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Diagnostik und Therapie der epidermalen Nekrolyse (Stevens-Johnson-Syndrom und toxisch epidermale Nekrolyse) –

Evidenzbericht

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DDG Deutsche Dermatologische Gesellschaft

Evidence report: Diagnosis and treatment of epidermal necrolysis (Stevens-Johnson syndrome and toxic epidermal necrolysis)

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Abbreviations

AMSTAR Assessing the methodological quality of systematic reviews
AMT Amniotic membrane transplantation
BCVA Best-corrected visual acuity
CI Confidence interval
COI Conflict of interestEN Epidermal necrolysis
GRADE Grading of recommendations, assessment, development, and evaluations
IQR Interquartile range
IVIG Intravenous immunoglobulines
MD Mean difference
MMG Mucous membrane graftingTBSA Total body surface area
RCT Randomized controlled trial
RR Relative risk
SCARS Severe cutaneous adverse reactions
SCORTEN Severity-of-illness score for toxic epidermal necrolysisSJS Stevens-Johnson syndrome
TBUT Tear film break-up time
TEN Toxic epidermal necrolysis
TNF-α Tumor-necrosis factor alpha
VAS Visual analog scale

SYSTEMIC IMMUNOMODULATORY TREATMENT OF EPIDERMAL NECROLYSIS

For patients with EN: what is the clinical efficacy of systemic immunomodulatory treatment compared with supportive therapy only or other systemic immunomodulatory treatments?	
POPULATION:	Patients with acute EN and disease progression within the last 24 hours; Patients below 18 years of age with acute EN and disease progression within the last 24 hours
INTERVENTION:	Systemic corticosteroids and/or cyclosporine A, intravenous immunoglobulins (IVIG), etanercept and other systemic immunomodulatory treatments or combinations thereof
COMPARISON:	Supportive therapy only or any of the previously mentioned interventions
MAIN OUTCOMES:	Primary outcomes: o Survival / in-hospital mortality (9 = critical) o Incidence of serious complications (9 = critical) o Quality of life / psychosocial well-being (7 = critical) o Sequelae of the eyes, group 1: blindness, limitation of reading ability, corneal perforations / ulcerations / epithelial defects, limbal stem cell insufficiency, chronic ocular dryness (8 = critical) o Sequelae of the eyes, group 2: entropion / ectropion, trichiasis, symblepharon: (7 = critical) o Sequelae of other organ systems, group 1, digestive system: ulcerations, perforations; urogenital system: urethral strictures, vaginal stenosis; respiratory system: acute respiratory distress syndrome (ARDS), bronchiolitis, bronchiectasis, chronic obstructive pulmonary dysfunction (COPD) (7 = critical) Secondary outcomes: o Sequelae of other organ systems, group 2, skin: scarring, nail loss, postinflammatory hypo- and / or hyperpigmentation; urogenital system: phimosis (6 = important) o Days with ventilation/requirement of ventilation (6 = important) o Mental health (6 = important) o Incidence of chronic pain (6 = important) o Time to complete reepithelialization / skin healing (5 important) o Time to return to school / work (5 = important) o Length of hospital stay (4 = important)
SETTING:	Hospital- or burn unit-based care, no regional limitations
PERSPECTIVE:	Clinical recommendations, population perspective
BACKGROUND:	o High mortality and prevalence of illness sequelae in EN call for the improvement of acute care o No consensus on whether to use systemic immunomodulatory treatments in EN and which treatment to choose o Research on the effectiveness of interventions is limited by low incidence rates o Existing systematic reviews are heterogeneous with respect to research methodologies and results o Several patient-important outcomes have not been systematically evaluated
STUDY DESIGNS:	For the meta-analysis o Randomized controlled trials o Comparative prospective or retrospective studies with at least 5 patients per treatment arm For descriptive results o Randomized controlled trials o Comparative prospective or retrospective cohort studies with at least 5 patients per treatment arm
CONFLICT OF INTERESTS:	Three members of the guideline panel have declared limited COI and have been excluded from leadership positions in the working group for this topic. One member of the guideline panel has declared moderate COI and has been excluded from leadership positions in the working group and voting on recommendations for this topic.

ASSESSMENT: SYSTEMATIC REVIEW BASED ON 38 STUDIES WITH 2248 PATIENTS

Is the problem a priority?	
Judgement: ○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies	Epidermal necrolysis (EN) is a severe adverse reaction with considerable mortality and morbidity, including life-long sequelae that is most frequently associated with drug intake but also with infectious processes. Due to its low incidence, no treatment standards have been established in Germany. This also pertains to systemic immunomodulatory treatments, which are hypothesized to have mechanistically plausible effects on the progression of EN. Even at the international level there is no consensus on whether systemic immunomodulatory treatments provide a benefit, which interventions are preferable and when they should be administered. Due to its assumed effects on mortality and other patient-important outcomes such as frequency of illness sequelae, obtaining reliable measures of treatment effectiveness for different systemic immunomodulatory treatment regimens is relevant to all stakeholders. **Patients' and family members' needs/preferences:** To assess the patient perspective on acute care needs, we conducted and analyzed 14 semi-structured interviews with survivors and family members of survivors. In the interviews, participants did not mention specific preferences regarding systemic immunomodulatory treatments, which is likely due to the extent of professional expertise involved in judgements based on pathophysiological reasoning rather than empirical evidence. However, the participants frequently reported the disease's long-term impact on their daily lives through sequelae affecting eyes, skin and appendages. We, therefore, put special emphasis on the potential role of systemic immunomodulatory treatments in reducing illness sequelae when making guideline recommendations. **Healthcare professional needs:** Providers are likely to place high importance in obtaining information on the effectiveness of systemic immunomodulatory treatment.
Methodological remarks Is there considerable methodological heterogeneity in the existing research?	
Judgement: ● Considerable heterogeneity ○ Possibly considerable heterogeneity ○ Probably no considerable heterogeneity ○ No considerable heterogeneity ○ Not known	There is widespread disagreement about the clinical effectiveness of systemic immunomodulatory treatment in acute EN across countries and in German health care providers. While some aggregated evidence on these interventions exist, treatment recommendations remain equivocal. Due to methodological challenges associated with the condition's low incidence rate, there is substantial heterogeneity in research approaches both within primary studies and systematic reviews. Medical providers faced with treating a progressive and potentially fatal condition consequently need to make decisions based on complex methodological considerations. In this report, we provide a comprehensive overview of existing research and discuss our confidence in the evidence. To meet the somewhat conflicting requirements of scientific rigor and clinical utility inherent to making recommendations in the context of rare diseases, we opted for conducting original research in conjunction with citing existing evidence alongside our own results. Considering the predominance of observational studies in this research domain, we included only studies comparing interventions across groups we judged similar with respect to characteristics likely to influence both outcome and treatment choice. Although our findings proof robust to sensitivity analyses, they represent one particular, contingent methodological decision regarding study inclusion. Accordingly, it is necessary to consider the wider research context in assessing certainty of evidence. In the following tables we will present results of existing high-level research in the respective comment sections.

SYSTEMIC IMMUNOMODULATORY THERAPIES: MONOTHERAPIES

Corticosteroids

Summary of Findings

What is the overall certainty of the evidence?

Corticosteroids vs supportive therapy

JUDGEMENT	RESEARCH EVIDENCE						COMMENTS
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
					Supportive therapy	Corticosteroids	
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	202 (8 observational studies)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.5** (0.26 – 0.96)	Risk of mortality 222 per 1.000	**112 fewer per 1.000** (166 fewer to 9 fewer)	Additional results for the outcome mortality: A 2013 comprehensive survival analysis with 61 patients by Sekula et al. (1) comparing corticosteroids with supportive therapy reports a hazard ratio (HR) of 1.3, 95% CI 0.8 to 1.9 for any given time within the first 365 days after hospital admission. Due to incommensurable outcome measures (365-days-based hazard ratio vs in-hospital mortality risk ratio), this study was excluded from our meta analysis. Including only prospective studies and applying Cochrane methodology, a 2022 systematic review by Jacobsen et al. (2) comparing the effect of corticosteroids with no corticosteroids on disease-specific mortality reports a risk ratio (RR) of 2.55, 95% confidence interval (CI) 0.72 to 9.03, including 2 studies and 56 participants (very low-certainty evidence). The results of an alternative statistical model incorporating multiple regression-adjusted outcome measures from 2 additional studies (1 with 2 national cohorts and propensity score-based analysis) is shown in the second row of this table. For details please see separately published methods report and conclusion section for corticosteroids in this report.
	Mortality (alternative statistical model)	541 (11 observational studies)	⊕⊕◯◯ LOW [a,b,d]	**RR 0.48** (0.28 – 0.8)	Risk of mortality 182 per 1.000	**94 fewer per 1.000** (130 fewer to 37 fewer)	
	Length of hospital stay	69 (4 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	-	Mean stay: 17.71 ± ± 23.02 days	**MD in days: 2.41 less** (9.24 less to 4.42 more)	
	Serious complications: sepsis	32 (2 observational studies)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.18** (0.02 – 1.44)	Risk of serious complications 250 per 1.000	**205 fewer per 1.000** (244 fewer to 110 more)	
	Serious complications: organ failure	57 (4 observational studies)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.31** (0.1 – 0.97)	Risk of serious complications 389 per 1.000	**269 fewer per 1.000** (351 fewer to 10 fewer)	
	Sequelae: eyes	35 (2 observational studies)	⊕◯◯◯ VERY LOW [a,b]	**RR 2.14** (0.31 – 14.56)	Risk of sequelae 50 per 1.000	**57 more per 1.000** (34 fewer to 678 more)	
	Sequelae: skin	15 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	**RR 4** (0.47 – 34.24)	Risk of sequelae 100 per 1.000	**300 more per 1.000** (53 fewer to 3324 more)	

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met
c. Inconsistency of results: CIs of effect estimates of individual studies do not overlap or evidence of substantial statistical heterogeneity
d. Large magnitude of effect

IVIG vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Corticosteroids	IVIG
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	48 (2 observational studies)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.4** (0.08 – 1.94)	Risk of mortality 226 per 1.000	**136 fewer per 1.000** (207 fewer

						to 212 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Cyclosporine A vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Corticosteroids	Cyclosporine A
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	62 (2 observational study)	⊕⊕◯◯ LOW [a,b]	**RR 0.45** (0.11 – 1.82)	Risk of mortality 262 per 1.000	**144 fewer per 1.000** (233 fewer to 215 more)
	Length of hospital stay	110 (3 observational studies)	⊕⊕◯◯ LOW [a,b]	-	Mean stay: 15.33 ± 11.78 days	**MD in days: 4.3 less** (10.41 less to 1.81 more)
	Time to complete reepithelialization	110 (3 observational studies)	⊕⊕◯◯ LOW [a,b]	-	Mean time: 12.46 ± 5.72 days	**MD in days: 3.85 less** (7.9 less to 0.21 more)
	Serious complications: sepsis	110 (3 observational study)	⊕⊕◯◯ LOW [a,b]	**RR 0.62** (0.21 – 1.81)	Risk of serious complications 190 per 1.000	**73 less per 1.000** (150 less to 154 more)
	Sequelae: eyes	17 (1 observational study)	⊕⊕◯◯ LOW [a,b]	**RR 1.75** (0.08 – 37.39)	Risk of serious complications 0 per 1.000	**Not calculable**

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Etanercept vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE						COMMENTS
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Additional results: Including only prospective studies and applying Cochrane methodology, a 2022 systematic review by Jacobsen et al. (2) comparing the effect of etanercept with corticosteroids on disease-specific mortality reports a risk ratio (RR) of 0.51, 95% confidence interval (CI) 0.16 to 1.63. Serious adverse events, such as sepsis and respiratory failure, were reported in 5 of 48 participants with etanercept and 9 of 43 participants with corticosteroids, but it was not clear if they led to discontinuation of therapy. All results were based on 1 study with 91 participants (low-certainty evidence).
					Corticosteroids	Etanercept	
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	91 (1 randomized controlled trial)	⊕⊕⊕◯ MODERATE [a]	**RR 0.51** (0.16 – 1.63)	Risk of mortality 163 per 1.000	**79 fewer per 1.000** (137 fewer to 102 more)	
	Time to complete reepithelialization	91 (1 randomized controlled trial)	⊕⊕⊕◯ MODERATE [a]	-	Mean time: 16 days	**MD in days: 1.7 less** (4.48 less to 1.08 more)	
	Serious complications: sepsis	91 (1 randomized controlled trial)	⊕⊕⊕◯ MODERATE [a]	**RR 0.45** (0.09 – 2.32)	Risk of serious complications 93 per 1.000	**51 less per 1.000** (85 less to 123 more)	

a. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Bibliography

Brand, 2000 (3); Chatproedprai, 2018 (4); Dicle, 2009 (5); Kim, 2005 (6); Koh, 2010 (7); Kridin, 2021 (8); Leaute-Labreze, 2000 (9); Sekula, 2010 (10); Sekula, 2013 (11); Shah, 2021 (12); Singh, 2013 (13); Thakur, 2021 (14); Torres-Navarro, 2020 (15); Wang, 2018 (16); Yip, 2005 (17)

Desirable Effects

Are the desirable effects large?

Judgement	Research evidence
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Corticosteroids vs supportive therapy • Significant advantage with corticosteroids for the critical outcomes mortality and serious complications: organ failure (GRADE: ⨁◯◯◯ VERY LOW) • No significant difference with corticosteroids for the critical outcome sequelae: eyes and the important outcome sequelae: skin and length of hospital stay (GRADE: ⨁◯◯◯ VERY LOW) IVIG vs corticosteroids • No significant difference with corticosteroids for the critical outcome mortality (GRADE: ⨁◯◯◯ VERY LOW) Cyclosporine A vs corticosteroids • No significant difference with corticosteroids for the critical outcomes mortality and serious complications: sepsis and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⨁⨁◯◯ LOW) Etanercept vs corticosteroids • No significant difference with corticosteroids for the critical outcomes mortality and serious complications sepsis and the important outcome time to complete reepithelialization (GRADE: ⨁⨁⨁◯ MODERATE)

Undesirable Effects

Are the undesirable effects small?

Judgement	Research evidence
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Corticosteroids vs supportive therapy • No significant difference with corticosteroids for the critical outcome sequelae: eyes and the important outcome sequelae: skin and length of hospital stay (GRADE: ⨁◯◯◯ VERY LOW) IVIG vs corticosteroids • No significant difference with corticosteroids for the critical outcome mortality (GRADE: ⨁◯◯◯ VERY LOW) Cyclosporine A vs corticosteroids • No significant difference with corticosteroids for the critical outcomes mortality and serious complications: sepsis and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⨁⨁◯◯ LOW) Etanercept vs corticosteroids • No significant difference with corticosteroids for the critical outcomes mortality and serious complications sepsis and the important outcome time to complete reepithelialization (GRADE: ⨁⨁⨁◯ MODERATE)

Differences in values

Is there important uncertainty about how much people value the main outcomes?

Judgement: ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty of variability ○ No important uncertainty of variability ○ Not known	• The guideline committee has judged the significant desirable effects as critical (mortality and incidence of serious complications: organ failure in corticosteroids compared with supportive therapy) • No significant undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group suggest a higher importance of illness sequelae relative to the judgement of the guideline committee. As no significant between-group differences could be identified for this set of outcomes, no conflict of values is expected.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Corticosteroids vs supportive therapy • Significant advantage with corticosteroids for the critical outcomes mortality and serious complications: organ failure (GRADE: ⊕◯◯◯ VERY LOW) • No significant difference with corticosteroids for the critical outcome sequelae: eyes and the important outcome sequelae: skin and length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW) • Very low confidence in the certainty of the evidence does not permit reliably estimating balance of effects IVIG vs corticosteroids • No significant difference with corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW) • Very low confidence in the certainty of the evidence does not permit reliably estimating balance of effects Cyclosporine A vs corticosteroids • No significant difference with corticosteroids for the critical outcomes mortality and serious complications: sepsis and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⊕⊕◯◯ LOW) • Low confidence in the certainty of the evidence does not permit reliably estimating balance of effects Etanercept vs corticosteroids • No significant difference with corticosteroids for the critical outcomes mortality and serious complications sepsis and the important outcome time to complete reepithelialization (GRADE: ⊕⊕⊕◯ MODERATE)
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No cost-benefit analysis for the German healthcare system was identified. • Corticosteroids can be considered routine care and likely represent a negligible burden to payers
Resource use Is the incremental cost small relative to the net benefits?	
Judgement:	• No cost-benefit analysis for the German healthcare system was identified

○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small benefits in critical outcomes
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No significant impact on equity expected
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated
Conclusion What is the final judgement considering the evidence, and are there important limitations?	
Judgement: ○ Strong recommendation against the intervention ○ Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	Regarding the outcomes in-hospital mortality and incidence of serious complications: organ failure, there is low to very low quality of evidence for an advantage of corticosteroids over supportive therapy based on data from 5 retrospective observational studies with 316 and 5 observational studies with 77 patients, respectively. Due to the generally small and selective sample sizes underlying our review, it is important to consider our results in conjunction with preexisting research and alternative methods of analysis. Comparing our pooled effect estimates for the outcome mortality against two previous systematic reviews of high methodological quality (own assessment using AMSTAR), only our study finds a significant advantage for corticosteroids. In addition, one of the reviews reports a different direction of effect based on 2 studies, albeit with no statistical significance. This estimated disadvantage of corticosteroids compared to supportive therapy is also mirrored in a methodologically rigorous study we had excluded from our analysis for reasons of conceptually incompatible outcome measures (365-days-based hazard ratio vs in-hospital-based odds ratio). To better reflect the impact of methodological choices on the review outcome, we also presented the results of a second statistical model incorporating 3 adjusted effect estimates from reported multiple regression analyses. Especially the inclusion of a register-based study reporting on 2 propensity-analyzed cohorts in Germany and France might have mitigated the impact of residual confounding in this model. However, due to statistical considerations related to pooling adjusted and unadjusted results, we do not recommend interpreting these results in isolation. Due to considerable variability in effect estimates for this outcome across systematic reviews and an underlying low to very low certainty evidence, we can neither make a recommendation for nor against the use of corticosteroids.

	Medical providers may want to consider empirical in conjunction with mechanistic evidence in making clinical decisions

Intravenuous immunoglobulines (IVIG)

Summary of Findings

What is the overall certainty of the evidence?

IVIG vs supportive therapy

JUDGEMENT

- o Trivial
- o Small
- o Moderate
- o Large
- o Varies
- ● Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Supportive therapy	IVIG
Mortality	462 (10 observational studies)	⊕◯◯◯ VERY LOW [a,c]	RR 1.25 (0.93 – 1.69)	Risk of mortality 260 per 1.000	66 more per 1.000 (19 fewer to 179 more)
Mortality (alternative statistical model)	571 (11 observational studies)	⊕◯◯◯ VERY LOW [a,c]	RR 1.25 (0.93 – 1.62)	Risk of mortality 253 per 1.000	62 more per 1.000 (19 fewer to 157 more)
Length of hospital stay	109 (3 observational studies)	⊕⊕◯◯ LOW [a,c]	-	Mean stay: 19.07 ± 22.38 days	MD in days: 3.04 more (1.29 fewer to 7.37 more)
Time to complete reepithelialization	45 (1 observational study)	⊕⊕◯◯ LOW [b,c]	-	Mean time: 12.4 ± 5.9 days	MD in days: 5.4 more (0.57 more to 10.23 more)
Serious complications: sepsis	63 (2 observational studies)	⊕⊕◯◯ LOW [b,c]	RR 1.15 (0.81 – 1.63)	Risk of serious complications 622 per 1.000	93 more per 1.000 (117 fewer to 391 more)
Serious complications: ventilation required	31 (1 observational study)	⊕⊕◯◯ LOW [b,c]	RR 1.02 (0.24 – 4.34)	Risk of serious complications 222 per 1.000	5 more per 1.000 (169 fewer to 742 more)

COMMENTS

Additional results:

Including only prospective studies and applying Cochrane methodology, a 2022 systematic review by Jacobsen et al. (2) comparing the effect of IVIG with no IVIG on disease-specific mortality reports a risk ratio (RR) of 0.33, 95% confidence interval (CI) 0.04 to 2.91. For the outcomes time to complete reepithelialization and length of hospital stay, they report a mean difference (MD) of -2.93 days, 95% confidence interval -4.4 to -1.46 and an MD of -2 days, 95% confidence interval -5.81 to 1.81, respectively. All results were based on 1 study with 36 participants (very low-certainty evidence).

A 2017 systematic review by Zimmermann et al. (18) comparing IVIG versus supportive therapy for the outcome disease-specific mortality reports three different effect estimates based on meta-analysis at the study- and patient level, where the latter analysis was conducted both stratified by study and unstratified. Based on 9 studies (including 3 studies omitted in our analysis due to baseline differences between groups and statistical considerations) with 344/611 patients (study-level/patient-level) reports a pooled odds ratio (OR) of 0.99, 95% CI 0.64 to 1.54 for the study-level analysis, and OR of 0.65, 95% CI 0.42 to 1 and 1.34, 95% CI 0.68 to 2.61 for the unstratified and stratified analysis, respectively.

The results of an alternative statistical model incorporating multiple regression-adjusted outcome measures instead of crude deaths rate (from 1 study also included in the original model) is shown in the second row of this table. For details please see separately published methods report.

a. Study limitations: serious risk of bias in multiple studies
b. Study limitations: moderate risk of bias in multiple studies
c. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not me

IVIG vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Corticosteroids	IVIG
	Mortality	48 (2 observational studies)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.4** (0.08 – 1.94)	Risk of mortality 226 per 1.000	**136 fewer per 1.000** (207 fewer to 212 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Cyclosporine A vs IVIG

JUDGEMENT	RESEARCH EVIDENCE						COMMENTS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Additional results: Including only prospective studies and applying Cochrane methodology, a 2022 systematic review by Jacobsen et al. (2) comparing the effect of cyclosporine with IVIG on disease-specific mortality reports a statistically significant risk ratio (RR) of 0.13, 95% confidence interval (CI) 0.02 to 0.98, based on 1 study with 22 participants (very low-certainty evidence).
					IVIG	Cyclosporine A	
	Mortality	91 (2 observational studies)	⊕⊕⊕◯ MODERATE [a,b,c]	**RR 0.18** (0.05 – 0.58)	Risk of mortality 376 per 1.000	**309 fewer per 1.000** (355 fewer to 156 fewer)	
	Length of hospital stay	54 (1 observational study)	⊕⊕◯◯ LOW [a,b]	-	Mean stay: 26.6 ± 28 days	**MD in days: 9.8 less** (19.63 less to 0.03 more)	

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met
c. Large magnitude of effect

Etanercept vs IVIG

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					IVIG	Etanercept
	Mortality	14 (1 observational studies)	⊕⊕◯◯ LOW [a,b]	**RR 0.12** (0.01 – 2.1)	Risk of mortality 400 per 1.000	**352 fewer per 1.000** (397 fewer to 440 more)

a. Study limitations: moderate risk of bias in mutliple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Bibliography

Brown, 2004 (19); Chan, 2019 (20); Dreyer, 2021 (21); Gonzalez-Herrada, 2017 (22); Gravante, 2007 (23); Imahara, 2006 (24); Kim, 2005 (6); Kirchhof, 2014 (25); Kridin, 2021 (8); Marchitto, 2018 (26); Paquet, 2006 (27); Schneck, 2008 (28); Sekula, 2013 (11), Shortt, 2004 (29); Williams, 2021 (30); Yip, 2005 (17)

Desirable Effects

Are the desirable effects large?

