	To find, appraise, and synthesise studies that reported the effectiveness, harms, and adverse events associated with antibiotic treatment for	n= 1391 participantsresiding in RACFs, who were diagnosed with an ASB or bacteriuria	therapeutic or prophy-lactic antibiotic treatment of any type, dose, duration, or administered by any route of delivery	placebo, and no therapy control groups	**<u>Elderly population: > 81.8 years</u>** **development of UTI symptoms** (n=4 RCTs; 317 participants) • Antibiotics: 36/176 • No antibiotic: 27/141 RR=1.18 (95% CI: 0.45-3.07, I^2 = 67%); p = 0.73) **mortality** (n=7 RCTs, n= 310 participants) antibiotics vs. no antibiotics	Overall, although antibiotic treatment was associated with bacteriological cure, it was also associated with significantly more adverse effects. The harms and lack of clinical benefit of antibiotic use for **older patients** in RACFs may outweigh the benefits. To provide a better indication of the effectiveness and safety of antibiotics in RACF-based patients, further primary studies are warranted.	**Conflict of interest**: None **Funding**: None Supplementary figures not found! only a small number of RCTs with relatively small sample sizes are included; limited to nursing home settings (based in an RACF); high heterogeneity across the included	1a - RoB: high

	were conducted in: USA, Greece, Canada,	older patients with ASB residing in RACFs				• <u>At 6 mo</u>: RR=0.53 (95% CI: 0.16-1.71, I^2 = 0%); p=0.29, • <u>1-3y</u>: RR=1.10 (95% CI: 0.74-1.66, I^2=0%); p = 0.63, • <u>5-9y</u>: RR=0.93 (95% CI: 0.74-1.18, I^2= 0%); p = 0.55 **Adverse events** (n=4 RCTs; 303 participants) • Antibiotics: 11/169 • No antibiotics: 1/134 RR=5.62 (95% CI: 1.07-29.55, I^2=0%); p=0.04 **Complications (epididymo-orchitis and bacteraemia)** (2 RCTs; 81 participants) (supplementary S3 not found) →no difference between groups in the number of participants experiencing complications: RR 1.89, 95% CI = 0.77 to 4.63, P = 0.16, I 2 = 0%) **Bacteriological cure** (n=9 RCTs; 888		studies. No prospero, so compliance with corresponding analysis etc. was not comprehensible.	

						participants) • Antibiotics: 271/496 • no antibiotics:76/392 RR= 1.89 (95% CI: 1.08-3.32, I^2= 81%); p=0.03			
Liu 2021 [88] 32763348	Systematic review and meta-analysis 8 RCTs Search date: through March/April 2020 Countries: not mentioned	To investigate the effect of antibiotic prophylaxis for consequent urinary tract infections (UTIs) after extraction of urinary catheter and further explore the association between the outcome and clinical characteristics of patients.	(n= 997) Patients with a duration of catheter-ization ≤14 days, specified definition of UTIs, antibiotic prophylaxis which was administered presently after the extraction of catheters rather than before it.	antibiotic prophylaxis (ciprofloxacin, Nitro-furantoin, TMP/SMX, cefotaxime)	No prophylaxis	<u>Effect of antibiotic prophylaxis for UTIs after removal of catheters</u> **<u>Older than 60</u>** (6 RCTs): Antibiotics (n=443) vs. no antibiotics (n= 427) • RR = 0.50, (95% CI: 0.33-0.76), P< 0.05, I^2 = 29% **<u>Ciprofloxacin</u>** (n= 2 RCTs): **Berrondo 2019** (167 laparoscopic radical prostatectomy; 2 doses, first before removal, second after removal; cases experimental: 3/83; cases control: 5/84; follow-up: 6 weeks; mean age older than 60; male) • RR 0.61 (95% CI 0.15-2.46) **Fang 2014** (dose: not reported; 160 laparoscopic radical Prostatectomy; cases experimental: 4/80; cases control: 9/80; mean age older than 60; follow-up time;	Patients with catheters removed might get benefit from antibiotic prophylaxis as a result of fewer consequent UTIs, and those **who have advanced age (over 60 years old) or long-term catheterization (over 5 days)** could get more benefit from prophylaxis. And TMP/SMX could be a good choice of prophylaxis for UTIs after extraction of urinary catheters. **This approach should apply to** high-risk patients (**advanced age or long-term catheterization**) due to the potential harm of widespread antibacterial agents such as side effects and bacterial resistance. Further research should reach a consensus of study design protocols (types of antibiotic agents, duration of catheterization, observation time, etc.) to provide more convincing evidence. **Meanwhile, clinicians must prescribe antibiotics cautiously according to the risk factors of their patient population**.	**Funding**: This study was found by 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD18011, ZY2016104). **Conflicts of interest**: None **Only 2 of the included studies comprised nonsurgical YOUNGER patients in hospital, and separate analyses of these 2 studies alone did not show benefit of the prophylaxis.** ➔ Presented population were all surgery patients! No Prospero, so analyses determined a priori cannot be reviewed; no information whether ROB was evaluated by 2 independent reviewers	1 a - RoB: high

						1,4,8 weeks male only) • RR 0.44 (95% CI 0.14-1.38) **<u>TMP/SMX or Ciprofloxacin</u>** <u>(2 RCT):</u> **Van Hees 2011** (91 general surgery, ciprofloxacin (n=31) or TMP/SMX (n=24) x1 dose before removal; cases experimental: 1/55; cases control: 1/36; follow up: 2 weeks; mean age older than 60; mixed gender) • RR 0.65 (95% CI 0.04-10.13) **Pfefferkorn 2009** (205 abdominal surgery; TMP/SMX (3 doses, first before removal) or ciprofloxacin; cases experimental: 5/103; cases: 22/102; follow up: 22/102 4 +/-2 days after catheter removal; mean age older than 60; mixed gender • RR 0.23 (95% CI 0.09-0.57) **<u>Cefotaxime</u>** <u>(1 RCT)</u> **Grabe 1984** (96 transurethral prostatectomy 3 doses, two daily, first before removal; cases experimental: 3/47; cases control: 8/49;			

						follow-up: 1 week; mean age older than 60; male) →no data **<u>Nitrofurantoin</u>** (1 RCT) **Lavelle 2019** (151 pelvic reconstructive Surgery; 100mg once daily; cases experimental: 13/75; cases control: 13/76; mean age older than 60; follow-up: 6 weeks, female) →no data! **<u>Catheters for more than 5 days</u>** (n= 4 RCTs) (Berrondo, Fang, Van Hees, Pfefferkorn) • Antibiotics (n= 321) vs. no antibiotics (n= 302) RR = 0.34, (95% CI: 0.19-0.63), P< 0.01, I^2 = 0%. **<u>catheters < 5 days</u>** (n= 2 RCTs) **Lavelle 2019 (s. above)** • RR 1.01 (95% CI 0.50-2.04) Grabe 1984 (s. above) • RR 0.39 (95% CI 0.11 – 1.39)			
Zeng 2020 [89]	Systematic review search: up to	This review aimed to outline the diagnostic, **treatment**	n=64 publications people over 65 years	• Cranberry juice • Hormonal • Fluid intaking • D-Mannose • Vaccine		**Long-term urinary catheter** • Antimicrobial-coated catheters could slightly decrease the	Management of UTI in elderly patients with long-term catheter remains challenging. There is evidence that prophylactic antibiotics are able to reduce	no study protocol, no complete search strategy and study characteristics of the included studies reported, no information	1a - (for the presented results)

32221713	March 2019	, and prevention of UTI in the frail aging population.		• Antibiotics	risk of catheter-associated UTI (disadvantages: more frequent catheter removal, more uncomfortable caused by catheter, and higher costs) • Systemic antibiotic prophylaxis does not reduce rates of bacteriuria, catheter-associated UTI, or death, and should not be recommended.	risk of recurrent UTI in correctly selected elderly patients.	if efforts were made to minimise error in data collection, no risk of bias assessment, unclear if all identified studies are included in the review, no funnel plot, bias risk of the included studies is not addressed Funding National Natural Science Foundation of China (No. 81870483 and No. 81800625), and Natural Science Foundation of Guangdong Province (2018A030310296) Conflict of interest The authors declare that they have no conflict of interest.	RoB: high

Schlüsselfrage

Geriatrie-Therapie: Welche weiteren Behandlungsalternativen zur Therapie einer Harnwegsinfektion in den definierten Gruppen können empfohlen werden?

Referenz	Studien-charakteristika	Studien-ziel	Patienten-Merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
Juthani-Mehta M 2016 [90] 27787564	RCT N= 185 English-speaking, female, nursing home	To test the effect of two oral cranberry capsules once per day on presence	N=185 Female, nursing home residents, age 65 or older, with or without	N= 92 Once per day two oral cranberry capsules, each capsule	N= 93 Placebo	**Mean age 86.4 years [± 8.2])** **Treatment (n= 92): Age: 87.1 ±8.4** **Control (n= 93): 85.6 ±8.0** Presence of bacteriuria plus pyuria (unadjusted) overall over 1 year treatment group: • 25.5% (95% CI 18.6, 33.9) of the control group:	After adjusting for missing data and covariates, there was no statistically significant difference in presence of	**Funding**: The funder (National Institutes of Health, National Institute on Aging, R01 AG041153, as well as K07 AG030093 and the Claude D. Pepper Older Americans Independence	1b Rob: low

	residents, age 65 or older USA August 24, 2012 through October 7, 2014 six follow-up time points (months 2-12).	of bacteriuria plus pyuria among women residing in (n=21) nursing homes	bacteriuria and pyuria at baseline	containing 36mg of the active ingredient proanthocyanidin (i.e., 72mg total, equivalent to 20 ounces of cranberry juice)		• 29.5% (95% CI 22.2, 37.9) of the Presence of bacteriuria plus pyuria (adjusted GEE model): **treatment (T) vs. control groups (CG)**: • 29.1% vs. 29.0%; • OR 1.01, (95% CI 0.61,1.66; p=0.984). number of symptomatic UTIs(T vs. CG) • 10 vs. 12 episodes **Adverse effects:** rates of death (T vs. CG) • 17 vs. 16, 20.4 vs. 19.1 deaths/100 person-years, • RR 1.07 (95% CI 0.54, 2.12), hospitalization (T vs. CG) • 33 vs. 50 episodes, 39.7 vs. 59.6 hospitalizations/100 person-years, • RR 0.67, (95% CI 0.32, 1.40), bacteriuria associated with multi-drug resistant gram-negative bacilli (T vs. CG) • 9 vs. 24 episodes, 10.8 vs. 28.6 episodes/100 person-years, • RR 0.38, 0.10, 1.46, antibiotics administered for suspected UTI (T vs. CG) • 692 vs. 909 antibiotic days, 8.3 vs. 10.8 antibiotic days/person-year, • RR 0.77, (95% CI 0.44, 1.33), total antimicrobial utilization (T vs. CG) • 1415 vs. 1883 antimicrobial days, 17.0 vs. 22.4 antimicrobial days/person-year, • RR 0.76, (95% CI 0.46, 1.25).	bacteriuria plus pyuria between the treatment (29.1%) and control (29.0%) groups over 1 year. Among older women residing in nursing homes, administration of cranberry capsules, compared with placebo, resulted in no significant difference in presence of bacteriuria plus pyuria over 1 year.	Center P30 AG021342) had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The cranberry and placebo capsule manufacturer had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Conflicts of Interest**: None High loss to follow-up in both groups (reasons not ☐ fully described)	
Jones 2019 [91] 30359646	Systematic Review N= 21 studies (4 RCT, **15 before-after study**, 1 cross-sectional,	To examine effectiveness of behavioural interventions to reduce E. coli bacteraemia and/or symptomatic UTIs for	Older adults (65+) in hospital or community care settings.	All behaviour-al interventions.	None speci-fied	**Outcomes**: Symptomatic UTI and E. coli bacteraemia. N= 6 **multi-faceted hospital interventions** including education, with audit and feedback or reminders reduced UTIs but only n= 3 supplied **statements of significance**: **Dickson 2016**: decreasing catheter-associated UTI (CAUTI) by 88% (F (1,20) = 7.25).	The heterogeneity of studies means that **one effective intervention cannot be recommended**. We suggest that feedback should be considered because it	**Conflict of interest statement** L. Jones and C. McNulty work for Public Health England's Primary Care Unit and are involved in the development and evaluation of the TARGET Antibiotics Toolkit.	3a - RoB: high

	1 non-randomized trial) Conducted in: USA, Netherlands, Italy, India, France, Australia, Taiwan, UK, Canada from 1990-summer 2017	older adults.				**Smith 2009**: reductions in CAUTI from 11.17 to 10.53 during Phase I and by 0.39 during Phase II (χ^2 = 254). **Van Gaal 2011:** fewer UTIs per patient week (RR = 0.39). N= 2 hospital studies of online training and catheter insertion and care simulations decreased CAUTIs from 33 to 14 and from 10.40 to 0. Increasing nursing staff, community continence nurses, and catheter removal reminder stickers reduced infection. N= 0 studies examining prevention of E. coli bacteraemias.	facilitated **reductions in UTI when used alone or in multi-faceted interventions** including education, audit or catheter removal protocols. Multi-faceted education is likely to be effective. **Catheter removal protocols, increased staffing**, and **patient education require further evaluation**.	**Funding source** This work was funded by Public Health England's Primary Care Unit. **Narrative synthesis approach** was chosen due to the heterogeneity of studies included in the review such as the intervention types, methodologies used, and data collected. Studies were excluded **if interventions aimed at reducing asymptomatic bacteriuria**, as this is very common in the elderly and treatment with antibiotics does not reduce mortality or symptomatic episodes Reviewed studies: all lacked methodological quality Missing 2 independent reviewers to minimize errors in study selection as well as risk of bias assessment.	
Aliyu 2022 [92] 34075829	N= 19 studies (n= 1 RCT; n= 5 cluster RCTs; n= 13 quasi experimantal)	To assess ASPs in Nursing homes and their effects on antibiotic use, multi-drug-	Residents of NHs or long-term care facilities	Antibiotic Steward-ship Interventions (education, antibiotic pocket cards,	persons who received the intervention, some were just	Inappropriate Antibiotic use in Nursing Home Residents Type of infection measured: UTI (n= 4 studies; studies & design unclear) • Pooled result: 24.4 (95% CI 15.1-33.8) Metaanalysis (10 studies): Inappropriate antibiotic use decreased	ASP interventions led to a 13.8% decline in inappropriate antibiotic use suggesting the need for enhanced ASP implementation.	No definition of the **mean age** of the nursing home residents. →No age-subgroup-analysis concerning the specific outcomes Overall, the risk of bias of the body of studies	LoE: 3a RoB: low

	Search: 1988 to 2020 USA	resistant organisms, antibiotic prescribing practices, and resident mortality.		videos, and group discussions in nursing homes →details s. Article p. 895)	physicians while the comparison group included physicians, nurses and pharmacists. Some facilities practiced standard care while the comparison group practiced the new intervention.	<u>following ASP intervention in eight studies:</u> • pooled decrease: 13.8% (95% CI: [4.7, 23.0]) • I^2 = 99.9%; Cochran Q = 166,837.8, p <.001	Decrease in inappropriate antibiotic use was **highest in studies that examined antibiotic use for urinary tract infection (UTI).** Among the interventions to reduce inappropriate antibiotic use, **education and algorithms** promoting antibiotic stewardship for UTIs were most effective. Evidence surrounding ASPs in NH is weak, with recommendations suited for UTIs.	included in the systematic review was weak to moderate. Methodological weaknesses noted in the included studies Findings of this article must be interpreted with caution due to methodological weaknesses noted in the included studies. **Funding**: None **Declaration of Conflicting Interests**: None	

Schlüsselfrage

Geriatrie-Therapie: Welche Antibiotika kommen für die Therapie einer unkomplizierten Zystitis in Frage?

