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S3 Guideline:

Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V.

# Oxygen Therapy in the Acute Treatment of Adult Patients

Long version 1.0 – June 2021 AWMF registration number: 020 - 021

**Authors:**
Jens Gottlieb
Philipp Capetian
Uwe Hamsen
Uwe Janssens
Christian Karagiannidis
Stefan Kluge
Marco König
Andreas Markewitz
Monika Nothacker
Sabrina Roiter
Susanne Unverzagt
Wolfgang Veit
Thomas Volk
Christian Witt
René Wildenauer
Heinrich Worth
Thomas Fühner

Bundesverband der Organtransplantierten e.V.

DGK. Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V.

DGIIN Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin

DEUTSCHE GESELLSCHAFT FÜR PFLEGEWISSENSCHAFT e.V.

DIVI Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin

DGIM Deutsche Gesellschaft für Innere Medizin

DGAI Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin

Deutsche Gesellschaft für Chirurgie

DBRD Deutscher Berufsverband Rettungsdienst e.V.

DGNI Deutsche Gesellschaft für Neurointensiv- und Notfallmedizin

# Contents

# 1 Introduction

Oxygen (O2) is a drug. In 2015, 14% of over 55,000 hospital patients in the UK were using oxygen. 42% of patients received this supplemental oxygen without a valid prescription (1). Healthcare professionals are often uncertain about the relevance of hypoxemia and little aware of the risks of hyperoxemia. Numerous randomized controlled trials and systematic reviews of the target ranges of oxygen therapy have been published in recent years. For lack of a formal guideline, oxygen is often used rather indiscriminately in acute medicine in Germany, for example, in non-hypoxemic patients presenting with shortness of breath. In addition, oxygen therapy is usually not properly prescribed and documented in writing. Several national guidelines on oxygen therapy for specific conditions are available—with partly diverging recommendations. A German national guideline on supplemental oxygen in acute medicine is therefore overdue.

In contrast to the Guideline for Long-Term Oxygen Therapy, the present guideline uses oxygen saturation as the key target parameter. This approach benefits from providing a common target parameter for both pulse oximetry ($SpO_2$) and blood gas analyses ($SaO_2$). The authors are aware that blood gas analyses predominantly measure the partial pressure of oxygen and that oxygen saturation is only at times derived. In addition, the meaningfulness of oxygen saturation is limited due to the flattening of the oxygen dissociation curve at oxygen saturations > 90%. For practical reasons, the authors decided to use target ranges of oxygen saturation where the lower and upper limits also indicate when supplemental oxygen should be started/discontinued. The guideline development group deliberately refrained from specifying target ranges for specific clinical conditions. This approach takes into account the increasing multimorbidity of patients and serves to improve the practical applicability of the guideline. The validity of these target ranges for relevant and common conditions (e.g., acute coronary syndrome, COVID-19, and neurological conditions) is supported by extensive scientific evidence.

There is currently no clear scientific evidence as to when and how much supplemental oxygen is needed to treat hypoxemia. Relevant for this guideline and the target ranges recommended in it are the points at which, based on current evidence, hypoxemia and hyperoxemia are likely to be harmful to acutely ill patients, and the range within which supplemental oxygen therapy is not harmful and, thus, can be safely used. The oxygen saturation limits indicated in this guideline are recommendations for initiating or escalating oxygen therapy and, if not met, may not be construed as criteria for intubation. The guideline includes 34 evidence-based recommendations in section 3.1.

Jens Gottlieb, Heinrich Worth, Thomas Fühner

# 2 About this guideline

## 2.1 Published by:

Program for National Disease Management Guidelines of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF)

## 2.2 Responsible medical association

German Respiratory Society (DGP)

## 2.3 Funding of the guideline

This guideline was sponsored by the German Respiratory Society (DGP) as part of their guideline program.

## 2.4 Contact

German Respiratory Society
(Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, DGP)
Robert-Koch-Platz 9
10115 Berlin
Tel.: 030-293 62 701
info@pneumologie.de

## 2.5 Citation

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Accessed on: 6/21/2021

## 2.6 Please note

Human medicine is continuously developing. The information and recommendations provided in this guideline can therefore only reflect the state of knowledge at the time of going to press of this guideline. The recommendations provided in this guideline were developed with utmost diligence. In the general interest, readers are asked to report any inconsistencies to the

guideline editorial team. All diagnostic and therapeutic applications remain the responsibility of the user of this guideline. Registered trademarks (protected trade names) are not identified in this guideline. It may therefore not be concluded from the absence of such identification that a trade name is not protected. The guideline as a whole is copyrighted. Any exploitation outside the intended scope requires the consent of the AWMF guideline program. No part of this work may be reproduced in any form without written consent. This applies in particular to the use and exploitation of this guideline in electronic systems, intranets, and on the Internet.

## 2.7 Available guideline documents and implementation

This document is the long version of the S3 Guideline on Oxygen Therapy in the Acute Treatment of Adult Patients. The document can be accessed via the following websites:

- German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin) (https://pneumologie.de/publikationen/leitlinien/)
- AWMF (https://www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- In addition, an English version of this guideline is planned to be published, as are topic-related versions in German journals, and a short version.

In addition to the long version, the following supplementary documents to this guideline are available:

- Disclosures regarding conflicts of interest
- Evidence report
- Guideline-based evidence
- Evaluation of evidence for the recommendations
- Short version

These documents can be accessed in the Appendix (Chapter 12) and/or on the AWMF website.

## 2.8 Coordination & editorial team

- Jens Gottlieb (Hannover)
- Heinrich Worth (Fürth)
- Thomas Fühner (Hannover)

## 2.9 Composition of the guideline development group, medical associations involved, authors

The following medical associations were intended to be included at the time of registering the guideline: German Society of Internal Medicine (DGIM), German Society of Surgery (DGCH), German Society of Medical Intensive Care Medicine and Acute Medicine (DGIIN), German Society of Anesthesiology and Intensive Care Medicine (DGAI), German Society of Neurocritical Care and Acute Medicine (DGNI), German Interdisciplinary Association for Intensive and Emergency Medicine (DIVI), German Cardiac Society (DGK), German Society of Nursing Science (DGP), German College of General Practitioners and Family Physicians

(DEGAM). DEGAM did not assign a representative for lack of resources; all other medical associations were represented.

The German Rescue Service Association (DBRD) and the German Association for Palliative Medicine (DGP) were designated advisors on specific issues. DBRD was represented by one delegate at the consensus meetings. Taking into account the current S3 guideline on palliative care, there was no need to obtain additional advice from the respective medical association.

| Medical associations and organizations involved | Representatives and experts involved |
|---|---|
| Federal Association of Organ Transplant Patients (BDO) | Wolfgang Veit, Marne |
| German Interdisciplinary Association for Intensive and Emergency Medicine (DIVI) | Prof. Dr. med. Andreas Markewitz, Koblenz |
| German Cardiac Society (DGK) | Prof. Dr. med. Uwe Janssens, Eschweiler |
| German Respiratory Society (DGP) | Prof. Dr. med. Jens Gottlieb, Hannover |
| German Respiratory Society (DGP) | Prof. Dr. med. Thomas Fühner, Hannover |
| German Respiratory Society (DGP) | Prof. Dr. med. Christian Witt, Berlin |
| German Society of Medical Intensive Care Medicine and Acute Medicine (DGIIN) | Prof. Dr. med. Stefan Kluge, Hamburg |
| German Society of Neurocritical Care and Acute Medicine (DGNI) | Dr. med. Philipp Capetian, Würzburg |
| German Society of Internal Medicine | Prof. Dr. med. Heinrich Worth, Fürth |
| German Society of Surgery | Dr. med. Uwe Hamsen, Bochum |
| German Society of Surgery | Dr. med. René Wildenauer, Wiesentheid |
| German Society of Medical Intensive Care Medicine and Acute Medicine (DGIIN) | Prof. Dr. med. Christian Karagiannidis, Cologne |
| German Rescue Service Association (DBRD) | Marco König, Lübeck |
| German Society of Nursing Science (DGP) | Sabrina Roiter, Hamburg |

| | |
|---|---|
| German Society of Anesthesiology and Intensive Care Medicine (DGAI) | Prof. Dr. med. Thomas Volk, Homburg/Saar |

Working group members:

| | Panel members/experts involved |
|---|---|
| Working group 1: | Heinrich Worth, Jens Gottlieb |
| Working group 2: | Uwe Janssens, Christian Karagiannidis, Heinrich Worth |
| Working group 3: | Sabrina Roiter, Uwe Hamsen, Christian Witt |
| Working group 4: | Jens Gottlieb, Thomas Fühner, Stefan Kluge |
| Working group 5: | Thomas Fühner, Christian Karagiannidis, Andreas Markewitz, Jens Gottlieb |
| Working group 6: | Sabrina Roiter, Philipp Capetian, René Wildenauer |
| Working group 7: | Thomas Volk, Jens Gottlieb |

Susanne Unverzagt prepared the evidence report, but did not participate in the consensus meetings for the recommendations.

## 2.10 Patient involvement

The guideline was developed with the direct involvement of a patient representative. Wolfgang Veit of the Federal Association of Organ Transplant Patients (BDO) was involved in the guideline development process and participated in the consensus meetings with voting rights.

## 2.11 Methodology support and review of evidence

- Monika Nothacker, MPH (AWMF), Berlin, methodology support
- Susanne Unverzagt, Department of General Medicine, Academic Hospital of Leipzig University, evidence review

The review of evidence included an independent guideline and literature search on the key questions for the guideline in the second half of 2019. The guideline report and the independent evidence report are based on this review (cf. Chapter 11). The guideline search identified 4 guidelines with high-level evidence, 2 of which were considered suitable for answering some of the key questions after being reviewed by the authors. After the independent evidence report had been evaluated by the clinical scientists, it was found that additional relevant studies had been published in the meantime and that some of the key questions were not sufficiently addressed in the evidence report. An independent literature

search and evidence assessment of the recommendations were therefore conducted, and another evidence report was created in the period from November 2020 to February 2021. The most recent literature search for the recommendations was conducted on February 1, 2021.