Judgement:	IVIG vs supportive therapy

<table>
<tr><td>o No
o Probably no
● Uncertain
o Probably yes
o Yes
o Varies</td><td>• No significant difference with IVIG for the critical outcomes mortality (GRADE: ⊕◯◯◯ VERY LOW) and serious complications sepsis (GRADE: ⊕⊕◯◯ LOW) and the important outcomes length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW), time to complete reepithelialization (GRADE: ⊕⊕◯◯ LOW) and serious complications: ventilation required (GRADE: ⊕⊕◯◯ LOW)

<u>IVIG vs corticosteroids</u>

• No significant difference with IVIG for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)

<u>Cyclosporine A vs IVIG</u>

• No significant difference with IVIG for the critical outcomes serious complications: sepsis (GRADE: ⊕◯◯◯ VERY LOW), serious complications: organ failure and the important outcomes length of hospital stay (GRADE: ⊕⊕◯◯ LOW) and serious complications: ventilation required (GRADE: ⊕⊕◯◯ LOW)

<u>Etanercept vs IVIG</u>

• No significant difference with IVIG for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW)</td></tr>
<tr><td colspan="2">Undesirable Effects
Are the undesirable effects small?</td></tr>
<tr><td>Judgement:

o No
● Probably no
o Uncertain
o Probably yes
o Yes
o Varies</td><td><u>IVIG vs supportive therapy</u>

• Significant disadvantage with IVIG for the important outcome time to complete reepithelialization (GRADE: ⊕⊕◯◯ LOW)
• No significant difference with IVIG for the critical outcomes mortality (GRADE: ⊕◯◯◯ VERY LOW) and serious complications sepsis (GRADE: ⊕⊕◯◯ LOW) and the important outcomes length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW), time to complete reepithelialization (GRADE: ⊕⊕◯◯ LOW) and serious complications: ventilation required (GRADE: ⊕⊕◯◯ LOW)

<u>IVIG vs corticosteroids</u>

• No significant difference with IVIG for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)

<u>Cyclosporine A vs IVIG</u>

• Significant disadvantage with IVIG for the critical outcome mortality (GRADE: ⊕⊕⊕◯ MODERATE)
• No significant difference with IVIG for the critical outcomes serious complications: sepsis (GRADE: ⊕◯◯◯ VERY LOW), serious complications: organ failure and the important outcomes length of hospital stay (GRADE: ⊕⊕◯◯ LOW) and serious complications: ventilation required (GRADE: ⊕⊕◯◯ LOW)

<u>Etanercept vs IVIG</u>

• No significant difference with IVIG for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW)</td></tr>
<tr><td colspan="2">Differences in values
Is there important uncertainty about how much people value the main outcomes?</td></tr>
<tr><td>Judgement:

o Important uncertainty or variability
o Possibly important uncertainty or</td><td>• No significant desirable effects have been reported
• The guideline committee has judged the significant undesirable effects as critical (mortality in IVIG compared to cyclosporine A) and important (longer time to complete reepithelialization in IVIG compared with supportive therapy)</td></tr>
</table>

variability ● Probably no important uncertainty of variability ○ No important uncertainty of variability ○ Not known	• Interviews with 14 survivors and family members of survivers conducted by our group suggest a higher importance of illness sequelae relative to the judgement of the guideline committee. As no significant between-group differences could be identified for this set of outcomes, no conflict of values is expected.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	IVIG vs supportive therapy • Significant disadvantage with IVIG for the important outcome time to complete reepithelialization (GRADE: ⨁⨁◯◯ LOW) • No significant difference with IVIG for the critical outcomes mortality (GRADE: ⨁◯◯◯ VERY LOW) and serious complications sepsis (GRADE: ⨁⨁◯◯ LOW) and the important outcomes length of hospital stay (GRADE: ⨁◯◯◯ VERY LOW), time to complete reepithelialization (GRADE: ⨁⨁◯◯ LOW) and serious complications: ventilation required (GRADE: ⨁⨁◯◯ LOW) • Low to very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects IVIG vs corticosteroids • No significant difference with IVIG for the critical outcome mortality (GRADE: ⨁◯◯◯ VERY LOW) • Very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects Cyclosporine A vs IVIG • No significant difference with IVIG for the critical outcomes • Significant disadvantage with IVIG for the critical outcome mortality (GRADE: ⨁⨁⨁◯ MODERATE) • No significant difference with IVIG for the critical outcomes serious complications: sepsis (GRADE: ⨁◯◯◯ VERY LOW), serious complications: organ failure and the important outcomes length of hospital stay (GRADE: ⨁⨁◯◯ LOW) and serious complications: ventilation required (GRADE: ⨁⨁◯◯ LOW) • low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects (applies to outcome length of hospital stay only) Etanercept vs IVIG • No significant difference with IVIG for the critical outcome mortality (GRADE: ⨁⨁◯◯ LOW) • Low to very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No comprehensive cost-benefit analysis for the German healthcare system was identified • Compared with corticosteroids, IVIG represenst a more significant burden to payers
Resource use Is the incremental cost small relative to the net benefits?	

Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No comprehensive cost-benefit analysis for the German healthcare system was identified • Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small benefits in critical outcomes
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No significant impact on equity expected
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated
Conclusion What is the final judgement in light of the evidence, and are there important limitations?	
Judgement: ○ Strong recommendation against the intervention ● Conditional recommendation against the intervention ○ Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	Pooled effect estimates provide evidence for a disadvantage of IVIG over cyclosporine A based on retrospective data from 3 observational studies with 139 patients suggesting a large effect on in-hospital mortality. For the outcome time to complete reepithelialization, we found low-certainty evidence for a significant disadvantage of intravenuous immunoglobulines over supportive therapy based on retrospective data from 1 observational study with 45 patients. However, as the confidence intervals of the reported effect estimate cross the threshold of minimal clinical importance (MD ≥ 2 days) and there is a high potential for measurement error in this outcome, it is unclear whether there is any meaningful effect. Considering the absence of pooled effect estimates suggesting an advantage for IVIG monotherapy in conjunction with the significant advantage of IVIG combined with corticosteroids over IVIG alone (very low certainty evidence, see EtD-Table Combined Therapies below), we conditionally recommend against using intravenuous immunoglobulines as monotherapy for the treatment of acute EN. Medical providers may want to consider empirical in conjunction with mechanistic evidence in making clinical decisions.

Cyclosporine A

Summary of Findings What is the overall certainty of the evidence?

Cyclosporine A vs supportive therapy

JUDGEMENT	RESEARCH EVIDENCE						COMMENTS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Additional results: A retrospective observational study by Poizeau et al., 2018 (31) applying a propensity score method to acount for residual confounding reports higher mortality with cyclosporin A compared with supportive therapy (hazard ratio (HR) 1.54, 95% confidence intervals: 0.2 to 9.28). The same study reports shorter time to complete reepithelialization with cyclosporin A (HR 0.75, 95% CI: 0.48-1.18) and mucosal re-epithelialization (≤ day 10 after response initiation: HR 0.48, 95% confidence intervals: 0.23 to 1.02). Due to incommensurable outcome meaasures (HR of dichotomized time difference vs mean difference in days) these results could not be pooled with effect estimates of other studies. The results of an alternative statistical model incorporating multiple regression-adjusted outcome measures instead of crude deaths rate (from 1 study also included in the original model) is shown in the second row of this table. For details please see separately published methods report.
					Supportive therapy	Cyclosporine A	
	Mortality	74 (1 observational study)	⊕⊕◯◯ LOW [b,c]	RR 1.5 (0.27 – 8.46)	Risk of mortality 54 per 1.000	27 more per 1.000 (40 fewer to 403 more)	
	Mortality (alternative statistical model)	175 (2 observational studies)	⊕◯◯◯ VERY LOW [a,c]	RR 1.2 (0.37 – 3.22)	Risk of mortality 107 per 1.000	21 more per 1.000 (68 fewer to 238 more)	
	Serious complications: sepsis	74 (1 observational studies)	⊕⊕◯◯ LOW [b,c]	RR 1.37 (0.62 – 3.03)	Risk of serious complications 216 per 1.000	81 more per 1.000 (81 more to 438 more)	
	Serious complications: organ failure	74 (1 observational studies)	⊕⊕◯◯ LOW [b,c]	RR 9 (0.5 – 161.44)	Risk of serious complications 0 per 1.000	Not calculable	

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Study limitations: moderate risk of bias in multiple or a substantial number of studies
c. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Cyclosporine A vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Corticosteroids	Cyclosporine A
	Mortality	62 (2 observational study)	⊕⊕◯◯ LOW [a,b]	RR 0.45 (0.11 – 1.82)	Risk of mortality 262 per 1.000	144 fewer per 1.000 (233 fewer to 215 more)
	Length of hospital stay	110 (3 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	-	Mean stay: 15.33 ± 11.78 days	MD in days: 4.3 less (10.41 less to 1.81 more)
	Time to complete reepithelialization	110 (3 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	-	Mean time: 12.46 ± 5.72 days	MD in days: 3.85 less (7.9 less to 0.21 more)
	Serious complications: sepsis	110 (3 observational study)	⊕⊕◯◯ LOW [a,b]	RR 0.62 (0.21 – 1.81)	Risk of serious complications 190 per 1.000	73 less per 1.000 (150 less to 154 more)
	Sequelae: eyes	17 (1 observational study)	⊕⊕◯◯ LOW [a,b]	RR 1.75 (0.08 – 37.39)	Risk of serious complications 0 per 1.000	Not calculable

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met
c. Inconsistency of results: CIs of effect estimates of individual studies do not overlap or evidence of substantial statistical heterogeneity

Cyclosporine A vs IVIG

JUDGEMENT	RESEARCH EVIDENCE						COMMENTS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Additional results: Including only prospective studies and applying Cochrane methodology, a 2022 systematic review by Jacobsen et al. (2) comparing the effect of cyclosporine with IVIG on disease-specific mortality reports a statistically significant risk ratio (RR) of 0.13, 95% confidence interval (CI) 0.02 to 0.98, based on 1 study with 22 participants (very low-certainty evidence).
					IVIG	Cyclosporine A	
	Mortality	91 (2 observational studies)	⊕⊕⊕◯ MODERATE [a,b,c]	RR 0.18 (0.05 – 0.58)	Risk of mortality 376 per 1.000	309 fewer per 1.000 (355 fewer to 156 fewer)	
	Length of hospital stay	54 (1 observational study)	⊕⊕◯◯ LOW [a,b]	-	Mean stay: 26.6 ± 28 days	MD in days: 9.8 days less (19.63 less to 0.03 more)	

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met
c. Large magnitude of effect

Bibliography

Gonzalez-Herrada, 2017 (22); Kirchhof, 2014 (25); Kridin, 2021 (8); Poizeau, 2018 (31); Shah, 2021 (12); Singh, 2013 (13); Thakur, 2021 (14)

Desirable Effects

Are the desirable effects large?

Judgement:	
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Cyclosporine A vs supportive therapy • No significant difference with cyclosporine A for the critical outcomes mortality and serious complications: sepsis (GRADE: ⊕⊕◯◯ LOW) Cyclosporine A vs corticosteroids • No significant difference with cyclosporine A for the critical outcomes mortality, sequelae: eyes and serious complications: sepsis and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⊕⊕◯◯ LOW) Cyclosporine A vs IVIG • Significant advantage with cyclosporine A for the critical outcome mortality (GRADE: ⊕⊕⊕◯ MODERATE) • No significant difference with cyclosporine A for the critical outcome serious complications: organ failure and the important outcomes length of hospital stay and serious complications: ventilation required (GRADE: ⊕⊕◯◯ LOW)

Undesirable Effects

Are the undesirable effects small?

Judgement:	
○ No ○ Probably no ● Uncertain ○ Probably yes	Cyclosporine A vs supportive therapy • No significant difference with cyclosporine A for the critical outcomes mortality and serious complications: sepsis (GRADE: ⊕⊕◯◯ LOW) Cyclosporine A vs corticosteroids

<table>
<tr>
<td>○ Yes
○ Varies</td>
<td>• No significant difference with cyclosporine A for the critical outcomes mortality, sequelae: eyes and serious complications: sepsis and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⊕⊕◯◯ LOW)

<u>Cyclosporine A vs IVIG</u>

• No significant difference with cyclosporine A for the critical outcome serious complications: organ failure and the important outcomes length of hospital stay and serious complications: ventilation required (GRADE: ⊕⊕◯◯ LOW)</td>
</tr>
<tr>
<td colspan="2">Differences in values
Is there important uncertainty about how much people value the main outcomes?</td>
</tr>
<tr>
<td>Judgement:
○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty of variability
○ No important uncertainty of variability
○ No known undesirable</td>
<td>• The guideline committee has judged the significant desirable effects as critical (mortality)
• No significant undesirable effects have been reported
• Interviews with 14 survivors and family members of survivers conducted by our group suggest a higher importance of illness sequelae relative to the judgement of the guideline committee. As no significant between-group differences could be identified for this set of outcomes, no conflict of values is expected.</td>
</tr>
<tr>
<td colspan="2">Balance of effects
Does the balance between desirable and undesirable effects favor the intervention?</td>
</tr>
<tr>
<td>Judgement:

○ No
○ Probably no
● Uncertain
○ Probably yes
○ Yes
○ Varies</td>
<td><u>Cyclosporine A vs supportive therapy</u>

• No significant difference with cyclosporine A for the critical outcomes mortality and serious complications: sepsis (GRADE: ⊕⊕◯◯ LOW)
• Low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects

<u>Cyclosporine A vs corticosteroids</u>

• No significant difference with cyclosporine A for the critical outcomes mortality, sequelae: eyes and serious complications: sepsis and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⊕⊕◯◯ LOW)
• Low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects

<u>Cyclosporine A vs IVIG</u>

• Significant advantage with cyclosporine A for the critical outcome mortality (GRADE: ⊕⊕⊕◯ MODERATE)
• No significant difference with cyclosporine A for the critical outcome serious complications: organ failure and the important outcomes length of hospital stay and serious complications: ventilation required (GRADE: ⊕⊕◯◯ LOW)
• Low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects (does not apply for outcome mortality)</td>
</tr>
<tr>
<td colspan="2">Resource use
Are the resources required small?</td>
</tr>
<tr>
<td>Judgement:

○ No
○ Probably no
○ Uncertain</td>
<td>• No comprehensive cost-benefit analysis for the German healthcare system was identified
• Compared with corticosteroids, cyclosporine A leads to slightly higher costs</td>
</tr>
</table>

● Probably yes ○ Yes ○ Varies	
Resource use Is the incremental cost small relative to the net benefits?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No comprehensive cost-benefit analysis for the German healthcare system was identified • Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small benefits in critical outcomes
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No significant impact on equity expected
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated
Conclusion What is the final judgement in light of the evidence, and are there important limitations?	
Judgement: ○ Strong recommendation against the intervention ○ Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	A comparison between cyclosporine A and supportive therapy based on 2 observational studies with 175 and 1 observational study with 101 patients for the outcomes mortality, serious complications: organ failure and serious complications: ventilation required did not produce significant findings. However, the former 2 observational studies provided low certainty evidence for a disadvantage with cyclosporine A over supportive therapy for the outcome serious complications: sepsis. As the pooled effect estimate for this outcome crosses the the threshold of minimal clinical importance (RR = 1.1) and there is a high potential for measurement error in this outcome, it is unclear whether there is any meaningful effect. Furthermore, there are conflicting directions of effects for different critical outcomes (mortality vs incidence of serious complications) based on low to very low certainty evidence. Even though there is moderate-certainty evidence for a statistically significant advantage of cyclosporine A over IVIG regarding the outcome mortality based on 2 observational studies with 91 and 1 observational study with 37 patients, this does not imply an overall benefit of cyclosporine A without first establishing non-inferiority of IVIG over supportive therapy. As it cannot be ruled out that the administration of IVIG increases mortality compared with supportive therapy, we can neither make a recommendation for nor against the use of cyclosporine A in acute EN.

	Medical providers might want to consider empirical in conjunction with mechanistic evidence in making clinical decisions

Etanercept

Summary of Findings

What is the overall certainty of the evidence?

Etanercept vs supportive therapy

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Supportive therapy	Etanercept
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	86 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	RR 0.32 (0.11 – 0.93)	Risk of mortality 263 per 1.000	**180 fewer per 1.000** (235 fewer to 18 fewer)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Etanercept vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE						COMMENTS
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		
					Corticosteroids	Etanercept	
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	91 (1 randomized controlled trial)	⊕⊕⊕◯ MODERATE [a]	RR 0.51 (0.16 – 1.63)	Risk of mortality 163 per 1.000	**79 fewer per 1.000** (137 fewer to 102 more)	Including only prospective studies and applying Cochrane methodology, a 2022 systematic review by Jacobsen et al. (2) comparing the effect of etanercept with corticosteroids on disease-specific mortality reports a risk ratio (RR) of 0.51, 95% confidence interval (CI) 0.16 to 1.63. Serious adverse events, such as sepsis and respiratory failure, were reported in 5 of 48 participants with etanercept and 9 of 43 participants with corticosteroids, but it was not clear if they led to discontinuation of therapy. All results were based on 1 study with 91 participants (low-certainty evidence).
	Time to complete reepithelialization	91 (1 randomized controlled trial)	⊕⊕⊕◯ MODERATE [a]	-	Mean time: 16 ± 7.2 days	**MD in days: 1.7 less** (4.48 less to 1.08 more)	
	Serious complications: sepsis	91 (1 randomized controlled trial)	⊕⊕⊕◯ MODERATE [a]	RR 0.45 (0.09 – 2.32)	Risk of serious complications 93 per 1.000	**51 less per 1.000** (85 less to 123 more)	

a. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Etanercept vs IVIG

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					IVIG	Etanercept
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	14 (1 observational studies)	⊕⊕◯◯ LOW [a,b]	RR 0.12 (0.01 – 2.1)	Risk of mortality 400 per 1.000	**352 fewer per 1.000**

						(397 fewer to 440 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Bibliography

Dreyer, 2021 (21); Wang, 2018 (16)

Desirable Effects

Are the desirable effects large?

Judgement:	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Etanercept vs supportive therapy • Significant advantage with etanercept for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW) Etanercept vs corticosteroids • No significant difference with etanercept for the critical outcomes mortality and serious complications sepsis and the important outcome time to complete reepithelialization (GRADE: ⊕⊕⊕◯ MODERATE) Etanercept vs IVIG • No significant difference with etanercept for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW)

Undesirable Effects

Are the undesirable effects small?

Judgement:	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Etanercept vs supportive therapy • No disadvantage with etanercept reported Etanercept vs corticosteroids • No significant difference with etanercept for the critical outcomes mortality and serious complications sepsis and the important outcome time to complete reepithelialization (GRADE: ⊕⊕⊕◯ MODERATE) Etanercept vs IVIG • No significant difference with etanercept for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW)

Differences in values

Is there important uncertainty about how much people value the main outcomes?

Judgement:	
Judgement: ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty of variability ○ No important uncertainty of variability ○ No known undesirable	• The guideline committee has judged the significant desirable effects as critical (in-hospital mortality in etanercept compared with supportive therapy) • No significant undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group suggest a higher importance of illness sequelae relative to the judgement of the guideline committee. As no significant between-group differences could be identified for this set of outcomes, no conflict of values is expected.

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention?

Judgement:	
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Etanercept vs supportive therapy • Significant advantage with etanercept for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW) • No disadvantage with etanercept reported • Very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects Etanercept vs corticosteroids • No significant difference with etanercept for the critical outcomes mortality and serious complications sepsis and the important outcome time to complete reepithelialization (GRADE: ⊕⊕⊕◯ MODERATE) Etanercept vs IVIG • No significant difference with etanercept for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW) • Low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects

Resource use

Are the resources required small?

Judgement:	
○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No comprehensive cost-benefit analysis for the German healthcare system was identified • Compared with corticosteroids, etanercept represents a more significant burden to payers

Resource use

Is the incremental cost small relative to the net benefits?

Judgement:	
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No comprehensive cost-benefit analysis for the German healthcare system was identified • Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small benefits in critical outcomes

Equity

What would be the impact on health inequities?

Judgement:	
○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No significant impact on equity expected

Acceptability, Implementability and Feasibility

Is the option acceptable to key stakeholders, can it be implemented and is it feasible?

Judgement:	
○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated

Conclusion

What is the final judgement in light of the evidence, and are there important limitations?

Judgement:	
○ Strong recommendation against the intervention ○ Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	Pooled effect estimates provide very low-certainty evidence for an advantage of etanercept over supportive therapy for the outcome mortality based on data reported as additional retrospective analysis (comparison with historical control group) in the context of a randomized controlled trial with 86 patients. However, as the confidence intervals of the reported effect estimate cross the threshold of clinical importance (0.9), we are uncertain whether there is any clinically significant effect. Moreover, in comparing etanercept with corticosteroid therapy in 91 patients, the RCT fails to find statistical significance. We therefore do not feel confident in making recommendations for or against the use of etanercept. Medical providers might want to consider empirical in conjunction with mechanistic evidence in making clinical decisions.

Thalidomide

Summary of Findings

What is the overall certainty of the evidence?

Thalidomide vs placebo

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Placebo	Thalidomide
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	22 (1 randomized controlled trial)	⊕⊕⊕⊕ HIGH	RR 2.78 (1.04 – 7.4)	Risk of mortality 300 per 1.000	533 more per 1.000 (13 more to 1920 more)

Bibliography

Wolkenstein, 1998 (32)

Desirable Effects

Are the desirable effects large?

Judgement:	Research evidence
Judgement: ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Thalidomide vs placebo • No advantage with thalidomide reported
Undesirable Effects Are the undesirable effects small?	
Judgement: ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Thalidomide vs placebo • Significant disadvantage with thalidomide for the critical outcome mortality (GRADE: ⊕⊕⊕⊕ HIGH)
Differences in values Is there important uncertainty about how much people value the main outcomes?	
Judgement: ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty of variability ● No important uncertainty of variability ○ No known undesirable	• The guideline committee has judged the significant undesirable effects as critical (in-hospital mortality in Thalidomide compared with placebo) • No significant desirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group suggest a higher importance of illness sequelae relative to the judgement of the guideline committee. As no significant between-group differences could be identified for this set of outcomes, no conflict of values is expected.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ● No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	Thalidomide vs placebo • No advantage with thalidomide reported • Significant disadvantage with thalidomide for the critical outcome mortality (GRADE: ⊕⊕⊕⊕ HIGH)
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No comprehensive cost-benefit analysis for the German healthcare system was identified
Resource use Is the incremental cost small relative to the net benefits?	

Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No comprehensive cost-benefit analysis for the German healthcare system was identified • Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small benefits in critical outcomes
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No significant impact on equity expected
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ No ● Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated
Conclusion What is the final judgement in light of the evidence, and are there important limitations?	
Judgement: ● Strong recommendation against the intervention ○ Conditional recommendation against the intervention ○ Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	There is high-certainty evidence for a detrimental effect on mortality of thalidomide based on a single placebo-controlled, randomized, double-blind trial in 22 patients. This study had to be stopped early due to an increased mortality rate in the thalidomide group. Paradoxically, patients in the thalidomide group presented with increased serum TNF-α levels (Wolkenstein et al. 1998) (32). We therefore strongly recommend against the use of thalidomide in acute EN.

SYSTEMIC IMMUNOMODULATORY THERAPIES: COMBINED THERAPIES

IVIG + corticosteroids

Summary of Findings

What is the overall certainty of the evidence?

IVIG + corticosteroids vs supportive therapy

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Supportive therapy	IVIG + corticosteroids

o Moderate o Large o Varies ● Don't know	Mortality	165 (3 observational studies)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 0.62** (0.3 – 1.24)	Risk of mortality 222 per 1.000	**86 fewer per 1.000** (155 fewer to 54 more)
	Serious complications: sepsis	19 (1 observational study)	⊕⊕◯◯ LOW [b,c]	**RR 0.9** (0.38 – 2.11)	Risk of serious complications 556 per 1.000	**56 fewer per 1.000** (342 fewer to 616 more)
	Serious complications: ventilation required	19 (1 observational study)	⊕◯◯◯ LOW [b,c]	**RR 0.45** (0.05 – 4.16)	Risk of serious complications 222 per 1.000	**122 fewer per 1.000** (211 fewer to 703 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Study limitations: moderate risk of bias in multiple studies
c. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met
d. Indirectness: studies with sequential treatment included

IVIG + corticosteroids vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Corticosteroids	IVIG + corticosteroids
o Trivial o Small o Moderate o Large o Varies ● Don't know	Mortality	548 (9 observational studies)	⊕◯◯◯ VERY LOW [a,c,e]	**RR 0.73** (0.46 – 1.18)	Risk of mortality 167 per 1.000	**44 fewer per 1.000** (91 fewer to 30 more)
	Length of hospital stay	261 (4 observational studies)	⊕◯◯◯ VERY LOW [a,c,d]	-	Mean stay: 21.6 ± 13.39 days	**MD in days: 4.48 less** (8.43 less to 0.54 less)
	Time to complete reepithelialization	36 (1 observational study)	⊕⊕◯◯ LOW [b,c]	-	Mean time: 10.93 ± 2.25 days	**MD in days: 2.93 less** (4.4 less to 1.46 less)
	Serious complications: sepsis	140 (3 observational studies)	⊕◯◯◯ VERY LOW [a,c,e]	**RR 0.77** (0.31 – 1.93)	Risk of serious complications 136 per 1.000	**31 less per 1.000** (94 less to 126 more)
	Serious complications: organ failure	75 (2 observational studies)	⊕◯◯◯ VERY LOW [a,c,e]	**RR 0.69** (0.29 – 1.66)	Risk of serious complications 220 per 1.000	**69 less per 1.000** (157 fewer to 145 more)

a. Study limitations: serious risk of bias in multiple studies
b. Study limitations: moderate risk of bias in multiple studies
c. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met
d. Inconsistency of results: CIs of effect estimates of individual studies do not overlap or evidence of substantial statistical heterogeneity
e. Indirectness: studies with sequential treatment included

IVIG + corticosteroids vs IVIG

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					IVIG	IVIG + corticosteroids
o Trivial o Small o Moderate o Large o Varies ● Don't know	Mortality	136 (3 observational studies)	⊕◯◯◯ VERY LOW [a,c,d]	**RR 0.46** (0.22 – 0.96)	Risk of mortality 312 per 1.000	**167 fewer per 1.000** (243 fewer to 11 fewer)

	Serious complications: sepsis	32 (1 observational study)	⊕⊕◯◯ LOW [b,c]	**RR 0.85** (0.42 – 1.72)	Risk of serious complications 591 per 1.000	**91 less per 1.000** (345 less to 427 more)
	Serious complications: ventilation required	32 (1 observational study)	⊕⊕◯◯ LOW [b,c]	**RR 0.44** (0.06 – 3.29)	Risk of serious complications 227 per 1.000	**127 less per 1.000** (214 fewer to 521 more)
	Sequelae: eyes	32 (1 observational study)	⊕⊕◯◯ LOW [b,c]	**RR 0.55** (0.2 – 1.53)	Risk of serious complications 545 per 1.000	**245 less per 1.000** (437 less to 287 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Study limitations: moderate risk of bias in multple or a substantial number of studies
c. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met
d. Indirectness: studies with sequential treatment included

Etanercept + corticosteroids vs IVIG + corticosteroids

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					IVIG + corticosteroids	Etanercept + corticosteroids
	Mortality	46 (1 observational studies)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.28** (0.01 – 6.58)	Risk of mortality 48 per 1.000	**34 less per 1.000** (47 less to 266 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Bibliography

Chan, 2019 (20);Hsieh, 2021 (33); Jagadeesan, 2013 (34); Schneck, 2008 (28); Williams, 2021 (30); Xiao, 2019 (35); Yang, 2009 (36); Yang, 2021 (37); Yeong, 2011 (38); Yun, 2008 (39); Zhang, 2022 (40); Zhu, 2012 (41)

Desirable Effects

Are the desirable effects large?