Referenz	Studien-charak-teristika	Studien-ziel	Patienten-merkmale	Inter-vention	Kon-trolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
Dawson-Hahn 2017 [93]	review of systematic reviews	To summarize the evidence comparing the	(6 studies; n= 431) Older women with acute uncomplicat	antibiotic prescriptions described as short course	longer duration courses of antibi	**Acute uncomplicated UTI in older women (Lutters 2008, RCT; n= 431 (>60 years))** Short (3-6 days) versus long courses (7-14 days) in:	There was no significant difference in the rates of clinical cure in participants given short (3–6 days) versus longer courses (7–14 days) when comparing	**Funding**: CCB is supported by the National Institute for Health Research Health Protection Research Unit, Healthcare Associated	1a - RoB: high

28486675	N= 9 SR of RCTs → 1 system. Review for women >60 years Canada, Denmark, France, Germany, Ireland, Israel, Italy, the Netherlands Search: inception until April 2016	effectiveness of short and long courses of oral antibiotics for infections treated in outpatient settings.	ed lower tract urinary tract infection		otics	<u>comparing different antibiotics</u> (4 studies; n= 395 patients): • RR* 0.98, (95% CI: 0.62, 1.54) <u>Bacteriological persistent UTI at 2 weeks</u> (3 studies; n= 431 →suppl. table 6) • RR* 0.85 (95% CI: 0.29, 2.47) <u>Bacteriological persistent UTI >2 weeks</u> (3 studies; n= 470→ suppl. table 6) • RR* 0.85 (95% CI: 0.54, 1.32) <u>Discontinuation due to adverse reactions</u> (2 studies; n=406→suppl. table 6) • RR* 0.11, (95% CI: 0.01, 1.97) <u>Reinfection (long term)</u> (n= 2 studies; n= 405→suppl. table 6) • RR* 1.30 (95% CI: 0.42, 4.01) [*RR > 1 supports long course]	different antibiotics. In addition, rates of bacteriological persistence of UTI at ≥2 weeks and adverse drug reactions were equivalent among women treated with short and long courses. The impact on antibiotic resistance and associated treatment failure requires further study.	Infections and Antimicrobial Resistance, at the University of Oxford. EED-H's time was supported by the Ruth L. Kirschstein National Research Service Award (#T32HP10002). All other funding was provided by departmental support. **Conflict of interest**: none. **Indirect evidence (no subgroup-analysis of the elderly population)** Moderate quality of included studies within reviews No Prospero, so it remains unclear to what extent a priori fixed analyses were performed; no other sources searched in addition to electronic search; presumably no robust results or tests performed accordingly	
Drekonja, D. M., et al. (2021) [94] 34313686	RCT (Randomized, double-blind, placebo-controlled Noninferiority trial)	To determine whether 7 days of treatment is noninferior to 14 days when using ciprofloxaci	N= 272 men with presumed symptomatic UTI treated with ciprofloxacin or trimethoprim/sulfameth	(n = 136) **Group 1:** 7 days of antimicrobial treatment*	(n = 136) **Group 1:** … to receive continued	**272 men (median [interquartile range] age, 69 [62-73] years** **Intervention-Group** Age, median (IQR), y 70 (62-73) **Control-Group** Age, median (IQR), y 70 (62-	The findings support the use of a 7-day course of ciprofloxacin or trimethoprim/ sulfamethoxazole as an alternative to a 14-day course for treatment of afebrile men with suspected UTI.	**Role of the Funder/Sponsor**: The funding organization (VA Merit Review Program, grant number I01BX007080.) reviewed the design and conduct of the study. The funder had no role in the collection, management,	1 b RoB: low

	N= 272 men USA April 2014 through December 2019 and from January 2018 through December 2019 final follow-up, January 28, 2020	n or trimethoprim/sulfamethoxazole to treat urinary tract infection (UTI) in afebrile men.	oxazole	**Group 2:** 7 days of antimicrobial treatment * *with ciprofloxacin or trimethoprim/sulfamethoxazole	7-day placebo group (placebo on day 8 through 14) **Group 2:** … to receive continued 7-days antibiotic therapy	75) **Resolution of UTI symptoms 14 days after stopping active antimicrobials** As-treated population (primary analysis): Symptom resolution (participants/%) 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group • 122/131 (93.1%) vs. 111/123 (90.2%) • difference, 2.9% [1-sided 97.5% CI, −5.2% to ∞] As-randomized analysis: Symptom resolution (participants/%) 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group • 125/136 (91.9%) vs. 123/136 (90.4%) • difference, 1.5% [1-sided 97.5% CI, −5.8% to ∞] **Recurrence of UTI symptoms within 28 days of stopping study medication (secondary outcome)** As-treated population: Recurrence of UTI symptoms (participants/%): 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group • 13/131 (9.9%) vs. 15/123 (12.9%) • difference, −3.0% [95% CI, −10.8% to 6.2%]; P = .70		analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. **Conflict of Interest Disclosures**: Dr Trautner reports research and consulting funding from Genentech and the National Institute of Allergy and Infectious Diseases for COVID trials; consultancy fees from Genentech; and grants from the US Department of Veterans Affairs (VA) rehabilitation Research & Development Service and the Agency for Healthcare Research and Quality. Ms Amundson reports receiving salary support for this trial during the conduct of the study from VA Merit Review grants. Dr. Johnson reports grant support from Allergan/Actavis, Cipla/Achaogen, Melinta, Merck, Shionogi, Synitron, Tetraphase; consulting fees from Crucell/Janssen; and pending patents for 2 E coli strain tests. No other conflicts were reported.	

						As-randomized population: <u>Recurrence of UTI symptoms</u> (participants/%): 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group • 14/136 (10.3) vs. 23/136 (16.9) • difference, −6.6 (−15.5 to 2.2); P = .20 <u>Adverse events</u> (participants/%): 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group **any adverse event**: As-treated-population: • 26/131 (19.8%) vs 29/123 (23.6%) As-randomized population vs. as-treated population: • 22.4% vs 21.7% Adverse event for each group in the as-randomized population: • 28/136 (20.6%) vs. 33/136 (24.3%) Individual adverse events: full text table 4			

Schlüsselfrage

Geriatrie-Therapie: Welche Antibiotika kommen für die Therapie der unkomplizierten Pyelonephritis in Frage?

Referenz	Studien-charakteristika	Studienziel	Patienten-merkmale	Intervention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
Malaisri, C., et al. (2017) [95]	RCT (prospective randomized controlled	To compare the clinical and bacteriological efficacy of	N= 36 patients with acute pyelonephriti	Sitafloxacin	Ertapenem.	**Median (IQR), years** **Sitafloxacin (n= 19 (52.8%))** • 72.3 (51.9-78.7)	In conclusion, our study demonstrated favorable clinical	**Conflict of interest**: none **Funding:** not	1b - RoB: High

28587974	trial) N= 36 patients Thailand November 2012 to June 2015 Follow-up: laboratory monitoring at day 3 and day 10; day 7 clinical assessment of treatment outcomes; day 30, UA and UC	sitafloxacin and ertapenem for non-bacteremic acute pyelonephritis caused by ESBL-EC for 10 days.	s caused by ESBL-E			**Ertapenem (n = 17 (47.2%))** • 65.0 (52.7e77.8) **P= 0.912** **Baseline characteritics - previous urinary catheter insertion:** Sitafloxacin vs. Ertapenem • 15.8% vs. 52.9%, p = 0.018 **Signs and symptoms** Sitafloxacin vs. Ertapenem • 68.4% vs. 29.4%, p ¼ 0.019 **Clinical cure** Sitafloxacin vs. Ertapenem Day 10: • 19 (100.0) vs. 16 (94.1), p= 0.472 Failure at day 10: none Died: • 0 (0.0) vs. 1 (5.9); p= 0.472 Recurrence at day 30: • 2 (10.5) vs. 0 (0.0); p= 0.607 **Bacteriological outcomes** Sitafloxacin vs. Ertapenem Eradication at day 10 • 16 (84.2) 12 (70.6), p= 0.532 Persistence at day 10 • 2 (10.5) vs. 0 (0.0); p= 0.487 Both groups: No significant **adverse effects**.	and microbiological outcomes for sitafloxacin as a switch therapy in the majority of patients with non-bacteremic acute pyelonephritis caused by ESBL-EC. A treatment regimen of carbapenem followed by sitafloxacin was effective and well-tolerated among patients with acute pyelonephritis. Sitafloxacin may be considered as an alternative choice of switch therapy in this clinical setting. A large prospective study to determine the clinical efficacy of sitafloxacin for treatment of ESBL-producing gram-negative bacterial infections is warranted.	mentioned The patient-trail was performed as a pilot study. Indirect evidence: range of patient-population is not precisely geriatric (just IQR is above 65+) Bacteriologial/microbiological data was misrepresented in the abstract/text. Data listed here are from table3 (full text) Open-label, loss to follow-up reasons not fully described	
Mir, M. A., et al.	RCT (phase 3,	To show the noninferiority of	(n= 143) Patients	CSE, 1034 (N = 74)	Meropenem (N = 69)	**Age ≥65 Mixed patient population (cUTI and**	CSE met the primary objective	**Funding:** This work was funded by Venus	1b -

(2019) [96] 31433059	prospective, randomized, multicenter, double-blind, double-dummy, parallel-group, noninferiority trial) December 2013 and April 2017 India n= 143 patients	CSE to meropenem at the test-of-cure visit (8–12 days after the end of therapy), with a noninferiority margin of 10%.	aged ≥18 years with a diagnosis of complicated urinary tract infections (cUTIs), including **acute pyelonephritis** (AP)	CSE-1034 is a novel antibiotic adjuvant entity (AAE). CSE is a novel combination of ceftriaxone, sulbactam, and disodium ethylenediaminetetraacetic acid (EDTA) with activity against multidrug-resistant Gram-negative pathogens.		**pyelonephritis patients)** CSE: n= 4 (5.4) Meropenem: n= 8 (11.6) **Subgroup Analysis at TOC visit (mMITT N= 143) (Suppl. S 10)**: **Symptom resolution**: Age: 65< Age <74 CSE-1034: 0.500 Meropenem: 0.857 Difference in proportions: -0.357 (95% CI -0.836:0.257) Age: 75< Age <90 CSE-1034: 1.000 Meropenem: 1.000 Difference in proportions: 0.000 (95% CI Not estimate) **Per-patient microbiological eradication and symptomatic resolution**: Age: 65< Age <74 CSE-1034: 0.500 Meropenem: 0.857 Difference in proportions: -0.357 (95% CI -0.836:0.257) Age: 75< Age <90 CSE-1034: 1.000 Meropenem: 1.000 Difference in proportions: 0.000 (95% CI Not estimate)	of showing noninferiority against meropenem in the treatment of patients with cUTI, including AP. The susceptibility profile of pathogens isolated in this study highlights the increasing antibiotic resistance trend and warrant a need for new effective antimicrobials. The results support the use of CSE as a potential alternative to carbapenems in the treatment of patients with cUTI or AP, including infections caused by ESBL-producing Gram-negative bacteria. **Sensitivity analyses** of the primary endpoints were generally consistent across baseline patient characteristics, and the point estimates of the	Remedies Limited. Medical writing support was provided by JSS Medical Research India Limited, funded by Venus Remedies Limited. **conflicts of interest:** M. A. M., S. C., and A. P. are employees of Venus Remedies Limited. CSE is being developed by Venus Remedies Limited. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed. Allocation concealment not clearly described, microbiologic modified intent-to-treat analysis used for statistical analysis	RoB: high

						Favorable per-patient microbiological response Age: 65< Age <74 CSE-1034: 0.500 Meropenem: 0.857 Difference in proportions: -0.357 (95% CI -0.836:0.257) Age: 75< Age <90 CSE-1034: 1.000 Meropenem: 1.000 Difference in proportions: 0.000 (95% CI Not estimate)	treatment difference generally favored CSE; **the exception being patients in the age group of 65–74.**		

Schlüsselfrage

Geriatrie-Prävention: Welche nicht-medikamentösen Maßnahmen verringern die Häufigkeit rezidivierender Harnwegsinfektionen?