## 2.12 Abbreviations used in this guideline

| Abbreviation | Explanation |
|---|---|
| ARDS | Acute respiratory distress syndrome |
| BGA | Blood gas analysis |
| BMI | Body mass index |
| $CaO_2$ | Arterial oxygen content |
| CF | Cystic fibrosis |
| CI | Confidence interval |
| CO | Carbon monoxide |
| $CO_2$ | Carbon dioxide |
| COPD | Chronic obstructive pulmonary disease |
| CPAP | Continuous positive airway pressure |
| $DO_2$ | Oxygen delivery |
| $FiO_2$ | Inspired oxygen concentration |
| HBO | Hyperbaric oxygenation |
| HR | Hazard ratio, ratio of the risks of a particular event in two groups during a given observation period |
| HFNC | High-flow nasal cannula |
| Hb | Hemoglobin |
| L/min | Liters per minutes |
| NIV | Non-invasive ventilation |
| NEWS2 | National early warning score 2 |
| NMD | Neuromuscular disease |
| $O_2$ | Oxygen |
| OR | Odds ratio, a measure of association of the probability of occurrence of a characteristic (e.g., a disease) between two groups |
| P/F | Oxygenation index as a ratio of $pO_2/FiO_2$ (Horovitz index) |
| $paO_2$ | Partial pressure of oxygen in arterial blood |
| $paCO_2$ | Partial pressure of carbon dioxide in arterial blood |
| $pvCO_2$ | Partial pressure of carbon dioxide in venous blood |
| RCT | Randomized controlled trial |
| RR | Relative risk, risk ratio in two different groups |
| $SaO_2$ | Arterial oxygen saturation |
| $SO_2$ | Oxygen saturation |
| $SpO_2$ | Oxygen saturation measured by pulse oximetry |
| $tcpCO_2$ | Transcutaneous partial pressure of carbon dioxide |
| $tcpO_2$ | Transcutaneous partial pressure of oxygen |
| VAS | Visual analog scale |

## 2.13 Scope

The Guideline on Oxygen therapy in the Acute Treatment of Adult Patients is intended for out-of-hospital and in-hospital emergency settings. This guideline is also intended to include recommendations for the treatment of critically ill patients, e.g., those treated in intensive care units, including patients on invasive ventilation and extracorporeal oxygenation. Furthermore, the guideline is intended to include recommendations for supplemental oxygen therapy during procedures, with the aim of preserving spontaneous breathing, e.g., in endoscopy. The scope of this guideline does not include the use of oxygen therapy in diving and high-altitude medicine, long-term oxygen therapy in the domestic setting, and the administration of oxygen in the context of general anesthesia, and in veterinary medicine.

## 2.14 Objectives and question

In their constitutive meeting, the members of the guideline development group defined the following objectives for the guideline:

- Promotion of local standards for oxygen therapy in pre-hospital and in-hospital settings
- Definition of indications for emergency $O_2$ therapy, preferably independent of medical condition
- Submission of proposals for target oxygen saturation ranges for patients on oxygen therapy
- Identification of risks and adverse drug reactions in connection with oxygen, and prevention of hyperoxemia
- Promotion of written orders for supplemental oxygen therapy
- Provision of practical recommendations for $O_2$ therapy (prescription, monitoring, documentation, discontinuation)

In their constitutive meeting in April 2019, the guideline development group determined that the following questions should be addressed:

1. When should oxygen therapy be started in acutely ill adults (lower limit of $SpO_2$)?
2. Is oxygen administration useful in acutely ill normoxemic adults (e.g., patients with sepsis, pulmonary embolism, etc.)?
3. How much oxygen should be given to acutely ill adult patients (upper limit of $SpO_2$)?
4. How should an acute oxygen therapy be administered (e.g., nasal cannula, mask)?
5. What is the target saturation range for critically ill adult patients on oxygen therapy?
6. How should oxygen therapy be monitored and managed in critically ill adult patients?
7. When and how should oxygen therapy be discontinued in critically ill adult patients?
8. How should oxygen therapy be prescribed in critically ill adult patients?
9. When should oxygen humidification be used in the acute treatment of critically ill patients?
10. When is high-flow nasal cannula therapy (HFNC) superior to conventional $O_2$ treatment?

## 2.15 Target group

This guideline is intended for healthcare professionals using oxygen in acute out-of-hospital and in-hospital settings. The target group is also reflected in the medical associations and organizations involved in the development of this guideline:

- German Respiratory Society (DGP)
- German Society of Internal Medicine (DGIM)
- German Society of Surgery (DGCH)
- German Society of Medical Intensive Care Medicine and Acute Medicine (DGIIN)
- German Society of Anesthesiology and Intensive Care Medicine (DGAI)
- German Society of Neurocritical Care and Acute Medicine (DGNI)
- German Interdisciplinary Association for Intensive and Emergency Medicine (DIVI)
- German Cardiac Society (DGK)
- German Society of Nursing Science (DGP)
- German College of General Practitioners and Family Physicians (DEGAM)
- German Association for Palliative Medicine (DGP)
- German Rescue Service Association (DBRD)

The guideline also intends to inform other users of oxygen in pre-hospital and in-hospital settings, such as healthcare and nursing staff, members of the emergency rescue services, and doctors.

## 2.16 Validity and updates

The S3 Guideline is valid until updated. The guideline will be valid for 3 years until June 30, 2024. The guideline as such is intended to be updated, and individual recommendations/topics may be revised, if an urgent need for revision arises.

Comments and suggestions in the context of the updating process are welcome. Please contact the guideline secretariat:

Prof. Dr. Jens Gottlieb
Klinik für Pneumologie OE 6870
Medizinische Hochschule Hannover
Carl-Neuberg-Str. 1
30625 Hannover
gottlieb.jens@mh-hannover.de
Fax: +49 (0)511-532-16-1118

## 2.17 Methods

The methodological approach is based on the AWMF guidelines (http://www.awmf-leitlinien.de).

## 2.18 Grading of evidence

This guideline uses the 2011 version of the Oxford Centre for Evidence-Based Medicine (CEBM) System ("The Oxford 2011 Levels of Evidence") to classify the types of studies in terms of validity. (Oxford Centre for Evidence-Based Medicine, http://www.cebm.net/index.aspx?o=5653, Table 1). This system provides for the classification of studies with regard to various clinical aspects (benefit of therapy, prognostic significance, diagnostic value) by levels of evidence.

Table 1: Classification of the identified studies

| Type of Study | Level of evidence (CEBM 2011) |
|---|---|
| Systematic review of randomized controlled trials | 1 |
| Randomized controlled trial or observational study with dramatic effect | 2 |
| Non-randomized cohort study | 3 |
| Case series, case control studies or historically controlled studies | 4 |
| Mechanism-based reasoning (case studies, anecdotes, and personal opinions) | 5 |

## 2.19 Grading of recommendations

The AWMF guidelines provide for the grading of recommendations by the authors of a guideline in the context of a formal consensus-building process. A total of 3 structured consensus conferences with impartial facilitation (M. Nothacker, AWMF Institute for Medical Knowledge Management) were held. They were structured in accordance with the model described by the National Institutes of Health, with the following sequence:

- Presentation of the recommendation including background text by the spokesperson of the working group/expert responsible for developing the recommendation
- Clarification of content-related queries
- Request for proposal of substantiated amendments and summarization of proposals, as necessary
- Voting on the original version and on the amendments
- Repeat discussion and voting if no consensus was reached.

As part of these processes, the representatives voted on the recommendations. Each representative had one vote (not just one vote per medical association). In the context of the 2019 in-person meeting, the votes were cast using a web-based smartphone application (Kahoot.it). The recommendations were initially assessed through preliminary surveys (https://www.soscisurvey.de/) in the run-up to the consensus meetings. During the video conferences, votes were cast via chat entries, which were documented by screen shots. The results of the respective ballots (consensus strength) are assigned to the recommendations according to the categories in Table 2:

Table 2: Consensus strength

| | |
|---|---|
| Strong consensus | Endorsed by < 95 % of participants |
| Consensus | Endorsed by 76–75% of participants |
| Majority approval | Endorsed by 50–75% of participants |
| No consensus | Endorsed by < 50% of participants |

Based on the vote, consensus (n=4) / strong consensus (n=30) was reached for all 34 recommendations.

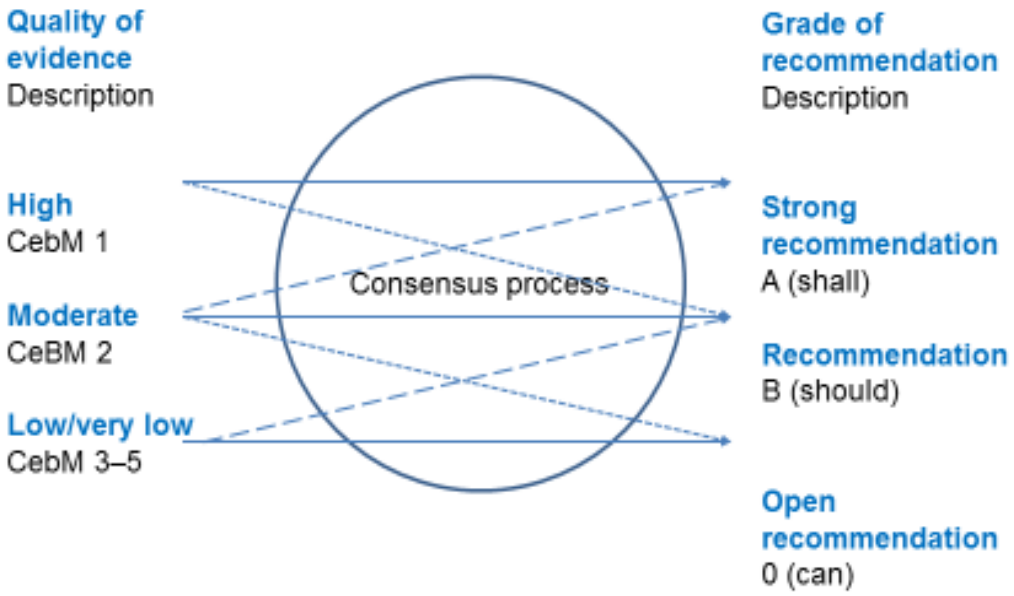
For all recommendations, the guideline indicates the level of evidence of the supporting studies as well as the strength of the recommendation (grade of recommendation). This guideline distinguishes three levels of recommendation in terms of strength of recommendation.

Table 3: Grades of recommendation

| Grade of | Description | Wording |
|---|---|---|
| A | Strong recommendation | Shall/shall not |
| B | Recommendation | Should/should not |
| 0 | Conditional | Can/can do without |

The grade of each recommendation results from the quality of the evidence and the rationale for the strength of recommendation (cf. Figure 1, modified based on AWMF). Thus, a strong recommendation could be issued even without a high degree of certainty, if the recommendation was based on clinical assessment/experience.

Figure 1: AWMF grades of recommendation based on quality of evidence and other decision criteria




GRADE-rated recommendations are presented according to the following template:

| **WG no.** | **Recommendation (% agreement)** | **Grade of recommendation / GRADE** | |
|---|---|---|---|
| **Recommen-dation no.** | Wording of recommendation (shall/should/can) | **A, B or 0** | |
| | | Quality of evidence endpoint 1 ⊕⊖⊖⊖ to ⊕⊕⊕⊕ | Endpoint 1 |
| | Supporting randomized controlled studies (RCT), meta analyses | Quality of evidence endpoint 2 ⊕⊖⊖⊖ to ⊕⊕⊕⊕ | Endpoint 2 |

## 2.20 GRADE System

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) is a system used for assessing the quality of evidence and for grading guideline recommendations. The guideline group started by drafting 9 questions and 8 patient-relevant endpoints.

Critical endpoints:

- Mortality
- Quality of life

Important (but not critical) endpoints:

- New ischemic cardiovascular events
- Relief of shortness of breath

- Correction of hypoxemia
- Monitoring effort and costs
- Necessity of ventilation (safety)
- Adverse effects: Immobility/disability, discomfort, claustrophobia, mucosal desiccation, hoarseness (safety).
- functional outcome (Rankin scale: http://www.neuroreha.at/assets/rankin-scale-deu.pdf)

GRADE initially rates the quality of cross-trial evidence gained from randomized controlled trials (RCTs) as high and evidence from observational studies as low. Five features (risk of bias, inconsistency, indirectness, imprecision, and publication bias) may result in a downgrading of the quality of evidence, and three features (large magnitude of effect, dose-response gradient, confounders) may increase the quality of evidence (Table 4). After assessing the quality of the evidence, the guideline development group evaluated all of the information collated in order to decide, which endpoints were critical and which were important for decision-making, and also to assess the quality of the evidence in general. At the end, the quality of evidence classified in one of four categories, ranging from high to very low. The overall quality of the evidence for all endpoints was then assessed based on the lowest quality of the critical end points.