Judgement:	
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	IVIG + corticosteroids • No significant difference with IVIG + corticosteroids for the critical outcomes mortality, serious complications: sepsis and the important outcome serious complications: ventilation required (GRADE: ⊕◯◯◯ VERY LOW) IVIG + corticosteroids vs corticosteroids • Significant advantage with IVIG + corticosteroids for the important outcomes length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW) and time to complete reepithelialization (GRADE: ⊕◯◯◯ LOW) • No significant difference for the critical outcomes mortality, serious complications: sepsis and serious complications: organ failure (GRADE: ⊕◯◯◯ VERY LOW) IVIG + corticosteroids vs IVIG • Significant advantage with IVIG + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW) • No significant difference with IVIG + corticosteroids for the critical outcomes serious complications: sepsis and sequelae: eyes and the important outcome serious complications: ventilation required (GRADE: ⊕◯◯◯ LOW) Etanercept + corticosteroids vs IVIG + corticosteroids

	• No significant difference for IVIG + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)
Undesirable Effects Are the undesirable effects small?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	IVIG + corticosteroids • No significant difference with IVIG + corticosteroids for the critical outcomes mortality, serious complications: sepsis and the important outcome serious complications: ventilation required (GRADE: ⊕◯◯◯ VERY LOW) IVIG + corticosteroids vs corticosteroids • No significant difference for the critical outcomes mortality, serious complications: sepsis and serious complications: organ failure (GRADE: ⊕◯◯◯ VERY LOW) IVIG + corticosteroids vs IVIG • No significant difference with IVIG + corticosteroids for the critical outcomes serious complications: sepsis and sequelae: eyes and the important outcome serious complications: ventilation required (GRADE: ⊕◯◯◯ LOW) Etanercept + corticosteroids vs IVIG + corticosteroids • No significant difference for IVIG + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)
Differences in values Is there important uncertainty about how much people value the main outcomes?	
Judgement: ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty of variability ○ No important uncertainty of variability ○ No known undesirable	• The guideline committee has judged the significant desirable effects as critical (mortality in IVIG + corticosteroids compared with supportive therapy) and important (length of hospital stay and time to complete reepithelialization in IVIG + corticosteroids compared with supportive therapy) • No significant undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group suggest a higher importance of illness sequelae relative to the judgement of the guideline committee. As no significant between-group differences could be identified for this set of outcomes, no conflict of values is expected.
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	IVIG + corticosteroids vs supportive therapy • No significant difference with IVIG + corticosteroids for the critical outcomes mortality, serious complications: sepsis and the important outcome serious complications: ventilation required (GRADE: ⊕◯◯◯ VERY LOW) • Very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects IVIG + corticosteroids vs corticosteroids • Significant advantage with IVIG + corticosteroids for the important outcomes length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW) and time to complete reepithelialization (GRADE: ⊕◯◯◯ LOW)

<table>
<tr><td></td><td>

No significant difference for the critical outcomes mortality, serious complications: sepsis and serious complications: organ failure (GRADE: ⊕◯◯◯ VERY LOW)
Low to very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects

<u>IVIG + corticosteroids vs IVIG</u>

Significant advantage with IVIG + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)
No significant difference with IVIG + corticosteroids for the critical outcomes serious complications: sepsis and sequelae: eyes and the important outcome serious complications: ventilation required (GRADE: ⊕◯◯◯ LOW)
Low to very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects

<u>Etanercept + corticosteroids vs IVIG + corticosteroids</u>

No significant difference with IVIG + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)
Very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects

</td></tr>
<tr><td colspan="2">Resource use
Are the resources required small?</td></tr>
<tr><td>Judgement:

○ No
○ Probably no
○ Uncertain
● Probably yes
○ Yes
○ Varies</td><td>

No cost-benefit analysis for the German healthcare system was identified
IVIGs represent a more significant burden to payers
Corticosteroids can be considered routine care and likely represent a negligible burden to payers

</td></tr>
<tr><td colspan="2">Resource use
Is the incremental cost small relative to the net benefits?</td></tr>
<tr><td>Judgement:

○ No
○ Probably no
● Uncertain
○ Probably yes
○ Yes
○ Varies</td><td>

No cost-benefit analysis for the German healthcare system was identified
Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small benefits in critical outcomes

</td></tr>
<tr><td colspan="2">Equity
What would be the impact on health inequities?</td></tr>
<tr><td>Judgement:

○ Increased
○ Probably increased
○ Uncertain
○ Probably reduced
○ Reduced
● Varies</td><td>

No significant impact on equity expected

</td></tr>
<tr><td colspan="2">Acceptability, Implementability and Feasibility
Is the option acceptable to key stakeholders, can it be implemented and is it feasible?</td></tr>
</table>

Judgement:	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated

Conclusion

What is the final judgement in light of the evidence, and are there important limitations?

Judgement	
Judgement: ○ Strong recommendation against the intervention ○ Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	There is low to very low certainty evidence for an advantage of IVIG + corticosteroids over corticosteroids alone for the outcomes length of hospital stay and time to complete reepithelialization based on 4 observational studies with 261 and 1 observational studies with 36 patients, respectively. In the comparison between IVIG + corticosteroids and IVIG alone, we found very low certainty evidence for lower mortality in combination therapy based on 3 observational studies with 136 patients. Considering the low certainty of the evidence and the imprecision of reported effect estimates, we can neither make a recommendation for nor against the use of IVIG + corticosteroids in acute EN Medical providers might want to consider empirical in conjunction with mechanistic evidence in making clinical decisions

Etanercept + corticosteroids

Summary of Findings

What is the overall certainty of the evidence?

Etanercept + corticosteroids vs corticosteroids

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Corticosteroids	Etanercept + corticosteroids
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	25 (1 observational studies)	⊕⊕◯◯ LOW [a,b]	**RR 0.69** (0.01 – 32.12)	Risk of mortality per 1.000 not estimable (no death in single control group)	Risk reduction of mortality per 1.000 not estimable (no death in single control group)
	Length of hospital stay	25 (1 observational study)	⊕⊕◯◯ LOW [a,b]	-	Mean stay: 17.5 ± 8.57 days	**MD in days: 4.9 less** (10.75 less to 0.95 more)
	Time to re-epithilialization	25 (1 observational study)	⊕⊕◯◯ LOW [a,b]	-	Mean time: 16.7 ± 8.5 days	**MD in days: 4.57 less** (10.38 less to 1.24 more)
	Serious complications: organ failure	25 (1 observational study)	⊕⊕◯◯ LOW [a,b]	**RR 0.67** (0.17 – 2.67)	Risk of serious complications 300 per 1.000	**100 less per 1.000** (250 less to 500 more)

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Etanercept + corticosteroids vs IVIG + corticosteroids

JUDGEMENT	RESEARCH EVIDENCE

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					IVIG + Corticosteroids	Etanercept + corticosteroids
	Mortality	46 (1 observational studies)	⊕◯◯◯ VERY LOW [a,b]	RR 0.28 (0.01 – 6.58)	Risk of mortality 48 per 1.000	34 less per 1.000 (47 less to 266 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Bibliography

Ao S, 2022 (42); Zhang, 2022 (40)

Desirable Effects

Are the desirable effects large?

Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	<u>Etanercept + corticosteroids vs corticosteroids</u> • No significant difference for etanercept + corticosteroids vs corticosteroids for the critical outcomes mortality and serious complications organ failure and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⊕◯◯◯ LOW) <u>Etanercept + corticosteroids vs IVIG + corticosteroids</u> • No significant difference with Etanercept + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)

Undesirable Effects

Are the undesirable effects small?

Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	<u>Etanercept + corticosteroids vs corticosteroids</u> • No significant difference for etanercept + corticosteroids vs corticosteroids for the critical outcomes mortality and serious complications organ failure and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⊕◯◯◯ LOW) <u>Etanercept + corticosteroids vs IVIG + corticosteroids</u> • No significant difference with Etanercept + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)

Differences in values

Is there important uncertainty about how much people value the main outcomes?

Judgement: ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty of variability ○ No important uncertainty of variability ○ No known undesirable	• No significant desirable effects have been reported • No significant undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group suggest a higher importance of illness sequelae relative to the judgement of the guideline committee. As no significant between-group differences could be identified for this set of outcomes, no conflict of values is expected

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention?

Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Etanercept + corticosteroids vs corticosteroids • No significant difference for etanercept + corticosteroids vs corticosteroids for the critical outcomes mortality and serious complications organ failure and the important outcomes length of hospital stay and time to complete reepithelialization (GRADE: ⊕◯◯◯ LOW) • Low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects Etanercept + corticosteroids vs IVIG + corticosteroids • No significant difference with Etanercept + corticosteroids for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW) • Very low confidence in the certainty of the evidence does not permit reliable estimation of balance of effects
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ Varies	• No cost-benefit analysis for the German healthcare system was identified. • Etanercept represent a more significant burden to insurers • Corticosteroids can be considered routine care and likely represent a negligible cumulative burden to payers
Resource use Is the incremental cost small relative to the net benefits?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No cost-benefit analysis for the German healthcare system was identified • Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small benefits in critical outcomes
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No significant impact on equity expected
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ No ○ Probably no ○ Uncertain ● Probably yes	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated

o Yes o Varies	
Conclusion What is the final judgement in light of the evidence, and are there important limitations?	
Judgement: o Strong recommendation against the intervention o Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison o Conditional recommendation for the intervention o Strong recommendation for the intervention	Low to very low certainty evidence based on non-significant findings from 2 observational studies with 25 and 46 patients was available for this treatment combination. Although this evidence is consistent with an advantage for etanercept + corticosteroids over corticosteroids and IVIG + corticosteroids, the lack of statistical significance combined with the low number of studies and sample sizes does not permit making recommendations for or against the use of etanercept + corticoseroids in acute EN. Medical providers might want to consider empirical in conjunction with mechanistic evidence in making clinical decisions

TOPICAL TREATMENT OF EPIDERMAL NECROLYSIS

For patients with EN, what is the clinical efficacy of biological or biosynthetic skin coverage compared with conventional wound dressings?	
POPULATION:	Patients with acute EN
INTERVENTION:	Biological (e.g. amnion membrane, allograft, xenograft), or biosynthetic (e.g. Suprathel®, Epicite®, Biobrane™) skin coverage
COMPARISON:	Other wound dressings
MAIN OUTCOMES:	Primary outcomes: o Survival / in-hospital mortality (9 = critical) o Incidence of serious complications (9 = critical) o Quality of life / psychosocial well-being (7 = critical) o Sequelae of the eyes, group 1: blindness, limitation of reading ability, corneal perforations / ulcerations / epithelial defects, limbal stem cell insufficiency, chronic ocular dryness (8 = critical) o Sequelae of the eyes, group 2: entropion / ectropion, trichiasis, symblepharon: (7 = critical) o Sequelae of other organ systems, group 1, digestive system: ulcerations, perforations; urogenital system: urethral strictures, vaginal stenosis; respiratory system: acute respiratory distress syndrome (ARDS), bronchiolitis, bronchiectasis, chronic obstructive pulmonary dysfunction (COPD) (7 = critical) Secondary outcomes: o Sequelae of other organ systems, group 2, skin: scarring, nail loss, postinflammatory hypo- and / or hyperpigmentation; urogenital system: phimosis (6 = important) o Days with ventilation/requirement of ventilation (6 = important) o Mental health (6 = important) o Pain (6 = important) o Time to complete reepithelialization / skin healing (5 important) o Time to return to school / work (5 = important) o Length of hospital stay (4 = important)
SETTING:	Hospital- or burn unit-based care, no regional limitations
PERSPECTIVE:	Clinical recommendations, population perspective
BACKGROUND:	o Although there is consensus on the centrality of supportive care in EN, no optimal wound care regimen has been established o Disease-specific evidence is currently limited due to the low incidence of EN and a resulting lack of statistical power to reliably detect treatment effects o Indirect evidence from burn patients may be transferable to EN patients where mechanistically justified
CONFLICT OF INTERESTS:	Two members of the guideline panel have declared moderate COI and have been excluded from leadership positions in the working group and voting on recommendations for this topic.

ASSESSMENT

Is the problem a priority?

Judgement:	
○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies	Epidermal necrolysis (EN) is a predominatly drug-induced mucocutaneous reaction with considerable mortality and morbidity, including life-long sequelae. Due to its low incidence, no treatment standards have been established in Germany. As EN patients commonly require extensive wound care to reduce the risk of wound infections, promote skin healing and reduce pain associated with incomplete wound closure, establishing optimal management is relevant to all stakeholders. Patients’ and family members’ needs/preferences: To assess the patient perspective on acute care needs, we conducted and analyzed 14 semi-structured interviews with survivors and family members of survivors. Although the participants did not mention specific preferences regarding wound care, they retrospectively evaluated the pain associated with dressing changes as traumatizing and potentially avoidable. Our findings therefore suggest that, considering the centrality of this aspect in the survivors’ reports, the outcome pain should receive special attention in making guideline recommendations. Healthcare professional needs: Not all wound care products might be readily available in given setting. As wound care needs to be initiated as soon as possible, substandard but locally available products may sometimes be preferable over more effective options with longer procurement times.

TOPICAL TREATMENT: BIOLOGICAL AND BIOSYNTHETIC SKIN SUBSTITUTES

Summary of Findings

What is the overall certainty of the evidence?

Systematic review based on 2 observational studies with 14 and 24 patients, respectively.

Indirect evidence:

As pain was regarded as critical in making guideline recommendations but no direct evidence of sufficient quality could be identified, an additional scoping review was carried out on May 25th, 2023 to assess the effect of biologic and biosynthetic skin substitutes on this outcome in patients with superficial and partial thickness burns.

One high-quality systematic review using Cochrane methodology (43) could be identified that compared the effect on pain associated with the application and removal, or both, of wound dressings in the following products: hydrocolloid dressings, hydrogel dressings, biosynthetic skin substitute dressings, antimicrobial (silver and iodine containing) dressings and fibre dressings. Even though data on other outcomes such as time to complete reepithelialization was also reported, due to pathophysiological differences between burn wounds and autogenous skin detachment, only results for the outcome pain were deemed transferable to EN patients. The reported quantitative synthesis has been adapted below under the category *indirect evidence*.

Biosynthetic skin substitute dressings (Biobrane™) vs. conventional wound dressings (paraffin gauze)

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Outcomes**	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Paraffin gauze	Biosynthetic skin substitute dressings (Biobrane™)
	Mortality	14 (1 observational study)	⊕⊕◯◯ LOW [a,b]	**RR 0.89** (0.21 – 3.76)	Risk of Mortality 375 per 1.000	**42 fewer per 1.000** (296 fewer to 1035 more)

	Length of hospital stay	14 (1 observational study)	⨁⨁◯◯ LOW [a,b]	-	Mean stay: 16.6 ± 5.3 days	**MD in days: 0.7 more** (4.17 less to 5.57 more)
	Time to complete reepithelialization	14 (1 observational study)	⨁⨁◯◯ LOW [a,b]	-	Mean time: 16 ± 3.1 days	**MD in days: 3.5 less** (6.38 less to 0.62 less)
	Pain (difference in mean VAS-score at days 1, 3, 5, 7, 9 and 11 [0=no pain, 10=unbearable pain])	14 (1 observational study)	⨁⨁◯◯ LOW [a,b]		Mean VAS-score: 7.5, 6.8, 6.8, 5.5, 4.5, 3.3	**Pain: statistically significant difference at α = 0.05: -0.7 , -3.3, -4.8, -3.7, -2.8,- 2.3** (no statistically significant difference at baseline [p=0.228])
	Sepsis	14 (1 observational study)	⨁⨁◯◯ LOW [a,b]	**RR 0.44** (0.06 to 3.29)	Risk of sepsis 375 per 1000	**208 fewer per 1000** (352 fewer to 857 more)

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold or optimal information size criterion not met

Porcine xenograft vs. conventional wound care (including silver impregnated dressings)

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Outcomes**	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Conventional wound care	Porcine xenograft
	Mortality	24 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	**RR 1** (0.11 to 9.44)	Risk of Mortality 125 per 1.000	**0 fewer per 1.000** (112 fewer to 1056 more)
	Length of hospital stay	24 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	-	Median time in days (IQR): 11.5 (9-16.5)	**Median time in days** (IQR): **13 (11.75-13.25)** (between-group comparison not statistically significant at 0.05 level, p=0.83 according to Mann-Whitney U test)
	Pain (1=lowest, 10=highest) reduction 24h after treatment	24 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	-	-	**Decrease in median pain (IQR) from 5.5 (2.5, 8.25) to 2.8 (0.75, 4)** (within-group comparison pre/post graft placement statistically significant at 0.05 level, p=0.03)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Indirect evidence:

Biosynthetic skin substitute dressings (Biobrane™) vs silver sulfadiazine

JUDGEMENT	RESEARCH EVIDENCE				
	Outcomes				**Anticipated absolute effects**

○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know		№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Silver sulfadiazine	Biosynthetic skin substitute dressings (Biobrane™)
	Pain (VAS 1 [no pain]-5 [severe pain])	99 (106 wounds) (2 randomized controlled trials)	⊕⊕◯◯ LOW [a,b]	-	Mean pain: 3.69 ± 0.95	**MD: 1.63 less** (2.2 less to 1.06 less)

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies (according to Wasiak, 2013: high risk of bias due to lack of blinding in both RCTs)
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Bibliography

Direct evidence: Boorboor (2008) (44); Young (2016) (45); Indirect evidence: Gerding (1988) (46), Gerding (1990) (47)

Desirable Effects

Are the desirable effects large?

Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Direct evidence: Biobrane vs. conventional wound dressings (paraffin gauze) • Statistically significant advantage with biosynthetic skin substitute dressings (Biobrane™) for the important outcomes time to complete reepithelialization and pain (GRADE: ⊕⊕◯◯ LOW) • No statistically significant difference with biosynthetic skin substitute dressings (Biobrane™) for the critical outcome mortality and serious complications: sepsis and the important outcome length hospital stay (GRADE: ⊕⊕◯◯ LOW) Porcine xenograft vs. Conventional wound care (including silver impregnated dressings) • Statistically significant advantage with porcine xenograft for the important outcome pain (GRADE: ⊕◯◯◯ VERY LOW) • No statistically significant difference with porcine xenograft for the critical outcome mortality and the important outcome length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW) Indirect evidence: Biosynthetic skin substitute (Biosynthetic skin substitute dressings (Biobrane™)) vs silver sulfadiazine • Statistically significant advantage with biosynthetic skin substitute dressings (Biobrane™) for the important outcome pain (GRADE: ⊕◯◯◯ VERY LOW)

Undesirable Effects

Are the undesirable effects small?

Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Direct evidence: Biosynthetic skin substitute dressings (Biobrane™) vs. conventional wound dressings (paraffin gauze) • No statistically significant difference with biosynthetic skin substitute dressings (Biobrane™) for the critical outcome mortality and serious complications: sepsis and the important outcome length hospital stay (GRADE: ⊕⊕◯◯ LOW) Porcine xenograft vs. conventional wound care (including silver impregnated dressings) • No statistically significant difference with porcine xenograft for the critical outcome mortality and the important outcome length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW) Indirect evidence:

	Biosynthetic skin substitute dressings (Biobrane™) vs silver sulfadiazine • No disadvantage with biosynthetic skin substitute dressings (Biobrane™) reported
Differences in values Is there important uncertainty about how much people value the main outcomes?	
Judgement: ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty of variability ○ No important uncertainty of variability ○ Not known	• The guideline committee has judged the statistically significant effects as important (time to complete reepithelialization and pain) • No statistically significant undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group suggest a higher importance of the outcome pain relative to the judgement of the guideline committee
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Biosynthetic skin substitute dressings (Biobrane™) vs. conventional wound dressings (paraffin gauze) • Statistically significant advantage with biosynthetic skin substitute dressings (Biobrane™) for the important outcomes time to complete reepithelialization and pain (GRADE: ⊕⊕◯◯ LOW) • No statistically significant difference with biosynthetic skin substitute dressings (Biobrane™) for the critical outcome mortality and serious complications: sepsis and the important outcome length hospital stay (GRADE: ⊕⊕◯◯ LOW) • Very low certainty of evidence does not permit reliably estimating balance of effects Porcine xenograft vs. conventional wound care (including silver impregnated dressings) • Statistically significant advantage with porcine xenograft for the important outcome pain (GRADE: ⊕◯◯◯ VERY LOW) • No statistically significant difference with porcine xenograft for the critical outcome mortality and the important outcome length of hospital stay (GRADE: ⊕◯◯◯ VERY LOW) • Very low certainty of evidence does not permit reliably estimating balance of effects Indirect evidence: Biosynthetic skin substitute dressings (Biobrane™) vs silver sulfadiazine • Statistically significant advantage with biosynthetic skin substitute dressings (Biobrane™) for the important outcome pain (GRADE: ⊕◯◯◯ VERY LOW) • No disadvantage with biosynthetic skin substitute dressings (Biobrane™) reported • Very low certainty of evidence does not permit reliably estimating balance of effects
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes	• No cost-benefit analysis for the German healthcare system was identified

<table>
<tr><td>○ Yes
○ Varies</td><td></td></tr>
<tr><td colspan="2">Resource use
Is the incremental cost small relative to the net benefits?</td></tr>
<tr><td>Judgement:

○ No
○ Probably no
● Uncertain
○ Probably yes
○ Yes
○ Varies</td><td>• In the absence of evidence regarding critical outcomes, secondary outcomes such as pain reduction should be considered when evaluating the role of costs in making treatment recommendations
• Several interlocking factors need to be considered on a case-by-case basis:
  ○ How large is the detached body surface area / what is the presumed timeframe to attain wound closure (i.e., the amount of product needed)?
  ○ How important is a reduction of pain for a given patient (considering their level of sedation, age, psychological comorbidities and personal preferences) relative to the product’s presumed effectiveness regarding this outcome?
  ○ Does the product have a potential for lowering indirect costs, such as staffing costs (e.g., fewer dressing changes required)?
• Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small treatment benefits</td></tr>
<tr><td colspan="2">Equity
What would be the impact on health inequities?</td></tr>
<tr><td>Judgement:

○ Increased
○ Probably increased
○ Uncertain
○ Probably reduced
○ Reduced
● Varies</td><td>• No important impact on equity expected</td></tr>
<tr><td colspan="2">Acceptability, Implementability and Feasibility
Is the option acceptable to key stakeholders, can it be implemented and is it feasible?</td></tr>
<tr><td>Judgement:

○ Increased
○ Probably increased
○ Uncertain
○ Probably reduced
○ Reduced
● Varies</td><td>• No conflicts regarding acceptability anticipated
• No conflicts regarding implementability anticipated
• No conflicts regarding feasibility anticipated</td></tr>
<tr><td colspan="2">Conclusion
What is the final judgement considering the evidence, and are there important limitations?</td></tr>
<tr><td>Judgement:

○ Strong recommendation against the intervention
○ Conditional recommendation against the intervention
● Conditional recommendation for either the intervention or the comparison</td><td><u>Biosynthetic skin substitute dressings (Biobrane™):</u>

Regarding the outcomes time to complete reepithelialization, pain (difference in mean VAS-score at days 1, 3, 5, 7, 9 and 11) and pain (unspecified), there is very low certainty evidence for an advantage of biosynthetic skin substitute dressings (Biobrane™) over conventional wound dressings (based on 1 observational study with 14 patients). For the outcome pain (unspecified), a pre-existing systematic review on wound care in burn patients provided indirect very low certainty evidence for an advantage of biosynthetic skin substitute dressings (Biobrane™) over silver sulfadiazine (based on 2 randomized controled trials with 99 patients [106 wounds]). Due to study size limitations, high risk of bias, indirectness, ambiguous reporting of the outcomes in question and uncertainty about whether the intervention provides a clinically important effect, we do not feel confident in making a recommendation for the use of biosynthetic skin substitute dressings (Biobrane™) in acute EN patients.</td></tr>
</table>

○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	<u>Porcine xenograft:</u> Regarding the outcome pain reduction (24h after treatment) there is very low certainty evidence for an advantage of porcine xenograft over conventional wound care including silver-impregnated dressings (based on 1 observational study with 24 patients). Due to study size limitations, high risk of bias, ambiguous reporting of the outcomes in question and uncertainty about whether the intervention provides a clinically important effect, we do not feel confident in making a recommendation for the use of porcine xenograft in acute EN patients.

TOPICAL TREATMENT: DEBRIDEMENT, CREAMS AND WOUND DRESSINGS (INCLUDING PRODUCTS CONTAINING SILVER)

Summary of Findings

What is the overall certainty of the evidence?

Systematic review based on 2 observational studies with 29 and 20 patients, respectively.

Indirect evidence:

As pain was regarded as critical in making guideline recommendations but no direct evidence of sufficient quality could be identified, an additional scoping review was carried out on May 25th, 2023 to assess the effect of biologic and biosynthetic skin substitutes on this outcome in patients with superficial and partial thickness burns.

One high-quality systematic review using Cochrane methodology (43) could be identified that compared the effect on pain associated with the application and removal, or both, of wound dressings in the following products: hydrocolloid dressings, hydrogel dressings, biosynthetic skin substitute dressings, antimicrobial (silver and iodine containing) dressings and fibre dressings. Even though data on other outcomes such as time to complete reepithelialization was also reported, due to pathophysiological differences between burn wounds and autogenous skin detachment, only results for the outcome pain were deemed transferable to EN patients. The reported quantitative synthesis has been adapted below under the category indirect evidence.