Referenz	**Studien-charakteristika**	**Studien-ziel**	**Patienten-merkmale**	**Inter-vention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Juthani-Mehta M 2016 [90] 27787564	RCT N= 185 English-speaking, female, nursing home residents, age 65 or older USA August	To test the effect of two oral cranberry capsules once per day on presence of bacteriuria plus pyuria among	N=185 Female, nursing home residents, age 65 or older, with or without bacteriuria and pyuria at baseline	N= 92 Once per day two oral cranberry capsules, each capsule containing 36mg of the active ingredient	N= 93 Placebo	**Mean age 86.4 years [± 8.2])** **Treatment (n= 92): Age: 87.1 ±8.4** **Control (n= 93): 85.6 ±8.0** Presence of bacteriuria plus pyuria (unadjusted) overall over 1 year treatment group: • 25.5% (95% CI 18.6, 33.9) of the control group: • 29.5% (95% CI 22.2,	After adjusting for missing data and covariates, there was no statistically significant difference in presence of bacteriuria plus pyuria between the treatment (29.1%) and control (29.0%) groups over 1 year. Among older women residing in nursing homes, administration of cranberry capsules, compared with placebo, resulted in no significant difference in presence of	**Funding**: The funder (National Institutes of Health, National Institute on Aging, R01 AG041153, as well as K07 AG030093 and the Claude D. Pepper Older Americans Independence Center P30 AG021342) had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the	1b Rob: low

	24, 2012 through October 7, 2014 six follow-up time points (months 2-12).	women residing in (n=21) nursing homes		proanthocyanidin (i.e., 72mg total, equivalent to 20 ounces of cranberry juice)		37.9) of the Presence of bacteriuria plus pyuria (adjusted GEE model): **treatment (T) vs. control groups (CG)**: • 29.1% vs. 29.0%; • OR 1.01, (95% CI 0.61,1.66; p=0.984). number of symptomatic UTIs(T vs. CG) • 10 vs. 12 episodes **Adverse effects:** rates of death (T vs. CG) • 17 vs. 16, 20.4 vs. 19.1 deaths/100 person-years, • RR 1.07 (95% CI 0.54, 2.12), hospitalization (T vs. CG) • 33 vs. 50 episodes, 39.7 vs. 59.6 hospitalizations/100 person-years, • RR 0.67, (95% CI 0.32, 1.40), bacteriuria associated with multi-drug resistant gram-negative bacilli (T vs. CG) • 9 vs. 24 episodes, 10.8 vs. 28.6 episodes/100 person-years, • RR 0.38, 0.10, 1.46, antibiotics administered for suspected UTI (T vs. CG) • 692 vs. 909 antibiotic days, 8.3 vs. 10.8 antibiotic days/person-year, • RR 0.77, (95% CI	bacteriuria plus pyuria over 1 year.	data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The cranberry and placebo capsule manufacturer had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Conflicts of Interest**: None High loss to follow-up in both groups (reasons not ☐ fully described)	

						0.44, 1.33), <u>total antimicrobial utilization (T vs. CG)</u> • 1415 vs. 1883 antimicrobial days, 17.0 vs. 22.4 antimicrobial days/person-year, RR 0.76, (95% CI 0.46, 1.25).			
Wu 2020 [97] 31971291	Systematic Review N= 4 studies (n= 2 Quasi-experimental, n= 1 descriptive study; n= 1 RCT) Serach: 2008–2018. Conducted in: Taiwan, USA, Australia, Netherlands	Aim is to assess the effectiveness of nurse-led interventions to prevent **urinary tract infection**, including **catheter-associated** urinary tract infection, in older adults in RACFs	older adults (65 years of age or over) living in RACFs, were included [regardless of their mobility, cognitive impairment or the presence of urinary catheters]	nurse-led interventions a) the appointment of advanced practice nurses, (b) those focused on a single specific nursing intervention, and (c) implementation of a multicomponent nursing intervention.	None or fluid intake	**Lin 2013** (quasi-experimental, age in INT & CON: 75.2 ± 11.9 years, urinary cath.: no (excluded); Nursing homes) <u>INT: (n = 30) Increase daily fluids to greater than 1,500 ml (6-week follow-up) vs. CON: (n = 44) Maintained fluid</u>: **ASB-prevalence** significantly reduced between baseline and 6-week follow-up (p < .001) for both groups of participants. **No significant difference** between pre- and postintervention in asymptomatic bacteriuria. Compared to the control group, the **intervention group** had significantly greater improvement on daily fluid intake (p < .001). **Morrison-Pandy 2015** (descriptive study; age in INT & CON: 79.6 ± 8.07(range 66–90) years; urinary cath.: no	Nurses are leaders in health care and are well placed to lead prevention of urinary tract infections in residential aged care; however, evidence of the effectiveness of a nurse-led approach is limited. High-quality randomised controlled trials are warranted to address the **knowledge gap** and **advance practice** in this area. <u>Relevance to clinical practice</u>: When developing an effective nurse-led intervention programme, the programme should be grounded in **nurse-led principles** and consider the complex staffing factors to ensure that nurse-led programmes are tailored to an effective level. Due to the relative lack of currently available evidence regarding the effectiveness of nurse-led interventions **for reducing catheter-associated** urinary tract infection in older adults in RACFs, this review is limited to only addressing review question 1preventing CAUTI in older	Prospero: CRD42018096889 Narrative summary to give an overview of current approaches and outcomes concerning nurse-led interventions for preventing urinary tract infections in older adults in residential aged care facilities. **Conflict of Interest**: None **Funding information**: This project was funded by research capacity-building seed funding from Griffith University. The funding body had no role in study design; collection; analysis or interpretation of the data; report writing or decisions on publication. There was no external funding. Highly heterogeneous included studies → it was impossible to determine	2a RoB: low

						(excluded); long-term care facilities) INT (n= 89): NPs provided evidence-based supportive strategies including increasing fluid intake and voiding frequency, and/or drinking cranberry juice (no control). Postemployment of a NP, significantly greater **improvement in management of aUTI** with the following supportive strategies: increased fluids ($p < .001$), frequent toileting ($p < .001$), and cranberry juice ($p < .05$). No significant differences in **antibiotic** prescribing rates from pre- to postemployment of the NP **Stuart et al. 2015** Quasi-experimental (urinary cath., age and sample size were not reported; Residential aged care facilities (RACFs) and hostel) INT (n= not reported): A nurse-led antimicrobial stewardship intervention (3-month follow-up) including an education programme, whicht highlights the importance of using antibiotics appropriately (no control) **Post-CNC-led intervention**, there was a statistically significant	adults in RACFs.	the most effective intervention approach. Limited available studies. Studies published in English→ increases the risk of publication bias. Review is unable to provide a summary of evidence of nurse-led intervention for CAUTI in older adults in RACFs due to insufficient studies in the field.	

						decrease in OBDs for UTI ($p < .001$). **Antibiotic usage** was significantly reduced ($p < .001$) **van Gaal et al. (2011)** Cluster RCT; urinary cath.: not reported; nursing homes <u>INT(n = 196; age: 80 ± 10.9 years): Patient safety programme (SAFE or SORRY?) (9-month follow-up)</u> <u>1.) Nurse education; 2.) patient involvement; 3.) nurses register patients's feedback vs. CON: usual care (n = 196; age: 79 ± 10.5 years)</u> **Incidence of UTI between groups**: • RR = 0.85, 95% CI: 0.43–1.67 **Fewer pressure ulcers per patient-week**: • RR= 0.34, 95% CI: 0.15–0.76) and • falls per patient-week: RR = 0.63, 95% CI: 0.35–1.16) for intervention group compared to control. **Incidence of adverse events**: • RR = 0.67, 95% CI: 0.47–0.97) for the intervention group compared to control.			

						None of the included studies reported outcomes for **change in mental status** (e.g. confusion or delirium), unusual behaviour changes or falls.			
Meddings 2017 [98] 28459908	Systematic Review N= 19 (8 RCTs, 10 non-randomized interventions, 1 non-randomized intervention with current controls) Search: through June 22, 2015	Strategies to reduce UTIs/CA UTI in nursing home residents	Participants with or without catheters (i.e., not limited to only catheterized patients) in nursing homes	patients/ residents who have undergone interventions → **Single and multiple interventions:** interventions involving urinary catheter use (improving appropriate use, aseptic placement, maintenance care, prompting removal of un-necessary catheters). Infection preventio	Available reported non-exposed group (either as a pre-intervention assessment/baseline, or concurrent type of control group).	**Interventions to reduce UTI, CAUTI or urinary catheter use*** **Mentes, 2003, US**, RCT, 42 elderly residents from 4 nursing homes: 2 VA nursing homes, 2 community nursing homes **Strategies to reduce or improve catheter use**: None specified **Infection prevention strategies**: None specified **Other strategies**: Increase hydration (single intervention, 8 weeks) **Reported Outcomes Types**: UTI **UTI, CAUTI, Bacteriuria Measures**: Hydration-linked event of UTI diagnosed by a provider (unclear if symptoms, catheter use or other criteria), proceeded by urine specific gravity of >=1.010 + decreased fluid intake **Comparison Group**: 1 UTI (4.1% of 24 control patients) **Intervention**: 0 UTI (0% of 25 treatment patients) **Urinary catheter use measures**: not reported	Several practices, often implemented in bundles, appear to reduce UTI or CAUTI in nursing home residents such as improving hand hygiene, reducing and improving catheter use, managing incontinence without catheters, and enhanced barrier precautions.	Performed narrative! Studies were often underpowered to assess statistical significance; none were pooled given variety of interventions and outcomes. **Mean-Age of the "elderly/aged" patients is not mentioned!** Limited information about their intervention and on how outcomes were defined Due to large trial heterogeneity among these studies with respect to interventions and outcomes reported. RoB was not identified; risk of bias was not mentioned; heterogeneity of studies was mentioned only in a subordinate sentence. **Conflicts of interests**: None **Financial Support:** Agency for Healthcare	3a - RoB: high

				n strategies (hand hygiene, barrier precautions, infection control strategies, infection surveillance, use of standardized infection definitions, interventions to improve antibiotic use). → defined as facilities providing short-stay skilled nursing care and/or rehabilitation, as well as long-term care.		**Stuart, 2015, Australia**, non-randomized trial, Residents in 2 urban aged care facilities 130 beds **Strategies to reduce or improve catheter use**: None specified **Infection prevention strategies**: (multiple interventions; pre- and post: à 3 months) Nurse-led antibiotic stewardship program, infection control and surveillance programs. **Other strategies**: Nurse-physician communications about antibiotics and data **Reported Outcomes Types**: UTI **UTI, CAUTI, Bacteriuria Measures**: UTI rates form surveillance data using McGeer's criteria **Comparison & intervention group**: Data not provided, but text indicates surveillance infection rates surveillance data remained stable over the 2 data collection periods **Urinary catheter use measures**: not reported **Yeung, 2011, China** RCT, 1268 elderly residents in 6 nursing homes **Strategies to reduce or improve catheter use**: None specified		Research and Quality (AHRQ) contract #HHSA290201000025I provided funding for this study which was developed in response to AHRQ Task Order #8 for ACTION II RFTO 26 CUSP for CAUTI in LTC. AHRQ developed the details of the task and provided comments on a draft report, which informed the report submitted to AHRQ in December 2013 used to inform the interventions for a national collaborative (http://www.hret.org/quality/projects/long-term-care-cauti.shtml). Author JM's effort on this project was funded by concurrent effort from her AHRQ (K08 HS19767); JM's other research is funded by AHRQ (2R01HS018334-04), the NIH-LRP program, the VA National Center for Patient Safety, and the VA Ann Arbor Patient Safety Center of Inquiry; SS's and SK's effort on this project was funded by concurrent effort from the Veterans Affairs National Center for Patient Safety, Patient Safety Center of Inquiry. SK's other research is	

						Infection prevention strategies: Hand hygiene (single intervention) **Other strategies**: None specified **Reported Outcomes Types**: UTI **UTI, CAUTI, Bacteriuria Measures**: UTIs requiring hospitalization, unclear if with or without catheters **Comparison group**: Baseline period:3 UTIs per 32,726 resident-days, calculated as 0.09 per 1,000 resident-days // Follow-up period:22 UTIs per 81,177 resident-days, calculated as 0.27 per 1,000 resident-days. p=0.06 **Intervention**: Baseline period:6 UTIs per 21,862 resident-days, calculated as 0.27 per 1,000 resident-days// Follow-up period: 8 UTIs per 50,441 resident-days, calculated as 0.16 per 1,000 resident-days). p=0.30 Urinary catheter use measures: not reported		funded by a VA Health Services Research and Development Award (RCS 11-222). LM's other research is funded by VA Healthcare System Geriatric Research Clinical Care Center (GRECC), NIA-Pepper Center, NIA (R01AG032298, R01AG041780, K24AG050685-01).	
Bruno 2021 [99] 34684642	Systematic review and meta-analysis N= 19 studies for qualitative synthesis	This study investigated the impact of interventions to improve hydration in	N=165 patients, Acutely unwell patients in hospital or residents in nursing homes (>65 years)	Oral methods to improve hydration or fluid intake	Comparator such as usual care	**Results of meta-analysis (n=2 studies)** groups receiving interventions to improve hydration consumed 300.93 mL more fluid per day than those in the intervention groups • MD=300.93 (95% CI: 289.27-312.59,	The major finding was that behavioural interventions utilising verbal prompting and increased availability or choice of drinks were associated with improvements in fluid intake and hydration. When pooled, interventions can improve fluid intake by approximately 300 mL per day. This is particularly	Conflict of interest None. Funding None. N=2 studies for meta-analysis (n=1 RCT, n=1 non randomized clinical trail)	1 a RoB: low

	(n=9 RCTs, n=7 pre-post studies, n=2 non randomized clinical trail, n=1 retroepctive analysis) Search date: up to 13 May 2020 Studies were conducted in: UK, Taiwan, USA, Japan, Australia,	acutely unwell or institutionalised older adults for hydration and hydration linked events (constipation, falls, urinary tract infections) as well as patient satisfaction.				I^2=0%), p<0.00001 **<u>Results of systematic review (n=19 studies)</u>** <u>Behavioural Strategies</u> (n= 7 studies) **Allen et al. 2013** participants consuming nutritional supplements through a • glass/beaker (64.6 ± 34.3%) compared • through a straw 57.3 ± 37.0%, • supplement volume p = 0.027 **Bak et. al 2018** • statistically significant increase in fluid intake at breakfast time (Mean intake at breakfast from 139mL (±84 mL) to 205 mL (±12 mL); p = 0.03). • this result is not clinically significant, change in intake was only 70 mL **Lin et. al 2013** provided unrestricted drinks choice to reduce bacteriuria rates in nursing home residents • intervention group from 1449 mL (± 421 mL) to 1732 mL (± 301 mL); p < 0.01 • control group from 1539 mL (± 565 mL) to 1548 mL (± 558	important in the acute clinical setting where a successful intervention could be implemented into practice and result in reduced dehydration related outcomes and length of stay. This is particularly important in the acute clinical setting where a successful intervention could be implemented into practice and result in reduced dehydration related outcomes and length of stay.		

						mL) per day (p = 0.643). **Schnelle et al. 2010** offered beverage choices to residents' multiple times a day and compared Intervention vs. Control: • 186 mL vs. 56.2 ± 118 mL); p < 0.001 **Simmons et al. 2001** provided daily verbal prompting to drink • Serum osmolality significantly declined in both groups overtime (p < 0.05) • fluid intake between meals with each phase of prompting (p < 0.001). **Spangler et al. 1984** offering beverage choices and assistance with toileting to nursing home residents every 1.5 h. • Urinometer scores at baseline indicated 25% of residents were dehydrated (score > 20) • post intervention all residents had scores < 20 indicating absence of dehydration (p < 0.002). **Tanaka et al. 2009**			

						provided residents with beverage choices in between meals and staff offered encouragement to drink • after the intervention was implemented (1146.4 ± 365.2) • compared to baseline (881.1 ± 263.8) • p < 0.001 <u>Environmental Strategies (n=4 studies)</u> **Dunne et al. 2004** assessed the effect of low and high contrast tableware compared to white tableware on fluid intake in nursing home residents with Alzheimer's disease. This occurred as two separate studies one year apart. • first study using high contrast red tableware demonstrated a significant mean percent increase of 84% for liquid between baseline and intervention (p = 0.001). • follow up study, the mean percent increase in liquid intake for high contrast blue was 29.8% (p < 0.05) **Holzapfel et al. 1996** assigned nursing home residents to three groups where a feeding			

						assistant would provide food and beverages to residents in a specific position (standing, sitting or position chosen by feeding assistant). • Statistically result were ob-served with fluid intake at day 5 • comparing the control group (choice of position by assistant) and experimental groups (sitting or standing or position chosen by feeding assistant) • no significant result (control vs. experimental group) **Kenkmann et al. 2010** implemented a program to increase the availability and choice of drinks as well as improve the social and physical environment at mealtimes • Rates of dehydration dropped in both intervention and control care homes (16% to 9% and 46% to 39% respectively) • RR of being dehydrated in an intervention home compared to a control home was 0.36 (CI 0.06 to 2.04, p = 0.25) **Robinson and Rosher**			