Table 4: Grading the quality of evidence based on the GRADE system

| | Evidence | Downgraded if | Upgraded if | Quality of evidence |
|---|---|---|---|---|
| Randomized controlled trial (CEBM 1,2) | High | • Risk of bias<br>• Inconsistency<br>• Indirectness<br>• Imprecision<br>• Publication bias | • Magnitude of effect<br>• Dose-response gradient<br>• Low confound-ders | High ⊕⊕⊕⊕<br>⇧<br>Moderate ⊕⊕⊕⊖<br>Low ⊕⊕⊖⊖<br>Very low ⊕⊖⊖⊖ |
| Observational study<br>(CEBM 3,4,5) | Low | | | |

A full endpoint-based assessment based on GRADE was carried out for the questions processed by Ms. Unverzagt (cf. evidence report). For the evidence researched in the actual working groups, the evaluation was oriented on the GRADE criteria.

## 2.21 Expert opinion

Recommendations were worded based on expert consensus if the systematic search failed to identify suitable studies or was deemed to be too time-consuming. In this case, a recommendation is identified as ‘expert consensus’ with no level of evidence or grading of recommendation. The degree of recommendation in this case is expressed only by the words “shall”/“should”/“can”. These recommendations generally reflect a modus operandi based on

good clinical practice, and no scientific studies with a high level of evidence are available or no scientific studies are necessary or can reasonably be expected.

Recommendations based on expert opinion are presented as shown below:

| **WG no.** | **Recommendation (% agreement)** | |
|---|---|---|
| **Recommen-dation no.** | Wording of recommendation (shall/should/can)<br><br>Expert opinion | Expert consensus |

## 2.22 Good practice

The "Good practice" sections include good practice recommendations the authors consider relevant for the users of oxygen therapy. They are identified by a simple text box. The recommendations are often based on case reports, isolated literature references, and include clinically significant observations. The good practice tips were not subject to a consensus voting process.

## 2.23 Independence and disclosure of potential conflicts of interest

The guideline was developed independent of the funding organization. All members of the guideline group submitted a written disclosure of conflicts of interest in accordance with the current AWMF template (version 2018). The conflicts of interest were screened by the guideline coordinator and the AWMF representative for any relevant conflicts and consequences for the consensus process. Criteria for conflicts of interest and their severity (low/moderate/high) were defined by the steering committee in consultation with the AWMF prior to the consensus conference and communicated and confirmed to the entire guideline group at the beginning of the consensus conference.

Presentations of companies or authorship based on a fee-for-service agreement were rated as low direct conflicts of interest. Membership in a scientific advisory board/expert activities for a company in the healthcare sector with a thematic relevance as well as the conduct of studies financed by these companies were rated as moderate direct conflicts of interest. Patents or ownership interests were rated as high conflicts of interest. As a result, no member of the guideline group was found to have a low conflict of interest, three were found to have a moderate conflict of interest and no one was found to have a high conflict of interest. Moderate conflicts of interest resulted in abstention from voting. The disclosed circumstances pointing to conflicts of interest can be viewed in the Appendix to the guideline (Chapter 12). Stefan Kluge and Christian Karagiannidis had a potential conflict of interest with regard to

extracorporeal procedures, which were rated as moderate in both cases. This guideline does not cover extracorporeal procedures and provides no recommendations in this regard. Thomas Volk had a possible moderate conflict of interest on the subject of humidification. He did not participate in voting on the recommendation of WG 6 No. 6 on the subject of humidification.

The relevance of conflicts of interest to the guideline was repeatedly discussed on the occasion of the constitutive meeting on April 15, 2019, which was held as in-person meeting in Hannover, Germany, and at the consensus conferences on December 7 and December 14, 2020, which were held as video conferences (Microsoft Teams).

The risk of bias as a result of conflicts of interest was reduced, among others, by commissioning a third party, Ms. Susanne Unverzagt, with the literature research, selection and evaluation. Formal consensus building and cross-disciplinary drafting were additional tools used to minimize industry influence.

## 2.24 Notes by the editorial team

In the interest of readability, we have chosen to refrain from using the feminine correspondents of masculine terms. All gendered references apply equally to both genders. All guideline recommendations are to be viewed as recommendations, which should be implemented as part of a joint decision-making process involving the clinician, the patient, and the patient's next of kin, as necessary. Nurses and respiratory therapists should also be involved in the decision-making process.

## 2.25 Implementation and dissemination

This guideline is planned to be implemented and rolled out in a multi-step process, ideally supported by a communication campaign. This strategy includes:

- Evaluation of the actual situation prior to implementing the guideline based on OXYBAR, an oxygen prevalence study conducted in hospitals in Germany (DRKS003360)
- Guideline publication on the Internet, and in medical journals
- The publication will follow the criteria recommended by the International Committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html)
- Implementation of the guideline through the national medical societies, healthcare and nursing care societies, as well as associations of emergency workers including commenting, adaptation, or adoption

- Development of educational materials for medical professionals on the use of oxygen
- Dissemination through continuing education programs, training programs at medical conferences
- Dissemination by stakeholders at European level, the EFP through European stakeholders, via national societies, i.e. Via the EFP members
- Evaluation of the successful implementation of the guideline by repeating the local oxygen prevalence study OXYBAR (DRKS003360) in German hospitals.

Table 5: Timeline of guideline development

| Date | Event |
|---|---|
| September 05, 2018 | Registration of the guideline with the Association of the Scientific Medical Societies in Germany (AWMF) |
| April 15, 2019 | Constitutive guideline meeting (in-person meeting) in Hannover (participants: Capetian, Gottlieb, Hamsen, Hoyer, Karagiannidis, Kluge, Nothacker, Roiter, Volk, Worth, Unverzagt) |
| May–December 2019 | Disclosure of conflicts of interest by all members of the guideline development group |
| June–December 2019 | Literature search including preparation of evidence report and guideline search report |
| 6/30/2020 | Working meeting (video conference) (participants: Capetian, Fühner, Gottlieb, Hamsen, Hoyer, Karagiannidis, Kluge, Markewitz, Roiter, Volk, Witt, Worth) |
| July–November 2010 | Development of the recommendations including background texts by the working groups |
| 12/7/2020 | First consensus-building guideline meeting (video conference) (participants: Capetian, Nothacker, Valtin, Fühner, Gottlieb, Hamsen, Janssens, Karagiannidis, Kluge, König, Markewitz, Roiter, Veit (patient representative), Volk, Wildenauer, Witt (from recommendation 4.1), Worth) |
| 12/14/2020 | Second consensus-building guideline meeting (video conference) (participants: Nothacker, Fühner, Gottlieb, Hamsen, Janssens, Kluge, König, Markewitz, Veit, Wildenauer, Witt, Worth) |
| December 2020–January 2021 | Evidence update, assessment by the working groups and revision of background texts |
| February 2021 | Finalization of guideline and background texts |
| April 2021 | Consultation with the medical societies |
| June 2021 | Publication of the guideline on the AWMF and DGP websites |
| N.N. | Publication of guideline in an international medical journal |
| N.N. | Publication of guideline in a national medical journal |

## 2.26 Acknowledgments

The authors thank the members of the guideline development group and the experts for their honorary work. The authors are grateful for the support of Ms. Susanne Hoyer, Hannover, and Ms. Christina Valtin, Hannover.

The authors would also like to extend their gratitude to the following experts for providing their advice: Bernd Schönhofer, Hannover; Terence Krauß, Hannover; Björn Jüttner, Hannover; Michael Westhoff, Hemer; Peter Haidl, Schmallenberg; Carsten Hermes, Bonn; Guido Michels, Eschweiler; Jan-Christopher Kamp, Hannover.

# 3 Introduction

## 3.1 List of recommendations

| Recommendation | Subject of recommendation | Grade of recommendation | Quality of evidence |
|---|---|---|---|
| 1.1. | Dyspnea in non-hypoxemic patients | A | ⊕⊕⊕⊕ |
| 2.2. | Vital signs | A | Expert opinion |
| 2.1. | Pulse oximetry | A | ⊕⊖⊖⊖ |
| 6.2. | Arterial BGA | B | Expert opinion |
| 2.3. | Capillary BGA | 0 | ⊕⊖⊖⊖ |
| 2.4. | Venous BGA | A | ⊕⊕⊕⊖ |
| 3.2. | $O_2$ for nebulized therapy | A | Expert opinion |
| 3.3. | Training in $O_2$ therapy | A | Expert opinion |
| 3.1. | Oxygen delivery systems | A | ⊕⊕⊕⊖ |
| 3.4. | Oxygen prescription | A | Expert opinion |
| 3.5. | Reevaluation of patients under $O_2$ therapy | B | Expert opinion |
| 4.1. | $O_2$ target range for patients not at risk of hypercapnia | A | ⊕⊕⊕⊖ |
| 4.3. | $O_2$ target range for patients at risk of hypercapnia | A | ⊕⊕⊖⊖ |
| 4.2. | $O_2$ target range for ventilated patients | A | ⊕⊕⊖⊖ |
| 4.4. | Drop in $SpO_2$ without hypoxemia | B | Expert opinion |
| 4.7. | Consultation of experienced clinicians | A | Expert opinion |
| 4.9. | Non-invasive ventilation in hypercapnia | A | ⊕⊕⊕⊖ |
| 4.11. | Non-invasive ventilation in hypoxemia | 0 | ⊕⊕⊖⊖ |
| 5.3. | $O_2$ in carbon monoxide poisoning | A | Expert opinion |
| 4.15. | $O_2$ therapy in the pre-hospital setting | A | ⊕⊖⊖⊖ |
| 5.1. | $O_2$ therapy during CPR | B | ⊕⊕⊖⊖ |
| 5.5. | $O_2$ therapy in infections transmitted by aerosols e.g., COVID-19 | A | ⊕⊕⊕⊖ |
| 5.4. | $O_2$ for patients with cluster headaches | A | ⊕⊕⊕⊕ |
| 4.12. | Pulse oximetry in sedated patients | A | Expert opinion |
| 4.13. | Hypoxemia during sedation | B | Expert opinion |
| 5.6. | Indications for high-flow oxygen | B | Expert opinion |
| 5.7. | Monitoring during high-flow oxygen | B | Expert opinion |
| 6.6. | Humidification of supplemental oxygen | A | ⊕⊕⊕⊖ |
| 6.3. | BGA check after change in $O_2$ flow rate | B | Expert opinion |
| 6.4. | Pulse oximetry after change in $O_2$ flow rate | B | Expert opinion |
| 7.1. | Reduction of $O_2$ therapy | B | Expert opinion |
| 7.2. | Discontinuation of $O_2$ therapy | B | Expert opinion |
| 7.4. | Temporary drop in $SpO_2$ | B | Expert opinion |
| 7.5. | Post-acute oxygen therapy | B | Expert opinion |

## 3.2 History of oxygen therapy

Oxygen, a colorless, odorless gas that liquefies at temperatures below -183°C, was discovered independently by Carl Wilhelm Scheele and Joseph Priestley in 1776. The ability to store oxygen in gas cylinders and the development of compressed gas technology and pressure regulation at the end of the 19th century made it possible to use oxygen for medical purposes. Karol Stanislaw Olszewski and Zygmunt Florenty Wróblewski succeeded in liquefying oxygen, and Carl von Linde in industrially producing liquid oxygen at a larger scale. One liter of liquid oxygen produces approximately 850 liters of gaseous oxygen.