Silver sulfadiazine vs. conventional wound care

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Conventional wound care	**Silver sulfadiazine**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	29 (1 observational study)	⊕⊕◯◯ LOW [a,b]	**RR 0.72** (0.31 to 1.67)	Risk of Mortality 696 per 1.000	**196 fewer per 1.000** (481 fewer to 468 more)

a. Study limitations: moderate risk of bias in multiple or a substantial number of studies (rated down one level)
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold or optimal information size criterion not met (rated down one level)

Fibre dressing (Aquacel™ AG) vs. silver sulfadiazine

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Silver sulfadiazine	Fibre dressing (Aquacel™ AG)
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	20 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	**RR 0.75** (0.18 to 3.17)	Risk of Mortality 333 per 1.000	**83 fewer per 1.000** (274 fewer to 724 more)
	Time to 95% re-epithelialization	20 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	-	Mean time: 17.5 ± 6.5 days	**MD in days: 0.75 less** (6.37 less to 4.87 more)
	Pain at second dressing change (0=no pain, 10=unbearable pain)	20 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	-	Mean VAS: 5.75 ± 1.39	**MD: 1.67 less** (2.99 less to 0.34 less)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies (rated down two levels)
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met (rated down one level)

Indirect evidence

Hydrocolloid dressing vs silver sulfadiazine

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Outcomes**	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Silver sulfadiazine	**Hydrocolloid dressing**
	Pain (0=no pain, 10=maximum)	42 (1 randomized controlled trial)	⊕◯◯◯ VERY LOW [a,b]	-	Mean pain: 2.3 ± 1.4	**MD: 1.19 less** (1.82 less to 0.56 less)

a. Study limitations: high risk of bias in multiple or a substantial number of studies (according to Wasiak, 2013: risk of bias due to improper blinding, incomplete outcome data and other biases) (rated down two levels).
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold or optimal information size criterion not met (rated down one level)

Silver-impregnated dressing vs silver sulfadiazine

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Outcomes**	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Silver sulfadiazine	Silver-impregnated dressing
	Pain (1=no pain, 10=unbearable pain)	135 (3 randomized controlled trials)	⊕⊕◯◯ LOW [a,b]	-	Mean pain: 5.96 ± 9.79	**MD: 2.84 less** (5.89 less to 0.21 more)

a. Study limitations: high risk of bias in multiple or a substantial number of studies (according to Wasiak, 2013: risk of bias due to improper blinding and incomplete outcome data) (rated down one level).
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met (rated down one level)

Fibre dressing (Aquacel™ AG) vs silver sulfadiazine

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Outcomes**	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Fibre dressing (Aquacel™ AG)	Silver sulfadiazine
	Pain at day 1	70 (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	-	Mean pain: 6.1 ± 2.3	**MD: 2 less** (3.03 less to 0.97 less)
	Pain at day 3	70 (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	-	Mean pain: 5.2 ± 2.1	**MD: 3.1 less** (4.02 less to 2.18 less)
	Pain at day 7	70 (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	-	Mean pain: 3.3 ± 1.9	**MD: 2.4 less** (3.18 less to 1.62 less)

a. Study limitations: high risk of bias in multiple or a substantial number of studies (according to Wasiak, 2013: risk of bias due to improper blinding) (rated down one level).
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Hydrogel dressing vs usual care

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small	**Outcomes**	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Usual care	Hydrogel dressing

○ Moderate ○ Large ○ Varies ● Don't know	Pain at baseline (scale unspecified)	118 (1 randomized controlled trial)	⊕◯◯◯ VERY LOW [a,b]	-	Mean pain: 6 ± 2.6	**MD: 0.01 less** (0.94 less to 0.92 more)
	Pain 30 minutes after treatment (scale unspecified)	118 (1 randomized controlled trial)	⊕◯◯◯ VERY LOW [a,b]	-	Mean pain: 4.6 ± 2.4	**MD: 0.79 less** (1.64 less to 0.06 more)
	Pain at end of study (scale unspecified)	118 (1 randomized controlled trial)	⊕◯◯◯ VERY LOW [a,b]	-	Mean pain: 4 ± 2.7	**MD: 1.31 less** (2.37 less to 0.25 less)

a. Study limitations: high risk of bias in multiple or a substantial number of studies (according to Wasiak, 2013: risk of bias due to selective reporting, other biases and unlear status with respect to remaining bias categories (rated down two levels).
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met (rated down one level)

Bibliography

Direct evidence: Das (2014) (48); Huang (2014) (49); Indirect evidence: Wyatt (1990) (50); Guilbaud 1992 (51); Muangman (2006) (52), Opasanon (2010) (53), Varas (2005) (54)

Desirable Effects

Are the desirable effects large?

Judgement:

○ No
○ Probably no
● Uncertain
○ Probably yes
○ Yes
○ Varies

Silver sulfadiazine vs. conventional wound care

- No statistically significant difference with silver sulfadiazine for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW)

Fibre dressing (Aquacel™ AG) vs. silver sulfadiazine

- Statistically significant advantage with fibre dressing (Aquacel™ AG) for the important outcome pain at second dressing change (GRADE: ⊕◯◯◯ VERY LOW), however, as pain was only measured once at time of second dressing change, between-group differences at baseline that could account for differences at later measurements cannot be ruled out. We therefore did not consider this comparison for the outcome pain in our final analysis.
- No statistically significant difference for the critical outcome mortality and the important outcome time to 95% re-epithelialization (GRADE: ⊕◯◯◯ VERY LOW)

Indirect evidence

Hydrocolloid dressing vs silver sulfadiazine

- Statistically significant advantage with hydrocolloid dressing for the important outcome pain (GRADE: ⊕◯◯◯ VERY LOW)

Hydrogel dressing vs usual care

- Statistically significant advantage with hydrogel dressing for the important outcome pain at end of study (GRADE: ⊕◯◯◯ VERY LOW)
- No statistically significant difference with hydrogel dressing for the important outcome pain 30 minutes after treatment (GRADE: ⊕◯◯◯ VERY LOW)

Silver-impregnated dressing vs silver sulfadiazine

- No statistically significant difference with silver-impregnated dressing for the important outcome pain (GRADE: ⊕◯◯◯ VERY LOW)

Fibre dressing (Aquacel™ AG) vs silver sulfadiazine

- Statistically significant advantage with fibre dressing (Aquacel™ AG) for the important outcome pain (at days 1, 3 and 7) (GRADE: ⊕◯◯◯ LOW). However, as there is evidence of statistically significant baseline differences (pain at day 1) that could account for differences between treatment groups at later measurements, we did not consider this comparison in our final analysis

Undesirable Effects

Are the undesirable effects small?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Silver sulfadiazine vs. conventional wound care • No statistically significant difference with silver sulfadiazine for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW) Fibre dressing (Aquacel™ AG) vs. silver sulfadiazine • No statistically significant difference for the critical outcome mortality and the important outcome time to 95% re-epithelialization (GRADE: ⊕◯◯◯ VERY LOW) Indirect evidence Hydrocolloid dressing vs silver sulfadiazine • No disadvantage with hydrocolloid dressing reported Hydrogel dressing vs usual care • No statistically significant difference with hydrogel dressing for the important outcome pain 30 minutes after treatment (GRADE: ⊕◯◯◯ VERY LOW) Silver-impregnated dressing vs silver sulfadiazine • No statistically significant difference with silver-impregnated dressing for the important outcome pain (GRADE: ⊕◯◯◯ VERY LOW) Fibre dressing (Aquacel™ AG) vs silver sulfadiazine • No disadvantage with Fibre dressing (Aquacel™ AG) reported
Differences in values Is there important uncertainty about how much people value the main outcomes?	
Judgement: ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty of variability ○ No important uncertainty of variability ○ Not known	• The guideline committee has judged the statistically significant effects as important: pain • No statistically significant undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group suggest a higher importance of the outcome pain relative to the judgement of the guideline committee
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes	Silver sulfadiazine vs. conventional wound care • No statistically significant difference with silver sulfadiazine for the critical outcome mortality (GRADE: ⊕⊕◯◯ LOW) Fibre dressing (Aquacel™ AG) vs. silver sulfadiazine

○ Yes ○ Varies	• Statistically significant advantage with fibre dressing (Aquacel™ AG) for the important outcome pain at second dressing change (GRADE: ⨁◯◯◯ VERY LOW), however, as pain was only measured once at time of second dressing change, between-group differences at baseline that could account for differences at later measurements cannot be ruled out. We therefore did not consider this comparison for the outcome pain in our final analysis. • No statistically significant difference for the critical outcome mortality and the important outcome time to 95% re-epithelialization (GRADE: ⨁◯◯◯ VERY LOW) Indirect evidence Hydrocolloid dressing vs silver sulfadiazine • Statistically significant advantage with hydrocolloid dressing for the important outcome pain (GRADE: ⨁◯◯◯ VERY LOW) • No disadvantage with hydrocolloid dressing reported Hydrogel dressing vs usual care • Statistically significant advantage with hydrogel dressing for the important outcome pain at end of study (GRADE: ⨁◯◯◯ VERY LOW) • No statistically significant difference with hydrogel dressing for the important outcome pain 30 minutes after treatment (GRADE: ⨁◯◯◯ VERY LOW) Silver-impregnated dressing vs silver sulfadiazine • No statistically significant difference with silver-impregnated dressing for the important outcome pain (GRADE: ⨁◯◯◯ VERY LOW) Fibre dressing (Aquacel™ AG) vs silver sulfadiazine • Statistically significant advantage with fibre dressing (Aquacel™ AG) for the important outcome pain (at days 1, 3 and 7) (GRADE: ⨁◯◯◯ LOW). However, as there is evidence of statistically significant baseline differences (pain at day 1) that could account for differences between treatment groups at later measurements, we did not consider this comparison in our final analysis.
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No cost-benefit analysis for the German healthcare system was identified
Resource use Is the incremental cost small relative to the net benefits?	

Judgement:
 	
○ No
○ Probably no
● Uncertain
○ Probably yes
○ Yes
○ Varies
	• In the absence of evidence regarding critical outcomes, secondary outcomes such as pain reduction should be considered when evaluating the role of costs in making treatment recommendations.
	• Several interlocking factors need to be considered on a case-by-case basis:
	  ○ How large is the detached body surface area / what is the presumed timeframe to attain wound closure (i.e., the amount of product needed)?
	  ○ How important is a reduction of pain for a given patient (considering their level of sedation, age, psychological comorbidities and personal preferences) relative to the product’s presumed effectiveness regarding this outcome?
	  ○ Does the product have a potential for lowering indirect costs, such as staffing costs (e.g., fewer dressing changes required)?

<table>
<tr><td></td><td>• Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small treatment benefits.</td></tr>
<tr><td colspan="2">Equity
What would be the impact on health inequities?</td></tr>
<tr><td>Judgement:

○ Increased
○ Probably increased
○ Uncertain
○ Probably reduced
○ Reduced
● Varies</td><td>• No important impact on equity expected</td></tr>
<tr><td colspan="2">Acceptability, Implementability and Feasibility
Is the option acceptable to key stakeholders, can it be implemented and is it feasible?</td></tr>
<tr><td>Judgement:

○ Increased
○ Probably increased
○ Uncertain
○ Probably reduced
○ Reduced
● Varies</td><td>• No conflicts regarding acceptability anticipated
• No conflicts regarding implementability anticipated
• No conflicts regarding feasibility anticipated</td></tr>
<tr><td colspan="2">Conclusion
What is the final judgement considering the evidence, and are there important limitations?</td></tr>
<tr><td>Judgement:

○ Strong recommendation against the intervention
○ Conditional recommendation against the intervention
● Conditional recommendation for either the intervention or the comparison
○ Conditional recommendation for the intervention
○ Strong recommendation for the intervention</td><td><u>Silver sulfadiazine:</u>

Regarding the outcome mortality, only 1 study comparing silver sulfadiazine with conventional wound care could be identified. As the confidence intervals of the study’s effect estimate are consistent with both substantial benefit and harm, no clear direction of effect can be established. For the outcomes pain (unspecified) and pain (at days 1, 3 and 7), a pre-existing systematic review on wound care in burn patients provided indirect very low certainty evidence for a disadvantage with silver sulfadiazine over hydrocolloid dressing (based on 1 randomized controlled trial with 42 patients) and Fibre dressing (Aquacel™ AG) (based on 1 randomized controlled trial with 70 patients) in addition to the results of our main analysis. However, the latter randomized controlled trial comparing silver sulfadiazine and fibre dressing (Aquacel™ AG) reports statistically significant baseline differences (pain at day 1) that could account for differences between treatment groups at later measurements. We have therefore excluded this comparison from our analysis. Moreover, due to study size limitations, high risk of bias, indirectness and uncertainty about whether the intervention provides a clinically important effect, we do not feel confident in making a recommendation for the use of silver sulfadiazine in acute EN patients.

<u>Fibre dressing (Aquacel™ AG):</u>

Regarding the outcome pain (at second dressing change), there is direct very low certainty evidence for an advantage of fibre dressings (Aquacel™ AG) over conventional wound dressings (paraffin gauze) (based on 1 observational study with 20 patients). However, as pain was only measured once at time of second dressing change, between-group differences at baseline that could account for differences at later measurements cannot be ruled out. We therefore did not consider this comparison for the outcome pain in our final analysis. For the outcome pain (at days 1, 3 and 7), a pre-existing sytematic review on wound care in burns patients was consulted for indirect evidence regarding the comparison between fibre dressings (Aquacel™ AG) over silver sulfadiazine (based on 1 randomized controlled trial with 70 patients). However, the latter randomized controlled trial comparing silver sulfadiazine and fibre dressing (Aquacel™ AG) reports statistically significant baseline differences (pain at day 1) that could account for differences between treatment groups at</td></tr>
</table>

	later measurements. We have therefore excluded this comparison from our analysis. Moreover, due to study size limitations, high risk of bias and uncertainty about whether the intervention provides a clinically important effect, we do not feel confident in making a recommendation for the use of fibre dressings (Aquacel™ AG) in acute EN patients. Hydrocolloid dressing: We did not identify any direct evidence pertaining to hydrocolloid dressings. For the outcome pain (unspecified), a pre-existing sytematic review on wound care in burn patients provided indirect evidence for an advantage of hydrocolloid dressings over silver sulfadiazine (based on 1 randomized controlled trial with 42 patients) in addition to the results of our main analysis. However, due to study size limitations, high risk of bias, indirectness and uncertainty about whether the intervention provides a clinically important effect, we do not feel confident in making a recommendation for the use of fibre dressings (Aquacel™ AG) in acute EN patients. Hydrogel dressing: We did not identify any direct evidence pertaining to hydrogel dressings. For the outcome pain (at end of study), a pre-existing sytematic review on wound care in burn patients provided indirect evidence for an advantage of hydrocolloid dressings over silver sulfadiazine (based on 1 randomized controlled trial with 118 patients) in addition to the results of our main analysis. However, due to study size limitations, high risk of bias, indirectness and uncertainty about whether the intervention provides a clinically important effect, we do not feel confident in making a recommendation for the use of hydrogel dressings in acute EN patients. Silver-impregnated dressing: We did not identify any direct evidence pertaining to silver-impregnated dressings. Furthermore, regarding the outcome pain (unspecified), a pre-existing sytematic review on wound care in burn patients did not provided any indirect evidence for or against treatment benefits with silver-impregnated dressings over silver sulfadiazine (based on 3 randomized controlled trials with 135 patients). Due to a lack of statistically statistically significant findings, study size limitations, high risk of bias and indirectness, we do not feel confident in making a recommendation for the use of silver impregnated dressings in acute EN patients.

TREATMENT OF ACUTE OPHTALMOLOGICAL MANIFESTATIONS OF EPIDERMAL NECROLYSIS

For patients with EN, what is the clinical efficacy of a coverage of the ocular surface with amniotic membrane (surgical transplant or apposition with therapeutic contact lens) compared with supportive therapy?	
POPULATION:	Patients with acute EN
INTERVENTION:	Coverage of the ocular surface with amniotic membrane (surgical transplant or apposition with therapeutic contact lens)
COMPARISON:	Supportive therapy
MAIN OUTCOMES:	Primary outcomes: o Survival / in-hospital mortality (9 = critical) o Incidence of serious complications (9 = critical) o Quality of life / psychosocial well-being (7 = critical) o Sequelae of the eyes, group 1: blindness, limitation of reading ability, corneal perforations / ulcerations / epithelial defects, limbal stem cell insufficiency, chronic ocular dryness (8 = critical) o Sequelae of the eyes, group 2: entropion / ectropion, trichiasis, symblepharon: (7 = critical) o Sequelae of other organ systems, group 1, digestive system: ulcerations, perforations; urogenital system: urethral strictures, vaginal stenosis; respiratory system: acute respiratory distress syndrome (ARDS), bronchiolitis, bronchiectasis, chronic obstructive pulmonary dysfunction (COPD) (7 = critical) Secondary outcomes: o Sequelae of other organ systems, group 2, skin: scarring, nail loss, postinflammatory hypo- and / or hyperpigmentation; urogenital system: phimosis (6 = important) o Days with ventilation/requirement of ventilation (6 = important) o Mental health (6 = important) o Pain (6 = important) o Time to complete reepithelialization / skin healing (5 important) o Time to return to school / work (5 = important) o Length of hospital stay (4 = important)
SETTING:	Hospital- or burn unit-based care, no regional limitations
PERSPECTIVE:	Clinical recommendations, population perspective
BACKGROUND:	o About 55-88% of all EN patients are affected by ophtalmic complications, which can often lead to severe long-term consequences, including blindness o Early treatment of ophthalmological manifestations of EN is hypothesized to improve the long-term prognosis and prevent subsequent disability o Preliminary research findings and the prevalence of clinical use suggests beneficial effects of ocular surface treatment with amniotic membrane that have not been systematically evaluated
CONFLICT OF INTERESTS:	None

ASSESSMENT

Is the problem a priority?

Judgement:	
○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies	Epidermal necrolysis (EN) is a predominatly drug-induced mucocutaneous reaction with considerable mortality and morbidity, including life-long sequelae. Due to its low incidence, no treatment standards have been established in Germany. This especially pertains to the treatment of ophthalmological manifestations of EN, which is hypothesized to significantly mitigate the long-term impact of the disease. Amniotic membrane treatment of the ocular surface is commonly applied in clinical practice based on mechanistic considerations and preliminary scientific evidence. Currently, different options exist for amniotic membrane treatment, which considerably differ in methods of apposition (surgical transplant vs. therapeutic contact lens with affixed amniotic membrane). A systematic evaluation of the effectiveness of the intervention and its different forms of application is therefore desirable for all stakeholders. Patients' and family members' needs/preferences: To assess the patient perspective on acute care needs, we conducted and analyzed 14 semi-structured interviews with survivors and family members of survivors. Two themes emerged regarding medical care for ophthalmological manifestations of EN. The importance of early eye-directed intervention seems to be often underestimated and therefore leaves patients questioning whether or not illness sequelae could have been prevented. Second, there is marked uncertainty about practical day-to-day considerations, such as managing symptoms of dry eyes. Healthcare professional needs: Providers are likely to place high importance in obtaining information on the effectiveness of amniotic membrane treatment.

Summary of Findings

What is the overall certainty of the evidence?

Systematic review based on 1 randomized controlled trial with 25 patients (50 eyes) and 1 observational study with 48 patients (96 eyes).

Amniotic membrane transplantation vs. supportive therapy (RCT)

JUDGEMENT	RESEARCH EVIDENCE				
	Outcomes	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Supportive therapy	AMT
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Ocular sequelae (group 1): corneal perforations / ulcerations / epithelial defects at 6 months	25 (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	**RR 1** (0.07 to 15.12)	Risk of outcome 40 per 1.000	**0 fewer per 1.000** (37 fewer to 565 more)
	Ocular sequelae (group 1): Limbal stem cell insufficiency at 6 months	25 (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	**RR 0.08** (0-1.3)	Risk of outcome 240 per 1000	**222 fewer per 1000** (239 fewer to 71 more)
	Ocular sequelae (group 1): Conjunctival congestion at 6 months	25 (1 randomized controlled trial)	⊕⊕⊕⊕ HIGH [a,c]	**RR 0.09** (0.01-0.65)	Risk of outcome 440 per 1.000	**400 fewer per 1000** (434 fewer to 153 fewer)

	Ocular sequelae (group 2): ectropion / entropion at 6 months	25 (1 randomized controlled trial)	⨁⨁◯◯ LOW [a,b]	**RR 0.2** (0.01-3.97)	Risk of outcome 80 per 1.000	**64 fewer per 1000** (79 fewer to 237 more)
	Ocular sequelae (group 2): trichiasis at 6 months	25 (1 randomized controlled trial)	⨁⨁◯◯ LOW [a,b]	**RR 0.08** (0-1.3)	Risk of outcome 240 per 1.000	**222 fewer per 1000** (239 fewer to 71 more)
	Ocular sequelae (group 2): symblepharon at 6 months	25 (1 randomized controlled trial)	⨁⨁◯◯ LOW [a,b]	**RR 0.11** (0.01-1.96)	Risk of outcome 160 per 1.000	**142 fewer per 1000** (159 fewer to 154 more)
	Best-corrected visual acuity (BCVA) at 6 months	25 (1 randomized controlled trial)		-	Mean LogMAR: 0.522 ± 0.52 units	MD in LogMAR units: 0.454 less (0.68 less to 0.23 less)
	Schirmer's test at 6 months	25 (1 randomized controlled trial)		-	Mean Schirmer's test: 8.64 ± 5.4 mm	**MD in mm: 6.8 more** (3.46 more to 10.14 more)
	Tear film break-up time (TBUT)	25 (1 randomized controlled trial)		-	Mean TBUT: 6.96 ± 4.5 sec	**MD in sec: 2.96 more** (0.51 more to 5.41 more)

a. Study limitations: some concerns for risk of bias (rated down one level)
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met (rated down one level)
c. Large effect: (rated up one level)

Amniotic membrane transplantation vs. supportive therapy (observational study)

JUDGEMENT	RESEARCH EVIDENCE					
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Outcomes**	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Supportive therapy	AMT
	Ocular sequelae (group 1): corneal perforations at 4 years	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.02** (0-0.31)	Risk of outcome 333 per 1.000	**327 fewer per 1000** (333 fewer to 229 fewer)
	Ocular sequelae (group 1): epithelial defects at 4 years	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.13** (0.05-0.3)	Risk of outcome 611 per 1.000	**534 fewer per 1000** (578 fewer to 431 fewer)
	Ocular sequelae (group 1): Blindness/restricted reading ability (best-corrected visual acuity <20/200) at 4 years	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.05** (0.01-0.22)	Risk of outcome 500 per 1.000	**474 fewer per 1000** (494 fewer to 391 fewer)
	Ocular sequelae (group 1): limbal stem cell insufficiency/total limbal stem cell deficiency at 4 years	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.06** (0.02-0.18)	Risk of outcome 667 per 1.000	**628 fewer per 1000** (655 fewer to 544 fewer)
	Ocular sequelae (group 1): chronic dry eyes (moderate and severe)	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.21** (0.12-0.37)	Risk of outcome 778 per 1.000	**611 fewer per 1000 (682 fewer to 488 fewer)**

	Ocular sequelae (group 2): entropion at 4 years	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.26** (0.12-0.58)	Risk of outcome 444 per 1.000	**329 fewer per 1000 (393 fewer to 187 fewer)**
	Ocular sequelae (group 2): ectropion at 4 years	48 (1 observational study)	⨁◯◯◯ VERY LOW [a,c]	**RR 1.2** (0.06-24.03)	Risk of outcome 0 per 1.000	**inestimable**
	Ocular sequelae (group 2): trichiasis / distichiasis at 4 years	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.42** (0.3-0.58)	Risk of outcome 889 per 1000	**517 fewer per 1000 (622 fewer to 371 fewer)**
	Ocular sequelae (group 2): symblepharon at 4 years	48 (1 observational study)	⨁⨁⨁◯ MODERATE [a,b]	**RR 0.32** (0.19-0.52)	Risk of outcome 722 per 1000	**491 fewer per 1000 (582 fewer to 343 fewer)**

a. Study limitations: some concerns for risk of bias (rated down two levesl)
b. Large effect: (rated up one level)
c. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met (rated down one level)

Bibliography

Shanbhag, 2020 (55); Sharma, 2016 (56)

Desirable Effects

Are the desirable effects large?

Judgement:	Amniotic membrane transplantation vs. supportive therapy
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• Statistically significant advantage with Amniotic membrane transplantation for the critical outcome ocular sequelae (group 1): conjunctival congestion at 6 months (GRADE: ⨁⨁⨁◯ MODERATE) • No statistically significant difference with with Amniotic membrane transplantation for the critical outcomes ocular sequelae (group 1): corneal perforations / ulcerations / epithelial defects at 6 months, limbal stem cell insufficiency at 6 months and ocular sequelae (group 2): ectropion / entropion at 6 months, trichiasis at 6 months, symblepharon at 6 months (GRADE: ⨁⨁◯◯ LOW) Amniotic membrane transplantation vs. supportive therapy • Statistically significant advantage with Amniotic membrane transplantation for the critical outcomes ocular sequelae (group 1): corneal perforations at 4 years, epithelial defects at 4 years, blindness/restricted reading ability (best-corrected visual acuity <20/200) at 4 years, limbal stem cell insufficiency/total limbal stem cell deficiency at 4 years, chronic dry eyes (moderate and severe), and ocular sequelae (group 2): entropion at 4 years,trichiasis / distichiasis at 4 years, symblepharon at 4 years (GRADE: ⨁⨁⨁◯ MODERATE) • No statistically significant difference with with Amniotic membrane transplantation for the critical outcome ocular sequelae (group 2): ectropion at 4 years (GRADE: ⨁◯◯◯ VERY LOW)

Undesirable Effects

Are the undesirable effects small?