						2002 implemented a five week hydration program (increased availability and choice of drinks using a colourful beverage cart) in a nursing home • percent of residents meeting the fluid goal was 53% with 24% not meeting the goal every time • No significance value was reported. <u>Multifaced Strategies (n=3 studies)</u> **Mentes and Culp 2003** provided 180 mL of fluid with medication administration, providing drinks in between meals as well as offering a one hour time period where non-alcoholic cocktails are served (also known as happy hour) twice a week in the afternoon. • meeting fluid goals, urine colour and specific gravity did not increase significantly for either intervention or control group (p = 0.08) • Incidence of HLEs was 3 events per 63 days of follow-up for the intervention group and 6 events per 60 days of follow-up for the control group but			

						this was not statistically significant (p = 0.39). **Smith et al. 2019** utilised a three-pronged approach (providing flavoured water, using larger cups and increased prompting to drink by nurses) • Fluid intake increased with the mean fluid intake at baseline being 1551 mL • compared to 2225 mL post intervention **Wilson et al. 2019** implemented an intervention that included drinks being provided in between main meals, implementation of protected drinks time and increasing choice through a drinks menu • Mean fluid intake at Home A < 1500 mL per day whilst mean fluid intake at Home B was >1500 mL. • No statistically significant value was reported. • There was no change in the incidence of HLEs however there was a significant decrease in the use of laxatives in both homes (p < 0.05)			

						Nutritional Strategies (n=5 studies) **Howard et al. 2018** patients with dysphagia who had received nectar thick and textured thin fluids during their hospital stay • Creatinine and sodium levels significantly vs. nectar thick diet (p = 0.047, p = 0.014 respectively). • Although serum urea increased when on a nectar thick diet this change was not statistically significant (p = 0.07). • When patients changed over to the textured thin liquids, serum urea dropped significantly (p = 0.06) • Creatinine decreased into the normal range, but the change was not significant (p = 0.63). **Karagiannis et al. 2011** implemented a water protocol in patients with dysphagia for five days, control group could only consume thickened fluids. • Fluid intake increased significantly in the intervention group receiving the water protocol (1428 ± 7.0			

						mL to 1767 ± 10.7 mL, p < 0.01). • The number of lung complications was significantly higher in the intervention group with 6 cases reported compared to zero in the control group (p < 0.05) **McCormick et al. 2006** determine if commercially thickened fluids or fluids thickened at the bedside increased fluid intake and influenced rates of constipation. • The difference in fluid intake between the two interventions were minimal with 795 mL of pre thickened liquids consumed • compared to 785 mL consumed prethickened drinks at the bedside (p = 0.47). No changes in constipation rates were observed. **Murray et al. 2016** applied the same water protocol as previously described by Karagiannis et al. to patients with dysphagia for two weeks. • Intervention- vs. control-intake: (1103 ± 215 mL, 1103 ± 247 mL respectively, p =			

						0.998). • UTI in control vs. intervention group (p = 0.024). **Taylor and Barr 2006** if a 3 day meal pattern compared to a five day meal pattern improved fluid intake. • Fluid intake was higher at with five meals (698 ± 156 mL) compared to three meals (612 ± 176 mL, p = 0.003). **<u>Metaanalysis: Fluid intake (baseline and post intervention)</u>** **Karagiannis 20211, Lin 2013** • MD 300.93 mL (95% CI 289.27 mL 312.59 mL, I^2 = 0%, p< 0.00001)			
Shepherd 2017 [100] (update from 2010; search inception till 2009) 28262925	Systematic Review N= 7 studies (n= 4 RCTs; n=3 randomized cross-over trials) 3xUSA, 2xUK, 1xCanada,	To determine if certain washout regimens are better than others in terms of eIectiveness, acceptability, complications,	N= 349 Adults, aged (≥65 years) at least 16 years, in any setting (i.e. hospital, nursing/ residential home, community) with an indwelling urethral, suprapubic or perineal catheter in	catheter washouts with water, saline, antiseptic, acidic, antimicrobial or antibiotic solutions alone or in any combination.	not using catheter-washout (cw), another type of cw, routine washout, short intervals, administration of cw, larger volume, weaker solution of washout or	**.Airaksinen 1979, RCT**; n=*40 randomly assigned participants, required a long-term indwelling catheter for a minimum of six months, age range: 50 to 59 years up to 85 to 99 years* <u>(treatment 1&2 group) Washout with saline (n=20) versus (control 1 & 2 group) no washout and also different types of silicone catheters (Silicath and Silastic) (n=20)</u> (6 months duration) **1. Any catheter**	**Data** from seven trials that compared different washout policies **were limited**, and generally, of **poor methodological** quality or were **poorly reported**. The evidence was not adequate to conclude **if washouts were beneficial or harmful**. **Further rigorous, high quality trials** that are adequately powered to detect benefits from washout being performed as opposed to no washout **are needed**. **Trials comparing different washout** solutions, washout volumes,	**Study funding sources**: The included studies were funded by Novobay Pharmaceuticals Inc (Linsenmeyer 2014); Alberta Heritage Foundation for Medical Research and the Canadian Nurses Foundation (Moore 2009); National institute of Aging, National Institutes of Health (Muncie 1989); Paralyzed Veterans of America	1 a - RoB. high

	1xFinland Search: (from last update?) to 23 May 2016	quality of life and critically appraise and summarise economic evidence for the management of long-term indwelling urinary catheterisation in adults.	situ for more than 28 days. Adults whose treatment combined intermittent catheterisation with periods of indwelling catheterisation were included only if the indwelling catheter had been in situ for more than 28 days at the time of data collection.		two or more sequential washout instillations of the same type.	**washout versus no washout** **1.1. Catheter removal rates due to blockage or infection** All participants received new catheters on day 0; participants in both Silicath catheter groups had these replaced at three months. Silicath catheter group with regular irrigation: 5/10 participants required a catheter change in the first three months of the study compared to those with similar catheters who were in the control group (no irrigation) in which 8/10 participants required a catheter change (stated $P < 0.01$). Silastic catheter intervention group: 2/11 participants required a catheter change compared with 2/9 participants in the silastic control group: • RR 0.67 (95% CI 0.34 to 1.31), • $P < 0.50$; 1 study. **Moore 2009, RCT**; 73 patients with community-dwelling or long-term care adults with long-term indwelling catheters that required changing every three weeks or less, requiring supportive or continuing care; m*ean age 66.24 years (Contisol*	and frequencies or timings are **also needed**.	Spinal Cord Research Foundation (Waites 2006). Three studies did not report funding sources. **Declaration of interest**: None Evidence was limited/insufficient to determine whether washout regimes were beneficial or harmful in long-term indwelling urinary catheterisation among adults. Limitations with the search meant that relevant studies were likely to have been missed. Further a large number of well-designed adequately powered high-quality RCTs are needed to support these findings Just studies with patients mean age 65+ AND without serious comorbidities are listed.	

						group mean 63.92 years, saline group mean 66.24 years, control group mean 68.56 years) <u>Parallel group RCT, 3 groups: catheter flush with saline vs acidic solution vs standard care (no washout)</u> (8 weeks) **1. Any catheter washout versus no washout** **1.1. Symptomatic UTI** No symptomatic UTIs in any study participants in the washout or non-washout groups. Self-reported UTIs (which did not meet the study criteria for symptomatic UTI) were noted in each group (citric acid 5/24, saline 2/18, no washout 3/23, P not reported). **1.2 Length of time each catheter in situ** (weeks until first catheter change): • citric acid 4.57 (SD 2.61) (N = 19); • saline 5.18 (SD 2.90) (N = 16); • no washout 4.55 (SD 2.91, N = 20) (P = 0.642) **2. One type of catheter washout solution versus another** **2.1 Symptomatic UTI** (Rate of participants discontinuing the use of washouts due to the			

						development of a symptomatic UTI): No symptomatic UTIs in any group in the trial using the citric acid or saline solutions. **2.2 Length of time each catheter in situ** (Mean time until first catheter change) No significant difference among trial groups, including the two groups receiving different washout solutions (citric acid versus saline, randomised cross-over trials (n= 136 participants) **Kennedy 1992 randomised cross-over trials**; *25 elderly women in long-term geriatric care with long-term catheter in situ, mean age 82 years, range 65 years to 100 years* -3 interventions: **A** 3 weeks of twice weekly sodium chloride washout, **B** 3 weeks of twice weekly Suby G washout, **C** 3 weeks of twice weekly Solution R washout - allocation by random number tables (i.e. to decide order in which 3 solutions administered) (12 weeks) **1. One type of catheter washout solution versus another**			

						1.1 Length of time each catheter in situ mean days the catheter was in situ: • saline16.3 days, • Suby G 14.3 days, • Solution R 14.2 days • P not reported. No standard deviations were reported. Authors reported no significant differences between groups. Only 3 participants retained their catheter for the full length of each trial period. **1.2 Catheter removal rates due to blockage or infection** 100 of 120 study catheters were examined for encrustation: • saline 18/44 catheters (41%), • Suby G 14/29 catheters (48%), • Solution R 7/27 catheters (26%). →no statistical tests were presented. Time effect was noted such that blocked catheters would be removed early (before they could be examined) thus distorting the data. → Reported: Little difference among the three solutions up to day 10, after which it was felt Solution R did not reduce encrustation. Mean encrustation scores were			

						presented but without standard deviations. →Mean number of episodes of bypassing per week: • saline 1.55, • Suby G 1.4, • Solution R 1.9, • P value not reported **1.3 Rates of ASB** comparing 3 solutions, the percentage of participants with bacteria observed in washout fluid at the end of a washout period with one of the trial solutions were: • saline 100%, • Suby G 75%, • Solution R 76%. → differences were not statistically significant (statistical test results were not presented). Further conclusion: treatment with acidic solutions (Suby G and Solution R) did not prevent or reduce urease-producer bacteria. Published data on presence of bacteria were inadequately reported. **1.4 Measures of complications or adverse effects** percentage of participants in each group who had red blood cells in their washout fluid at the end of each treatment period: • saline 21%, • Suby G 17%, • Solution R 14%. • P = 0.028 (higher red			

						blood cell count in the Suby G group compared to other groups). Furthermore: significant difference among treatment groups for urothelial cells over time (P = 0.068), → unlikely to be clinically significant. **2. A stronger solution of washout versus a weaker solution** (Comparision of two acidic solutions with different compositions.) • solution R, 6% • Suby G, 3.23% →Other elements of the solutions also differed. Any differences may not be attributable to the strength of the citric acid solution. **Muncie 1989, randomised cross-over trials**; *44 patients with indwelling urethral catheters in place for 30 consecutive days or longer; mean age 71 years, range 37 years to 88 years, 33 women were aged 65 years or over* Single centre cross-over RCT, 2 interventions: Group A: normal saline irrigation, Group B: no irrigation (24 weeks) **1. Any catheter washout versus no**			

						washout **1.1 Catheter removal rates due to blockage or infection** mean catheter replacement rate per 100 days of catheterisation: • saline washout periods: mean= 5.5 catheters replaced (n = 32), • no washout periods: mean= 4.7 catheters replaced (n = 32). Daily saline washouts had no significant effect on the incidence of total number of catheter replacements. No details of statistical tests were presented. **1.2 Rates of ASB** (Urine specimens obtained every 2 weeks). • Saline washout periods: mean= 4.0, • no washout periods: mean= 3.8. No test of statistical difference was reported. Percentage of specimens in which each strain was present was similar in the saline washout and no washout periods of the study. **1.3 Complications and adverse events** episodes of high temperature with possible urinary origin (per 100 days of catheterisation for the three periods) as a			

						proxy for symptomatic UTI: • saline washout period: Mean 1.2 (SD 1.3); • no washout period: mean= 0.9 (SD 1.1). (period 1, irrigation versus none; period 2, irrigation versus none): Same results for all episodes of high temperature as well as those of urinary origin. Difference between episodes of high temperature with possible urinary origin as a proxy for symptomatic UTI was not statistically significant, although no details were given.			
Li 2019 [101] 30259542	Systematic review and meta-analysis N= 10 studies (n= 6 case-control studies, n=3 retrospective cohort studies, n= 2 prospektive cohort study)	to identify the risk factors for **catheter-associated urinary** tract infection among hospitalized patients. We also tried to explore its potential effect on	N= 8785 participants with or without catheter-associated urinary tract infection	615 patients with CAUTI	8,170 patients without CAUTI	**Kim et al. 2017 (sample age: 64 (50–74)** effect of gender on CAUTI occurrence • OR 1.15 (95% CI 0.49, 2.67) effect of diabetes on CAUTI occurrence • OR 1.19 (95% CI: 0.46, 3.04) effect of previous catheterization on CAUTI occurrence • OR=2.67 (95% CI: 1.61, 4.42) **Vincitorio et al. 2014 (sample age: 85.4 SD 8.5)**	Many risk factors are associated with the development of CAUTI in hospitalized patients, which may further cause an increase in patient mortality. Recognizing patients at high risk for CAUTI can target our nursing practice and improve patient safety. Healthcare staff should focus on the identified risk factors for catheter-associated urinary tract infection. Further research is needed to investigate the microbial isolates and focus on the intervention strategies of catheter-associated urinary tract infection, so as to reduce its incidence and related	Conflict of interest None Funding This project was funded by a programme from the Sichuan Department of Science and Technology (Grant number: 2016SZ0062). **Indirect evidence**: N= 2 studies relevant for geriatric patients. only observational studies included and all data were collected through hospital HIS system or patients'	3 a - RoB: high