In 1890, Albert Blodgett from Boston reported the impressive case of a 37-year-old female patient with severe pneumonia, in whom mental confusion and cyanosis were reduced after two days of oxygen supplementation, with the symptoms returning when the O2 supply had been exhausted. After the therapy was resumed, the patient fully recovered over four and a half days (4).

## 3.3 Physiology of blood gases

Our body cells use the oxygen we breathe to get energy from the food we eat. The primary function of the human lungs is to deliver oxygen ($O_2$) to the blood and to take up carbon dioxide ($CO_2$) from the blood, which is then exhaled. The respiratory system is composed of two parts. The lungs regulate the uptake of oxygen and the release of carbon dioxide (gas exchange), while the respiratory pump takes care of the supply and removal of the gases (ventilation). In pulmonary insufficiency (type 1 respiratory failure), only the $O_2$ uptake, but not the excretion of $CO_2$, is compromised due to superior tissue solubility as compared to $O_2$, whereas in ventilatory insufficiency (type 2 respiratory failure), both $O_2$ uptake and $CO_2$ excretion are compromised.

In the blood, $O_2$ binds mostly to the heme component of hemoglobin (Hb) in red blood cells in a reversible reaction. Hemoglobin binds or releases oxygen depending on the partial pressure of oxygen. According to the equation, the physically dissolved oxygen is negligible under normobaric conditions due to the low solubility of $O_2$ in blood. The oxygen content ($CaO_2$) is calculated as follows:

$$CaO_2 = 1.34 \times Hb \times SO_2 + 0.0031 \times paO_2$$

$O_2$ content ($CaO_2$ in ml $O_2$/dl blood), hemoglobin concentration in blood (Hb) in g/dl, $O_2$ saturation ($SO_2$), $pO_2$ (partial pressure of $O_2$, in mm Hg), 1.34 is the Hufner's factor

The amount of $O_2$ in blood can be expressed by measuring the oxygen saturation ($SO_2$) of hemoglobin or by measuring the partial pressure of $O_2$ ($PaO_2$). The arterial oxygen saturation ($SaO_2$) indicates the percentage of hemoglobin saturated with oxygen at the time of measurement. The oxygen saturation of hemoglobin ($SO_2$, in %) can be measured from arterial blood ($SaO_2$) and also by pulse oximetry ($SpO_2$). Arterial saturation should be measured photometrically. Alternatively, it can be calculated, with lesser accuracy, from the partial pressure of oxygen using various formulas (5, 6).

$paO_2$ is a key parameter for assessing the pulmonary gas exchange. $SaO_2$, in comparison, is more sensitive to minor disturbances, but the process is painful for the patient and also more time-consuming. This is why the $SO_2$ is preferred over $paO_2$ measurements in emergency settings where $SO_2$ levels are frequently below 90%.

Neither oxygen saturation nor the partial pressure of oxygen in arterial blood are suitable key parameters for determining the tissue oxygenation. The supply of $O_2$ to tissue ($DO_2$) is calculated using the following formula:

$DO_2 = Q \times CaO_2$

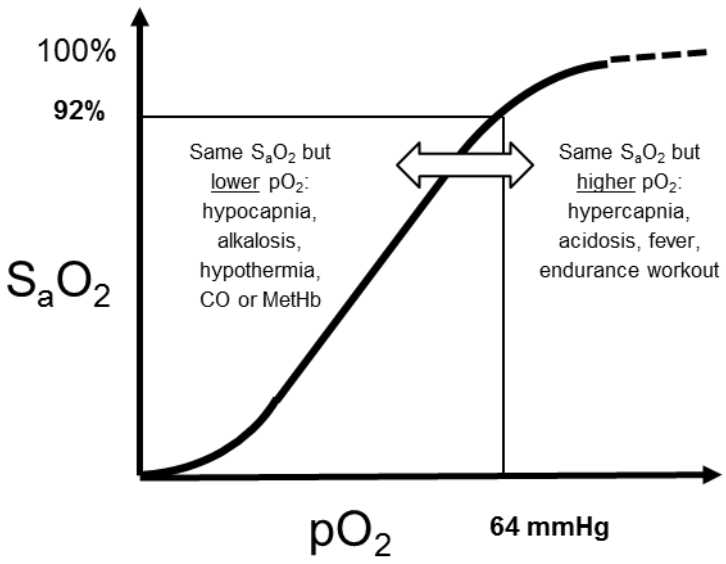
from the cardiac output (Q) and the arterial $O_2$ content ($CaO_2$).

Hypoxemia, i.e. low blood oxygen levels, is often confused with hypoxia. The formulas for calculating oxygen supply and oxygen content make it clear that tissue oxygenation is essentially determined by hemoglobin levels and cardiac output, and is only inadequately characterized by $SaO_2$ or $paO_2$. Nevertheless, much more attention is paid to hypoxemia in clinical practice than to these key parameters, which are not immediately available.

The oxygen binding curve (Figure 2) characterizes the relationship between arterial oxygen saturation ($SaO_2$) as a function of the partial pressure of $O_2$ ($paO_2$). An oxygen saturation of 100% is not achievable as a small amount of blood does not take part in pulmonary gas exchange and, instead, goes into the arterial circulation (shunt blood), reducing the $SO_2$ by 1–3%.

Figure 2: Relationship between oxygen saturation and the partial pressure of oxygen

| $S_aO_2$ | $pO_2$, mmHg | $pO_2$, kPa |
|---|---|---|
| 10 | 10 | 1.3 |
| 30 | 19 | 2.5 |
| 40 | 23 | 3.1 |
| 60 | 31 | 4.1 |
| 70 | 37 | 4.9 |
| 80 | 45 | 6.0 |
| 85 | 50 | 6.7 |
| 88 | 55 | 7.3 |
| 89 | 57 | 7.6 |
| 90 | 58 | 7.7 |
| 91 | 60 | 8.0 |
| 92 92 | 64 | 8.5 |
| 93 | 67 | 8.9 |
| 94 | 71 | 9.5 |
| 95 | 74 | 9.9 |
| 96 | 82 | 10.9 |
| 97 | 91 | 12.1 |
| 98 | 130 | 17.3 |
| 99.95 | 700 | 93.3 |




$SaO_2$: arterial oxygen saturation; $pO_2$: partial pressure of oxygen; kPa: kilo Pascal; CO: carbon monoxide; Met-Hb: methemoglobin. Mechanisms for the shift of the oxygen dissociation curve to the right/left.

Figure 2 shows that a linear relationship exists only in the steep part of the $O_2$ binding curve ($SaO_2$ between approx. 40% and 90%). At $O_2$ saturation levels > 90%, i.e., when the pulmonary gas exchange is only slightly impaired, an increase in the $paO_2$ results in only a minor $SO_2$ change.

The partial pressure of carbon dioxide ($paCO_2$) is an important marker of alveolar ventilation. In addition, $paCO_2$ is a key parameter for the interpretation of the pH. Given the good solubility of $CO_2$ in blood, a linear relationship is usually found between $CO_2$ levels in blood and $paCO_2$. The generally accepted normal $paCO_2$ range is 36–44 mmHg.

When measuring the waking $paCO_2$, particular attention should be paid to deliberate hyperventilation, which goes along with a drop in $paCO_2$ and at times high $paO_2$ levels. In case of hyperventilation ($paCO_2$ < 40 mmHg), the following formula can be used to determine the so-called standard $paO_2$, standardizing the $paO_2$ to normoventilation (= $paCO_2$ 40 mmHg):

Standard $paO_2$ (mmHg) = measured $paO_2$ (mmHg) – 1,66 × (40 – measured $paCO_2$ (mmHg)) (7)

The normal pO2 values when lying down and sitting vary depending on age (8, 9), with the latter being higher.

In a large UK study on 37,000 patients, the median SpO2 was 98% for adults aged 18–64 years, and 96% for the elderly.

Normal oxygen saturation in a population depends on altitude. A sample group of 3,812 people living in Tibet at an altitude of approx. 4,000 m, for example, had a mean SaO2 of only 88% (11). This effect is of minor relevance in Germany.

While pulse oximetry is more sensitive, its specificity for detecting hypoxemia is low. In 64 patients with exacerbation of chronic obstructive pulmonary disease (COPD), a blood oxygen saturation < 92% measured by pulse oximetry had a sensitivity to predict arterial hypoxemia (pO2 < 60 mmHg) of 100% and a specificity of 86% (12). In 664 arterial blood gas analyses and simultaneous pulse oximetry readings taken in an emergency department, pulse oximetry had a sensitivity of less than 92% in 92% of cases and a specificity of 90% for predicting arterial oxygen saturation (SaO2) of 90% (13). Errors in pulse oximeter readings also need to be considered when defining the target ranges. Even in critically ill patients, the 95% confidence interval for the difference between pulse oximetry and arterial saturation is + 4% (14).

### 3.4 Causes of hypoxemia

Hypoxemia is a decrease in the partial pressure of oxygen or oxygen saturation in arterial blood. Hypoxia, on the other hand, means insufficient organ and tissue oxygenation. In adults, hypoxemia is mostly defined as PaO2 < 60 mmHg and SaO2 < 90% (15).

The following types of tissue hypoxia are distinguished: hypoxemic, anemic, stagnant, and histotoxic (e.g., in cyanide poisoning). Oxygen therapy usually serves to correct hypoxemic hypoxia.

Hypoxemic hypoxia is present when the partial pressure of oxygen in the blood is reduced. This may be caused by high altitude, right-to-left shunts, marked pulmonary ventilation-perfusion mismatch, diffusion impairment, or alveolar hypoventilation (Table 6).

Table 6: Causes, examples, and responsiveness to $O_2$ treatment of various types of hypoxemic hypoxia

| Cause | $paCO_2$ | Alveolar-arterial partial pressure gradient | Response to $O_2$ supply | Example |
|---|---|---|---|---|
| Ventilation-perfusion mismatch | variable | increased | good | Pneumonia, ARDS |
| Pulmonary shunt | normal | increased | poor | Pulmonary arteriovenous malformation |
| Diffusion disorder | mostly reduced | increased | good | Emphysema, diffuse parenchymal lung disease |
| Hypoventilation | increased | normal | moderate | Neuromuscular disease |
| Low-$O_2$ environment | reduced | normal | good | Extreme altitude |

$O_2$: oxygen; $CO_2$: partial pressure of carbon dioxide; ARDS: acute respiratory distress syndrome in adult patients; $FiO_2$: inspired oxygen concentration.