Judgement:	Amniotic membrane transplantation vs. supportive therapy
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No statistically significant difference with with Amniotic membrane transplantation for the critical outcomes ocular sequelae (group 1): corneal perforations / ulcerations / epithelial defects at 6 months, limbal stem cell insufficiency at 6 months and ocular sequelae (group 2): ectropion / entropion at 6 months, trichiasis at 6 months, symblepharon at 6 months (GRADE: ⨁⨁◯◯ LOW)

	Amniotic membrane transplantation vs. supportive therapy • No statistically significant difference with with Amniotic membrane transplantation for the critical outcome Ocular sequelae (group 2): ectropion at 4 years (GRADE: ⊕◯◯◯ VERY LOW)
Differences in values Is there important uncertainty about how much people value the main outcomes?	
Judgement: ○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty of variability ○ No important uncertainty of variability ○ Not known	• The guideline committee has judged the statistically significant effects as critical: ocular sequelae (group 1): blindness, limitation of reading ability, corneal perforations / ulcerations / epithelial defects, limbal stem cell insufficiency, chronic ocular dryness,Ocular sequelae (group 2): entropion / ectropion, trichiasis, symblepharon • No statistically significant undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group did not suggest any difference in values between the judgement of the guideline committee and that of EN survivors
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Amniotic membrane transplantation vs. supportive therapy • Statistically significant advantage with Amniotic membrane transplantation for the critical outcome ocular sequelae (group 1): conjunctival congestion at 6 months (GRADE: ⊕⊕⊕◯ MODERATE) • No statistically significant difference with with Amniotic membrane transplantation for the critical outcomes ocular sequelae (group 1): corneal perforations / ulcerations / epithelial defects at 6 months, limbal stem cell insufficiency at 6 months and ocular sequelae (group 2): ectropion / entropion at 6 months, trichiasis at 6 months, symblepharon at 6 months (GRADE: ⊕⊕◯◯ LOW) Amniotic membrane transplantation vs. supportive therapy • Statistically significant advantage with Amniotic membrane transplantation for the critical outcomes ocular sequelae (group 1): corneal perforations at 4 years, epithelial defects at 4 years, blindness/restricted reading ability (best-corrected visual acuity <20/200) at 4 years, limbal stem cell insufficiency/total limbal stem cell deficiency at 4 years, chronic dry eyes (moderate and severe), and ocular sequelae (group 2): entropion at 4 years,trichiasis / distichiasis at 4 years, symblepharon at 4 years (GRADE: ⊕⊕⊕◯ MODERATE) • No statistically significant difference with with Amniotic membrane transplantation for the critical outcome Ocular sequelae (group 2): ectropion at 4 years (GRADE: ⊕◯◯◯ VERY LOW)
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes	• No cost-benefit analysis for the German healthcare system was identified

○ Yes ○ Varies	
Resource use Is the incremental cost small relative to the net benefits?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small treatment benefits
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No important impact on equity expected
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated
Conclusion What is the final judgement considering the evidence, and are there important limitations?	
Judgement: ○ Strong recommendation against the intervention ○ Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	Regarding the outcomes ocular sequelae (group 1): conjunctival congestion at 6 months, corneal perforations at 4 years, epithelial defects at 4 years, blindness/restricted reading ability (best-corrected visual acuity <20/200) at 4 years, limbal stem cell insufficiency/total limbal stem cell deficiency at 4 years, chronic dry eyes (moderate and severe), and ocular sequelae (group 2): entropion at 4 years,trichiasis / distichiasis at 4 years, symblepharon at 4 years there is moderate certainty evidence for an advantage amniotic membrane transplantation over supportive therapy (based on 1 RCT and 1 observational study with 25 and 48 patients, respectively. Due to the consistently high effect sizes, we feel confident in making a recommendation for the use of amniotic membrane transplantation in acute EN patients, despite the underlying low sample sizes and number of studies.

TREATMENT OF POSTACUTE OPHTALMOLOGICAL MANIFESTATIONS OF EPIDERMAL NECROLYSIS

For patients with EN, what is the clinical efficacy of surgical interventions (lid-directed procedures, keratoplasty, keratoprosthesis) compared with supportive therapy?	
POPULATION:	Patients with postacute EN
INTERVENTION:	Surgical interventions (lid-directed procedures, keratoplasty, keratoprosthesis)
COMPARISON:	Supportive therapy
MAIN OUTCOMES:	Primary outcomes: o Survival / in-hospital mortality (9 = critical) o Incidence of serious complications (9 = critical) o Quality of life / psychosocial well-being (7 = critical) o Sequelae of the eyes, group 1: blindness, limitation of reading ability, corneal perforations / ulcerations / epithelial defects, limbal stem cell insufficiency, chronic ocular dryness (8 = critical) o Sequelae of the eyes, group 2: entropion / ectropion, trichiasis, symblepharon: (7 = critical) o Sequelae of other organ systems, group 1, digestive system: ulcerations, perforations; urogenital system: urethral strictures, vaginal stenosis; respiratory system: acute respiratory distress syndrome (ARDS), bronchiolitis, bronchiectasis, chronic obstructive pulmonary dysfunction (COPD) (7 = critical) Secondary outcomes: o Sequelae of other organ systems, group 2, skin: scarring, nail loss, postinflammatory hypo- and / or hyperpigmentation; urogenital system: phimosis (6 = important) o Days with ventilation/requirement of ventilation (6 = important) o Mental health (6 = important) o Pain (6 = important) o Time to complete reepithelialization / skin healing (5 important) o Time to return to school / work (5 = important) o Length of hospital stay (4 = important)
SETTING:	Hospital- or burn unit-based care, no regional limitations
PERSPECTIVE:	Clinical recommendations, population perspective
BACKGROUND:	o About 55-88% of all EN patients are affected by ophtalmic complications, which can often lead to severe long-term consequences, including blindness o Early treatment of ophthalmological manifestations of EN is hypothesized to improve the long-term prognosis and prevent subsequent disability o Preliminary research findings and the prevalence of clinical use suggests beneficial effects of ocular surface treatment with amniotic membrane that have not been systematically evaluated
CONFLICT OF INTERESTS:	None

ASSESSMENT

Is the problem a priority?

Judgement:	
○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies	Epidermal necrolysis (EN) is a predominatly drug-induced mucocutaneous reaction with considerable mortality and morbidity, including life-long sequelae. Due to its low incidence, no treatment standards have been established in Germany. In the postacute phase, especially lid-related keratopathies present a common cause of distress for survivors due to the constant irritation caused by morphological changes of the involved mucous membranes. Different surgical procedures have been proposed to reduce mechanical irritation and mitigate the long-term impact of the disease. A systematic evaluation of the effectiveness of these surgical interventions is therefore desirable for all stakeholders. Patients' and family members' needs/preferences: To assess the patient perspective on care needs, we conducted and analyzed 14 semi-structured interviews with survivors and family members of survivors. While often not yet present in the acute phase, ophthalmological manifestations of EN can develop into a significant cause of suffering at a later stage, as the degenerative changes become more and more salient and necessitate rigorous symptom management. Healthcare professional needs: Providers are likely to place high importance in obtaining information on the effectiveness of amniotic membrane treatment.

Summary of Findings

What is the overall certainty of the evidence?

Systematic review based on 1 randomized controlled trial with 20 patients (40 eyes).

Mucous membrane grafting (fibrin-glue) vs. mucous membrane grafting (continuous 8-0 polygalactin suture-assisted)

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					Supportive therapy	AMT
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Ocular sequelae (group 1): improvement in conjunctival and corneal parameters at 6 months follow-up	40 eyes of 20 patients (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	RR: improvement in conjunctival hyperemia: **1.11** (0.93-1.31), conjunctival staining: **1.11** (0.93-1.31), corneal staining: **0.94** (0.71-1.25), corneal conjunctivalization: **1** (0.23-4.37), corneal neovascularization: **0.2** (0.01-3.92), corneal opacification: **3** (0.13-69.52), corneal keratinization: **1** (0.07-14.9)	Risk of outcome: improvement in conjunctival hyperemia: 900 per 1000, conjunctival staining 900 per 1000, corneal staining: 850 per 1000, corneal conjunctivalization: 150 per 1000, corneal neovascularization: 100 per 1000, corneal opacification: 0 per 1000, corneal keratinization: 50 per 1000	Risk of outcome: improvement in conjunctival hyperemia: **97 more per 1000** (59 fewer to 283 more), conjunctival staining: **97 more per 1000** (59 fewer to 283 more), corneal staining: **50 fewer per 1000** (249 fewer to 215 more), corneal conjunctivalization: **0 fewer/more per 1000** (116 fewer to 506 more), corneal neovascularization: **80 fewer per 1000** (99 fewer to 292 more), corneal opacification: **not estimable**, corneal

						keratinization: **0 fewer/more per 1000** (47 fewer to -695 more)
	Ocular sequelae (group 1): BCVA	40 eyes of 20 patients (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	-	Mean LogMAR: 0.77 (estimated from median and range after Wan et al, 2014)	**MD in LogMAR units: 0.05 less** (0.47 less to 0.37 more) (estimated from median and range after Wan et al, 2014)
	Schirmer's test at 6 months	40 eyes of 20 patients (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	-	Mean Schirmer's test: 14.42 ± 3.53 mm	**MD in mm: 1.87 less** (4.40 less to 0.66 more)
	Tear film break-up time (TBUT)	40 eyes of 20 patients (1 randomized controlled trial)	⊕⊕◯◯ LOW [a,b]	-	Mean TBUT: 5.75 ± 2.68 sec (estimated from median and range after Wan et al, 2014)	**MD in sec: 0.75 more** (1.14 less to 2.64 more) (estimated from median and range after Wan et al, 2014)

a. Study limitations: some concerns for risk of bias (rated down one level)
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met (rated down one level)

Bibliography

Pushker, 2021 (57)

Desirable Effects

Are the desirable effects large?

Judgement:	Mucous membrane grafting (fibrin-glue) vs. mucous membrane grafting (continuous 8-0 polygalactin suture-assisted)
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No statistically significant difference with with mucous membrane grafting (fibrin glue) for the critical outcome ocular sequelae (group 1): improvement in conjunctival and corneal parameters and BCVA at 6 months follow-up (GRADE: ⊕⊕◯◯ LOW)

Undesirable Effects

Are the undesirable effects small?

Judgement:	Mucous membrane grafting (fibrin-glue) vs. mucous membrane grafting (continuous 8-0 polygalactin suture-assisted)
○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No statistically significant difference with with mucous membrane grafting (fibrin glue) for the critical outcome ocular sequelae (group 1): improvement in conjunctival and corneal parameters and BCVA at 6 months follow-up (GRADE: ⊕⊕◯◯ LOW)

Differences in values

Is there important uncertainty about how much people value the main outcomes?

Judgement:	• No statistically significant desirable or undesirable effects have been reported • Interviews with 14 survivors and family members of survivors conducted by our group did not suggest any difference in values between the judgement of the guideline committee and that of EN survivors.

○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty of variability ○ No important uncertainty of variability ○ Not known	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	Mucous membrane grafting (fibrin-glue) vs. mucous membrane grafting (continuous 8-0 polygalactin suture-assisted) • No statistically significant difference with with mucous membrane grafting (fibrin glue) for the critical outcome ocular sequelae (group 1): improvement in conjunctival and corneal parameters and BCVA at 6 months follow-up (GRADE: ⨁⨁◯◯ LOW)
Resource use Are the resources required small?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No cost-benefit analysis for the German healthcare system was identified
Resource use Is the incremental cost small relative to the net benefits?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• Mucous membrane grafting using fibrin glue is costlier than the same procedure using a continuous suturing technique. Additionally, the fibrin glue group received addditional polygalactin sutures, albeit less than in the control group • Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small treatment benefits
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced	• No important impact on equity expected

○ Reduced ● Varies	
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated
Conclusion What is the final judgement considering the evidence, and are there important limitations?	
Judgement: ○ Strong recommendation against the intervention ○ Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	Regarding the outcome ocular sequelae (group 1): improvement in conjunctival and corneal parameters and BCVA at 6 months follow-up (GRADE: ⊕⊕◯◯ LOW), there is insufficient evidence for mucous membrane grafting using fibrin glue over mucous mebrane grafting using a continuous 8-0 polygalactin suture (based on 1 RCT wit 20 patients). Due to the lack of significant effect estimates and the higher cost of fibrin glue compared with continuous 8-0 polygalactin suture, we do not feel sufficiently certain to give a recommendation for or against the use of mucous membrane grafting with fibring glue. No evidence could be identified that compared mucous membrane grafting with supportive therapy. We therefore do not feel sufficiently certain to give a recommendation for or against the use of mucous membrane with supportive therapy.

ANTIMICROBIAL THERAPY

For patients with EN, what is the clinical efficacy of prophylactic antibiotic therapy compared with no prophylactic antibiotic therapy?	
POPULATION:	Patients with acute EN
INTERVENTION:	Prophylactic systemic antibiotic therapy
COMPARISON:	No prophylactic systemic antibiotic therapy
MAIN OUTCOMES:	Primary outcomes: o Survival / in-hospital mortality (9 = critical) o Incidence of serious complications (9 = critical) o Quality of life / psychosocial well-being (7 = critical) o Sequelae of the eyes, group 1: blindness, limitation of reading ability, corneal perforations / ulcerations / epithelial defects, limbal stem cell insufficiency, chronic ocular dryness (8 = critical) o Sequelae of the eyes, group 2: entropion / ectropion, trichiasis, symblepharon: (7 = critical) o Sequelae of other organ systems, group 1, digestive system: ulcerations, perforations; urogenital system: urethral strictures, vaginal stenosis; respiratory system: acute respiratory distress syndrome (ARDS), bronchiolitis, bronchiectasis, chronic obstructive pulmonary dysfunction (COPD) (7 = critical) Secondary outcomes: o Sequelae of other organ systems, group 2, skin: scarring, nail loss, postinflammatory hypo- and / or hyperpigmentation; urogenital system: phimosis (6 = important) o Days with ventilation/requirement of ventilation (6 = important) o Mental health (6 = important) o Pain (6 = important) o Time to complete reepithelialization / skin healing (5 important) o Time to return to school / work (5 = important) o Length of hospital stay (4 = important)
SETTING:	Hospital- or burn unit-based care, no regional limitations
PERSPECTIVE:	Clinical recommendations, population perspective
BACKGROUND:	o Infections caused by direct bacterial colonization of the skin or indirectly through catheterization frequently lead to sepsis, which is a major cause of morbidity and mortality in epidermal necrolysis o Prophylactic systemic antibiotics may help mitigate the risk of developing infections and thereby improve disease outcomes but also aggravate the patient’s condition through systemic side effects and facilitating the emergence of resistent organisms o The efficacy of prophylactic antibiotics in patients with epidermal necrolysis has not been systematically evaluated
CONFLICT OF INTERESTS:	None

ASSESSMENT

Is the problem a priority?

Judgement:	
○ No ○ Probably no ○ Uncertain ○ Probably yes ● Yes ○ Varies	Epidermal necrolysis (EN) is a predominatly drug-induced mucocutaneous reaction with considerable mortality and morbidity, including life-long sequelae. Due to its low incidence, no treatment standards have been established in Germany. As septicaemia is the major cause of death in patients with the condition, measures to prevent bacterial colonization of the affected tissues are highly desirable. Aside from its potential to suppress bacterial colonization, detrimental effects have been reported in relation to prophylactic antibiotic treatment, such as an increase in the risk of devloping resistant microbial strains. It is yet unclear whether the benefits outweigh the harms of this treatment. Patients’ and family members’ needs/preferences: To assess the patient perspective on care needs, we conducted and analyzed 14 semi-structured interviews with survivors and family members of survivors. However, the interviews did not touch on the subject of prophylactic antibiotic treatment. Healthcare professional needs: Providers are likely to place high importance in obtaining information on the effectiveness of prophylactic antibiotic treatment.

Summary of Findings

What is the overall certainty of the evidence?

Systematic review based on 1 observational study with 50 patients.

Prophylactic antibiotics vs. no prophylactic antibiotics

JUDGEMENT	RESEARCH EVIDENCE					
	Outcomes	**№ of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
					No prophylactic antibiotics	Prophylactic antibiotics
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	Mortality	50 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	**RR 1.74** (0.04 – 84.03)	Risk of mortality per 1.000 not estimable (no death in single control group)	Risk reduction of mortality per 1.000 not estimable (no death in single control group)
	Length of hospital stay	50 (1 observational study)	⊕◯◯◯ VERY LOW [a,b]	-	Mean stay: 13.1 ± 4.8 days	**MD in days: 3.8 more** (0.29 more to 7.31 more)

a. Study limitations: serious risk of bias in multiple or a substantial number of studies
b. Imprecision: CI of pooled effect estimate crosses clinical decision threshold and optimal information size criterion not met

Bibliography

Diao, 2020 (58)

Desirable Effects

Are the desirable effects large?

Judgement:	Prophylactic antibiotics vs. no prophylactic antibiotics
○ No ○ Probably no ● Uncertain ○ Probably yes	• No statistically significant difference with prophylactic antibiotics for the critical outcome mortality (GRADE: ⊕◯◯◯ VERY LOW)

o Yes o Varies	
Undesirable Effects Are the undesirable effects small?	
Judgement: o No o Probably no ● Uncertain o Probably yes o Yes o Varies	Prophylactic antibiotics vs. no prophylactic antibiotics • Statistically significant disadvantage with Prophylactic antibiotics for the important outcome length of hospital stay (GRADE: ⨁◯◯◯ VERY LOW) •
Differences in values Is there important uncertainty about how much people value the main outcomes?	
Judgement: o Important uncertainty or variability ● Possibly important uncertainty or variability o Probably no important uncertainty of variability o No important uncertainty of variability o Not known	• The guideline committee has judged the statistically significant undesirable effects as important (length of hospital stay)
Balance of effects Does the balance between desirable and undesirable effects favor the intervention?	
Judgement: o No o Probably no ● Uncertain o Probably yes o Yes o Varies	Prophylactic antibiotics vs. no prophylactic antibiotics • Statistically significant disadvantage with Prophylactic antibiotics for the important outcome time length of hospital stay (GRADE: ⨁◯◯◯ VERY LOW) • No statistically significant difference with prophylactic antibiotics for the critical outcome mortality (GRADE: ⨁◯◯◯ VERY LOW) • Very low certainty of evidence does not permit reliably estimating balance of effects
Resource use Are the resources required small?	
Judgement: o No o Probably no ● Uncertain o Probably yes o Yes o Varies	• No cost-benefit analysis for the German healthcare system was identified
Resource use	

Is the incremental cost small relative to the net benefits?	
Judgement: ○ No ○ Probably no ● Uncertain ○ Probably yes ○ Yes ○ Varies	• No cost-benefit analysis for the German healthcare system was identified • Considered in conjunction with the low incidence rate of EN, disease severity may justify above average costs and resource investment even for small treatment benefits
Equity What would be the impact on health inequities?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No important impact on equity expected
Acceptability, Implementability and Feasibility Is the option acceptable to key stakeholders, can it be implemented and is it feasible?	
Judgement: ○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ● Varies	• No conflicts regarding acceptability anticipated • No conflicts regarding implementability anticipated • No conflicts regarding feasibility anticipated
Conclusion What is the final judgement considering the evidence, and are there important limitations?	
Judgement: ○ Strong recommendation against the intervention ○ Conditional recommendation against the intervention ● Conditional recommendation for either the intervention or the comparison ○ Conditional recommendation for the intervention ○ Strong recommendation for the intervention	Regarding the outcome length of hospital stay there is very low certainty evidence for a disadvantage of prophylactic antibiotics over no prophylactic antibiotics based on 1 observational study with 50 patients. Considering the low certainty of the evidence and the imprecision of reported effect estimates, we can neither make a recommendation for nor against the use of prophylactic antibiotic treatment in acute EN patients. Medical providers may want to consider empirical in conjunction with mechanistic evidence in making clinical decisions.

SUPPLEMENT

Characteristics of included studies

Table 1: Characteristics of included studies

First author, year	Study period	Title	Comparison	Overall sample size	Comments	Risk of Bias
Ao, 2022	01/2017-09/2021	Inhibition of tumor necrosis factor improves conventional steroid therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis in a cohort of patients	Etanercept + corticosteroids vs. corticosteroids	25		Moderate risk of bias
Boorboor, 2008	01/2002-12/2006	Toxic epidermal necrolysis: use of Biobrane or skin coverage reduces pain, improves mobilisation and decreases infection in elderly patients	Biobrane^{TM} vs. other dressings (paraffin gauze)	14	Likely no systemic co-therapy: "Immunosupressive or immunomodulating therapy with steroids or immunglobulins or any prophylactic antibiotic therapy was avoided"	Moderate risk of bias
Brand, 2000	07/1978-06/1998	Toxic epidermal necrolysis in Western Australia	Corticosteroids vs. supportive therapy	12		Serious risk of bias
Brown, 2004	05/1997-09/2002	Toxic epidermal necrolysis: does immunoglobulin make a difference?	IVIG vs. supportive therapy	45	Therapy before burn-center admission with steroids in 16/24 (IVIG) and 13/21 (no IVIG), respectively; differential classification of TEN: "TEN was diagnosed by documentation of greater than 30% TBSA skin slough or with less than 30% TBSA slough and sloughing of one or more mucosal surfaces (oral, tracheal, urogenital)."	Moderate risk of bias

Chan, 2019	01/2006-12/2016	A 10-year retrospective cohort study of the management of toxic epidermal necrolysis and Stevens-Johnson syndrome in a New South Wales state referral hospital from 2006 to 2016	IVIG + corticosteroids vs. supportive therapy	19		Moderate risk of bias
Chan, 2019	01/2006-12/2016	A 10-year retrospective cohort study of the management of toxic epidermal necrolysis and Stevens-Johnson syndrome in a New South Wales state referral hospital from 2006 to 2016	IVIG vs. supportive therapy	22		Moderate risk of bias
Chan, 2019	01/2006-12/2016	A 10-year retrospective cohort study of the management of toxic epidermal necrolysis and Stevens-Johnson syndrome in a New South Wales state referral hospital from 2006 to 2016	IVIG + corticosteroids vs. IVIG	29		Moderate risk of bias
Chatproedprai, 2018	1/1997-12/2016	Clinical Features and Treatment Outcomes among Children with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A 20-Year Study in a Tertiary Referral Hospital	Corticosteroids vs. supportive therapy	32	Extracted data received from study authors upon request; patients receiving co-therapy with IVIG are excluded from SR	Serious risk of bias
Das, 2014	07/2004-10/2012	Unidentified drugs in traditional medications causing toxic epidermal necrolysis: A developing country experience	Silver sulfadiazine vs. traditional wound care	29		Moderate risk of bias
Diao, 2020	2010-2017	A retrospective analysis of infections and antibiotic treatment in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis	Prophylactic antibiotics vs. no prophylactic antibiotics	50	Reported outcomes only sufficient for analysis of non-infected patients (n=50); co-interventions received: IVIG + corticosteroids	Serious risk of bias
Dicle, 2009		Stevens-Johnson syndrome and toxic epidermal necrolysis: A	Corticosteroids vs. supportive therapy	20	2 patients reported as having received IVIG in addition to corticosteroids, but both	Moderate risk of bias

		retrospective evaluation. [Turkish]			patients (uniquely identifiable by described characteristics) are absent in results table of corticosteroids group (supportive therapy group may be inflated).	
Dreyer, 2021	2013-2016	Efficacy of Etanercept in the Treatment of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis	Etanercept vs. IVIG	14	Skin detachment from patient-level data <10 extracted as 9, <5 as 4 and "mucosal only" as 0	Moderate risk of bias
Gerding, 1988		Biosynthetic skin substitute vs 1% silver sulfadiazine for treatment of inpatient partial-thickness thermal burns	Biosynthetic dressing (Biobrane™) vs. twice-daily application of silver sulfadiazine	50 wounds in 47 patients		Serious risk of bias (high risk of bias in at least one domain according to systematic review by Wasiak et al., 2013)
Gerding, 1990		Outpatient management of partial-thickness burns: Biobrane versus 1% silver sulfadiazine	Biosynthetic dressing (Biobrane™) vs. twice-daily application of silver sulfadiazine	64		Serious risk of bias (high risk of bias in at least one domain according to systematic review by Wasiak et al., 2013)
Gonzalez-Herrada, 2017	2001-2015	Cyclosporine Use in Epidermal Necrolysis Is Associated with an Important Mortality Reduction: Evidence from Three Different Approaches	Cyclosporine A vs. IVIG	37	SCORTEN reporting based on imputation	Moderate risk of bias
Gravante, 2007	1/1995-12/2005	Toxic epidermal necrolysis and Steven Johnson syndrome: 11-years experience and outcome	IVIG vs. supportive therapy	32	Therapy group allocation according to reference in text (IVIG was used routinely after February 1999). However, Individual patient data was not reported at month-level.	Moderate risk of bias
Guilbaud, 1992		European comparative clinical study of Inerpan: a new wound dressing in treatment of partial skin thickness burns	Hydrogel dressing vs. silver sulfadiazine, paraffin gauze or paraffin gauze with antibiotics	62		Serious risk of bias (high risk of bias in at least one domain according to systematic review by Wasiak et al., 2013)

Hsieh, 2021	01/2000-03/2019	Recent Dermatological Treatments for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Japan	IVIG + corticosteroids vs. corticosteroids	40		Serious risk of bias
Huang, 2014	1995-2009	Clinical evaluation comparing the efficacy of aquacel Ag with vaseline gauze versus 1% silver sulfadiazine cream in toxic epidermal necrolysis	Aquacel Ag with vaseline gauze vs. sulfadiazine cream	20	Only time to 95% healing reported; unbalanced sex distribution (p< 0.05)	Serious risk of bias
Imahara, 2006	02/1987-03/2004	SCORTEN overestimates mortality in the setting of a standardized treatment protocol	IVIG vs. supportive therapy	109	Unclear whether IVIG group also contains non-IVIG patients: "IVIG was considered for patients with progressive disease after its routine institution in January 1999."	Serious risk of bias
Jagadeesan, 2013	02/2008-01/2012	Low dose intravenous immunoglobulins and steroids in toxic epidermal necrolysis: A prospective comparative open-labelled study of 36 cases	IVIG + corticosteroids vs. corticosteroids	36		Moderate risk of bias
Kim, 2005	11/1990-10/2003	Toxic epidermal necrolysis: analysis of clinical course and SCORTEN-based comparison of mortality rate and treatment modalities in Korean patients	IVIG vs. corticosteroids	35	38 patients in original sample, 2 deaths in excluded group: unclear whether deceased patients received treatment	Moderate risk of bias
Kirchhof, 2014	2001-2011	Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine	Cyclosporine A vs. IVIG	54	2 patients receiving both treatments included in both treatment groups; unclear whether all patients were treated at the same hospital: "9 patients with SJS/TEN were identified from our dermatology consult service database"	Moderate risk of bias