	Search date: up to January 2018 Studies were conducted in: Italy, USA, Saudi Arabia, Korea, Serbia, Egypt	patient outcomes if possible.				effect of the duration of catheterization on CAUTI occurrence • MD=6.40 (95% CI: 3.77, 9.03) effect of gender on CAUTI occurrence • OR 1.50 (95% CI 0.89, 2.52) effect of age on CAUTI occurrence • MD=2.20 (95% CI: –0.82, 5.22) effect of hospital length of stay on CAUTI occurrence • MD= 7.20 (95% CI: 2.55, 11.85) CAUTI occurrence and related mortality • OR= 1.86 95% CI: 0.98, 3.53)	mortality.	medical histories, leading to a varying degree of selection bias and information bias; differing study designs among the included studies; high heterogeneity for most risk factors interfere with the reliable pooling of the data. No prospero, so that no statements can be made about the achievement of the a priori defined goals	
Durant 2017 [102] 28982611	systematic review N= 29 case-control studies (of a single group, with a pre-post design) Searches were limited to studies published	This review aims to discover the effect of nursedriven protocols on the clinical predictors and prevalence of CAUTI.	United States-Patients on a unit, units, or hospital-wide, with a urinary catheter, in a given time period, compared with a retrospective chart review of the same.	nurse-driven protocol on acute care patients in the United States related to CAUTI	compared with prior practice on acute care patients in the United States related to CAUTI	**(Only 1 study, that explicitly focused on the elder patients) Gotelli et al, 2008**, houses the acute care for the **elderly unit** and provides nursing care for general medicine patients admitted to the hospital Intervention: • 1-y baseline, 3-mo intervention period, 5-mo intervention evaluation period • Implementation of an NDP, which involved regular assessment of catheter necessity and	General: Nurse-driven protocols to facilitate appropriate catheter use and timely removal appear to have a positive impact on the clinical predictors and prevalence of CAUTI. However, with only low levels of evidence available and existing research lacking in methodologic integrity, there is a need to improve the study design of quality improvement projects conducted within the patient care setting. For elderly patients: indirect evidence.	**Fund**: not mentioned **Conflicts of interest**: In addition to being a PhD student at Rockefeller College of Public Affairs & Policy, University at Albany-State University of New York, D.J.D. works for the Healthcare Association of New York State. A qualitative synthesis of data extracted was conducted. The heterogeneity of outcomes and methods	3a - RoB: high

	since 2006. (unclear end of search!) USA					removal by the bedside nurse without a physician order if no indication was identified <u>Results</u>: • Urinary catheter UR decreased from **24% to 17%** pre- to post-intervention; 14 mo later, indwelling urinary catheter use rate **dropped to 16.33%,** indicating ongoing effectiveness of the intervention • The number of CAUTIs remained the same at 5 months, pre- and post-intervention; a reduction in the number of CAUTIs was not shown		used made a statistical metaanalysis inappropriate. No Prospero, so no conclusions can be made about adherence to a priori planned analyses; inadequate search strategy; no inormation regarding two independent reviewers (minimizing risk of bias).	
Fasugba 2017 [103] 27986361	N= 14 studies (3 quasi-experimental studies and 11 RCTs) Serach: inception to December 2015 USA, UK, Saudi Arabia, South	To undertake a systematic review of the literature and meta-analysis of studies investigating the effectiveness of antiseptic cleaning before urinary catheter	Patients requiring short- or long-term IDCs or inter-mittent catheterization in hospitals, community settings and long-term care facilities.	antiseptic (povidone-iodine, chlorhexidine or antibacterial); sometimes in addition with alcohol-containing agent	non-antiseptic (water, saline, soap and water, or routine care)	**Geriatric population: n= 4 studies (3 RCTs; 1 quasi experimental study)** ***Effect of <u>meatal cleaning</u> on the incidence of catheter-associated urinary tract infections (results stratified by meatal cleaning agent)*** **Carapeti 1996** (RCT; General surgery patients; Intervention mean age: 67.5; Control mean age: 65.3) <u>0.3% CHG and 3% centrimide Savlon solution and 2.84%</u>	**Effect of meatal cleaning on the incidence of CAUTIs** No subgroup analysis of elderly people ➔ Indirect evidence **Effect of alcohol-containing antiseptic agents on the incidence of CAUTIs:** Although no specific information was provided on the presence of alcohol in the intervention agents in the included Studies, antiseptic interventions (Carpeti, Duffy, Lynch) may have included alcohol as an agent to deliver the ointment, cream or liquid. Given the difficulty in ascertaining the level of alcohol that intervention agents may contain, further	Demographic data on age of participants was not stated in the majority of papers. The only papers presenting data of geriatric people were old. There was considerable diversity in the types of interventions used, frequency of administration of the intervention, and laboratory definitions of UTI. **Funding sources**: This study was partially	1 a RoB: low

	Korea, Iran, Australia	insertion and during catheter use for prevention of CAUTIs.				isopropyl alcohol, 0.056% benzyl benzoate and terpineol as excipient ingredients (UTI-rates: 7/74) vs. Tap water (9/82) *(Once for surgery)* • OR 0.85 (95% CI 0.30, 2.40) **Duffy 1995** (RCT Male veterans in long-term care; Intervention mean age 72.6 (SD= 10.8); Control mean age: 70.9 (SD 12.1)) 10% povidoneiodine Betadine Solution and pareth-25-9 as inactive ingredient (UTI-rates: 26/42) vs. Soap and water (UTI-rates: 21/38) *(Pre-IC,~thrice daily)* • OR 1.32 (95% CI 0.54, 3.21) **Ibrahim 2002** (RCT, Male transurethral surgery patients; intervention mean age: 66.7 (SD= 10.1), control mean age: 66 (SD 10.4)) Povidoneiodine solution and alcohol containing agent Unclear, assumed no (UTI-rate: 19/64) vs. saline (UTI-rate 18/66) *(once/day)* • OR 1.13 (95% CI 0.53, 2.41) **Lynch 1991** (quasi experimental: Male transurethral surgery Patients; intervention	analysis on this potential confounder was not possible. There were **no differences in CAUTI rates**, although methodological issues hamper generalizability of this finding. Antibacterial agents may prove to be significant in a well-conducted study. The present results provide good evidence to inform infection control guidelines in catheter management.	funded by a seed grant from the Australasian College for Infection Prevention and Control and an Australian Catholic University Health Sciences Vacation Scholarship grant. **Conflict of interest:** None	

						mean age: 67 (SD= 9.7); control mean age: 68.4 (SD 8.4)) 2% polynoxylin Anaflex spray and formaldehyde as active ingredient (UTI-rate: 6/50) vs. no comparator agent-intervention (UTI-rate 11/50) *(once/day)* • OR 0.48 (95% CI 0.16, 1.43) ***Effect of using an antiseptic meatal cleaning agent (povidone-iodine, chlorhexidine or antibacterial) vs a non-antiseptic agent (no treatment/ usual care, soap and water, water or saline) on the incidence of catheterassociated urinary tract infections. (same data as above!)***			
Mitchell 2021 [104] 34103320 **(Mitchell wrote a joint SR with Fasugba 2017 (see above). This is an update! The exact**	updated systematic review and meta-analysis N= 18 RCTs (inkl. n=3 quasi-RCTs) USA, UK,	To present an updated systematic review on the effectiveness of antiseptic cleaning of the meatal area for	patients requiring short-term or long-term indwelling catheters or intermittent catheterisation in hospitals, community settings, and long-term/ aged care	the use of antiseptic, antibacterial agents for cleaning the meatal, periurethral or perineal areas	non-medicated agents (such as soap and water)	**Carapeti 1996 (27)** (UK, RCT; General surgery patients; Intervention mean age: 67.5; Control mean age: 65.3) 0.3% CHG and 3% centrimide Savlon solution and 2.84% isopropyl alcohol, 0.056% benzyl benzoate and terpineol as excipient ingredients (UTI-rates: 7/74) vs. Tap water (9/82) (Once for surgery)	There is emerging evidence of the role of some specific antiseptics (chlorhexidine) prior to urinary catheterisation, in reducing CAUTIs, and some potential benefit to the role of antiseptics more generally in reducing bacteriuria.	There was considerable heterogeneity in intervention and population groups. Pooled OR. Just indirect evidence (no subgroup-analysis of elderly patients) **Funding**: None **Competing interests**: BM reports personal fees	1a - RoB: high

same studies are listed here. Kara 2017 has been added!!!).	Australia, Saudi Arabia, South Korea, Turkey, Iran, Java Search: period between 1 January 2016 and 29 February 2020 (1 January 2016 represents the end date of the search from the initial review)	the prevention of CAUTIs and bacteriuria in patients who receive a urinary catheter.	facilities	before indwelling catheter insertion or intermittent catheterisation or during routine meatal care.		• OR 0.85 (95% CI 0.30, 2.40) **Duffy 1995 (29)** (RCT Male veterans in long-term care; Intervention mean age 72.6 (SD= 10.8); Control mean age: 70.9 (SD 12.1)) 10% povidoneiodine Betadine Solution and pareth-25-9 as inactive ingredient (UTI-rates: 26/42) vs. Soap and water (UTI-rates: 21/38) (Pre-IC,~thrice daily) • OR 1.32 (95% CI 0.54, 3.21) **Ibrahim 2002 (31)** (USA, RCT, Male transurethral surgery patients; intervention mean age: 66.7 (SD= 10.1), control mean age: 66 (SD 10.4)) Povidoneiodine solution and alcohol containing agent Unclear, assumed no (UTI-rate: 19/64) vs. saline (UTI-rate 18/66) (once/day) • OR 1.13 (95% CI 0.53, 2.41) **Kara 2017 (32);** (Turkey, RCT; ICU, surgical and medical patients) Intervention mean age: 66.34 (SD 14), 63.5 (SD 12); control mean age: 67.96 (12) Sterile water		from MSD, grants from Cardinal Health, grants from Senver, outside the submitted work. Prospero: „If sufficient studies are identified, subgroup analyses will be done by sex, age,..“ All 5 studies represents elderly people but no subgroup-analysis of age was done → a priori analysis was different	

						10% povidone-iodine vs. sterile water (once daily) • OR 0.49 (95% CI 0.13, 1.88) **Lynch 1991** (UK, quasi RCT: Male transurethral surgery Patients; intervention mean age: 67 (SD= 9.7); control mean age: 68.4 (SD 8.4)) 2% polynoxylin Anaflex spray and formaldehyde as active ingredient (UTI-rate: 6/50) vs. no comparator agent-intervention (UTI-rate 11/50) (once/day) • OR 0.48 (95% CI 0.16, 1.43)			

Schlüsselfrage

Geriatrie-Prävention: Welche medikamentösen Maßnahmen verringern die Häufigkeit rezidivierender Harnwegsinfektionen?

Referenz	Studien-charakteristika	Studien-ziel	Patienten-merkmale	Inter-vention	Kontrolle	Ergebnisse	Schlussfolgerungen des Autors	Methodische Bemerkungen	LoE/ RoB
Duenas-Garcia, O. F., et al. (2016). [69] 26825411	Systematic review n=9 RCTs Search date: 1970-2015	The purpose of this systematic review was to evaluate and summarize pharmacological	postmenopausal women with rUTI	pharmacological interventions	pharmacological interventions or placebo	**Antibiotics** (n=3 RCTs, Zhong 2011; Raz 2003; Beerepoot 2012; n=491 patients) Beerepoot 2012 - *Sulfamethoxazole plus trimethoprim (mean age, 65.4 ± 8.3 yr)* - *Vaginal lactobacilli*	This review supports the use of antibiotic suppression, vaginal estrogen, and oral lactobacillus for prevention of recurrent UTIs in postmenopausal women.	complete search strategy was not reported, no efforts were made to minimise error in: the study selection process, the data extraction and risk of bias assessment, no funnel plot CAVE: • some incorrectly assigned reference numbers	1a - RoB: high

	China, Israel, Netherlands, UK, Norway, Italy	interventions evaluated in randomized clinical trials designed to prevent recurrent episodes of UTIs in postmenopausal women.				*(mean age, 63.2 ± 8.6 yr)* • No significant difference in outcome using sulfamethoxazole plus trimethoprim vs. vaginal lactobacilli (MD=2.9 vs. 3.3, p=0.42) Zhong 2011 - *Intermittent antibiotic therapy (mean age, 62.7 ± 7 yr)* - *Continuous antibiotic therapy (mean age, 62.8 ± 7.3 yr)* • continuous vs. intermittent dosing of various antibiotics • continuous group showed a higher number of UTIs over 1 year of follow-up (59.4% vs. 35.5%; p<0.05) • as well as a higher rate of side effects Raz 2003 - *estrogen pessary (mean age, 68 yr; range, 49–82 yr)* - *Nitrofurantoin (mean age, 66.9 yr; range, 46–84 yr)* nitrofurantoin vs. estriol pessary patients using nitrofurantoin		Funding None. Conflict of interest None.	

						suppression had fewer UTIs compared to estriol pessary users (48 vs. 124, p<0.0003).			
Chwa, A., et al. (2019) [105] 31579504	Systematic Review January 1960 through September 2018 N= 10 studes (6 RCTs; 3 case studies; 1 cohort study) Countries of included studies: not mentioned	to evaluate the existing literature and discuss the use of methenamine in older adults for prevention of UTI.	Patients with a mean age of 58 years and older; receiving methenamine for prevention of UTI (just m. or in combination with a placebo).	methenamine	placebo, when applicable	**Incidence of UTI or bacteriuria (methenamine versus placebo, when applicable) (n= 5 studies)** **Freeman 1968** Methenamine (mandelate 1 g QID × 25 months) vs. placebo (N= 1 RCT; n= 122 patients; 58% > 60 years) • 25% versus 86% **Freeman 1975** Methenamine mandelate 1 g QID × 2 years vs. placebo (N= 1 RCT; n= 249 patients; mean age: 59 (21–83) • 9% versus 40% (p < 0.001) **Bohensky 1969** Methenamine mandelate 2 g QID × 25 days (n= 1 case series; n= 90 participants; mean age: 81.5 (67–102)) • 28% (no placebo) **Parvio 1976** Methenamine hippurate 1 g BID × 6 Months (n= 1 case series; n= 52 participants; mean age:	**Recurrent UTI:** Included studies shows that evaluated effectiveness of methenamine hippurate or mandelate in recurrent UTI prevention collectively resulted in positive results, with each showing a **reduction in incidence of UTI** or **bacteriuria**. The doses ranged from 500 mg twice daily to 1 g four times daily. Although the studies were able to show positive results, a collaborative recommendation for use of methenamine as a preventative strategy at doses lower than the FDA-approved doses remains unclear. All studies reviewed reported reduced rates of bacteriuria, but not all documented the incidence of symptomatic UTI. Bacteriuria may be a risk factor for UTI but does not always lead to a symptomatic UTI. **Long-term catheterization** The 2 studies provided positive results that supported methenamine hippurate 1 g twice daily	**Funding**: none **Conflict of interests**: none **Old** included studies. Included the reporting of **case studies**, which could introduce bias and may impact the validity of the findings. Many of the studies were of **low quality** and did not include statistical analysis to evaluate the significance of the rate of bacteriuria or UTI occurrence. No Prospero →statements on a priori analyses are not available; only one database; no information on 2 independent reviewers regarding minimization of errors in data collection; presumably not all central data to the synthesis were extracted; no RoB tool used and thus no corresponding reviewers; divergences between study types were not adequately considered; no funnel plots or sensitivity analyses; no analyses regarding risk of bias.	1a - RoB: high

						84.7 (65–96)) • 42.5% (no placebo) **McAllister 2014** Methenamine hippurate 500 mg BID (Case reports; n= 4 participants; mean age: 89) • Not applicable **Long-term catheterization (n= 2 studies)** **Kostiala 192** Methenamine hippurate 1 g BID + 0.5 g ascorbic acid TID × 8 days (n= 1RCT; n=123 patients; mean age 75) • 39% versus 100% at 1 week 77% versus 100% at 2 weeks Both 100% at 6 Weeks **Norrman 1976** Methenamine hippurate 1 g BID × 4 months (1 prosp. Cohort study, n= 22 patients; mean age: 75 (70–80)) • 18.2% versus 77.3%	as an effective off-label prophylactic option to prevent UTI in some patients with long-term need for catheterization. Methenamine hippurate may not be as effective at preventing UTI in patients with catheters compared with patients with recurrent UTI or postgenitourinary surgery, these studies demonstrated that it can delay acute occurrence of UTI postcatherization in some patients and decrease the future rate of UTI. Also methenamine hippurate was found to be antibiotic-sparing, a quality that may attenuate the development of antibiotic resistance in patients with recurrent UTI. Studies have not evaluated the **safety** of methenamine in patients with impaired renal function or CrCl <30 ml/min. When selecting a treatment approach to preventing UTI in older adults with adequate renal function, clinicians may consider methenamine as a viable option.		
Bakhit 2021 [79]	systematic review and	To systematically review	n=557 adult women (aged ≥18	methenamine hippurate	Placebo/ no treatment	In general n=6 studies, n=557 participants!	There is insufficient evidence to be certain of the benefits of	*The included studies also featured: considerable clinical and statistical heterogeneity;*	1a RoB:

34001538	meta-analysis n=6 RCTs Search date: up to 2020 UK, Australia, Norway, US	RCTs of adult women in the community with a history of recurrent UTIs and who use methenamine hippurate prophylactically	y) with a history of recurrent or confirmed UTIs		or any antibiotic	N= 3 RCT with data of geriatric people (Gunderson 1986, Høivik 1984, Botros 2020) **Prevention of UTI** *Patients remaining asymptomatic after 6 or 12 mo:* Methenamine hippurate vs. antibiotics: (**Botros** 2020, RCTs; N=92 (AGE: intervention: 70; comparison: 73)) • Methenamine: 15/43 • Any antibiotic: 15/43 RR 1.00 (95% CI 0.56 to 1.78) Methenamine hippurate vs. control (**Gundersen** 1986, RCTs; N= 30 participants; AGE: intervention: 74.5; Comparator: 74.0) (Placebo or antiseptic iodine perineal wash) • Methenamine Hippurate: 8/14 • Antibiotic: 4/14 RR=2.0 (95% CI: 0.78-5.14) *Patients remaining abacteriuric after 12 mo:* Methenamine hippurate vs. any antibiotic no geriatric data	methenamine hippurate to prevent UTI.	*poor reporting of bacterial resistance as one of the harms of using antibiotics in trials with an antibiotic arm; and general unclear risk of bias.* **Indirect evidence:** No subgroup-analysis of older people! Funding No funding or other material support was sought or received to perform this work specifically. Conflict of interest The authors have declared no competing interests.	low

						Number of symptomatic UTI episodes after 6 or 12 mo: <u>Methenamine hippurate vs. any antibiotic</u> no geriatric data **Adverse events** The most common adverse events reported in all studies were nausea, headache, and abdominal pain <u>Methenamine hippurate vs. antibiotic</u> (Botros 2020, RCTs) • methenamine hippurate:6/47 • any antibiotic: 4/45 OR= 1.50 (95% CI 0.39 to 5.71) <u>Methenamine hippurate vs. placebo or antiseptic iodine perineal wash (n=2 RCTs)</u> • methenamine hippurate:6/55 • any antibiotic: 2/27 OR=1.32 (95% CI: 0.23-7.77, I^2=0%); p=0.76			
Botros 2022 [106] 34115162	RCT N=92 women receiving daily prophylaxis with	**1**.to find an alternative treatment to a low-dose antibiotic for the	N=92 Women over 18 with a diagnosis of recurrent UTI, having at least two culture-	Methenamine hippurate (as a daily prophylaxis for a minimum	Trimethoprim (as a daily prophylaxis for a minimum of 6 months)	**Age overall (n= 92): 71.9±13.0; P= 0.35; postmenopausal: n= 86 (93.5%) p= 0.44 [mean ± standard deviation or n (%)]** <u>Trimethoprim (n= 47)</u>	Our findings support the Cochrane review of **methenamine hippurate** possibly being an **effective prevention strategy**, especially in the short term. In addition, methenamine hippurate	Study was not blinded and did not include a placebo arm. Open-label **Funding**: none **Conflicts of interest:** None	1b - RoB: high

	methenamine hippurate or trimethoprim for a minimum of 6 months. June 2016 to May 2018 Country: probably US (authors are from the USA) Follow-up: 6 and 12 months after starting treatment.	prevention of recurrent urinary tract infections (UTI) **2.** to evaluate the difference in rates of reinfection within 1 year when treated with methenamine hippurate for prophylaxis compared with trimethoprim.	positive UTI in the prior 6 months or three in the prior year.	of 6 months)		• Age (n =47): 70.6±15.0 • Postmenopausal: n= 43 (91.5) <u>Methenamine hippurate (n= 45)</u> • Age (n =45): 73.2±10.5 • Postmenopausal: n= 43 (95.6) **During prophylaxis [mean ± standard deviation or n (%)]** <u>Recurrent UTI at 1 year (ITT; trimethoprim n = 43; methenamine n = 43)</u> • Full Cohort (FC): 56 (65.1) • Trimethoprim (T): 28 (65.1) • Methenamine hippurate (Mh): 28 (65.1) • p= 1.00 <u>Recurrent UTI at 1 year (PP trimethoprim n = 40; methenamine n = 46)</u> • T: 26 (65.0) // Mh: 30 (65.2) • P= 0.98 <u>Time to subsequent infection (ITT)</u> • FC: 110±89.1 • T: 100.7±84.4 //Mh: 119.3±94.1 • P= 0.52 <u>Time to subsequent infection (PP)</u> • T: 106.5±84.9 // Mh: 113.0±93.9	may be **an acceptable long-term prophylaxis alternative** in the prevention of recurrent UTI, with similar adverse effects to trimethoprim. A significantly lower number of infections are seen with initiation of either treatment, with greater than 100 days to subsequent UTI after starting treatment.	variability in follow-up of participants and management at follow-up visits based on both patient and provider preference	

						• P= 0.88 <u>Number of UTI recurrences at 1 year (ITT)</u> • FC: 1.7±1.9 • T: 1.5±1.7 //Mh: 1.6±1.9 • P= 0.72 <u>Number of UTI recurrences at 1 year (PP)</u> • T: 1.8±2.1 // Mh: 1.4±1.5 • P= 0.36 **Decrease in number of UTIs per year [mean ± standard deviation or n (%)]** <u>Full cohort (mean ± standard devi.)</u> No. of UTI recur. prior to prophyl.: • 3.9 ± 1.8 No. of UTI recurrences within 1 yr after prophyl.: 1.6 ± 1.8 • p <0.01 <u>Trimethoprim (ITT)</u> No. of UTI recur. prior to prophyl.: • 4.0 ± 2.1 No. of UTI recurrences within 1 yr after prophyl.: • 1.5 ± 1.7 <u>Methenamine hippurate (ITT)</u> No. of UTI recur. prior to prophyl.: • 3.7 ± 1.5 No. of UTI recurrences within 1 yr after			

						prophyl.: • 1.6 ± 1.9 <u>Trimethoprim (PP)</u> No. of UTI recur. prior to prophyl.: • 4.3 ± 2.2 No. of UTI recurrences within 1 yr after prophyl.: • 1.8 ± 2.1 <u>Methenamine hippurate (PP)</u> No. of UTI recur. prior to prophyl.: • 3.5 ± 1.3 No. of UTI recurrences within 1 yr after prophyl.: • 1.4 ± 1.5 **Adverse effects and cost factors hindering use:** **T (n= 47)** **Mh (n= 45) [n [%]]** Diarrhea: • T: 1 (2.1); Mh: 2 (4.4); p= 0.54 Rash: • T:2 (4.3); Mh: 0; p= 0.17 Clostridium difficile colitis: • T: 1 (2.1); Mh: 0; p= 0.33 Weakness: • T: 2 (4.3); Mh: 0; p= 0.17 Abdominal pain: • T:0; Mh: 1 (2.2); p= 0.31 Nephrolithiasis: • T: 0; Mh: 1 (2.2);			

						p= 0.31 Cost of medication: • T: 0; Mh: 2 (4.4); p= 0.15			
Juthani-Mehta M 2016 [90] 27787564	RCT N= 185 English-speaking, female, nursing home residents, age 65 or older USA August 24, 2012 through October 7, 2014 six follow-up time points (months 2-12).	To test the effect of two oral cranberry capsules once per day on presence of bacteriuria plus pyuria among women residing in (n=21) nursing homes	N=185 Female, nursing home residents, age 65 or older, with or without bacteriuria and pyuria at baseline	N= 92 Once per day two oral cranberry capsules, each capsule containing 36mg of the active ingredient proanthocyanidin (i.e., 72mg total, equivalent to 20 ounces of cranberry juice)	N= 93 Placebo	**Mean age 86.4 years [± 8.2])** **Treatment (n= 92): Age: 87.1 ±8.4** **Control (n= 93): 85.6 ±8.0** Presence of bacteriuria plus pyuria (unadjusted) overall over 1 year treatment group: • 25.5% (95% CI 18.6, 33.9) of the control group: • 29.5% (95% CI 22.2, 37.9) of the Presence of bacteriuria plus pyuria (adjusted GEE model): **treatment (T) vs. control groups (CG)**: • 29.1% vs. 29.0%; • OR 1.01, (95% CI 0.61,1.66; p=0.984). number of symptomatic UTIs(T vs. CG) • 10 vs. 12 episodes **Adverse effects:** rates of death (T vs. CG) • 17 vs. 16, 20.4 vs. 19.1 deaths/100 person-years, • RR 1.07 (95% CI 0.54, 2.12), hospitalization (T vs. CG) • 33 vs. 50 episodes, 39.7 vs. 59.6	After adjusting for missing data and covariates, there was no statistically significant difference in presence of bacteriuria plus pyuria between the treatment (29.1%) and control (29.0%) groups over 1 year. Among older women residing in nursing homes, administration of cranberry capsules, compared with placebo, resulted in no significant difference in presence of bacteriuria plus pyuria over 1 year.	**Funding**: The funder (National Institutes of Health, National Institute on Aging, R01 AG041153, as well as K07 AG030093 and the Claude D. Pepper Older Americans Independence Center P30 AG021342) had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The cranberry and placebo capsule manufacturer had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. **Conflicts of Interest**: None High loss to follow-up in both groups (reasons not → fully described)	1b Rob: low

						hospitalizations/100 person-years, • RR 0.67, (95% CI 0.32, 1.40), <u>bacteriuria associated with multi-drug resistant gram-negative bacilli (T vs. CG)</u> • 9 vs. 24 episodes, 10.8 vs. 28.6 episodes/100 person-years, • RR 0.38, 0.10, 1.46, <u>antibiotics administered for suspected UTI (T vs. CG)</u> • 692 vs. 909 antibiotic days, 8.3 vs. 10.8 antibiotic days/person-year, • RR 0.77, (95% CI 0.44, 1.33), <u>total antimicrobial utilization (T vs. CG)</u> • 1415 vs. 1883 antimicrobial days, 17.0 vs. 22.4 antimicrobial days/person-year, RR 0.76, (95% CI 0.46, 1.25).			
Drekonja, D. M., et al. (2021) [94] 34313686	RCT (Rando-mized, double-blind, placebo-controlled Noninferi-ority trial) N= 272 men	To determine whether 7 days of treatment is noninferior to 14 days when using ciprofloxacin or trimethopri	N= 272 men with presumed symptomatic UTI treated with ciprofloxacin or trimethoprim/sulfa	(n = 136) **Group 1:** 7 days of antimicrobial treatment* **Group 2:** 7 days of antimicrobial treatment*	(n = 136) **Group 1:** … to receive continued 7-day placebo group (placebo on day 8 through	**272 men (median [interquartile range] age, 69 [62-73] years** **Intervention-Group** Age, median (IQR), y 70 (62-73) **Control-Group** Age, median (IQR), y 70 (62-75)	The findings support the use of a 7-day course of ciprofloxacin or trimethoprim/ sulfamethoxazole as an alternative to a 14-day course for treatment of afebrile men with suspected UTI.	**Role of the Funder/Sponsor**: The funding organization (VA Merit Review Program, grant number I01BX007080.) reviewed the design and conduct of the study. The funder had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or	1 b RoB: low

	USA April 2014 through December 2019 and from January 2018 through December 2019 final follow up, January 28, 2020	m/sulfamethoxazole to treat urinary tract infection (UTI) in afebrile men.	methoxazole	*with ciprofloxacin or trimethoprim/sulfamethoxazole	14) **Group 2:** … to receive continued 7-days antibiotic therapy	**Resolution of UTI symptoms 14 days after stopping active antimicrobials** As-treated population (primary analysis): Symptom resolution (participants/%) 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group • 122/131 (93.1%) vs. 111/123 (90.2%) • difference, 2.9% [1-sided 97.5% CI, –5.2% to ∞] As-randomized analysis: Symptom resolution (participants/%) 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group • 125/136 (91.9%) vs. 123/136 (90.4%) • difference, 1.5% [1-sided 97.5% CI, –5.8% to ∞] **Recurrence of UTI symptoms within 28 days of stopping study medication (secondary outcome)** As-treated population: Recurrence of UTI symptoms (participants/%): 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial		decision to submit the manuscript for publication. **Conflict of Interest Disclosures**: Dr Trautner reports research and consulting funding from Genentech and the National Institute of Allergy and Infectious Diseases for COVID trials; consultancy fees from Genentech; and grants from the US Department of Veterans Affairs (VA) rehabilitation Research & Development Service and the Agency for Healthcare Research and Quality. Ms Amundson reports receiving salary support for this trial during the conduct of the study from VA Merit Review grants. Dr. Johnson reports grant support from Allergan/Actavis, Cipla/Achaogen, Melinta, Merck, Shionogi, Synitron, Tetraphase; consulting fees from Crucell/Janssen; and pending patents for 2 E coli strain tests. No other conflicts were reported.	

						group • 13/131 (9.9%) vs. 15/123 (12.9%) • difference, −3.0% [95% CI, −10.8% to 6.2%]; P = .70 As-randomized population: <u>Recurrence of UTI symptoms</u> (participants/%): 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group • 14/136 (10.3) vs. 23/136 (16.9) • difference, −6.6 (−15.5 to 2.2); P = .20 <u>Adverse events</u> (participants/%): 7-Day antimicrobial + 7-day placebo group vs 14-day antimicrobial group **any adverse event**: As-treated-population: • 26/131 (19.8%) vs 29/123 (23.6%) As-randomized population vs. as-treated population: • 22.4% vs 21.7% Adverse event for each group in the as-randomized population: • 28/136 (20.6%) vs. 33/136 (24.3%) Individual adverse events: full text table 4			