Alveolar-arterial partial pressure gradient* = $(FiO_2^{\#} \times 760^{+}) - (paCO_2 / 0.8) - paO_2$

* according to (16); the normal value at sea level is < (age/4) + 4 mmHg, $^{+}$ atmospheric pressure (760 mm Hg at sea level) #$FiO_2$ = 0.21 + $O_2$ flow in liters per minute (L/min) x 0.038 (17) ,

Type 1 respiratory failure with reduced $paO_2$ and normal or reduced $paCO_2$ is caused by hypoxemic hypoxia consistent with hypoxemic respiratory failure. Hypercapnic respiratory failure (type 2 respiratory failure) has a $paCO_2 \geq 45$ mmHg, potentially resulting in reduced SaO2 and pO2 levels. In chronic hypercapnia, e.g., in COPD, hyperoxemia may result in a dangerous increase in the paCO2 as the pulmonary vasoconstriction of non-ventilated areas is reversed in hyperoxemia. In addition, hypoxemia reduces the respiratory minute volume; in addition, oxygenated hemoglobin has decreased carbon dioxide carriage (Haldane effect) (18).

Hypoxemia is a warning sign and requires immediate medical attention, differential diagnosis and subsequent treatment. This is why both hypoxemia as well as the presence of oxygen therapy were included as parameters in early warning scores (e.g., NEWS2) (19), to serve as indicators of increased mortality and the necessity of intensive medical care.

| WG1 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **1** | The underlying causes of hypoxemia shall be identified and treated. Oxygen shall be given to treat hypoxemia, not dyspnea.<br><br>Uronis 2007 (20), Uronis 2011 (21), Cranston 2008 (22) | **A** | |
| | | High quality of evidence<br>⊕⊕⊕⊕ | Quality of life |

The authors identified 3 meta-analyses on the relief of dyspnea through oxygen therapy in different patient groups (COPD, cancer) in the context of their own literature search (20-22). There was strong evidence that oxygen is not superior to compressed air in relieving dyspnea. The guideline search did not reveal any evidence-based recommendation in other guidelines. The authors identified the S3 Palliative Care Guideline, which also advocated against using oxygen in non-hypoxemic patients presenting with dyspnea (23).

In palliative care, 134 cancer patients (72% had an $SpO2 \geq 90\%$) with refractory dyspnea were observed in 5 studies comparing oxygen vs. compressed air therapy (20). 8 studies were covered in a more recent Cochrane meta-analysis (22). Study endpoints were patient-reported dyspnea measured on various scales. In none of the studies was the perceived dyspnea improved by oxygen. In a third Cochrane meta-analysis of 18 studies with 702 COPD patients (21), only a small effect was seen regarding the impact of oxygen on dyspnea, whereby the placebo effect of an airflow could not be reliably differentiated. In the largest randomized trial including 239 patients suffering from dyspnea (24), the relief provided by oxygen therapy was not superior to that provided by insufflation of compressed air. Most of the studies did not show a correlation between the degree of dyspnea and that of hypoxemia.

In pre-hospital settings, it may be difficult to obtain a usable pulse oximeter signal in patients presenting with dyspnea. In this situation, oxygen administration is justifiable according to expert opinion. In an inpatient setting, blood gas analysis of arterial or, alternatively, of capillary blood, should be performed for clarification.

Good practice:

In addition to oxygen therapy, general measures such as positioning the patient to improve oxygenation are useful in hypoxemia.

When positioning hypoxemic patients who are awake, the patient's preference should be taken into account in addition to the oxygen therapy. Putting the upper body in an upright position may improve oxygenation in some patients. Acute respiratory failure has been described in morbidly obese patients (BMI > 50 kg/m2) when lying on their back (25).

There are no RCTs supporting a beneficial effect of prone positioning in hypoxemic patients who are awake and breathing spontaneously. Before the development of this guideline, individual case series of COVID-19 patients described a positive effect ("self-proning").

To treat and prevent the aortocaval compression syndrome, hypoxemic pregnant women need to be positioned on their left side.

In palliative care, non-pharmacological measures are initially used to manage dyspnea in non-hypoxemic patients: relaxation exercises, cooling of the face, airflow from a table fan, and walking aids.

Opioids have been thoroughly studied for the treatment of dyspnea and have proven to be an effective intervention in non-hypoxemic patients with dyspnea.

## 3.5 Permissive hypoxemia as a routine therapy

Permissive hypoxemia has been proposed as a treatment option to avoid damage as a result of invasive ventilation. This strategy presupposes sufficient hemoglobin levels (usually > 10 g/dl) and a supranormal cardiac index (> 4.5 L/min/$m^2$) to maintain adequate oxygen supply ($DO_2$). The concept aims for critically ill patients to tolerate a target oxygen saturation between 85% and 89%.

There are so far no randomized trials comparing permissive hypoxemia vs. normoxemia in adults. The effect remains speculative. In contrast, oxygen therapy to treat chronic hypoxemia in COPD patients with a $pO_2 \leq 55$ mmHg (corresponding to an arterial saturation< 89%) improved the prognosis of patients in two historical randomized trials (26, 27).

A 2014 meta-analysis did not identify any studies comparing permissive hypoxemia in ventilated patients vs. a control group with normoxemia or mild hypoxemia (28). Based on our own literature search, the only study investigating the concept of permissive hypoxemia in a randomized approach was the NeOProM collaboration (29), in which 4,965 pre-term infants were randomized to receive oxygen therapy with a target $SpO_2$ of 85–89% or 91–95%. The study did not include adult patients. There was no difference in mortality, but more cases (9% vs. 7%) in the restrictive oxygen group required surgery for necrotizing enterocolitis or died. Interestingly, in a recently published study comparing liberal and restrictive oxygen

therapy in adult ARDS patients, isolated mesenteric ischemia was also observed in 5% of patients with a target SpO2 of 88–92% (30). Hence, the range of hypoxemia that can be tolerated by critically ill patients in the medium term remains unclear.

Occasionally, the view is expressed that oxygen saturation and partial pressure of oxygen are not suitable as indicators for oxygen therapy. An association of hypoxemia and increased mortality has repeatedly been described for large inpatient collectives and patients treated in a resuscitation context (31, 32). In 27,722 hospitalized patients, a pulse oximeter reading of less than 92% measured at least once was associated with in-hospital mortality of 6% vs. 2% in patients without hypoxemia (31).

It was suggested that, instead of $SaO_2$ and $pO_2$, oxygen content ($CaO_2$) should be used as the target parameter of oxygen therapy. However, no reference ranges exist for $CaO_2$. The parameter has not yet been tried in a single clinical trial and demonstrated its suitability as $O_2$ therapy target range. In a randomized controlled trial on 838 patients, 82% of whom were ventilated, a liberal transfusion strategy (hemoglobin > 10 g/dl) vs. a conservative strategy (hemoglobin > 7 g/dl) did not produce a significant difference in the 30-day survival rate, which was 18.7% in the restrictive and 23.3% in the liberal transfusion arm (33). In addition, to maintain tissue oxygenation and avoid hypoxemia, perfusion needs to be considered along with the oxygen content of the blood. This is often done using the cardiac output, which provides the oxygen supply ($DO_2$) by multiplying the oxygen content ($CaOO_2$) and the cardiac output. However, cardiac output is not easily measured at the bedside.

The results of increasing the $DO_2$ in critically ill patients on survival, organ failure, length of hospitalization in RCTs were contradictory (34, 35). Studies indicating improved survival had significant methodological flaws and were based on small case numbers. A systematic review provided insufficient data to support a routine increase of $DO_2$ in critically ill patients (36). The administration of inotropic agents to increase cardiac output may also produce adverse drug reactions (ADR) in some patients, and, for example, may negatively affect the cardiac function in ARDS patients and patients with coronary artery disease.

The fetal oxygenation is approx. 70% (37). This leads some authors to argue that even adult patients may be fully stable at a $SpO_2$ of 70%. This a valid observation as there are people who have adjusted to chronic hypoxemia (e.g., fetus, patients with mixed cyanosis, populations living at high altitudes, or people with chronic hypoventilation) who report no shortness of breath and also would not benefit from oxygen therapy despite being hypoxemic. Adjustment processes to chronic hypoxemia take several weeks and go along with an increase in hemoglobin levels, minute volume, and respiratory output. However, the experience that there are people who have adjusted to chronic hypoxemia cannot be transferred to patients with acute hypoxemia.

We know from historical high-altitude and aviation medicine publications (38) that, without adaptation process, altitude-induced hypoxemia at an altitude of 6,700 m above sea level with saturation levels below 70% leads to loss of consciousness within a short period of time and is fatal, even after several days of acclimatization. Acute patients do not go through the

adaptive processes associated with chronic hypoxemia. Even healthy subjects showed cognitive impairment in hypoxemia below 80% (39).

The exact range within which hypoxemia is tolerated in the medium term is unknown for lack of controlled trials, and the question of "How low can you go?" cannot be answered with certainty based on current knowledge. Lactate levels are often used as a surrogate parameter for tissue hypoxia, both in clinical practice and in studies. An increase in lactic acid content was demonstrated after 15 minutes in seven healthy subjects at an arterial saturation rate of 78% (40). In a case series of 12 healthy male subjects, myocardial lactate was released at a saturation of 70%–75% (41) when exercising in a low-oxygen environment. In three of nine patients with coronary artery disease aged 41–62 years, myocardial lactate was produced at rest during hypoxemia (SaO2 64%–85%) (42). No lactate production at rest was detected above a saturation rate of 85%. An oxygen saturation of 85% is therefore frequently described as the likely critical threshold of acute hypoxemia, although levels probably vary between individuals.

In the absence of randomized trials on oxygen therapy in acutely ill hypoxemic adults, the impact of oxygen therapy on survival and other patient-relevant outcomes remains unclear. For the purpose of this guideline and the limit values recommended in it, it is relevant from what level hypoxemia is likely to be harmful for the patient and in which range oxygen therapy is not harmful and, hence, safe. The recommendations take account of the limitations of pulse oximetry, whose 95% CI in terms of actual consistency with arterial saturation (SaO2) ranges from 84–92% for a SpO2 of 88%, for example.

Good practice:

The following questions need to be answered to decide whether or not oxygen therapy is necessary in hypoxemic patients:

1. Does the patient have symptoms and is he clinically stable?

It is important to record dyspnea, all vital signs, the mental state in particular (including confusion), and the respiration rate. In case of doubt, the presence of hypoxemia should be confirmed by blood gas analysis.

2. How severe is the hypoxemia and is it persistent?

Even severe hypoxemia that is transient (e.g., lasts less than 1 minute) and self-limiting—e.g., during exercise/coughing attacks or in the context of hypoventilation (during sleep, endoscopy)—is usually noncritical. Moderate hypoxemia with an arterial $O_2$ saturation of 85–89% most likely is of little concern, event in the long term. For the reasons mentioned above, acutely ill patients with extended severe hypoxemia whose $SaO_2$ (alternatively $SpO_2$) is well below this range are at risk from tissue hypoxia, and therefore have a poorer prognosis.

3. Has the patient adapted to hypoxemia?

Chronic hypoxemia (i.e. hypoxemia lasting for at least a couple of weeks) is common, for example, in patients with chronic hypoventilation, congenital heart defects, people living at high altitude, and generally also in patients at risk of hypercapnia. A frequently seen indicator for this condition is the presence of polycythemia with increased blood hemoglobin levels.