Koh, 2010	01/2001-12/2006	Stevens-Johnson syndrome and toxic epidermal necrolysis in Asian children	Corticosteroids vs. supportive therapy	133	15 patients in original sample (4 receiving IVIG)	Serious risk of bias
Kridin, 2021	01/2015-12/2019	Assessment of Treatment Approaches and Outcomes in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Insights From a Pan-European Multicenter Study	IVIG vs. supportive therapy	109		Serious risk of bias
Kridin, 2021	01/2015-12/2019	Assessment of Treatment Approaches and Outcomes in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Insights From a Pan-European Multicenter Study	Corticosteroids vs. supportive therapy	212		Serious risk of bias
Kridin, 2021	01/2015-12/2019	Assessment of Treatment Approaches and Outcomes in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Insights From a Pan-European Multicenter Study	Cyclosporine A vs. supportive therapy	101		Serious risk of bias
Kridin, 2021	01/2015-12/2019	Assessment of Treatment Approaches and Outcomes in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Insights From a Pan-European Multicenter Study	IVIG vs. corticosteroids	280		Serious risk of bias
Kridin, 2021	01/2015-12/2019	Assessment of Treatment Approaches and Outcomes in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Insights From a Pan-European Multicenter Study	Cyclosporine A vs. IVIG	48		Serious risk of bias
Kridin, 2021	01/2015-12/2019	Assessment of Treatment Approaches and Outcomes in Stevens-Johnson Syndrome and	Cyclosporine A vs. corticosteroids	72		Serious risk of bias

		Toxic Epidermal Necrolysis: Insights From a Pan-European Multicenter Study				
Léauté-Labrèze, 2000		Diagnosis, classification, and management of erythema multiforme and Stevens-Johnson syndrome	Corticosteroids vs. supportive therapy	15	20 patients in original sample (2 receiving thalidomide)	Serious risk of bias
Marchitto, 2018	1994-2014	Toxic epidermal necrolysis: a review of 20 years of data	IVIG vs. supportive therapy	40		Serious risk of bias
Muangman, 2006		Comparison of efficacy of 1% silver sulfadiazine and Acticoat for treatment of partial thickness burn wounds	Silver-impregnated dressing (Acticoat, Smith & Nephew, UK) vs. silver sulfadiazine	50		Serious risk of bias (high risk of bias in at least one domain according to systematic review by Wasiak et al., 2013)
Opasanon, 2010		Clinical effectiveness of alginate silver dressing in outpatient management of partial-thickness burns	Ionic silver dressing (Askina Calgitrol Ag) changed every 5 days until wound closure vs. daily silver sulfadiazine changes	65		Serious risk of bias (high risk of bias in at least one domain according to systematic review by Wasiak et al., 2013)
Paquet, 2006		Skin immunoglobulin deposition following intravenous immunoglobulin therapy in toxic epidermal necrolysis	IVIG vs. supportive therapy	11		Serious risk of bias
Poizeau, 2018	2005-2016	Cyclosporine for Epidermal Necrolysis: Absence of Beneficial Effect in a Retrospective Cohort of 174 Patients-Exposed/Unexposed and Propensity Score-Matched Analyses	Cyclosporine A vs. supportive therapy	174	Extraction based on entire cohort not propensity score analysis; TBSA measured on day 5	Moderate risk of bias
Pushker, 2021	09/2016 and 10/2017	Mucous membrane grafting (fibrin glue vs. suture) for lid margin pathologies in Stevens-Johnson syndrome: randomized comparative study	Fibrin glue-assisted MMG vs. continuous 8-0 polygalactin suture-assisted MMG	40 eyes of 20 patients		Some concerns

Schneck, 2008	04/1997-12/2001	Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study	IVIG + corticosteroids vs. supportive therapy	127		Serious risk of bias
Schneck, 2008	04/1997-12/2001	Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study	IVIG + corticosteroids vs. IVIG	75		Serious risk of bias
Schneck, 2008	04/1997-12/2001	Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study	IVIG + corticosteroids vs. corticosteroids	159		Serious risk of bias
Schneck, 2008	04/1997-12/2001	Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study	IVIG vs. supportive therapy	122		Serious risk of bias
Schneck, 2008	04/1997-12/2001	Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study	Corticosteroids vs. supportive therapy	206		Serious risk of bias
Sekula, 2010	04/1997-12/2001	An application of propensity score methods to estimate the treatment effect of corticosteroids in patients with severe cutaneous adverse reactions	Corticosteroids vs. supportive therapy	121	German cohort; re-analysis of Schneck et al., 2008	Moderate risk of bias

Sekula, 2010	04/1997-12/2001	An application of propensity score methods to estimate the treatment effect of corticosteroids in patients with severe cutaneous adverse reactions	Corticosteroids vs. supportive therapy	85	French cohort; re-analysis of Schneck et al., 2008	Moderate risk of bias
Sekula, 2013	01/2003-03/2007	Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis	IVIG vs. supportive therapy	178		Moderate risk of bias
Sekula, 2013	01/2003-03/2007	Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis	Corticosteroids vs. supportive therapy	414		Moderate risk of bias
Sekula, 2013	01/2003-03/2007	Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis	IVIG vs. corticosteroids	178		Moderate risk of bias
Shah, 2021		Use of cyclosporine for the treatment of Stevens-Johnson syndrome/toxic epidermal necrolysis	Cyclosporine A vs. corticosteroids	93	48 of 93 admitted patients included in the study (only patients receiving cyclosporine A or intravenously administered steroids)	Moderate risk of bias
Shanbhag, 2019	01/2000-09/2007	Long-Term Effect of a Treatment Protocol for Acute Ocular Involvement in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis	Standardized protocol (incl. AMT) vs. no protocol	96 eyes of 48 patients	group without protocol: 01/2000-01/2008, group with protocol: 02/2008-09/2017	Serious risk of bias
Sharma, 2016	05/2013-05/2014	Adjuvant Role of Amniotic Membrane Transplantation in Acute Ocular Stevens-Johnson Syndrome: A Randomized Control Trial	Amniotic membrane transplantation vs. supportive therapy	50 eyes of 25 patients	Severity at presentation classified according to Power, 1995. [Mild: complications requiring routine eye care with full resolution of signs and symptoms before hospital discharge. Moderate: ocular complications that required	Some concerns

					specific treatment and normal vision and near complete resolution of all active disease on discharge. Severe complications: sight-threatening disease, ongoing ocular inflammation with reduced vision, and the need for specific, ongoing eye care after discharge.]	
Shortt, 2004	04/1995-12/2002	Intravenous immunoglobulin does not improve outcome in toxic epidermal necrolysis	IVIG vs. supportive therapy	32	Acute physiology and chronic health evaluation (APACHE) 2 used for basline comparison of groups instead of SCORTEN; "Two cases in the control group (both survivors) had missing data for determination of systemic inflammatory response syndrome (SIRS), sepsis, multiple organ dysfunction (MOD), cutaneous progression, and ventilator support, so that the results on these parameters are based on analysis of 30 cases (14 in the control group, and 16 in the IVIG group)."	Moderate risk of bias
Singh, 2013	07/2011-06/2012	Cyclosporine in Stevens Johnson syndrome and toxic epidermal necrolysis and retrospective comparison with systemic corticosteroid	Cyclosporine A vs. corticosteroids	17	Historical cohort (corticosteroids); TBSA measured on day 5	Moderate risk of bias
Thakur, 2021	01/2014-12/2018	Factors Predicting the Outcome of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A 5-Year Retrospective Study	Cyclosporine A vs. corticosteroids	45		Moderate risk of bias

Torres-Navarro, 2020	01/2013-01/2018	Accuracy of SCORTEN and ABCD-10 to predict mortality and the influence of renal function in Stevens-Johnson syndrome/toxic epidermal necrolysis	Corticosteroids vs. supportive therapy	14	TBSA "<10" in patient-level data coded as 1 in order not to inflate treatment effectiveness	Serious risk of bias
Varas, 2005		A prospective, randomized trial of Acticoat versus silver sulfadiazine in the treatment of partial thickness burns: which method is less painful?	Silver-impregnated dressing (Acticoat) vs. silver sulfadiazine application and removal twice daily	14		Serious risk of bias (high risk of bias in at least one domain according to systematic review by Wasiak et al., 2013)
Wang, 2018	2009-2015	Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions	Etanercept vs. corticosteroids	91		Some concerns
Wang, 2018	2009-2015	Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions	Etanercept vs. supportive therapy	86	Historical cohort in supportive therapy group	Serious risk of bias (pertains to comparison with historical control group only)
Wang, 2018	2009-2015	Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions	Corticosteroids vs. supportive therapy	81	Historical cohort in supportive therapy group	Serious risk of bias (pertains to comparison with historical control group only)
Williams, 2021	01/2009-12/2018	Intensive care needs and long-term outcome of pediatric toxic epidermal necrolysis - A 10-year experience	IVIG vs. supportive therapy	31	Omnibus test used for baseline comparison (all > 0.05)	Moderate risk of bias
Williams, 2021	01/2009-12/2018	Intensive care needs and long-term outcome of pediatric toxic epidermal necrolysis - A 10-year experience	IVIG + corticosteroids vs. supportive therapy	19	Omnibus test used for baseline comparison (all > 0.05)	Moderate risk of bias
Williams, 2021	01/2009-12/2018	Intensive care needs and long-term outcome of pediatric toxic epidermal necrolysis - A 10-year experience	IVIG + corticosteroids vs. IVIG	32	Omnibus test used for baseline comparison (all > 0.05)	Moderate risk of bias

Wolkenstein, 1998	05/1995-09/1996	Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis	Thalidomide vs. placebo	22		Low risk of bias
Wyatt, 1990		Comparison of a hydrocolloid dressing and silver sulfadiazine cream in the outpatient management of second-degree burns	Hydrocolloid dressing (DuoDerm, ConvaTec, Squibb) vs. silver sulfadiazine (Silvadene, Marion Laboratories)	50		Serious risk of bias (high risk of bias in at least one domain according to systematic review by Wasiak et al., 2013)
Xiao, 2019	06/2009-03/2013	Clinical analysis of severe drug eruption treated with hemoperfusion combined with continuous renal replacement therapy	IVIG + corticosteroids vs. corticosteroids	15	Cases might have been selected contingent on favorable outcome: "10 cases of Stevens-Johnson syndrome (SJS) and 19 Toxic epidermal necrolysis (TEN) with favorable outcome after treatment from June 2009 to June 2013 were analyzed"; data received from study authors	Moderate risk of bias
Yang, 2009	01/1993-10/2007	Combination therapy of intravenous immunoglobulin and corticosteroid in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome: a retrospective comparative study in China	IVIG + corticosteroids vs. corticosteroids	65	Individual patient data for full cohort	Serious risk of bias
Yang, 2021	01/2008-12/2019	Intravenous Immunoglobulin Combined With Corticosteroids for the Treatment of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: A Propensity-Matched Retrospective Study in China	IVIG + corticosteroids vs. corticosteroids	145	IVIG administration contingent upon disease progression; 224 in unmatched sample (matched cohort of 145 patients reported here)	Moderate risk of bias
Yeong, 2011	01/2000-12/2006	Serum bicarbonate as a marker to predict mortality in toxic epidermal necrolysis	IVIG + corticosteroids vs. corticosteroids	14	16 patients in original sample (1 ivig only, 1 supportive therapy); reported steroid use	Serious risk of bias

					likely before admission to burn-center	
Yip, 2005	07/1995-06/2001 and 07/2001-06/2002	High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits	IVIG vs. supportive therapy	18	7 and 5 patients received corticosteroids in addition to main treatment regimen in intervention and control group, respectively. Baseline characteristics only available for survivors with eye complications	Serious risk of bias
Yip, 2005	07/1995-06/2001 and 07/2001-06/2002	High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits	Corticosteroids vs. supportive therapy	17	7 and 5 patients received corticosteroids in addition to main treatment regimen in intervention and control group, respectively. Baseline characteristics only available for survivors with eye complications	Serious risk of bias
Yip, 2005	07/1995-06/2001 and 07/2001-06/2002	High-dose intravenous immunoglobulin in the treatment of toxic epidermal necrolysis: a study of ocular benefits	IVIG vs. corticosteroids	13	7 and 5 patients received corticosteroids in addition to main treatment regimen in intervention and control group, respectively. Baseline characteristics only available for survivors with eye complications	Serious risk of bias
Young, 2016	2006-2014	The use of porcine xenografts in patients with toxic epidermal necrolysis	Porcine xenograft vs. traditional wound care	24	Historical control group (16/90, matched for baseline characteristics); unclear silver impregnated dressings were used in all control patients	Serious risk of bias
Yun, 2008	10/2001-03/2007	Serum lactate dehydrogenase is a novel marker for the evaluation of disease severity in the early stage of toxic epidermal necrolysis	IVIG + corticosteroids vs. corticosteroids	13	33 patients in original sample but outcome only reported for TEN cases	Serious risk of bias

Zhang, 2022	01/2014-12/2019	Evaluation of Combination Therapy With Etanercept and Systemic Corticosteroids for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Multicenter Observational Study	Etanercept + corticosteroids vs. IVIG + corticosteroids	46		Moderate risk of bias
Zhu, 2012	01/2000-04/2010	Toxic epidermal necrolysis: performance of SCORTEN and the score-based comparison of the efficacy of corticosteroid therapy and intravenous immunoglobulin combined therapy in China	IVIG + corticosteroids vs. corticosteroids	61	Patients from same hospital as Yang, 2009	Moderate risk of bias

Studies excluded in full-text screening

Reasons for exclusion:

- Less than 5 patients per treatment arm or non-comparative study
- Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
- Baseline characteristics associated with outcome significantly different between intervention groups
- Investigated treatment not pertinent to German context
- No full-text available after authors have been contacted
- Study not peer-reviewed (e.g., conference abstract)
- Diagnosis inadequately described / cases of differential diagnoses included
- Other reasons (e.g., duplicate, non-empirical research article)

Table 2: Studies excluded in full-text screening

First author, year	Reason for exclusion
Abdulah, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Abe, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Abela, 2014	Less than 5 patients per treatment arm or non-comparative study
Abou-Taleb, 2020	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Abtahi-Naeini, 2022	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Acar, 2022	Diagnosis inadequately described / cases of differential diagnoses included
Adedapo, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Adegbidi, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Agrawal, 2015	Less than 5 patients per treatment arm or non-comparative study
Agrawal, 2013	Study not peer-reviewed (e.g., conference abstract)
Ahluwalia, 2014	Less than 5 patients per treatment arm or non-comparative study
Ahmad, 2017	Less than 5 patients per treatment arm or non-comparative study
Ahmed, 2004	Other reasons (e.g., duplicate, non-empirical research article)
Aihara, 2015	Less than 5 patients per treatment arm or non-comparative study
Aihara, 2004	Less than 5 patients per treatment arm or non-comparative study

Aires, 2013	Less than 5 patients per treatment arm or non-comparative study
Al Lawatiya, 2020	Study not peer-reviewed (e.g., conference abstract)
Alajaji, 2020	Less than 5 patients per treatment arm or non-comparative study
Al-Benna, 2021	Less than 5 patients per treatment arm or non-comparative study
Alen Coutinho, 2019	Study not peer-reviewed (e.g., conference abstract)
Ali, 2014	Less than 5 patients per treatment arm or non-comparative study
Ali, 2018	Diagnosis inadequately described / cases of differential diagnoses included
Alizadeh, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Allenova, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Al-Mutairi, 2004	Less than 5 patients per treatment arm or non-comparative study
Ang, 2013	Less than 5 patients per treatment arm or non-comparative study
Ang, 2011	Less than 5 patients per treatment arm or non-comparative study
Ang, 2006	Less than 5 patients per treatment arm or non-comparative study
Antoon, 2017	Study not peer-reviewed (e.g., conference abstract)
Antoon, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Antoon, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Aoyama, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Araki, 2009	Less than 5 patients per treatment arm or non-comparative study
Arellano Ocampo, 1996	No full-text available after authors have been contacted
Arevalo, 1999	Less than 5 patients per treatment arm or non-comparative study
Arevalo, 2000	Investigated treatment not pertinent to German context
Asada, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Atipo-Tsiba, 2011	Less than 5 patients per treatment arm or non-comparative study
Atzori, 2006	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS

Avadhanam, 2020	Less than 5 patients per treatment arm or non-comparative study
Aydin, 2017	Less than 5 patients per treatment arm or non-comparative study
Azfar, 2010	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Aziza, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Baba, 2003	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Bachot, 2003	Less than 5 patients per treatment arm or non-comparative study
Bagga, 2018	Less than 5 patients per treatment arm or non-comparative study
Bai, 2017	Investigated treatment not pertinent to German context
Balai, 2021	Less than 5 patients per treatment arm or non-comparative study
Bamichas, 2002	Less than 5 patients per treatment arm or non-comparative study
Ban, 2016	Less than 5 patients per treatment arm or non-comparative study
Bang, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Bansal, 2015	Less than 5 patients per treatment arm or non-comparative study
Barrera-Ochoa, 2022	Less than 5 patients per treatment arm or non-comparative study
Barvaliya, 2011	Less than 5 patients per treatment arm or non-comparative study
Baskan, 2005	Less than 5 patients per treatment arm or non-comparative study
Bastuji-Garin, 1993	Other reasons (e.g., duplicate, non-empirical research article)
Basu, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Beck, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Bernal, 2015	Less than 5 patients per treatment arm or non-comparative study
Bettuzzi, 2022	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Bhattacharya, 2011	Less than 5 patients per treatment arm or non-comparative study
Boccia, 2004	Other reasons (e.g., duplicate, non-empirical research article)

Botelho, 2016	Less than 5 patients per treatment arm or non-comparative study
Cabanas Weisz, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Cachafeiro Fucinos, 2015	Less than 5 patients per treatment arm or non-comparative study
Campione, 2003	Less than 5 patients per treatment arm or non-comparative study
Cao, 2021	Study not peer-reviewed (e.g., conference abstract)
Capek, 2016	Study not peer-reviewed (e.g., conference abstract)
Capek, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Capper, 2013	Less than 5 patients per treatment arm or non-comparative study
Carneiro-Leao, 2018	Study not peer-reviewed (e.g., conference abstract)
Carneiro-Leao, 2020	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Carpenter, 2021	Diagnosis inadequately described / cases of differential diagnoses included
Carrasquillo, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Cartotto, 2008	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Casalita, 2020	Less than 5 patients per treatment arm or non-comparative study
Castaneda, 2009	Other reasons (e.g., duplicate, non-empirical research article)
Catt, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Catt, 2016	Less than 5 patients per treatment arm or non-comparative study
Cekic, 2016	Less than 5 patients per treatment arm or non-comparative study
Celiksoy, 2014	Less than 5 patients per treatment arm or non-comparative study
Chaidemenos, 1997	Less than 5 patients per treatment arm or non-comparative study
Chan, 2016	Less than 5 patients per treatment arm or non-comparative study
Chan, 2018	Less than 5 patients per treatment arm or non-comparative study
Chan, 2012	Study not peer-reviewed (e.g., conference abstract)
Chang, 2007	Other reasons (e.g., duplicate, non-empirical research article)

Chantachaeng, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Chantaphakul, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Chateau, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Chatterjee, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Chattopadhyay, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Chee, 2012	Less than 5 patients per treatment arm or non-comparative study
Chen, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Chen, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Chen, 2010	Baseline characteristics associated with outcome significantly different between intervention groups
Chen, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Chen, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Chen, 2021	Less than 5 patients per treatment arm or non-comparative study
Cheriyan, 1995	Less than 5 patients per treatment arm or non-comparative study
Cheung, 2020	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Cheung, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Chew, 2009	Other reasons (e.g., duplicate, non-empirical research article)
Chew, 2010	Other reasons (e.g., duplicate, non-empirical research article)
Chhipa, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Choi, 2018	Less than 5 patients per treatment arm or non-comparative study
Choi, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Choon, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Choonhakarn, 2016	Less than 5 patients per treatment arm or non-comparative study

Chua, 2016	Study not peer-reviewed (e.g., conference abstract)
Ciccacci, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Clarivet, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Colic-Hadzic, 2002	Less than 5 patients per treatment arm or non-comparative study
Cooney, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Cooper, 2015	Study not peer-reviewed (e.g., conference abstract)
Copaescu, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Corne, 2001	Less than 5 patients per treatment arm or non-comparative study
Criton, 1997	Less than 5 patients per treatment arm or non-comparative study
Crowder, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Crowder, 2022	Less than 5 patients per treatment arm or non-comparative study
Cruger, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Curtis, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Czubkowska, 2000	Less than 5 patients per treatment arm or non-comparative study
Das, 2013	Less than 5 patients per treatment arm or non-comparative study
De Prost, 2010	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
De Rojas, 2007	Diagnosis inadequately described / cases of differential diagnoses included
De Siqueira, 2010	Less than 5 patients per treatment arm or non-comparative study
Degboe, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Del Buey, 2016	Less than 5 patients per treatment arm or non-comparative study
Del Pozzo-Magana, 2021	Other reasons (e.g., duplicate, non-empirical research article)
DenAdel, 2022	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Deniro, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Deshmukh, 2022	Less than 5 patients per treatment arm or non-comparative study

Devarbhavi, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Devarbhavi, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Devi, 2005	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Devi, 2016	Less than 5 patients per treatment arm or non-comparative study
Di Pascuale, 2005	Other reasons (e.g., duplicate, non-empirical research article)
Dibek Misirlioglu, 2017	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Didona, 2010	Less than 5 patients per treatment arm or non-comparative study
Didona, 2015	Less than 5 patients per treatment arm or non-comparative study
Didona, 2019	Less than 5 patients per treatment arm or non-comparative study
Dillon, 2010	Less than 5 patients per treatment arm or non-comparative study
Dilokthornsakul, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Ding, 2010	Other reasons (e.g., duplicate, non-empirical research article)
Djordjevic, 2012	Less than 5 patients per treatment arm or non-comparative study
Dorafshar, 2008	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Dore, 2007	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Dsouza, 2019	Less than 5 patients per treatment arm or non-comparative study
Ducic, 2002	Less than 5 patients per treatment arm or non-comparative study
Duplisea, 2022	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Durand, 2009	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
East-Innis, 2009	Other reasons (e.g., duplicate, non-empirical research article)
East-Innis, 2013	Other reasons (e.g., duplicate, non-empirical research article)

Egan, 1999	Investigated treatment not pertinent to German context
el-Azhary, 2021	Less than 5 patients per treatment arm or non-comparative study
El-Hamd, 2017	Less than 5 patients per treatment arm or non-comparative study
El-Nabarawy, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Engelhardt, 1997	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Esposito, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Falsini, 2005	Less than 5 patients per treatment arm or non-comparative study
Fang, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Farhat, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Faye, 2005	Other reasons (e.g., duplicate, non-empirical research article)
Feldmeyer, 2010	Less than 5 patients per treatment arm or non-comparative study
Fellahi, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Fernandes, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Ferrandiz-Pulido, 2011	Less than 5 patients per treatment arm or non-comparative study
Ferrandiz-Pulido, 2011	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Finkelstein, 2009	Other reasons (e.g., duplicate, non-empirical research article)
Finkelstein, 2009	Other reasons (e.g., duplicate, non-empirical research article)
Finkelstein, 2011	Study not peer-reviewed (e.g., conference abstract)
Fiorelli, 2010	Less than 5 patients per treatment arm or non-comparative study
Firoz, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Forman, 2002	Diagnosis inadequately described / cases of differential diagnoses included
Foster, 2010	Less than 5 patients per treatment arm or non-comparative study
Franca, 2009	Less than 5 patients per treatment arm or non-comparative study
Francesia Berta, 2013	Less than 5 patients per treatment arm or non-comparative study

Frederiks, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Frederiks, 2022	Less than 5 patients per treatment arm or non-comparative study
Frey, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Frey, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Frizon, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Fu, 2011	Less than 5 patients per treatment arm or non-comparative study
Fujita, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Fukasawa, 2021	Less than 5 patients per treatment arm or non-comparative study
Furubacke, 1999	Less than 5 patients per treatment arm or non-comparative study
Gacto-Sanchez, 2018	Less than 5 patients per treatment arm or non-comparative study
Gaist, 1996	Other reasons (e.g., duplicate, non-empirical research article)
Galvis, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Gange, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Gao, 2021	Less than 5 patients per treatment arm or non-comparative study
Garcia-Doval, 2000	Other reasons (e.g., duplicate, non-empirical research article)
Gardezi, 2013	Less than 5 patients per treatment arm or non-comparative study
Garg, 2011	Less than 5 patients per treatment arm or non-comparative study
Garg, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Gaudin, 2022	Less than 5 patients per treatment arm or non-comparative study
Gerdts, 2007	Less than 5 patients per treatment arm or non-comparative study
Ghiasi, 2017	Less than 5 patients per treatment arm or non-comparative study
Giraud-Kerleroux, 2021	Less than 5 patients per treatment arm or non-comparative study
Giudice, 2017	Less than 5 patients per treatment arm or non-comparative study
Goh, 2019	Study not peer-reviewed (e.g., conference abstract)
Goldblatt, 2017	Other reasons (e.g., duplicate, non-empirical research article)

Goldman, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Gomes, 2003	Less than 5 patients per treatment arm or non-comparative study
Gomez-Criado, 2004	Less than 5 patients per treatment arm or non-comparative study
Gomez-Flores, 2019	Less than 5 patients per treatment arm or non-comparative study
Goutam, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Grando, 2014	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Gravante, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Green, 1993	Less than 5 patients per treatment arm or non-comparative study
Gregory, 2011	Less than 5 patients per treatment arm or non-comparative study
Gregory, 2011	Less than 5 patients per treatment arm or non-comparative study
Gregory, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Gueudry, 2009	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Guibal, 1995	Other reasons (e.g., duplicate, non-empirical research article)
Gurumurthy, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Guvenir, 2016	Study not peer-reviewed (e.g., conference abstract)
Haber, 2005	Less than 5 patients per treatment arm or non-comparative study
Haddad, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Hali, 2022	Less than 5 patients per treatment arm or non-comparative study
Hall, 2021	Less than 5 patients per treatment arm or non-comparative study
Hamilton, 2013	Less than 5 patients per treatment arm or non-comparative study
Hamilton, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Hamoy, 2012	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Han, 2011	Less than 5 patients per treatment arm or non-comparative study