Ferrante, K. L., et al. (2021) [107] 31232721	RCT (1:1:1 fashion) N= 35; 34 initiated therapy USA 3-year-duration (exact dates: unclear) Rates of UTI were assesses over the course of the 12-months study in all patients treated. QoL-question naires at basline, 6 months or unblende d. And 12 months. Expected follow-up visits.	To compare the efficacy of 2 commonly used contempora ry vaginal estrogen administrati ons versus placebo for the prevention of urinary tract infection (UTI) in postmeno-pausal women with a clinical diagnosis of recurrent UTI (rUTI) for 6 months	(N= 35 with 9 dropouts → 26) Postmen opausal women with an active diagnosis of rUTI.	**Vaginal Estrogen** (estradiol ring (2 mg estradiol placed vaginally every 3 months) or **conjugate estrogen cream*** (0.625 mg/g) doesd at 0.5 g (0.312 mg) twice a week) *creme patients were asked to return tubes for weighing at months 3,6, 9, 12.	Placebo creme	**Demographic Data subjects completing the primary outcome Placebo**(n= 11): <u>mean age</u> (SD) 65.73 (12.38) **Vag. Estro**. (n=15): <u>mean age</u> (SD) 71.25 (8.50) **P= 0.220** **<u>UTI by 6 months</u>: Vaginal estrogen vs. placebo:** <u>ITT (assuming dropout as faiures)</u>: • (50% [9/18] vs. 94% [16/17]; p=0.041) <u>As-treated analyses</u>: • (53% [8/15] vs. 91% [10/11]; p= 0.036) <u>Subgroup-Analyses of the as-treated analyses – RING vs. placebo</u>: • (38% [3/8] vs. 91% [10/11; p= 0.041]) <u>Subgroup-Analyses of the as-treated analyses – CREME vs. placebo:</u> • (71% [5/7] vs. 91% [10/11]; p= 0.245 **Decrease of UTI-occurrence** in women initially taken placebo and continued on to open-label vaginal estrogen (n=10): • (90% with UTI preestrogen vs. 30%	Commonly prescribed forms of vaginal estrogen with contemporary dosing schedules prevent UTIs in postmeno-pausal women with an active diagnosis of rUTI. Further study is needed to compare effectiveness between the modes of estrogen delivery.	Data from the abstract (ITT) differ from the full text. **Interests**: not mentioned **Fund**: not mentioned Random sequence generation and allocation concealment not described, after two years of recruitment, the study group revised the sample size and randomization schema, because they were not able to achieve the initial planned sample size, outcome assessors were not blinded. Single blind nature of the trial and although women were blinded to which formulations had estrogen, the ring group was likely incompletely blinded. The study was underpowered for secondary outcomes. Small sample size	1 b - RoB: high

TABLE 3. Six-Month Comparison of Quality of Life Measures

Questionnaire	Estradiol Ring (n = 8)	Conjugated Estrogen Cream (n = 7)	P*	Placebo (n = 11)	P†
FSFI, mean (SD)	35.29 (34.63)	26.0 (24.93)	0.576	43.45 (27.83)	0.277
MESA I, mean (SD)	4.71 (4.57)	15.0 (4.62)	0.001*	7.00 (7.27)	0.330
MESA II, mean (SD)	2.86 (1.77)	6.71 (3.25)	0.022*	4.82 (5.76)	0.987
PFDI, mean (SD)	43.75 (30.25)	65.62 (31.58)	0.229	65.88 (56.29)	0.596
PFIQ, mean (SD)	3.39 (8.98)	16.33 (17.36)	0.114	22.08 (44.01)	0.396
EPI, mean (SD)	76.43 (28.39)	72.86 (25.14)	0.808	33.00 (35.48)	0.004†

*Comparison between estrogen groups.
†Comparison between placebo and estrogen.

						postestrogen, p=0.042) • Median of UTI before the end of randomization: 1 in each group, p= 0.53 **<u>At 6 months</u>**: <u>Adherence to treatment in as-treated group (all RING-patients)</u>: • 100%= n= 8 <u>UTI in estrogen creme-patients (n=7)</u>: • 4 adherent to treatment; 75% had a UTI. <u>UTI in estrogen creme vs. placebo</u>: • (75% [3/4] vs. 91% [10/11], p= 0.48) <u>UTI in Ring vs. Placebo</u>: • 75% vs. 38% [3/8], p= 0.24) **<u>At 12 months</u>** Ring-adherence: 100%, n=17 Estrogen creme group: • 60% [3/5], p= 0.04 **Adverse events (s. also Table 3)**: n= 2 in placebo arm had 3 UTIs prior to the end of randomization and were placed to open-label vaginal estrogen. No other			

						related events reported.			
Fasugba 2017 [103] 27986361	N= 14 studies (3 quasi-experimental studies and 11 RCTs) Serach: inception to December 2015 USA, UK, Saudi Arabia, South Korea, Iran, Australia	To undertake a systematic review of the literature and meta-analysis of studies investigating the effectiveness of antiseptic cleaning before urinary catheter insertion and during catheter use for prevention of CAUTIs.	Patients requiring short- or long-term IDCs or inter-mittent catheterization in hospitals, community settings and long-term care facilities.	antiseptic (povidone-iodine, chlorhexidine or antibacterial); sometimes in addition with alcohol-containing agent	non-antiseptic (water, saline, soap and water, or routine care)	**Geriatric population: n= 4 studies (3 RCTs; 1 quasi experimental study)** ***Effect of <u>meatal cleaning</u> on the incidence of catheter-associated urinary tract infections (results stratified by meatal cleaning agent)*** **Carapeti 1996** (RCT; General surgery patients; Intervention mean age: 67.5; Control mean age: 65.3) <u>0.3% CHG and 3% centrimide</u> <u>Savlon solution and 2.84% isopropyl alcohol, 0.056% benzyl benzoate and terpineol as excipient ingredients (UTI-rates: 7/74) vs. Tap water (9/82)</u> *(Once for surgery)* • OR 0.85 (95% CI 0.30, 2.40) **Duffy 1995** (RCT Male veterans in long-term care; Intervention mean age 72.6 (SD= 10.8); Control mean age: 70.9 (SD 12.1)) <u>10% povidoneiodine Betadine Solution and pareth-25-9</u>	**Effect of meatal cleaning on the incidence of CAUTIs** No subgroup analysis of elderly people ➔ Indirect evidence **Effect of alcohol-containing antiseptic agents on the incidence of CAUTIs:** Although no specific information was provided on the presence of alcohol in the intervention agents in the included Studies, antiseptic interventions (Carpeti, Duffy, Lynch) may have included alcohol as an agent to deliver the ointment, cream or liquid. Given the difficulty in ascertaining the level of alcohol that intervention agents may contain, further analysis on this potential confounder was not possible. There were **no differences in CAUTI rates**, although methodological issues hamper generalizability of this finding. Antibacterial agents may prove to be significant in a well-conducted study. The present results provide good evidence to inform	Demographic data on age of participants was not stated in the majority of papers. The only papers presenting data of geriatric people were old. There was considerable diversity in the types of interventions used, frequency of administration of the intervention, and laboratory definitions of UTI. **Funding sources**: This study was partially funded by a seed grant from the Australasian College for Infection Prevention and Control and an Australian Catholic University Health Sciences Vacation Scholarship grant. **Conflict of interest:** None	1 a RoB: low

						as inactive ingredient (UTI-rates: 26/42) vs. Soap and water (UTI-rates: 21/38) *(Pre-IC,~thrice daily)* • OR 1.32 (95% CI 0.54, 3.21) **Ibrahim 2002** (RCT, Male transurethral surgery patients; intervention mean age: 66.7 (SD= 10.1), control mean age: 66 (SD 10.4)) Povidoneiodine solution and alcohol containing agent Unclear, assumed no (UTI-rate: 19/64) vs. saline (UTI-rate 18/66) *(once/day)* • OR 1.13 (95% CI 0.53, 2.41) **Lynch 1991** (quasi experimental: Male transurethral surgery Patients; intervention mean age: 67 (SD= 9.7); control mean age: 68.4 (SD 8.4)) 2% polynoxylin Anaflex spray and formaldehyde as active ingredient (UTI-rate: 6/50) vs. no comparator agent-intervention (UTI-rate 11/50) *(once/day)* • OR 0.48 (95% CI 0.16, 1.43) ***Effect of using an antiseptic meatal cleaning agent (povidone-iodine,***	infection control guidelines in catheter management.		

						chlorhexidine or antibacterial) <u>vs a non-antiseptic agent</u> (no treatment/ usual care, soap and water, water or saline) on the incidence of catheterassociated urinary tract infections. (same data as above!)			
Mitchell 2021 [104] 34103320 **(Mitchell wrote a joint SR with Fasugba 2017 (see above). This is an update! The exact same studies are listed here. Kara 2017 has been added!!!).**	updated systematic review and meta-analysis N= 18 RCTs (inkl. n=3 quasi-RCTs) USA, UK, Australia, Saudi Arabia, South Korea, Turkey, Iran, Java Search: period between 1 January 2016 and 29	To present an updated systematic review on the effective-ness of antiseptic cleaning of the meatal area for the prevention of CAUTIs and bacteriuria in patients who receive a urinary catheter.	patients requiring short-term or long-term indwelling catheters or intermittent catheterisation in hospitals, community settings, and long-term/ aged care facilities	the use of antiseptic, antibacterial agents for cleaning the meatal, periureth ral or perineal areas before indwellin g catheter insertion or intermitt ent catheteri sation or during routine meatal care.	non-medicated agents (such as soap and water)	**Carapeti 1996 (27)** (UK, RCT; General surgery patients; Intervention mean age: 67.5; Control mean age: 65.3) <u>0.3% CHG and 3% centrimide Savlon solution and 2.84% isopropyl alcohol, 0.056% benzyl benzoate and terpineol as excipient ingredients (UTI-rates: 7/74) vs. Tap water (9/82)</u> (Once for surgery) • OR 0.85 (95% CI 0.30, 2.40) **Duffy 1995 (29)** (RCT Male veterans in long-term care; Intervention mean age 72.6 (SD= 10.8); Control mean age: 70.9 (SD 12.1)) <u>10% povidoneiodine Betadine Solution and pareth-25-9 as inactive ingredient</u>	There is emerging evidence of the role of some specific antiseptics (chlorhexidine) prior to urinary catheterisation, in reducing CAUTIs, and some potential benefit to the role of antiseptics more generally in reducing bacteriuria.	There was considerable heterogeneity in intervention and population groups. Pooled OR. Just indirect evidence (no subgroup-analysis of elderly patients) **Funding**: None **Competing interests**: BM reports personal fees from MSD, grants from Cardinal Health, grants from Senver, outside the submitted work. Prospero: „If sufficient studies are identified, subgroup analyses will be done by sex, age,..” All 5 studies represents elderly people but no subgroup-analysis of age was done → a priori analysis was different	1a - RoB: high

	February 2020 (1 January 2016 represents the end date of the search from the initial review)					(UTI-rates: 26/42) vs. Soap and water (UTI-rates: 21/38) (Pre-IC,~thrice daily) • OR 1.32 (95% CI 0.54, 3.21) **Ibrahim 2002 (31)** (USA, RCT, Male transurethral surgery patients; intervention mean age: 66.7 (SD= 10.1), control mean age: 66 (SD 10.4)) Povidoneiodine solution and alcohol containing agent Unclear, assumed no (UTI-rate: 19/64) vs. saline (UTI-rate 18/66) (once/day) • OR 1.13 (95% CI 0.53, 2.41) **Kara 2017 (32);** (Turkey, RCT; ICU, surgical and medical patients) Intervention mean age: 66.34 (SD 14), 63.5 (SD 12); control mean age: 67.96 (12) Sterile water 10% povidone-iodine vs. sterile water (once daily) • OR 0.49 (95% CI 0.13, 1.88) **Lynch 1991** (UK, quasi RCT: Male transurethral surgery Patients; intervention mean age: 67 (SD= 9.7); control mean age: 68.4 (SD 8.4))			

						2% polynoxylin Anaflex spray and formaldehyde as active ingredient (UTI-rate: 6/50) vs. no comparator agent-intervention (UTI-rate 11/50) (once/day) OR 0.48 (95% CI 0.16, 1.43)			
Liu 2021 [88] 32763348	Systematic review and meta-analysis 8 RCTs Search date: through March/April 2020 Countries: not mentioned	To investigate the effect of antibiotic prophylaxis for consequent urinary tract infections (UTIs) after extraction of urinary catheter and further explore the association between the outcome and clinical characteristics of patients.	(n= 997) Patients with a duration of catheter-ization ≤14 days, specified definition of UTIs, antibiotic prophylaxis which was administered presently after the extraction of catheters rather than before it.	antibiotic prophylaxis (ciprofloxacin, Nitro-furantoi, TMP/SM, cefotaxime)	No prophylaxis	<u>Effect of antibiotic prophylaxis for UTIs after removal of catheters</u> **<u>Older than 60</u>** (6 RCTs): Antibiotics (n=443) vs. no antibiotics (n= 427) • RR = 0.50, (95% CI: 0.33-0.76), P< 0.05, I^2 = 29% **<u>Ciprofloxacin</u>** (n= 2 RCTs): **Berrondo 2019** (167 laparoscopic radical prostatectomy; 2 doses, first before removal, second after removal; cases experimental: 3/83; cases control: 5/84; follow-up: 6 weeks; mean age older than 60; male) • RR 0.61 (95% CI 0.15-2.46) **Fang 2014** (dose: not reported; 160 laparoscopic radical Prostatectomy; cases experimental: 4/80; cases control: 9/80;	Patients with catheters removed might get benefit from antibiotic prophylaxis as a result of fewer consequent UTIs, and those **who have advanced age (over 60 years old) or long-term catheterization (over 5 days)** could get more benefit from prophylaxis. And TMP/SMX could be a good choice of prophylaxis for UTIs after extraction of urinary catheters. **This approach should apply to** high-risk patients (**advanced age or long-term catheterization**) due to the potential harm of widespread antibacterial agents such as side effects and bacterial resistance. Further research should reach a consensus of study design protocols (types of antibiotic agents, duration of catheterization, observation time, etc.) to provide more convincing evidence. **Meanwhile, clinicians must**	**Funding**: This study was found by 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD18011, ZY2016104). **Conflicts of interest**: None **Only 2 of the included studies comprised nonsurgical YOUNGER patients in hospital, and separate analyses of these 2 studies alone did not show benefit of the prophylaxis.** Presented population were all surgery patients! No Prospero, so analyses determined a priori cannot be reviewed; no information whether ROB was evaluated by 2 independent reviewers	1 a - RoB: high

						mean age older than 60; follow-up time; 1,4,8 weeks male only) • RR 0.44 (95% CI 0.14-1.38) **TMP/SMX or Ciprofloxacin** (2 RCT): Van Hees 2011 (91 general surgery, ciprofloxacin (n=31) or TMP/SMX (n=24) x1 dose before removal; cases experimental: 1/55; cases control: 1/36; follow up: 2 weeks; mean age older than 60; mixed gender) • RR 0.65 (95% CI 0.04-10.13) Pfefferkorn 2009 (205 abdominal surgery; TMP/SMX (3 doses, first before removal) or ciprofloxacin; cases experimental: 5/103; cases: 22/102; follow up: 22/102 4 +/-2 days after catheter removal; mean age older than 60; mixed gender • RR 0.23 (95% CI 0.09-0.57) **Cefotaxime** (1 RCT) Grabe 1984 (96 transurethral prostatectomy 3 doses, two daily, first before removal; cases experimental: 3/47; cases control: 8/49;	**prescribe antibiotics cautiously according to the risk factors of their patient population**.		