4. Does the patient have concomitant diseases?

Patients with coronary heart disease or other cardiovascular conditions are likely to have a reduced tolerance for tissue hypoxia. Organs susceptible to hypoxia are especially the central nervous system, the myocardium, and the intestines. End-organ damage shall be assessed, for example through neurocognitive testing, ECG, and myocardial biomarkers. Lactate levels obtained from arterial, arterialized, or venous blood (normal value < 2 mmol/L) are used as surrogate markers of occult tissue hypoxia, despite little evidence in this regard.

## 3.6 Hyperoxemia

Hyperoxemia, like hypoxemia, is not precisely defined. The normal $O_2$ saturation at sea level is 96% (10). In the studies on $O_2$ therapy in normoxemic patients with acute coronary syndrome, stroke, and during surgery, $SpO_2$ values of more than 96% were measured in the treatment groups with liberal oxygen administration (43). Patients at risk of hypercapnic respiratory failure were generally excluded in these studies.

Numerous arguments speak against hyperoxia and hyperoxemia as a therapy target:

- The unnecessary use of oxygen causes claustrophobia, dehydration of mucosa, hoarseness, and in some patients and negatively affects patient mobilization, food and fluid intake, and communication (3). In addition, a number of deleterious side effects of hyperoxemia resulting from the administration of $O_2$ with the goal of achieving hyperoxia have been described (44).
- A meta-analysis of 25 randomized controlled $O_2$ trials in which 16,037 subjects with various acute conditions, including sepsis, stroke, trauma, myocardial infarction, and cardiac arrest had been enrolled, provided strong evidence of an increased relative risk of in-hospital mortality (43).
- In 10 studies on 1,458 ICU patients, the relative risk of 3-month mortality was 1.18 with a higher oxygen target range. The incidence of severe adverse events was higher in the group with liberal $O_2$ therapy (45).
- A randomized trial with patients with septic shock showed an increased overall incidence of serious adverse events in the hyperoxia group (100% oxygen for 24 hours) vs. the normoxia control group. The number of patients suffering from critical-illness polyneuropathy and myopathy was almost double in the hyperoxia group (46).
- High $O_2$ concentrations have a direct toxic effect on the lungs of healthy persons by causing an inflammatory airway response. In addition, resorption atelectasis has been described under high oxygen concentrations, especially in obese healthy subjects (47, 48).
- High oxygen concentrations in the context of hyperbaric oxygen therapy at atmospheric pressures greater than 1.8 have shown to have a toxic effect on the central nervous system to the point of causing seizures (49).
- The increased free radical generation during hyperoxia can result in cell damage (50).
- Hyperoxemia may result in falsely reassuring $SpO_2$ levels and delay the detection of a deterioration in hypoxemic patients. If the condition then worsens, options to further intensify the oxygen therapy are limited (11, 51).
- In patients with COPD, pre-hospital hyperoxia was associated with greater in-hospital mortality (2% vs. 9%). Hyperoxemia often went along with hypercapnic respiratory failure (52).
- Hyperoxemia leads to coronary vasoconstriction (53) and routine supplemental oxygen therapy does not improve the mortality after myocardial infarction (54). In a randomized trial, the rate of recurrent coronary events was increased more than fivefold in patients treated with oxygen vs. those treated with compressed air (55).
- In 21 studies on 7,597 patients, hyperoxia did not improve intra- and postoperative wound healing (56). In the follow-up of a randomized clinical trial, the long-term mortality of patients after surgery was even increased in those with a high perioperative inspiratory oxygen fraction (57).

# 4 Patient assessment

## 4.1 Clinical assessment of hypoxemia and hypercapnia

| WG2 | Recommendation (100% agreement) | |
|---|---|---|
| **2** | The assessment of patients presenting with dyspnea shall include respiration rate, pulse rate, blood pressure, body temperature, mental state as well as oxygen saturation.<br><br>Expert opinion | Expert consensus |

Our literature search identified no randomized controlled trials comparing different clinical assessment systems for acutely ill patients. The recommendations for the clinical assessment of these patients are based on expert opinion and retrospective studies, which were contributed in the context of our own literature search (2).

$SpO_2$ is only one of several physiological parameters—so-called vital parameters—for the assessment of patients, which are easily obtainable at the bedside by nursing staff. 1.15 million vital signs were measured in 27,722 patients upon admission (31). A critical level for any of the vital signs measured was defined as the limit which, when undercut or exceeded, resulted in in-hospital mortality ≥ 5% (31). The critical levels identified in this context were: systolic blood pressure < 85 mmHg, heart rate > 120/min, body temperature < 35 °C or > 38.9 °C, oxygen saturation < 91%, respiration rate ≤ 12/min or ≥ 24/min, and altered mental state.

Respiratory signs and symptoms of hypoxemia include: dyspnea, tachypnea, mouth breathing, increasing use of accessory respiratory muscles, changes in respiratory muscle activity (e.g., paradoxical abdominal breathing, rapid alternation of thoracic and abdominal breathing – respiratory alternans pattern), and nasal flaring.

Despite some limitations in assessing a patient's oxygenation in the context of a physical exam, hypoxemia has the potential to influence vital signs and symptoms (58). Relevant hypoxemia can, for example, result in impaired consciousness, pectoral angina, arrhythmia or hypotensive/hypertensive circulatory response (15). A respiration rate > 30 breaths/min is a prognostic indicator of poor outcome and predictive of respiratory failure and increased mortality (15).

Cyanosis of the skin should be seen as a warning sign rather than an indicator of hypoxemia (15, 59-62). An early sign may be pallor of the skin as a result of vasoconstriction (63). The severity of cyanosis also depends on other factors such as circulation, hemoglobin concentration, as well as light conditions (60, 62).

However, arterial hypoxemia does not necessarily lead to changes in vital signs. For example, no association between arterial hypoxemia and heart rate, respiration rate, and blood pressure

was found in 16 adult subjects (64). Hypoxemia often goes along with tachycardia (63, 65-68). Blood pressure changes are also described, such as mild hypertension in early mild hypoxemia and hypotension in progressive, marked hypoxemia (63, 68). Other studies also indicate that vital signs are insufficient in terms of predicting arterial hypoxemia (69-71).

Changes in consciousness may already be seen in the early stages of hypoxemia (63, 68). Warning signs are anxiety, restlessness and agitation followed by confusion and loss of consciousness (15). Neurological symptoms may be seen in hypercapnia with concomitant cerebral vasodilation, along with headache, muscle twitching and spasms (68).

The clinical examination of critically ill patients should be guided by the "ABC" algorithm of emergency medicine (A = airway, B = breathing, C = circulation) (2). The following physiological parameters should be obtained during the initial assessment of patients with dyspnea and when monitoring patients on supplemental oxygen (72):

- Oxygen saturation
- Respiration rate
- Mental state (e.g., The ACVPU scale: alert, confused, verbal responsive, pain responsive, unresponsive)
- Systolic blood pressure
- Temperature
- Heart rate

These so-called "track and trigger" systems are point-based scores of vital signs and serve as an early warning system with regard to emerging or relevant changes. One of these systems is the National Early Warning Score (NEWS2) (19). The NEWS2 system assigns a point score to the above-mentioned 6 vital signs, and in addition for the presence of supplemental oxygen therapy. The total NEWS2 score can range from 0 to 20, with patients with a score < 5 being considered clinically stable.

Good practice:

The respiration rate is of key importance among the vital signs, since it is not only used in track and trigger systems (e.g., NEWS2), but also in prognostic scores (qSOFA, CRB65). The respiration rate is of particular importance in hypoxemia and in patients on supplemental oxygen.

The normal respiration rate is 12–20 breaths per minute.

Patients are considered clinically stable when they have a NEWS2 score < 5 and their vital signs are predominantly in the non-critical range (19).

Training oxygen users in how to measure their respiration rate is useful in circumstances where this cannot be done using a device (73). Regularly measuring the respiration rate is particularly important in hospitalized patients.

Smartphone-based timers are useful tools for measuring the respiration rate (e.g., Android: "Stopwatch and Tally counter", IOS: "Tap counter with sets").

## 4.2 Pulse oximetry

| WG2 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **1** | Pulse oximetry shall be available in all clinical situations where oxygen is used for medical purposes and shall be used for regularly monitoring the supplemental oxygen therapy.<br><br>Pedersen 2014(74) | **A** | |
| | | Low quality of evidence<br>⊕⊕⊖⊖ | Mortality |
| | | Moderate quality of evidence<br>⊕⊕⊕⊖ | Hypoxemia |
| | | Moderate quality of evidence<br>⊕⊕⊕⊖ | Cardiovascular events |

Pulse oximetry uses light at two separate wavelengths to measure hemoglobin saturation: Oxygenated hemoglobin has a different absorption profile than deoxygenated hemoglobin. For instance, the absorption of oxygenated hemoglobin is higher at approx. 900 nm. Common pulse oximeters use light-emitting diodes, which alternately emit wavelengths of 660 nm and approx. 910 nm. Newer generation laser diodes measure at wavelengths at 750 nm and 850 nm, respectively. The oxygen saturation ($SpO_2$) is calculated using the ratio of both absorptions at the photodiode.

Pulse oximetry is a simple, non-invasive method for estimating arterial oxygen saturation and is universally used in out-of-hospital and in-hospital settings, in intensive care units as well as in the periprocedural environment. It is a simple, non-invasive method that can significantly reduce the number of blood gas tests required, and hence the invasiveness and costs of a treatment, without compromising on the quality of healthcare (75, 76). In a small RCT, pulse oximetry significantly reduced the number of blood gas tests ($p < 0.005$), significantly lowered the number of days on supplemental oxygen ($p < 0.001$), improved patient discomfort due to fewer painful punctures, reduced time effort for clinicians and, hence, lowered the cost (75). Pulse oximetry is less accurate than measuring the $O_2$ saturation of arterial blood, especially in the range below 80% (77, 78). In the clinically relevant range (oxygen saturation 80–100%), $SaO_2$ and $SpO_2$ have acceptable correlation. In clinically stable COPD patients, a SpO2 < 92% has high sensitivity and specificity for detecting an arterial saturation < 90%.

Our guideline search found an identical recommendation in the BTS guideline (79). It is supported by a number of observational studies (12, 13, 35, 80-82). An additional literature search conducted by the guideline authors identified a Cochrane analysis of pulse oximetry in postoperative monitoring (74). This systematic review looked at the use of pulse oximetry in 22,992 patients in five RCTs and showed that both in the theater and in the recovery room, hypoxemic episodes were 1.5 to 3 times less likely when pulse oximetry was used for patient monitoring than without pulse oximetry monitoring. No significant differences were found between the group with $SpO_2$ monitoring and the group without $SpO_2$ monitoring with regard to mortality, ICU necessity, length of hospitalization, frequency of respiratory, cardiac, neurological complications as well as complications caused by infections.

According to the authors' own literature search, the use of pulse oximeters improved the detection of hypoxemia vs. clinical monitoring alone, and this was demonstrated in various populations, and in the pre-hospital setting (12, 13, 69, 70, 80, 81).