Han, 2017	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Hanada, 2017	Less than 5 patients per treatment arm or non-comparative study
Hanken, 2010	Less than 5 patients per treatment arm or non-comparative study
Haravu, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Harwood, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Hasegawa, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Hassan, 2022	Less than 5 patients per treatment arm or non-comparative study
He, 2021	Less than 5 patients per treatment arm or non-comparative study
Heinzerling, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Hekman, 2021	Study not peer-reviewed (e.g., conference abstract)
Heng, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Heng, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Hernandez Fernandez Rojas, 1998	No full-text available after authors have been contacted
Hernandez-Mondragon, 2011	Study not peer-reviewed (e.g., conference abstract)
Herndon, 1995	Other reasons (e.g., duplicate, non-empirical research article)
Heur, 2014	Less than 5 patients per treatment arm or non-comparative study
Heymann, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Hii, 2014	Diagnosis inadequately described / cases of differential diagnoses included
Hinko, 2014	Study not peer-reviewed (e.g., conference abstract)
Hino, 2012	Less than 5 patients per treatment arm or non-comparative study
Hirahara, 2013	Less than 5 patients per treatment arm or non-comparative study
Hirapara, 2017	Baseline characteristics associated with outcome significantly different between intervention groups
Honavar, 2000	Less than 5 patients per treatment arm or non-comparative study

Hosaka, 2010	Less than 5 patients per treatment arm or non-comparative study
Houschyar, 2021	Less than 5 patients per treatment arm or non-comparative study
Hsu, 2012	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Hsu, 2021	Less than 5 patients per treatment arm or non-comparative study
Hu, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Huang, 2009	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Huang, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Huang, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Huang, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Huang, 1993	Less than 5 patients per treatment arm or non-comparative study
Huang, 2010	Less than 5 patients per treatment arm or non-comparative study
Hung, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Hutchens, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Huyen, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Ichihara, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Ikezawa, 2010	Less than 5 patients per treatment arm or non-comparative study
Imatoh, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Imatoh, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Inatomi, 2006	Less than 5 patients per treatment arm or non-comparative study
Ingen-Housz-Oro, 2022	Less than 5 patients per treatment arm or non-comparative study
Ioannides, 1994	Baseline characteristics associated with outcome significantly different between intervention groups
Iqbal, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Irungu, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS

Isah, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Ishida, 2014	Less than 5 patients per treatment arm or non-comparative study
Itoi, 2020	Less than 5 patients per treatment arm or non-comparative study
Ivanyushko-Nazarko, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Iyer, 2010	Less than 5 patients per treatment arm or non-comparative study
Iyer, 2010	Less than 5 patients per treatment arm or non-comparative study
Iyer, 2014	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Iyer, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Iyer, 2014	Less than 5 patients per treatment arm or non-comparative study
Jabbour, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Jackson, 2020	Study not peer-reviewed (e.g., conference abstract)
Jain, 2020	Less than 5 patients per treatment arm or non-comparative study
Jain, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Janeth, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Jantararoungtong, 2009	Other reasons (e.g., duplicate, non-empirical research article)
Jatana, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Jayanthi, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Jayaraman, 2020	Study not peer-reviewed (e.g., conference abstract)
Jeung, 2010	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Jha, 2018	Less than 5 patients per treatment arm or non-comparative study
Ji, 2020	Study not peer-reviewed (e.g., conference abstract)
Jin, 2021	Less than 5 patients per treatment arm or non-comparative study
Jovanovic, 2021	Less than 5 patients per treatment arm or non-comparative study

Kadhim, 2021	Less than 5 patients per treatment arm or non-comparative study
Kaido, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Kaido, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Kakourou, 1997	Other reasons (e.g., duplicate, non-empirical research article)
Kamaliah, 1998	Diagnosis inadequately described / cases of differential diagnoses included
Kang, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Kang, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Kang, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Kannabiran, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Kano, 2007	Other reasons (e.g., duplicate, non-empirical research article)
Kanus, 1993	Less than 5 patients per treatment arm or non-comparative study
Kanwar, 2004	Other reasons (e.g., duplicate, non-empirical research article)
Kara, 2019	Less than 5 patients per treatment arm or non-comparative study
Kara, 2020	Less than 5 patients per treatment arm or non-comparative study
Kardaun, 2007	Less than 5 patients per treatment arm or non-comparative study
Kasemsarn, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Katilov, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Katilov, 2019	Study not peer-reviewed (e.g., conference abstract)
Kaufman, 2001	Other reasons (e.g., duplicate, non-empirical research article)
Kelemen, 1995	Investigated treatment not pertinent to German context
Khakimova, 2020	Less than 5 patients per treatment arm or non-comparative study
Kheirkhah, 2013	Less than 5 patients per treatment arm or non-comparative study
Kherlopian, 2022	Less than 5 patients per treatment arm or non-comparative study
Khoo, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Kiguba, 2018	Other reasons (e.g., duplicate, non-empirical research article)

Kim, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Kim, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Kim, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Kim, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Kim, 2012	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Kim, 2004	Other reasons (e.g., duplicate, non-empirical research article)
Kim, 2013	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Kim, 2002	Other reasons (e.g., duplicate, non-empirical research article)
Kim, 2018	Less than 5 patients per treatment arm or non-comparative study
Kittipibul, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Klaewsongkram, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Klama-Baryla, 2018	Less than 5 patients per treatment arm or non-comparative study
Koduri, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Koizumi, 2001	Less than 5 patients per treatment arm or non-comparative study
Komatsu-Fujii, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Kompella, 2002	Less than 5 patients per treatment arm or non-comparative study
Krajewski, 2019	Less than 5 patients per treatment arm or non-comparative study
Krysik, 2022	Less than 5 patients per treatment arm or non-comparative study
Kuhn-Cordova, 2007	Less than 5 patients per treatment arm or non-comparative study
Kumar, 2021	Less than 5 patients per treatment arm or non-comparative study
Kunimi, 2011	Less than 5 patients per treatment arm or non-comparative study
Kuntoji, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Kura, 2001	Less than 5 patients per treatment arm or non-comparative study
Kurle, 2018	Other reasons (e.g., duplicate, non-empirical research article)

Kwan, 2021	Study not peer-reviewed (e.g., conference abstract)
Laguna, 2006	Less than 5 patients per treatment arm or non-comparative study
Lalevee, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lalevee, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Lalosevic, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lam, 2004	Less than 5 patients per treatment arm or non-comparative study
Lamireau, 2001	Other reasons (e.g., duplicate, non-empirical research article)
Latha, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Lee, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Lee, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Lee, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Lee, 2017	Baseline characteristics associated with outcome significantly different between intervention groups
Lee, 2013	Less than 5 patients per treatment arm or non-comparative study
Lee, 2010	Other reasons (e.g., duplicate, non-empirical research article)
Lee, 2010	Other reasons (e.g., duplicate, non-empirical research article)
Lee, 2005	Other reasons (e.g., duplicate, non-empirical research article)
Lee, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lee, 2013	Less than 5 patients per treatment arm or non-comparative study
Lee, 2013	Less than 5 patients per treatment arm or non-comparative study
Leenutaphong, 1993	Less than 5 patients per treatment arm or non-comparative study
Lefaucheur, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lehloenya, 2019	Less than 5 patients per treatment arm or non-comparative study
Lehloenya, 2011	Less than 5 patients per treatment arm or non-comparative study

Lehrer-Bell, 1998	Less than 5 patients per treatment arm or non-comparative study
Lekhanont, 2019	Less than 5 patients per treatment arm or non-comparative study
Leung, 2019	Study not peer-reviewed (e.g., conference abstract)
Levi, 2009	Other reasons (e.g., duplicate, non-empirical research article)
Li, 2017	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Li, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Li, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Li, 2009	Less than 5 patients per treatment arm or non-comparative study
Liao, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Liccioli, 2021	Less than 5 patients per treatment arm or non-comparative study
Liccioli, 2020	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lim, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Limpawattana, 2014	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lin, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lin, 2014	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Ling, 2016	Study not peer-reviewed (e.g., conference abstract)
Lipovy, 2017	Less than 5 patients per treatment arm or non-comparative study
Lipovy, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lissia, 2005	Less than 5 patients per treatment arm or non-comparative study
Liu, 2001	Other reasons (e.g., duplicate, non-empirical research article)
Liu, 2008	Less than 5 patients per treatment arm or non-comparative study
Liu, 2012	Study not peer-reviewed (e.g., conference abstract)

Liu, 2016	Less than 5 patients per treatment arm or non-comparative study
Loh, 1998	Less than 5 patients per treatment arm or non-comparative study
Long, 2015	Study not peer-reviewed (e.g., conference abstract)
Loo, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Lopez-Garcia, 2014	Less than 5 patients per treatment arm or non-comparative study
Ma, 2021	Less than 5 patients per treatment arm or non-comparative study
Ma, 2015	Study not peer-reviewed (e.g., conference abstract)
Ma, 2016	Less than 5 patients per treatment arm or non-comparative study
Ma, 2021	Less than 5 patients per treatment arm or non-comparative study
Ma, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Machado, 2010	Study not peer-reviewed (e.g., conference abstract)
Maenthaisong, 2014	Study not peer-reviewed (e.g., conference abstract)
Maggio, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Magina, 2003	Other reasons (e.g., duplicate, non-empirical research article)
Mahar, 2014	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Mahar, 2013	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Mahar, 2015	Less than 5 patients per treatment arm or non-comparative study
Mame Thierno, 2001	Other reasons (e.g., duplicate, non-empirical research article)
Mamishi, 2009	Less than 5 patients per treatment arm or non-comparative study
Mangla, 2005	Less than 5 patients per treatment arm or non-comparative study
Manivannan, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Mannor, 1994	Less than 5 patients per treatment arm or non-comparative study
Manriquez, 2016	Other reasons (e.g., duplicate, non-empirical research article)

Manvi, 2022	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Manzini, 2016	Less than 5 patients per treatment arm or non-comparative study
Maqsood, 2021	Less than 5 patients per treatment arm or non-comparative study
Marandiuc, 2014	Less than 5 patients per treatment arm or non-comparative study
Martins, 2019	Study not peer-reviewed (e.g., conference abstract)
Matsuyama, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Matvieiev, 2013	Other reasons (e.g., duplicate, non-empirical research article)
McCullough, 2017	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
McEnery-Stonelake, 2014	Study not peer-reviewed (e.g., conference abstract)
McGee, 1998	Less than 5 patients per treatment arm or non-comparative study
Medeiros, 2020	Less than 5 patients per treatment arm or non-comparative study
Medic, 2013	Less than 5 patients per treatment arm or non-comparative study
Mehregan, 2016	Less than 5 patients per treatment arm or non-comparative study
Meneux, 1997	Other reasons (e.g., duplicate, non-empirical research article)
Meng Yu, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Metry, 2003	Less than 5 patients per treatment arm or non-comparative study
Meyer, 2009	Less than 5 patients per treatment arm or non-comparative study
Micheletti, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Mieno, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Mifsud, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Miliszewski, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Miller, 2021	Less than 5 patients per treatment arm or non-comparative study
Mireskandari, 2009	Study not peer-reviewed (e.g., conference abstract)

Mittal, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Mittal, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Mittmann, 2004	Other reasons (e.g., duplicate, non-empirical research article)
Mockenhaupt, 2003	Other reasons (e.g., duplicate, non-empirical research article)
Mockenhaupt, 2008	Other reasons (e.g., duplicate, non-empirical research article)
Modi, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Mohanty, 2017	Baseline characteristics associated with outcome significantly different between intervention groups
Mokhtari, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Molgo, 2009	Less than 5 patients per treatment arm or non-comparative study
Moniz, 2011	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Monteiro, 2017	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Moodie, 2012	Study not peer-reviewed (e.g., conference abstract)
Moon, 2022	Less than 5 patients per treatment arm or non-comparative study
Morici, 2000	Less than 5 patients per treatment arm or non-comparative study
Morita, 2019	Investigated treatment not pertinent to German context
Mortazavi, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Mortazavi, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Mouafik, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Moussala, 2000	Other reasons (e.g., duplicate, non-empirical research article)
Moutaouakkil, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Movahedan, 2017	Less than 5 patients per treatment arm or non-comparative study
Murata, 2008	Less than 5 patients per treatment arm or non-comparative study
Murphy, 1997	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS

Nakae, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Napoli, 2006	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Naveen, 2013	Less than 5 patients per treatment arm or non-comparative study
Neal, 2016	Study not peer-reviewed (e.g., conference abstract)
Neff, 2005	Less than 5 patients per treatment arm or non-comparative study
Van Nguyen, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Nizamoglu, 2018	Less than 5 patients per treatment arm or non-comparative study
Noe, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Noel, 2004	Other reasons (e.g., duplicate, non-empirical research article)
Nomura, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Nouri, 2001	Less than 5 patients per treatment arm or non-comparative study
Nowsheen, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Oen, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Oh, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Olson, 2017	Less than 5 patients per treatment arm or non-comparative study
Olson, 2015	Less than 5 patients per treatment arm or non-comparative study
Olteanu, 2021	Less than 5 patients per treatment arm or non-comparative study
Olteanu, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Ong, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Ong, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Ota, 2022	Less than 5 patients per treatment arm or non-comparative study
Ozkaya, 2018	Less than 5 patients per treatment arm or non-comparative study

Paipool, 2015	Less than 5 patients per treatment arm or non-comparative study
Palappallil, 2017	Less than 5 patients per treatment arm or non-comparative study
Palmares, 1993	Less than 5 patients per treatment arm or non-comparative study
Palmieri, 2002	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Papp, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Paquet, 2010	Less than 5 patients per treatment arm or non-comparative study
Paquet, 2005	Less than 5 patients per treatment arm or non-comparative study
Paquet, 2014	Investigated treatment not pertinent to German context
Paquet, 2000	Other reasons (e.g., duplicate, non-empirical research article)
Paradisi, 2014	Less than 5 patients per treatment arm or non-comparative study
Paradisi, 2020	Less than 5 patients per treatment arm or non-comparative study
Paret, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Parihar, 2017	Less than 5 patients per treatment arm or non-comparative study
Park, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Park, 2012	Less than 5 patients per treatment arm or non-comparative study
Park, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Park, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Pasic, 2006	Less than 5 patients per treatment arm or non-comparative study
Pasricha, 1996	Less than 5 patients per treatment arm or non-comparative study
Patterson, 1994	Less than 5 patients per treatment arm or non-comparative study
Perello, 2014	Less than 5 patients per treatment arm or non-comparative study
Perwitasari, 2021	Less than 5 patients per treatment arm or non-comparative study
Pham, 2018	Other reasons (e.g., duplicate, non-empirical research article)

Pham, 2019	Baseline characteristics associated with outcome significantly different between intervention groups
Phasukkijwatana, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Pinheiro, 2013	Investigated treatment not pertinent to German context
Pinna, 2017	Less than 5 patients per treatment arm or non-comparative study
Pitche, 2005	Other reasons (e.g., duplicate, non-empirical research article)
Poggiali, 2010	Less than 5 patients per treatment arm or non-comparative study
Polak, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Porro, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Power, 1995	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Prabhasawat, 2000	Less than 5 patients per treatment arm or non-comparative study
Prabhasawat, 2013	Less than 5 patients per treatment arm or non-comparative study
Pradeep, 2022	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Prins, 2003	Less than 5 patients per treatment arm or non-comparative study
Prins, 2003	Less than 5 patients per treatment arm or non-comparative study
Pujari, 2011	Less than 5 patients per treatment arm or non-comparative study
Punrin, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Pushker, 2000	Less than 5 patients per treatment arm or non-comparative study
Qayoom, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Quirke, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Radenkova-Saev, 2022	Less than 5 patients per treatment arm or non-comparative study
Radford, 2012	Less than 5 patients per treatment arm or non-comparative study
Rahman, 1997	Other reasons (e.g., duplicate, non-empirical research article)
Rajaratnam, 2010	Less than 5 patients per treatment arm or non-comparative study

Raksha, 2008	Other reasons (e.g., duplicate, non-empirical research article)
Ramsali, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Rapuano, 2006	Other reasons (e.g., duplicate, non-empirical research article)
Rathi, 2017	Less than 5 patients per treatment arm or non-comparative study
Raucci, 2013	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Reed, 2019	Less than 5 patients per treatment arm or non-comparative study
Rhodes, 1999	Other reasons (e.g., duplicate, non-empirical research article)
Rijal, 2009	Less than 5 patients per treatment arm or non-comparative study
Ripa, 2020	Less than 5 patients per treatment arm or non-comparative study
Rishi, 2022	Less than 5 patients per treatment arm or non-comparative study
Rizzo, 2015	Less than 5 patients per treatment arm or non-comparative study
Rodriguez, 2017	Less than 5 patients per treatment arm or non-comparative study
Rodriguez-Martin, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Rodriguez-Martin, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Rogers, 2016	Study not peer-reviewed (e.g., conference abstract)
Rogers, 2017	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Rojas Mejia, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Romanelli, 2008	Less than 5 patients per treatment arm or non-comparative study
Roongpisuthipong, 2014	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Rootman, 2015	Less than 5 patients per treatment arm or non-comparative study
Rosenthal, 2000	Less than 5 patients per treatment arm or non-comparative study
Rosli, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Ross, 2011	Less than 5 patients per treatment arm or non-comparative study

Roujeau, 1995	Other reasons (e.g., duplicate, non-empirical research article)
Roy, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Roy, 2020	Less than 5 patients per treatment arm or non-comparative study
Rusek, 2012	Less than 5 patients per treatment arm or non-comparative study
Rzany, 1995	Other reasons (e.g., duplicate, non-empirical research article)
Rzany, 1994	Other reasons (e.g., duplicate, non-empirical research article)
Sadek, 2021	Other reasons (e.g., duplicate, non-empirical research article)
Saeed, 2017	Study not peer-reviewed (e.g., conference abstract)
Saida, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Saini, 2022	Less than 5 patients per treatment arm or non-comparative study
Saito, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Saka, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Saka, 2010	Other reasons (e.g., duplicate, non-empirical research article)
Sakamoto, 2017	Less than 5 patients per treatment arm or non-comparative study
Salvo, 2007	Other reasons (e.g., duplicate, non-empirical research article)
Sangasapasviliya, 2010	Other reasons (e.g., duplicate, non-empirical research article)
Sant' Anna, 2012	Less than 5 patients per treatment arm or non-comparative study
Santos, 2005	Less than 5 patients per treatment arm or non-comparative study
Saoji, 2020	Less than 5 patients per treatment arm or non-comparative study
Saraogi, 2016	Study not peer-reviewed (e.g., conference abstract)
Sasidharanpillai, 2015	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Sato, 2018	Less than 5 patients per treatment arm or non-comparative study
Sawicki, 2013	Less than 5 patients per treatment arm or non-comparative study
Schmidt, 2021	Less than 5 patients per treatment arm or non-comparative study
Schmidt-Westhausen, 1998	Less than 5 patients per treatment arm or non-comparative study

Schulz, 2000	Less than 5 patients per treatment arm or non-comparative study
Schulze Schwering, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Sehgal, 2003	Other reasons (e.g., duplicate, non-empirical research article)
Serrano, 2018	Less than 5 patients per treatment arm or non-comparative study
Sethuraman, 2012	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Shah, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Shammas, 2010	Less than 5 patients per treatment arm or non-comparative study
Shanbhag, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Shanbhag, 2020	Less than 5 patients per treatment arm or non-comparative study
Shanbhag, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Sharma, 2016	Less than 5 patients per treatment arm or non-comparative study
Sharma, Venugopal, Singhal, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Sharma, Venugopal, Maharana, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Sharma, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Sharma, 1995	Less than 5 patients per treatment arm or non-comparative study
Sharma, 2001	Other reasons (e.g., duplicate, non-empirical research article)
Sharma, 2008	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Sheridan, 1999	Less than 5 patients per treatment arm or non-comparative study
Shimazaki, 2002	Less than 5 patients per treatment arm or non-comparative study
Shimazaki, 2007	Investigated treatment not pertinent to German context
Shimazaki, 2000	Less than 5 patients per treatment arm or non-comparative study
Shrestha, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Sibbald, 2020	No full-text available after authors have been contacted
Sims, 2022	No full-text available after authors have been contacted

Singalavanija, 2011	No full-text available after authors have been contacted
Singh, 2015	No full-text available after authors have been contacted
Singh, 2014	Less than 5 patients per treatment arm or non-comparative study
Siqueira, 2010	Less than 5 patients per treatment arm or non-comparative study
Sivagnanalingam, 2022	No full-text available after authors have been contacted
Sivagourounadin, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Smith, 2015	Less than 5 patients per treatment arm or non-comparative study
Soifer, 2022	No full-text available after authors have been contacted
Solomon, 2002	Less than 5 patients per treatment arm or non-comparative study
Son, J., 2011	No full-text available after authors have been contacted
Son, Y.M., 2011	Other reasons (e.g., duplicate, non-empirical research article)
Sotozono, 2007	Other reasons (e.g., duplicate, non-empirical research article)
Sotozono, 2013	Less than 5 patients per treatment arm or non-comparative study
Sotozono, 2010	Other reasons (e.g., duplicate, non-empirical research article)
Sotozono, 2009	No full-text available after authors have been contacted
Sotozono, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Sotozono, 2014	Less than 5 patients per treatment arm or non-comparative study
Sousa-Pinto, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Speiser, 2013	Less than 5 patients per treatment arm or non-comparative study
Spies, 2001	Less than 5 patients per treatment arm or non-comparative study
Spornraft-Ragaller, 2006	Less than 5 patients per treatment arm or non-comparative study
Srinivas, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Stella, 2001	Less than 5 patients per treatment arm or non-comparative study
Stella, 2007	No full-text available after authors have been contacted
Struzyna, 2022	No full-text available after authors have been contacted

Su, 2014	No full-text available after authors have been contacted
Sudershan, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Sudusinghe, 2018	No full-text available after authors have been contacted
Sukasem, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Sun, 2014	No full-text available after authors have been contacted
Sunaga, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Suthumchai, 2018	Less than 5 patients per treatment arm or non-comparative study
Suwarsa, 2016	Less than 5 patients per treatment arm or non-comparative study
Syed, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Syu, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Szczeklik, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Takehara, 2016	Less than 5 patients per treatment arm or non-comparative study
Talebi, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Tan, 2005	Less than 5 patients per treatment arm or non-comparative study
Tan, 2021	Less than 5 patients per treatment arm or non-comparative study
Tan, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Tan, 2012	No full-text available after authors have been contacted
Tanno, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Tanno, 2013	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Tao, 2013	Less than 5 patients per treatment arm or non-comparative study
Tat, 2017	Less than 5 patients per treatment arm or non-comparative study
Tchanque-Fossuo, 2012	No full-text available after authors have been contacted
Techasatian, 2017	Less than 5 patients per treatment arm or non-comparative study
Teo, 2009	No full-text available after authors have been contacted

Teraki, 2013	Less than 5 patients per treatment arm or non-comparative study
Thakur, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Tham, 2003	Other reasons (e.g., duplicate, non-empirical research article)
Thammakumpee, 2013	No full-text available after authors have been contacted
Thierno, 2001	No full-text available after authors have been contacted
Thiyanaratnam, 2010	Less than 5 patients per treatment arm or non-comparative study
Thong, 2003	Other reasons (e.g., duplicate, non-empirical research article)
Thorel, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Tian, 2022	No full-text available after authors have been contacted
Tian, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Tocco-Tussardi, 2017	Less than 5 patients per treatment arm or non-comparative study
Tougeron-Brousseau, 2009	Less than 5 patients per treatment arm or non-comparative study
Tozer, 2014	Less than 5 patients per treatment arm or non-comparative study
Tran, 2019	No full-text available after authors have been contacted
Tran, 2022	No full-text available after authors have been contacted
Trautmann, 1998	Less than 5 patients per treatment arm or non-comparative study
Trent, 2003	Less than 5 patients per treatment arm or non-comparative study
Trent, 2004	Other reasons (e.g., duplicate, non-empirical research article)
Tripathi, 2000	Less than 5 patients per treatment arm or non-comparative study
Tristani-Firouzi, 2002	Less than 5 patients per treatment arm or non-comparative study
Trivedi, 2017	Less than 5 patients per treatment arm or non-comparative study
Tsai, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Tseng, 2017	Less than 5 patients per treatment arm or non-comparative study
Tseng, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Tsubota, 1999	Less than 5 patients per treatment arm or non-comparative study

Turk, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Ueta, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Ueta, H., 2015	Other reasons (e.g., duplicate, non-empirical research article)
Ueta, 2007	Other reasons (e.g., duplicate, non-empirical research article)
Ueta, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Ueta, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Ueta, K., 2015	Other reasons (e.g., duplicate, non-empirical research article)
Ugburo, 2008	Less than 5 patients per treatment arm or non-comparative study
Ukida, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Ukida, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Ukponmwan, 2010	Less than 5 patients per treatment arm or non-comparative study
Valdez, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Valeyrie-Allanore, 2010	Less than 5 patients per treatment arm or non-comparative study
Vassallo, 2021	Less than 5 patients per treatment arm or non-comparative study
Vazirani, 2021	Less than 5 patients per treatment arm or non-comparative study
Venn, 2000	Less than 5 patients per treatment arm or non-comparative study
Venugopal, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Venugopal, 2021	Less than 5 patients per treatment arm or non-comparative study
Verneuil, 2009	Other reasons (e.g., duplicate, non-empirical research article)
Vertieva, 2014	Other reasons (e.g., duplicate, non-empirical research article)
Viard, 1998	Less than 5 patients per treatment arm or non-comparative study
Vinay, 2019	Less than 5 patients per treatment arm or non-comparative study
Wakamatsu, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Wambier, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Wanat, 2009	No full-text available after authors have been contacted