						follow-up: 1 week; mean age older than 60; male) →no data **<u>Nitrofurantoin</u>** (1 RCT) <u>Lavelle 2019</u> (151 pelvic reconstructive Surgery; 100mg once daily; cases experimental: 13/75; cases control: 13/76; mean age older than 60; follow-up: 6 weeks, female) →no data! **<u>catheters for more than 5 days</u>** (n= 4 RCTs) (Berrondo, Fang, Van Hees, Pfefferkorn) Antibiotics (n= 321) vs. no antibiotics (n= 302) • RR = 0.34, (95% CI: 0.19-0.63), P< 0.01, I^2 = 0%. **<u>catheters < 5 days</u>** <u>(n= 2 RCTs)</u> **Lavelle 2019** • RR 1.01 (95% CI 0.50-2.04) **Grabe 1984** • RR 0.39 (95% CI 0.11 – 1.39)			

Schlüsselfrage Geriatrie-Prävention: Welche Antibiotika sind zur Langzeitprävention geeignet?									
Referenz	**Studien-charakteristika**	**Studienziel**	**Patienten-merkmale**	**Inter-vention**	**Kontrolle**	**Ergebnisse**	**Schlussfolgerungen des Autors**	**Methodische Bemerkungen**	**LoE/ RoB**
Ahmed 2017 [74] 28554926	Systematic review and meta-analysis n=3 RCTs Literature search: up to 2016 Recruitment countries: Israel, the Netherlands, Croatia	To determine the clinical effectiveness and safety of long-term antibiotic therapy for preventing recurrent UTIs in older adults	n=534 postmenopausal women with rUTI <u>Inclusion</u> women who were postmenopausal or over the age of 65 and men aged over 65	Long-term antibiotic therapy (defined as antibiotic dosing for at least 6 mo).	Non-antibiotic intervention • vaginal oestrogens (n=150) • oral lactobacilli (n=238) • D-mannose powder (n=94)	**Frequency of UTI recurrences during the prophylaxis period** *Narrative analyses* Beerepoot, 2012 <u>480 mg trimethoprim-sulfamethoxazole vs. capsule of lactobacilli for 12 mo (n=1)</u> Microbiologically-confirmed UTI episodes per patient-year • trimethoprim-sulfamethoxazole:1.2 • capsule of lactobacilli: 1.8 MD=0.6 episodes (95% CI: 0.0-1.4); p=0.02 Microbiologically confirmed UTI during prophylaxis • trimethoprim-sulfamethoxazole: 49.4% • capsule of lactobacilli: 62.9% RR=0.79 (95% CI: 0.63-1.0) Microbiologically confirmed UTI episodes	Findings from three small trials with relatively short follow-up periods suggest long-term antibiotic therapy reduces the risk of recurrence in postmenopausal women with recurrent UTI. We did not identify any evidence to inform several clinically important scenarios including, benefits and harms in older men or frail care home residents, optimal duration of prophylaxis, recurrence rates once prophylaxis stops and effects on urinary antibiotic resistance.	**KSR-Bewertung** (*https://ksrevidence.com/index.php?recordID=KSRA35758#recordpage*) Studies were restricted based on publication format and language, meaning relevant studies may have been missed. Only a single author was involved in study screening and data extraction, meaning that bias may have been introduced. Insufficient study characteristics were provided, making it challenging for the reader to interpret results. Study heterogeneity was high for adverse event outcomes. *Slightly differing information on the literature search period: abstract till August 2016 and in the method part it is stated March 2016* <u>Funding</u> This report is independent research arising from the National Institute of Health Research (NIHR) Doctoral	1a - RoB: high

						3 mo after cessation of prophylaxis • trimethoprim-sulfamethoxazole:0.1 • capsule of lactobacilli: 0.2 MD=0.0 (95% CI: -0.1-0.3); p=0.64 Raz, 2003 <u>nitrofurantoin (100g) for 9 mo vs. vaginal oestrogen pessaries</u> UTI during prophylaxis • nitrofurantoin: 42.3% • vaginal oestrogen pessaries: 64.6% RR 0.65 (95% CI: 0.8-0.90) Kranjčec, 2014 <u>Nitrofurantoin (50g) for 6 mo vs. D-mannose powder (2g)</u> UTI during prophylaxis • nitrofurantoin: 24% • d-mannose: 19% RR=1.24 (95% CI: 0.57-2.69) **Adverse events** *Pooled analysis* Mild adverse events (n=3 RCTs) • Antibiotic: 118/242 • Non-antibiotic: 107/261 RR=1.52 (95% CI: 0.76-3.03, I^2=86%); p=0.23 <u>Serious adverse events</u>		Research Fellowship awarded to Haroon Ahmed, and supported by Health and Care Research Wales (HCRW). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS Wales, HCRW or the Welsh Government. The funders had no role in the design or preparation of this manuscript. <u>Conflict of interest</u> None declared.	

						resulting in treatment withdrawal (n=2 RCTs) • Antibiotic: 21/200 • Non-antibiotic: 22/209 RR=0.90 (95% CI: 0.31-2.66, I^2=67%); p=0.85 **Effect of long-term antibiotic therapy on bacterial resistance** <u>Beerepoot, 2012</u> % of urinary and faecal E coli isolates that were resistant to trimethoprim–sulfamethoxazole, trimethoprim and amoxicillin: • baseline: 20%–40% • after 1 mo of treatment with trimethoprim–sulfamethoxazole: 80%–95%			
Dueñas-Garcia 2016 [69]	Systematic review n=9 RCTs Search date: 1970-2015	The purpose of this systematic review was to evaluate and summarize pharmacologic al interventions evaluated in randomized clinical trials designed to prevent recurrent episodes of	postmenopausal women with rUTI	pharmacological interventions	pharmacological interventions or placebo	**Antibiotics** (n=3 RCTs, Zhong 2011; Raz 2003; Beerepoot 2012; n=491 patients) <u>Beerepoot 2012</u> - *Sulfamethoxazole plus trimethoprim (mean age, 65.4 ± 8.3 yr)* - *Vaginal lactobacilli (mean age, 63.2 ± 8.6 yr)* • No significant	This review supports the use of antibiotic suppression, vaginal estrogen, and oral lactobacillus for prevention of recurrent UTIs in postmenopausal women.	complete search strategy was not reported, no efforts were made to minimise error in: the study selection process, the data extraction and risk of bias assessment, no funnel plot <u>CAVE:</u> • some incorrectly assigned reference numbers <u>Funding</u> None.	1a - RoB: high

		UTIs in postmenopausal women.				difference in outcome using sulfamethoxazole plus trimethoprim vs. vaginal lactobacilli (MD=2.9 vs. 3.3, p=0.42) <u>Zhong 2011</u> - *Intermittent antibiotic therapy (mean age, 62.7 ± 7 yr)* - *Continuous antibiotic therapy (mean age, 62.8 ± 7.3 yr)* • continuous vs. intermittent dosing of various antibiotics • continuous group showed a higher number of UTIs over 1 year of follow-up (59.4% vs. 35.5%; p<0.05) • as well as a higher rate of side effects <u>Raz 2003</u> - *estrogen pessary (mean age, 68 yr; range, 49–82 yr)* - *Nitrofurantoin (mean age, 66.9 yr; range, 46–84 yr)* • nitrofurantoin vs. estriol pessary patients using nitrofurantoin suppression had fewer UTIs compared		<u>Conflict of interest</u> None.	

						to estriol pessary users (48 vs. 124, p<0.0003).			
Botros 2022 [106] 34115162 (aus der Suchstrategie für Ger-P. SF 1&2)	RCT N=92 women receiving daily prophylaxis with methenamine hippurate or trimethoprim for a minimum of 6 months. June 2016 to May 2018 Country: probably US (authors are from the USA) Follow-up: 6 and 12 months after starting treatment.	**1**.to find an alternative treatment to a low-dose antibiotic for the prevention of recurrent urinary tract infections (UTI) **2.** to evaluate the difference in rates of reinfection within 1 year when treated with methenamine hippurate for prophylaxis compared with trimethoprim.	N= 92 Women over 18 with a diagnosis of recurrent UTI, having at least two culture-positive UTI in the prior 6 months or three in the prior year.	Methenamine hippurate (as a daily prophylaxis for a minimum of 6 months)	Trimethoprim (as a daily prophylaxis for a minimum of 6 months)	**Age overall (n= 92): 71.9±13.0; P= 0.35; postmenopausal: n= 86 (93.5%) p= 0.44 [mean ± standard deviation or n (%)]** Trimethoprim (n= 47) • Age (n =47): 70.6±15.0 • Postmenopausal: n= 43 (91.5) Methenamine hippurate (n= 45) • Age (n =45): 73.2±10.5 • Postmenopausal: n= 43 (95.6) **During prophylaxis [mean ± standard deviation or n (%)]** Recurrent UTI at 1 year (ITT; trimethoprim n = 43; methenamine n = 43) • Full Cohort (FC): 56 (65.1) • Trimethoprim (T): 28 (65.1) • Methenamine hippurate (Mh): 28 (65.1) • p= 1.00 Recurrent UTI at 1 year (PP trimethoprim n = 40; methenamine n = 46) • T: 26 (65.0) // Mh: 30 (65.2)	Our findings support the Cochrane review of **methenamine hippurate** possibly being an **effective prevention strategy**, especially in the short term. In addition, methenamine hippurate may be **an acceptable long-term prophylaxis alternative** in the prevention of recurrent UTI, with similar adverse effects to trimethoprim. A significantly lower number of infections are seen with initiation of either treatment, with greater than 100 days to subsequent UTI after starting treatment.	Study was not blinded and did not include a placebo arm. Open-label **Funding**: none **Conflicts of interest:** None variability in follow-up of participants and management at follow-up visits based on both patient and provider preference	1b - RoB: high

						• P= 0.98 Time to subsequent infection (ITT) • FC: 110±89.1 • T: 100.7±84.4 //Mh: 119.3±94.1 • P= 0.52 Time to subsequent infection (PP) • T: 106.5±84.9 // Mh: 113.0±93.9 • P= 0.88 Number of UTI recurrences at 1 year (ITT) • FC: 1.7±1.9 • T: 1.5±1.7 //Mh: 1.6±1.9 • P= 0.72 Number of UTI recurrences at 1 year (PP) • T: 1.8±2.1 // Mh: 1.4±1.5 • P= 0.36 **Decrease in number of UTIs per year [mean ± standard deviation or n (%)]** Full cohort (mean ± standard devi.) No. of UTI recur. prior to prophyl.: • 3.9 ± 1.8 No. of UTI recurrences within 1 yr after prophyl.: 1.6 ± 1.8 • p <0.01 Trimethoprim (ITT) No. of UTI recur. prior to prophyl.: • 4.0 ± 2.1			

						No. of UTI recurrences within 1 yr after prophyl.: • 1.5 ± 1.7 <u>Methenamine hippurate (ITT)</u> No. of UTI recur. prior to prophyl.: • 3.7 ± 1.5 No. of UTI recurrences within 1 yr after prophyl.: • 1.6 ± 1.9 <u>Trimethoprim (PP)</u> No. of UTI recur. prior to prophyl.: • 4.3 ± 2.2 No. of UTI recurrences within 1 yr after prophyl.: • 1.8 ± 2.1 <u>Methenamine hippurate (PP)</u> No. of UTI recur. prior to prophyl.: • 3.5 ± 1.3 No. of UTI recurrences within 1 yr after prophyl.: • 1.4 ± 1.5 **Adverse effects and cost factors hindering use: T (n= 47) Mh (n= 45) [n [%]]** Diarrhea: • T: 1 (2.1); Mh: 2 (4.4); p= 0.54 Rash: • T:2 (4.3); Mh: 0; p= 0.17 Clostridium difficile			

						colitis: • T: 1 (2.1); Mh: 0; p= 0.33 Weakness: • T: 2 (4.3); Mh: 0; p= 0.17 Abdominal pain: • T:0; Mh: 1 (2.2); p= 0.31 Nephrolithiasis: • T: 0; Mh: 1 (2.2); p= 0.31 Cost of medication: • T: 0; Mh: 2 (4.4); p= 0.15			
Rego 2016 [108] No PMID (research gate)	Systematic review n=43 articles Last search date: 2014	To evaluate the available literature on reported pulmonary, liver and nerve adverse reactions to long-term nitrofurantoin suppression in older women patients treated for urinary tract infections.	Older women with urinary tract infection	nitrofurantoin use for long-term		**Pulmonary reaction** United Kingdom: 2% Sweden: 5.3% Holland: 3.4% • nitrofurantoin-related pulmonary adverse reactions compared to total nitrofurantoin prescriptions differed worldwide (USA: 0.001%; France: 0.001%) **Liver damage** United Kingdom: 3.9% Sweden: not available Holland: 9.1% • nitrofurantoin-related hepatic adverse reactions compared to total nitrofurantoin prescriptions: 0.001% (France) **Peripheral**	The current evidence suggests that the rate of pulmonary, hepatic and nerve adverse reactions resulting from long-term nitrofurantoin prophylaxis in older patients treated for urinary tract infections are likely to be serious, but very small, hence this population should not be discouraged from the cautious use of nitrofurantoin.	**KSR-Bewertung** (*https://ksrevidence.com/index.php?recordID=KSRA28148#recordpage*) Only English language studies were included. Only one database was searched for the study selection process. Search terms were provided, but a full search strategy was not reported. There was no information on whether the searches were restricted by publication format or language. No information was provided regarding the number of authors involved in the study selection process and data extraction. The number of studies included in the synthesis was unclear. There were insufficient study details available to allow the	3a - RoB: high

					neuropathy United Kingdom: 14.1% Sweden: 2.2% Holland: 9.1%		reader to interpret the results. There was no formal assessment of the methodological quality of included studies. The analysis section of the review is not sufficiently elucidated. <u>Funding</u> None. <u>Conflict of interest</u> Glazer is a speakter for Genentech.	
Zeng 2020 [89] 32221713	Systematic review search: up to March 2019	This review aimed to outline the diagnostic, treatment, and prevention of UTI in the frail aging population.	n=64 publications people over 65 years	• Cranberry juice • Hormonal • Fluid intaking • D-Mannose • Vaccine • Antibiotics	**Long-term urinary catheter** • Antimicrobial-coated catheters could slightly decrease the risk of catheter-associated UTI (disadvantages: more frequent catheter removal, more uncomfortable caused by catheter, and higher costs) • Systemic antibiotic prophylaxis does not reduce rates of bacteriuria, catheter-associated UTI, or death, and should not be recommended.	Management of UTI in elderly patients with long-term catheter remains challenging. There is evidence that prophylactic antibiotics are able to reduce risk of recurrent UTI in correctly selected elderly patients.	no study protocol, no complete search strategy and study characteristics of the included studies reported, no information if efforts were made to minimise error in data collection, no risk of bias assessment, unclear if all identified studies are included in the review, no funnel plot, bias risk of the included studies is not addressed <u>Funding</u> National Natural Science Foundation of China (No. 81870483 and No. 81800625), and Natural Science Foundation of Guangdong Province (2018A030310296) <u>Conflict of interest</u> The authors declare that they have no conflict of	1a - (for the presented results) RoB: high

							interest.	

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