Simultaneous pulse oximetry and arterial oxygen saturation recordings found that approximately 80% of the saturation levels measured by pulse oximetry on 396 patients in 2 intensive care units were by 2% above or below the arterial oxygen saturation, and 100% were in the +4% range (14). In this Australian study, 92% of the measurements were taken on fingers and the standard deviation of pulse oximetry vs. arterial saturation was 2.2%. Body temperature, skin color, and pulse oximeter model influenced the deviation, and at low values ($SpO_2 < 89\%$), pulse oximetry tended to underestimate $O_2$ saturation more frequently.

Pulse oximetry sensors can measure on fingers, earlobes or toes. Transient changes in $SpO_2$ are detected faster when measuring on earlobes than on fingers (83).

The systems are calibrated according to the normal oxygen saturation range of a healthy person; manufacturers are ethically prohibited from calibrating the devices in the range below 80%, and measurements below this limit are an extrapolation at best. Ultimately, the continuous use of pulse oximetry in critically or acutely ill patients serves “only” to detect sudden drops in oxygen saturation. Being aware of the flattening of the oxygen binding above 95% and the resulting harmful hyperoxia, pulse oximetry should also be interpreted with caution in this range (80).

Pulse oximetry may also provide falsely high readings, if the reduced oxygen binding capacity of red blood cells is caused by the presence of carbon monoxide or methemoglobin or is the result of skin pigmentation (below 85%) (84). Smokers, for example, have falsely normal $SpO_2$ values immediately after cigarette smoking due to a high carboxyhemoglobin (COHb) level (up to 15%).

With the exception of special algorithms for capturing the respiration rate, pulse oximetry does not provide direct information concerning the ventilation (85). $SpO_2$ has a high sensitivity, but a low specificity for predicting $paO_2$. Pulse oximeter oxygen saturation readings of less than 92% had a sensitivity of 100% and a specificity of 86% for detecting arterial saturation levels below 90% in 64 patients with COPD exacerbation (12).

Artifacts are a frequent occurrence in pulse oximetry, and trigger alerts. The devices do not require calibration, but it was found in 29 UK hospitals that 10.5% of sensors were defective and 22.3% had a deviation of more than 4% (86) from the arterial saturation levels which was attributable to technical reasons.

Pulse oximeter readings can also be affected by dark nail polish (blue, green and black, less so by red nail polish), skin pigmentation and possibly by the light emitted from surgical lamps. In a large cohort study of almost 10,000 patients, occult hypoxemia was three times as high among African Americans patients vs. Caucasians (87). This needs to be considered in real life situations, as was shown to be the case across various pulse oximeter brands (88). Overestimation of oxygen saturation by pulse oximetry has also been described in crises situations of patients with sickle cell disease (89).

In conclusion, $SpO_2$ shall be measured in all patients presenting with acute dyspnea and in all clinical situations where supplemental oxygen therapy is used, as well as in the monitoring of oxygen therapy. We found no high-level randomized trials on this topic to support this recommendation. The recommendation is consistent with those provided in other guidelines and supported by high-level evidence. It is also backed by a systematic review in the sub-area of emergency medicine (2).

Good practice:

It is useful to record the $SpO_2$ at the time of drawing arterial or capillary blood gas samples. A plausibility check in the event of major deviations between $SpO_2$ and $SaO_2$.

If a patient's oxygen saturation is below the prescribed target range, check the oxygen system and the pulse oximeter for errors (e.g., sensor signal) first.

Devices displaying the pulse oximetry plethysmographic curve or indicating the signal strength are useful for the assessment of pulse oximetry.

Repeated $SpO_2$ measurements are useful for all patients on $O_2$ therapy. Continuous pulse oximetry monitoring may be indicated in patients with risk factors.

Pulse oximetry may overestimate oxygen saturation in patients with a dark skin color or in sickle cell crises. A lower trigger threshold should be set for blood gas analyses in patients with a darker skin color.

It is useful to train medical staff on the interpretation and limitations of pulse oximetry.

Pulse oximetry, in combination with other vital signs (especially respiration rate) is an important prognostic tool, especially for hospitalized patients (e.g., NEWS2 score) and those on oxygen therapy (e.g., ROX index).

## 4.3 Alternative measuring methods

Transcutaneous partial pressure of oxygen ($tcpO_2$) is frequently used in neonatal intensive medicine and in angiology. It is a non-invasive procedure in which a sensor is heated to 42 degrees and more to determine the partial pressure of oxygen on the surface of the skin and the (derived) systemic partial pressure of oxygen. Many factors can influence the measurement (e.g., body and room temperature, local perfusion, measurement site and ambient humidity), which limits the meaningfulness of the readings. For these reasons, and due to the difficult reproducibility of the results, the method did not become established for the assessment of patients in acute settings and the monitoring of oxygen therapy. Transcutaneous carbon dioxide pressure ($tcpCO_2$) correlates better with $paCO_2$ than $tcpO_2$ and $paO_2$. $TcpCO_2$ is usually higher than $paCO_2$ and less dependent on skin changes at the site of measurement than $tcpO_2$ measurement. The method is useful in hemodynamically stable patients to record the $CO_2$ development over time; however, no reference ranges have been defined so far. In comparison to pulse oximetry, transcutaneous methods are associated with a delayed response time and the risk of skin damage from overheating (85). A 2019 meta-analysis of 44 studies and 3,974 matched measurements found that tcCO2 can be up to 15 mmHg higher or lower than paCO2 (90).

In the pre-hospital setting, where blood gas analyses are not available, capnometry has also been studied in spontaneously breathing patients to detect hypercapnia. In 50 spontaneously breathing patients attended by emergency rescue staff, the mean difference between arterial

and integral CO2 was 12 mmHg, with a poor correlation between the two (91). The measurements are often not usable in patients with severe obstructive ventilation disorder. According to expert opinion, commercially available capnometry devices do not provide sufficient correlation with the partial pressure of carbon dioxide and are not able to detect hypercapnia with sufficient certainty.

Good practice:

Alternative measuring methods such as capnometry and the transcutaneous measurement of $O_2$ or partial pressures of $CO_2$ have not gained acceptance in the acute care setting for determining whether or not oxygen therapy is indicated or for the monitoring of an oxygen therapy.

## 4.4 Arterial blood gas analysis

| WG6 | Recommendation (92 % agreement) | |
|---|---|---|
| **2** | Monitoring of oxygen by blood gas analyses should be performed in the following in-patient groups:<br><br>▪ Critically ill patients, e.g., those suffering from shock or metabolic disorders<br>▪ Ventilated patients<br>▪ Patients with severe hypoxemia (> 6 L $O_2$/min, or $FiO_2$ >0,4)<br>▪ Patients at risk of hypercapnia (e.g., COPD, severe asthma, obesity with BMI > 40 kg/$m^2$)<br>▪ Patients where no reliable pulse oximetry signal can be obtained<br><br>No routine blood gas measurements should done in patients who are stable and do not fall into any of the above-mentioned patient groups.<br><br>Expert opinion | Expert consensus |

The statements on patient selection and indication for blood gas analysis are essentially based on expert opinion. The authors' own literature search identified two guidelines addressing the role of blood gas analysis in COPD and asthma (79, 92). The COPD NICE guideline generally recommends blood gas analysis for all in-patients with acute COPD exacerbation, even those without hypoxemia on admission (79). The UK SIGN guideline recommends blood gas analysis in patients with asthma if saturation is below 92%. The recommendation was based on a cohort study (CeBM Grade 2) with 89 emergency department patients with acute asthma, which identified respiratory insufficiency for an SpO2 above 92% in less than 5% of blood gas analyses (93).

Blood gases should be measured in emergency situations in critically ill (94) hypoxemic patients and are recommended for ventilated patients in the S3 guideline on ventilation (95). According to expert opinion, blood gas analyses are required to monitor oxygen therapy if pulse oximetry is not available or fails to provide a reliable signal. Due to the high intubation rate (35–40%) of patients with severe hypoxemia (oxygenation index < 150 mmHg corresponding to an oxygen flow rate > 6 L/min or $FiO_2$ > 0.4) (96-98) it is imperative, according to expert opinion, to measure blood gases in order to exclude hypercapnia, among other conditions.

Stable hypoxemic patients who are not at risk of hypercapnic respiratory failure can generally be clinically assessed without blood gas analysis (2). Clinically stable patients are defined as having a NEWS2 score (19) < 5, with vital signs predominantly in the non-critical range.

Arterial blood gas analysis continues to be the gold standard for diagnosing respiratory failure and confirming hypoxemia. Alternative methods for detecting hypercapnia (capnometry and transcutaneous $CO_2$ measurement, see Chapter 4.3) did not prove successful in the acute treatment of adult patients. The downside of arterial puncture, according to expert opinion, are the potential of complications and the fact that they are painful for the patients.

Good practice:

Indwelling arterial catheters are useful in situations where patients are likely to require multiple arterial blood gas analyses over a short period of time.

It is not necessary to perform routine blood gas analyses in stable patients without critical illness or risk of hypercapnia. This applies if an oxygen flow rate of 6 L/min (or $FiO_2$ 0.4) is not exceeded.

Blood gas analyses from arterial or arterialized blood are indicated in inpatients at risk of hypercapnia.

## 4.5 Capillary blood gas analysis

<table>
<tr><th>WG 2</th><th>Recommendation (100% agreement)</th><th colspan="2">Grade of recommendation / GRADE</th></tr>
<tr><td rowspan="3">3</td><td rowspan="3">Blood gas analysis of arterialized capillary blood from the earlobe can be used to assess non-ICU patients.<br><br>Zavorsky 2007 (99), Magnet 2017 (100), Ekkernkamp 2015 (101)</td><td colspan="2">0</td></tr>
<tr><td>Low quality of evidence<br>⊕⊕⊖⊖<br><br>Very low quality of evidence<br>⊕⊖⊖⊖</td><td>Hypoxemia<br><br>Quality of life</td></tr>
<tr><td colspan="2"></td></tr>
</table>

Due to the increased complication rate associated with arterial puncture, blood gas analysis (BGA) for non-ICU patients is often done using earlobe blood, which is arterialized by rendering it hyperemic (= capillary BGA) (102).

The benefit of a less invasive method must be weighed against the lesser accuracy of the result. Our guideline search found an identical recommendation in the BTS guideline (2). It was based on a meta-analysis of 29 studies of 664 matched earlobe samples and 222 samples from the fingertip to determine capillary and arterial $paO_2$ (99). In this analysis, the $pO_2$ from earlobe blood was found to be lower by 3.9 mmHg on average, and from the fingertip by as much as 11.5 mmHg.

Two other studies with 83 and 120 matched samples of stable LTOT patients showed the capillary $pO_2$ to be lower than the arterial $pO_2$ by 5.6 and 6.0 mm, respectively, on average (100, 101). Major sources of error in capillary BGA include inadequate hyperemization, shunts in the earlobe region, and hemolysis due to mechanical pressure as well as clot formation or air in capillary samples. In addition, the studies also looked at patient comfort; arterial sampling was significantly more painful for patients (measured by visual analog scale) (100, 101). According to expert opinion, capillary blood gas analysis can be used in stable patients outside the intensive care setting after thorough hyperemization of the earlobe blood, but not in emergency situations when patients are unstable.

Good practice:

It is recommended that a standard be followed for capillary blood gas analysis. At least 5 minutes at a constant $O_2$ flow rate, at least 10 minutes of hyperemization, and at least 15 minutes of physical rest are considered necessary preparatory steps for capillary blood gas analysis (102).