Wang, C.W., 2021	Other reasons (e.g., duplicate, non-empirical research article)
Wang, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Wang, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Wang, L., 2017	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Wang, L.L., 2021	Other reasons (e.g., duplicate, non-empirical research article)
Wang, 2003	Single case report
Wang, F., 2017	Other reasons (e.g., duplicate, non-empirical research article)
Wang, L., 2021	Less than 5 patients per treatment arm or non-comparative study
Wang, S., 2014	Other reasons (e.g., duplicate, non-empirical research article)
Wang, Y.M., 2014	Less than 5 patients per treatment arm or non-comparative study
Wanh, 2009	No full-text available after authors have been contacted
Wasuwanich, 2019	Other reasons (e.g., duplicate, non-empirical research article)
Watanabe, 2011	Other reasons (e.g., duplicate, non-empirical research article)
Watanabe, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Watkins, 2017	Other reasons (e.g., duplicate, non-empirical research article)
Wee, 2015	Less than 5 patients per treatment arm or non-comparative study
Weinand, 2013	Less than 5 patients per treatment arm or non-comparative study
Wester, 2015	Other reasons (e.g., duplicate, non-empirical research article)
Westman, 2017	No full-text available after authors have been contacted
Wetter, 2010	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Williams, 2014	Less than 5 patients per treatment arm or non-comparative study
Wolkenstein, 1996	Other reasons (e.g., duplicate, non-empirical research article)
Wong, 1999	Patient recruitment started in 1985
Worswick, 2020	No full-text available after authors have been contacted
Wu, 2015	Less than 5 patients per treatment arm or non-comparative study

Xia, 2016	Diagnosis inadequately described / cases of differential diagnoses included
Xiang, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Xiang, 2020	No full-text available after authors have been contacted
Xiao, 2013	Other reasons (e.g., duplicate, non-empirical research article)
Xiao, 2014	No full-text available after authors have been contacted
Xu, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Yamada, 2008	Secondary analysis of case reports
Yamane, 2007	Secondary analysis of case reports
Yamane, 2009	Secondary analysis of case reports
Yamane, 2016	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Yang, 2016	Other reasons (e.g., duplicate, non-empirical research article)
Yang, 2011	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Yang, L., 2020	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Yang, 2007	Less than 5 patients per treatment arm or non-comparative study
Yang, F., 2020	Other reasons (e.g., duplicate, non-empirical research article)
Yang, 2012	Other reasons (e.g., duplicate, non-empirical research article)
Yang, 2013	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Yang, 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Yang, 2018	Aggregated reporting of single hospital cases and collected case reports
Yang, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Yang, 2015	Less than 5 patients per treatment arm or non-comparative study
Yarbrough, 1996	Patient recruitment started 1986
Yaytokgil, 2021	Other reasons (e.g., duplicate, non-empirical research article)

Yeung, 2005	Less than 5 patients per treatment arm (taking co-therapy with corticosteroids into account)
Yin, 2019	Less than 5 patients per treatment arm or non-comparative study
Ying, 2001	Less than 5 patients per treatment arm or non-comparative study
Yoon, 2019	Less than 5 patients per treatment arm or non-comparative study
Yoshikawa, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Yoshikawa, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Yu, 2022	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Zajicek, 2012	Less than 5 patients per treatment arm or non-comparative study
Zavala, 2018	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Zhang, A.J.., 2019	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Zhang, C.X., 2019	Less than 5 patients per treatment arm or non-comparative study
Zhang, C, 2019	Less than 5 patients per treatment arm or non-comparative study
Zhang, 2017	Less than 5 patients per treatment arm or non-comparative study
Zhao, 2018	Other reasons (e.g., duplicate, non-empirical research article)
Zhao, 2015	Less than 5 patients per treatment arm or non-comparative study
Zhao, 2009	Less than 5 patients per treatment arm or non-comparative study
Zharnasek, 2016	Less than 5 patients per treatment arm or non-comparative study
Zheng, 2020	Other reasons (e.g., duplicate, non-empirical research article)
Zhou, 1999	Less than 5 patients per treatment arm or non-comparative study
Zhou, 2004	Less than 5 patients per treatment arm or non-comparative study
Ziemer, 2022	Other reasons (e.g., duplicate, non-empirical research article)
Zilliox, 2021	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS
Zilliox, 2020	Baseline characteristics or outcomes not reported or aggregated across interventions or different SCARS

Zouhair, 2002	No full-text available after authors have been contacted; data collection started 1967
Van Zyl, 2014	Other reasons (e.g., duplicate, non-empirical research article)

Search strategies

Guidelines: search strategy for MEDLINE (via Ovid)

Table 3: Guideline search MEDLINE via Ovid, searched on 07.07.2023

1	toxic epidermal necrolysis.ti,ab.
2	stevens johnson syndrome.ti,ab.
3	Lyell's disease.ti,ab.
4	Lyell's syndrome.ti,ab.
5	erythema multiforme.ti,ab.
6	exp Epidermal Necrolysis, Toxic/
7	exp Stevens-Johnson Syndrome/
8	exp Erythema Multiforme/
9	OR/1-8
10	((clinical adj3 pathway) or (clinical adj3 pathways) or (practice adj3 parameter) or (practice adj3 parameters)).ti,ab,kw. or algorithms/ or care pathway.ti,ab,kw. or care pathways.ti,ab,kw. or clinical protocols/ or Consensus/ or Consensus Development Conference.pt. or Consensus Development Conference, NIH.pt. or Consensus Development Conferences as Topic/ or Consensus Development Conferences, NIH as Topic/ or critical pathway/ or guidance.ti,ab. or guideline*.ti. or guidelines as topic/ or practice guidelines as topic/ or Health Planning Guidelines/ or practice guideline/
11	9 AND 10

Table 4: Systematic review search MEDLINE via Ovid, searched on 07.07.2023

1	Meta-Analysis as Topic/
2	meta analy$.tw.
3	metaanaly$.tw.
4	Meta-Analysis/
5	(systematic adj (review$1 or overview$1)).tw.
6	exp Review Literature as Topic/
7	or/1-6

8	cochrane.ab.
9	embase.ab.
10	(psychlit or psyclit).ab.
11	(psychinfo or psycinfo).ab.
12	(cinahl or cinhal).ab.
13	science citation index.ab.
14	bids.ab.
15	cancerlit.ab.
16	or/8-15
17	reference list$.ab.
18	bibliograph$.ab.
19	hand-search$.ab.
20	relevant journals.ab.
21	manual search$.ab.
22	or/17-21
23	selection criteria.ab.
24	data extraction.ab.
25	23 or 24
26	Review/
27	25 and 26
28	Comment/
29	Letter/
30	Editorial/
31	animal/
32	human/
33	31 not (31 and 32)
34	or/28-30,33
35	7 or 16 or 22 or 27
36	35 not 34
37	toxic epidermal necrolysis.ti,ab.

38	stevens johnson syndrome.ti,ab.
39	Lyell's disease.ti,ab.
40	Lyell's syndrome.ti,ab.
41	erythema multiforme.ti,ab.
42	exp Epidermal Necrolysis, Toxic/
43	exp Stevens-Johnson Syndrome/
44	exp Erythema Multiforme/
45	OR/37-44
46	36 AND 45

Table 5: Primary study search MEDLINE (1993 onwards), searched on 05.03.2023

1	"toxic epidermal necrolys*".ti,ab,kw.
2	(toxic and epidermal and necrolys*).ti,ab,kw.
3	"steven* johnson syndrom*".mp.
4	"Steven*-Johnson-Syndrom*".ti,ab,kw.
5	"Steven* Johnson*".ti,ab,kw.
6	"Stevens-Johnson-Syndrom".ti,ab,kw.
7	"Steven*Johnson*Syndrom*".ti,ab,kw.
8	Lyell*.ti,ab,kw.
9	SJS.ti,ab,kw.
10	(epiderm* adj10 necro*).tw.
11	exp Stevens-Johnson Syndrome/
12	or/1-11
13	systemic immun* therap$.mp.
14	STEROIDS/
15	(steroid$ or corticosteroid$).mp.
16	Adrenal Cortex Hormones/
17	corticoid$.mp.
18	Glucocorticoids/
19	(glucocorticosteroid$ or glucocorticoid$).mp.

20	dexamethasone.mp. or DEXAMETHASONE/
21	prednisolone.mp. or PREDNISOLONE/
22	METHYLPREDNISOLONE/ or methylprednisolone.mp.
23	C#closporin*.mp. or CYCLOSPORINE/
24	Immunoglobulins/
25	(immunoglobulin$ or IVIG).mp.
26	etanercept.mp. or ETANERCEPT/
27	Enbrel.mp.
28	Tumor Necrosis Factor-alpha/
29	anti-tumo?r necrosis factor$.mp.
30	anti-tnf.mp.
31	TNF-alpha inhibitor$.mp.
32	anti-interleukin$.mp.
33	infliximab.mp. or INFLIXIMAB/
34	remicade.mp.
35	exp PLATELETPHERESIS/
36	Plateletpheres$.mp.
37	(platelet and rich and pheres$).mp.
38	PLASMAPHERESIS/
39	plasmapheres$.mp.
40	THALIDOMIDE/
41	Thalidomid$.mp.
42	ACETYLCYSTEINE/
43	Acetylcystein$.mp.
44	N?acetylcystein$.mp.
45	NAC.mp.
46	cyclophosphamide.mp. or CYCLOPHOSPHAMIDE/
47	granulocyte stimulating factor$.mp.
48	hemoperfusion.mp. or HEMOPERFUSION/
49	Azathioprine/

50	azathiop*.mp.
51	Adalimumab/
52	Adalimumab.mp.
53	Golimumab.mp.
54	Certolizumab Pegol/
55	Certolizumab.mp.
56	debrid*.mp.
57	Anti-Infective Agents, Local/
58	Silver Nitrate/
59	(silver* adj3 nitr?t*).mp.
60	Silver Sulfadiazine/
61	(silver* adj3 sulfadiazin*).mp
62	aquacel*.mp.
63	flamazine*.mp. and dressing*.mp.
64	(skin* adj3 allograft*).mp.
65	(skin* adj3 xenograft*).mp.
66	skin* coverage*.mp.
67	biobrane*.mp.
68	suprathel*.mp.
69	epigard*.mp.
70	Epicite.mp.
71	Skin, Artificial/
72	Skin Transplantation/
73	biological dressing.mp.
74	Amnion/
75	Amnio* membran*.mp.
76	skin transplantation.mp.
77	debrid*.mp.
78	Anti-Infective Agents, Local/
79	Silver Nitrate/

80	(silver* adj3 nitr?t*).mp.
81	Lubricant Eye Drops.mp.
82	Restasis.mp.
83	Ikervis.mp.
84	Anti-bacterial agents/ and ophthalmic solutions/tu
85	Symblephar*.mp.
86	Ocular shell*.mp.
87	exp serum/
88	(autologous adj2 serum$).tw.
89	Eyelid Diseases/
90	Tretinoin/
91	Vagina/ and Dilatation/
92	Psychotherapy/
93	Anti-bacterial agents/
94	or/13-93
95	12 and 94
96	95 and 1993:current.(sa_year).

Table 6: Primary study search Embase (1993 onwards), searched on 05.03.2023

Global Search	
1	"toxic epidermal necrolys*".ti,ab,kw.
2	(toxic and epidermal and necrolys*).ti,ab,kw.
3	"steven* johnson syndrom*".mp.
4	"Steven*-Johnson-Syndrom*".ti,ab,kw.
5	"Steven* Johnson*".ti,ab,kw.
6	"Stevens-Johnson-Syndrom".ti,ab,kw.
7	"Steven*Johnson*Syndrom*".ti,ab,kw.
8	Lyell*.ti,ab,kw.
9	SJS.ti,ab,kw.
10	(epiderm* adj10 necro*).tw.
11	exp Stevens-Johnson Syndrome/
12	or/1-11
13	systemic immun* therap$.mp.
14	STEROIDS/
15	(steroid$ or corticosteroid$).mp.
16	Adrenal Cortex Hormones/
17	corticoid$.mp.
18	Glucocorticoids/
19	(glucocorticosteroid$ or glucocorticoid$).mp.
20	dexamethasone.mp. or DEXAMETHASONE/
21	prednisolone.mp. or PREDNISOLONE/
22	METHYLPREDNISOLONE/ or methylprednisolone.mp.
23	C#closporin*.mp. or CYCLOSPORINE/
24	Immunoglobulins/
25	(immunoglobulin$ or IVIG).mp.
26	etanercept.mp. or ETANERCEPT/
27	Enbrel.mp.
28	Tumor Necrosis Factor-alpha/

29	anti-tumo?r necrosis factor$.mp.
30	anti-tnf.mp.
31	TNF-alpha inhibitor$.mp.
32	anti-interleukin$.mp.
33	infliximab.mp. or INFLIXIMAB/
34	remicade.mp.
35	exp PLATELETPHERESIS/
36	Plateletpheres$.mp.
37	(platelet and rich and pheres$).mp.
38	PLASMAPHERESIS/
39	plasmapheres$.mp.
40	THALIDOMIDE/
41	Thalidomid$.mp.
42	ACETYLCYSTEINE/
43	Acetylcystein$.mp.
44	N?acetylcystein$.mp.
45	NAC.mp.
46	cyclophosphamide.mp. or CYCLOPHOSPHAMIDE/
47	granulocyte stimulating factor$.mp.
48	hemoperfusion.mp. or HEMOPERFUSION/
49	Azathioprine/
50	azathiop*.mp.
51	Adalimumab/
52	Adalimumab.mp.
53	Golimumab.mp.
54	Certolizumab Pegol/
55	Certolizumab.mp.
56	debrid*.mp.
57	Anti-Infective Agents, Local/
58	Silver Nitrate/

59	(silver* adj3 nitr?t*).mp.
60	Silver Sulfadiazine/
61	(silver* adj3 sulfadiazin*).mp
62	aquacel*.mp.
63	flamazine*.mp. and dressing*.mp.
64	(skin* adj3 allograft*).mp.
65	(skin* adj3 xenograft*).mp.
66	skin* coverage*.mp.
67	biobrane*.mp.
68	suprathel*.mp.
69	epigard*.mp.
70	Epicite.mp.
71	Skin, Artificial/
72	Skin Transplantation/
73	biological dressing.mp.
74	Amnion/
75	Amnio* membran*.mp.
76	skin transplantation.mp.
77	debrid*.mp.
78	Anti-Infective Agents, Local/
79	Silver Nitrate/
80	(silver* adj3 nitr?t*).mp.
81	Lubricant Eye Drops.mp.
82	Restasis.mp.
83	Ikervis.mp.
84	Anti-bacterial agents/ and ophthalmic solutions/
85	Symblephar*.mp.
86	Ocular shell*.mp.
87	exp serum/
88	(autologous adj2 serum$).tw.

89	Eyelid Diseases/
90	Tretinoin/
91	Vagina/ and Dilatation/
92	Psychotherapy/
93	Anti-bacterial agents/
94	or/13-93
95	12 and 94
96	95 and 1993:current.(sa_year).

Table 7: Primary study search (psychotherapy) MEDLINE (1993 onwards), searched on 01.13.2023 (adapted from O’Reilly et al., 2022)

1	"toxic epidermal necrolys*".ti,ab,kw.
2	(toxic and epidermal and necrolys*).ti,ab,kw.
3	"steven* johnson syndrom*".mp.
4	"Steven*-Johnson-Syndrom*".ti,ab,kw.
5	"Steven* Johnson*".ti,ab,kw.
6	"Stevens-Johnson-Syndrom".ti,ab,kw.
7	"Steven*Johnson*Syndrom*".ti,ab,kw.
8	Lyell*.ti,ab,kw.
9	SJS.ti,ab,kw.
10	(epiderm* adj10 necro*).tw.
11	exp Stevens-Johnson Syndrome/
12	(psych* adj3 (care or manag* or intervention* or strateg* or technique* or approach or approaches)).mp OR (psych* adj3 (support or nursing or nurse*)).mp OR (psych* adj3 (accompaniment or accompagnement or treatment or treating)).mp OR (psychotherap* adj3 (care or manag* or intervention* or strateg* or technique* or approach or approaches)).mp OR (psychotherap* adj3 (support or nursing or nurse*)).mp OR (psychotherap* adj3 (accompaniment or accompagnement or treatment or treating)).mp
13	(counselling or counsellor).mp OR ("patient centered nursing" OR "patient centred nursing").mp OR ("patient centered care" OR "patient centred care").mp
14	("affirmative therapy" or "affirmative therapies" OR "cognitive therapy" or "cognitive therapies" OR "emotion focused therapy" or "emotion focused therapies").mp OR "emotional support".mp OR diary adj1 writaring.mp OR distract* adj1 technique*.mp OR (meditation or mindfulness or hypnosis).mp

15	(anxiety adj2 (manag* or intervention* or support or technique*)).mp OR (ptsd adj2 (manag* or intervention* or support or technique*)).mp OR ("post traumatic stress disorder" adj2 (manag* or intervention* or support or technique*)).mp
16	("self esteem" adj2 (manag* or intervention* or support or technique*)).mp OR ("self-esteem" adj2 (manag* or intervention* or support or technique*)).mp OR ("body image" adj2 (manag* or intervention* or support or technique*)).mp OR (panic adj2 (manag* or intervention* or support or technique*)).mp OR (stress adj2 (manag* or intervention* or support or technique*)).mp OR (fear adj2 (manag* or intervention* or support or technique*)).mp
17	(premorbid adj2 (manag* or intervention* or support or technique*)).mp OR ("pre-morbid" adj2 (manag* or intervention* or support or technique*)).mp OR ("pre morbid" adj2 (manag* or intervention* or support or technique*)).mp
18	or/1-11
19	or/12-17
20	18 AND 19

Table 8: Primary study search (psychotherapy) Embase (1993 onwards), searched on 01.13.2023 (adapted from O'Reilly et al., 2022)

1	"toxic epidermal necrolys*,kw.".tw.
2	(toxic AND epidermal AND necrolys*).tw. ,kw.
3	"steven* johnson syndrom*".mp.
4	Steven*-Johnson-Syndrom*,kw..tw.
5	"Steven* Johnson*,kw.".tw.
6	Stevens-Johnson-Syndrom,kw..tw.
7	Steven*Johnson*Syndrom*,kw..tw.
8	Lyell*,kw..tw.
9	SJS,kw..tw.
10	(epiderm* ADJ10 necro*).tw.
11	exp "Stevens-Johnson Syndrome"/
12	(psych* ADJ3 (care OR manag* OR intervention* OR strateg* OR technique* OR approach OR approaches)).mp. OR (psych* ADJ3 (support OR nursing OR nurse*)).mp. OR (psych* ADJ3 (accompaniment OR accompagnement OR treatment OR treating)).mp. OR (psychotherap* ADJ3 (care OR manag* OR intervention* OR strateg* OR technique* OR approach OR approaches)).mp. OR (psychotherap* ADJ3 (support OR nursing OR nurse*)).mp. OR (psychotherap* ADJ3 (accompaniment OR accompagnement OR treatment OR treating)).mp.

13	(counselling OR counsellor).mp. OR ("patient centered nursing" OR "patient centred nursing").mp. OR ("patient centered care" OR "patient centred care").mp.
14	("affirmative therapy" OR "affirmative therapies" OR "cognitive therapy" OR "cognitive therapies" OR "emotion focused therapy" OR "emotion focused therapies").mp. OR "emotional support".mp. OR diary ADJ1 writaring.mp. OR distract* ADJ1 technique*.mp. OR (meditation OR mindfulness OR hypnosis).mp.
15	(anxiety ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR (ptsd ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR ("post traumatic stress disorder" ADJ2 (manag* OR intervention* OR support OR technique*)).mp.
16	("self esteem" ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR (self-esteem ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR ("body image" ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR (panic ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR (stress ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR (fear ADJ2 (manag* OR intervention* OR support OR technique*)).mp.
17	(premorbid ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR (pre-morbid ADJ2 (manag* OR intervention* OR support OR technique*)).mp. OR ("pre morbid" ADJ2 (manag* OR intervention* OR support OR technique*)).mp.
18	OR /1-11
19	OR /12-17
20	(OR /1-11) AND (OR /12-17)

Results of interviews with EN-survivors / relatives

Table 9: Recovery periods at time of interview and age of participants

Age / Time after reaction	<25	25-59	>59
<3 years	2 survivors	2 survivors, 4 family members	2 survivors
3-5 years	-	1 survivor, 1 family member	-
>5 years	1 survivor	1 survivor	-

Table 10: Synopsis of main findings

Initial contact / diagnosis	Acute phase	Postacute / follow-up care	Impact on quality of life / psychological impact	General information flow
Delayed diagnosis and transfer to intensive care unit (ICU) / burn unit	Deficits in physician-patient communication (inadequate language, jargon)	Limited support for eye conditions in follow-up rehabilitation	Psychological distress due to pain-related trauma	Information overwhelming / not individualized / problem-oriented, inappropriately complex
Incomplete communication of necessary treatment steps	Dampened state of consciousness in the first weeks makes it difficult to process information	Time of follow-up rehabilitation not always optimal, spatial distance to relatives perceived as stressful	Lack of psychological support of family members (sometimes more emotionally affected than patients due to clearer perception of critical phase)	Increased need for safety regarding newly prescribed medication

Lack of early ophthalmological involvement	Disturbed sleep; unnecessarily restrictive supply of sleep medication	No measures against cognitive impact of disease (e.g., concentration / memory training)	Lack of understanding of the exceptional character of the disease in psychotherapists (e.g., “just an allergy”)	Difficulties in finding SJS/TEN experts (postacute care)
	Pronounced feeling of shame (bandages as only coverage)		Fear of taking medications also in infection-induced cases	Desire for regular „check-up visits“
	Pain relief of central importance; no clear understanding why certain measures are being taken		Difficulties in communicating the impact of the disease on one’s life; feeling of social alienation	Patients do not feel seen during phone consultations: video consultations desirable
	Inadequate education on prognosis (e.g., presumed hospital discharge)			Need for exchange with other patients

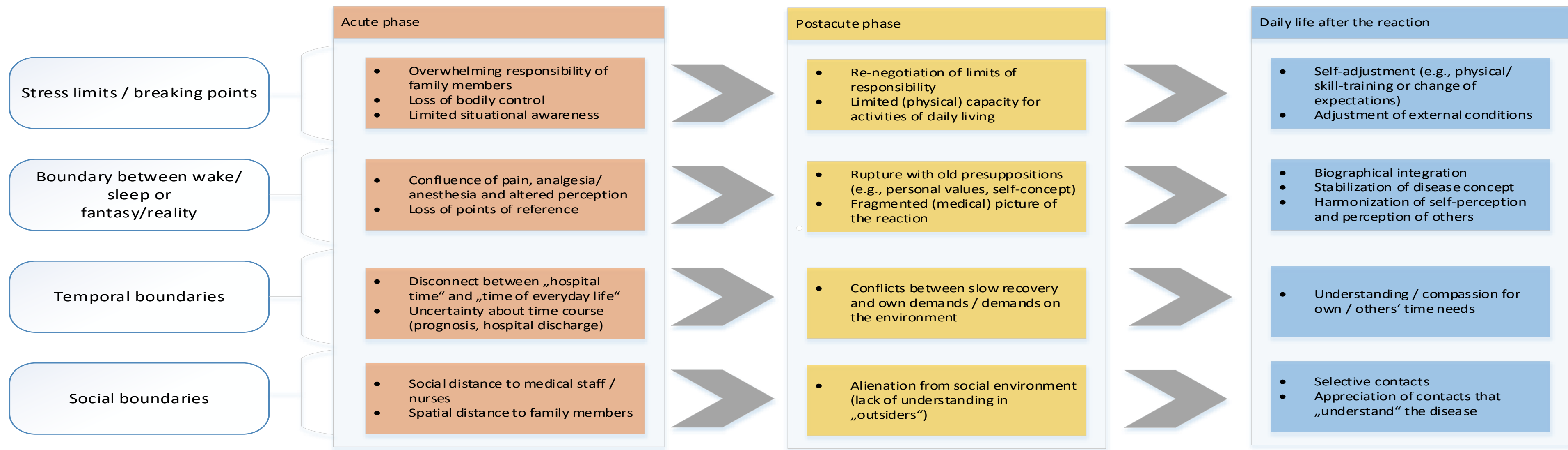

Figure 1: Dimensions of SJS/TEN-induced boundary violations across time

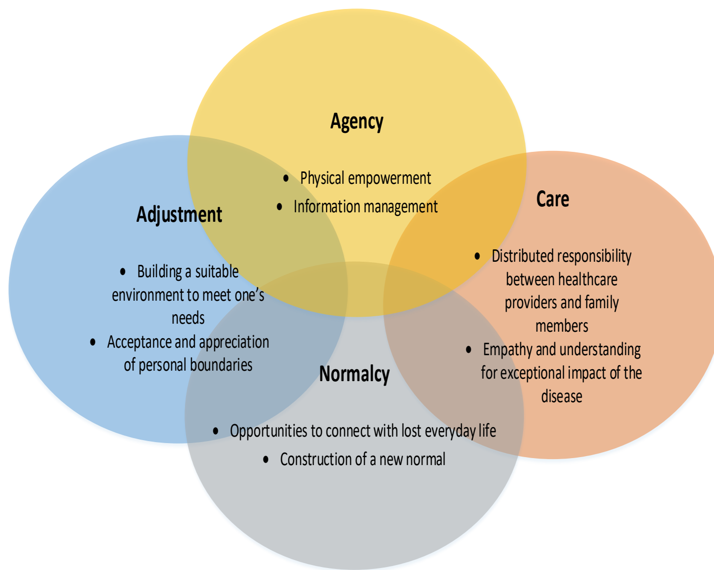

Figure 2: Cross-temporal fields of action in SJS/TEN care

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