Both capillary blood gas analysis and pulse oximetry may underestimate arterial oxygen saturation. If $SpO_2$ and $SaO_2$ are measured simultaneously, oxygen therapy should be based on the higher of the two readings; alternatively, arterial blood gas analysis should be performed.

## 4.6 Venous blood gas analysis

| **WG2** | **Recommendation (100% agreement)** | **Grade of recommendation / GRADE** | |
|---|---|---|---|
| **4** | Venous blood gas analysis shall not be used to monitor oxygen therapy. Venous blood gas analysis are able to exclude hypercapnia only at a $pvCO_2$ < 45 mmHg. | **A** | |
| | | Moderate quality of evidence ⊕⊕⊕⊖ | Hypoxemia |
| | Lim 2010 (103), Byrne 2014 (104), Bingheng 2019 (105), Bloom 2014 (106) | | |

The authors' own literature search found four meta-analyses on venous blood gas analysis during oxygen therapy, which essentially focus on the question of excluding hypercapnia (100, 101, 103-106). Blood gas measurements from venous blood samples go along with significantly fewer complications than those obtained through arterial puncture, they are less painful, and readily available. The partial pressure of oxygen in venous blood is by 13–37 mmHg lower than in arterial blood. It is therefore not suitable for measuring oxygenation. This has been shown by the meta-analyses independently of each other (103-105). In addition, there is a physiological difference between the upper and lower half of the body. Venous blood gas analyses are therefore not suitable for monitoring oxygen therapy. There is also a difference of +3–6 mmHg in the partial pressure of carbon dioxide partial compared to arterial measurements (103-106). Three studies with matched arterial and venous blood gas analyses used a cut-off of 30–46 mmHg (107-110). These three studies, in which the $pCO_2$ was determined in a core lab using matched samples, were able to exclude arterial hypercapnia with a negative predictive value of 100% at a venous $pCO_2$ cutoff of < 45 mmHg. The study by Ibrahim (110) used a cut-off von 30 mmHg for $pCO_2$ in point of care testing. Most studies with matched blood gas analyses (venous/arterial) were performed on patients with acute

COPD exacerbation. No analysis is available regarding the clinical outcomes of oxygen therapy managed based on venous blood gas analysis. However, the metabolic parameters (pH, bicarbonate, lactate) in the meta-analyses of studies on matched blood gas analyses of arterial and venous samples were consistent (103-105).

# 5 Oxygen prescription

## 5.1 Sources of oxygen

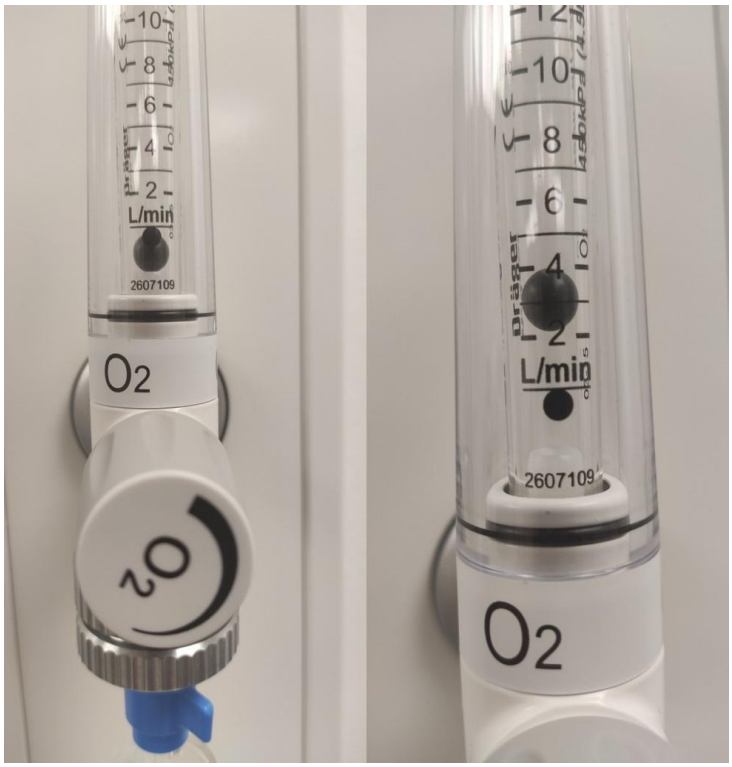
It needs to be ensured in an inpatient setting that oxygen is delivered via wall outlets providing pure oxygen, not from other outlets for compressed air or other gases. The ISO 7396-1 standard (most recent 2019 version) specifies the requirements to pipeline systems for oxygen, other gases for medicinal applications, medical gases, gases for operating surgical tools, and vacuum in healthcare facilities and covers their design, installation, function, performance, testing, commissioning, and documentation. This includes requirements to the supply systems, distribution pipeline, regulating, monitoring and alert systems, and the non-interchangeability of outlets and plug systems of the various gas or vacuum systems (Figure 3).

In Germany, medical $O_2$ in healthcare facilities is commonly provided by a central system supplying pure, compressed oxygen (100%). Central storage tanks must be refilled on a regular basis. In other countries (e.g., Canada), hospitals use oxygen concentrators to obtain oxygen 93% (111). The oxygen content in this administration form is 90–96% according to the European pharmacopoeia, with the remainder being argon and nitrogen. No adverse events have been reported in connection with this form of $O_2$ administration. If oxygen 93% is used, the equipment needs to be adjusted accordingly, as malfunctions or even equipment failures, e.g., due to incorrect calibration, are possible otherwise. The use of oxygen 90% instead of pure oxygen goes along with the theoretical risk of inadequate compensation in cases of extremely severe gas exchange disorders (e.g., COVID-19, CO poisoning). In these cases, only extracorporeal procedures can provide the necessary oxygenation.

ISO standard 10524-1-2019 specifies technical requirements for pressure regulators. Pressure regulators are used to reduce high gas cylinder pressure to a lower pressure suitable for use with medical equipment or for delivering gas directly to a patient. Tube flow meters can be set from 0.5–4 L/min, 2–16 L/min, and 4–32 L/min with a flow accuracy of +10% (+15% at the lowest setting). It can happen that medical staff are unable to correctly read the $O_2$ flow rate on a tube flow meter (for example, some manufacturers have the reading on the “north pole” of the floating ball (cf. Figure 4) while others may provide it on the “equator”). Compact flow meters with notches may offer advantages in terms of readability, but may be somewhat more inaccurate, depending on the manufacturer. Digital flow meters are currently not really used in real life settings. They are, however, the most accurate, with a display deviation of only +5% from the measured value.

Figure 3: Connectors and plugs for oxygen (hexagonal) and compressed air (square)


Figure 4: Correct reading of the floating ball (here on the “north pole”) on a tube flow meter (the flow rate is set to 4 L $O_2$/min, as shown in the right image)




Compressed $O_2$ gas cylinders with pressure regulators and notches are the mobile oxygen sources commonly used in acute medicine. It is important to ensure that portable oxygen

cylinders have sufficient oxygen, e.g., for transporting a patient. Cylinder volume, filling level and oxygen flow rate must be checked (Table 7).

Table 7: Oxygen reserve of a 10-liter oxygen gas cylinder, depending on filling pressure and $O_2$ flow rate (using the ideal gas law)

| | Flow rate | | | | |
|---|---|---|---|---|---|
| Filling pressure | 1 L $O_2$/min | 2 L $O_2$/min | 4 L $O_2$/min | 6 L $O_2$/min | 12 L $O_2$/min |
| 200 bar | ~ 33 hrs. | ~ 16 hrs. | ~ 8 hrs. | ~ 5 h 30 min. | ~ 2 hrs. 45 min. |
| 150 bar | ~ 25 hrs. | ~ 12 hrs. | ~ 6 hrs. | ~ 4 hrs. | ~ 2 hrs. |
| 100 bar | ~ 16 hrs. | ~ 8 hrs. | ~ 4 hrs. | ~ 2 h 45 min. | ~ 1 h 20 min. |
| 50 bar | ~ 8 hrs. | ~ 4 hrs. | ~ 2 hrs. | ~ 1 h 10 min. | ~ 40 min |

Calculation of oxygen supply: Cylinder volume in L x cylinder pressure in bar = oxygen volume in liters.

Portable oxygen concentrators and mobile liquid oxygen play only a minor role in acute medicine and are used in domiciliary long-term oxygen therapy.

Oxygen-gas mixtures (e.g., oxygen-helium, Heliox) do not play a major role in the routine acute care provided in a clinical setting. Care must be taken to ensure that the gases and their connections are clearly labeled to avoid mix-ups. Oxygen outlets are hexagonal (cf. Figure 3). Nitrous oxide/oxygen mixtures (Livopan®) for analgesia shall not be used in patients at risk of hypercapnia.

| **WG3** | **Recommendation (100% agreement)** | |
|---|---|---|
| **2** | Oxygen shall not be used as driving gas or used for a short time only (generally less than 10 minutes, if compressed air is not available) for the nebulized administration of drugs in patients at risk of hypercapnia.<br><br>Expert opinion | Expert consensus |

Our guideline search found a similar recommendation in the BTS guideline (2). The BTS guideline recommends limiting the use of $O_2$ as a driving gas to 6 minutes for patients at risk of hypercapnia. The guideline recommendation is based mainly on a randomized controlled trial with COPD patients (112). The authors' literature search identified another randomized controlled trial. As the previous one, it did not explore the predefined clinically important endpoints of the guideline (113). Both studies analyzed the increase in the partial pressure of carbon dioxide during high-dose oxygen therapy vs. compressed air. The randomized controlled double-blind study by Bardsley evaluated 90 patients with acute COPD exacerbation who inhaled 2.5 mg of salbutamol nebulized with either oxygen at 8 L/min or

compressed air at 8 L/min (113). In the treatment arm with $O_2$-driven nebulization, the proportion of patients in whom the transcutaneously measured partial pressure of carbon dioxide (PtCO2) had increased by ≥ 4 mmHg vs. the baseline after 6 minutes was significantly lower than after 15 minutes. No patient in the treatment arm with compressed air-driven nebulization had an increase in $PtCO_2$ ≥ 4 mmHg. In addition, the mean time for nebulized salbutamol to dissipate from the chamber was 5.2 minutes.

For optimum nebulization performance in connection with inhalation masks, manufacturers generally recommend a flow rate of the driving gas of no less than 8 L/min.

This is important in emergency situations if COPD patients at risk of hypercapnia, for example, are administered drugs (e.g., bronchodilators) via nebulizers using high-dose oxygen as a driving gas instead of compressed air. The inhalation time in this constellation shall be less than 10 minutes to limit the increase in the partial pressure of carbon dioxide (112-114).

High-dose oxygen administration may result in hyperoxemia with acute hypercapnic respiratory failure (52). Compressed air-driven nebulizers or ultrasonic nebulizers shall be preferred. If the defined target saturation range cannot be reached under nebulization, additional oxygen is recommended to be administered during inhalation, e.g., via nasal prongs. For patients not at risk of hypercapnic respiratory failure, on the other hand, inhaled drugs can be nebulized using driving oxygen, as the risk of short-term hyperoxemia (atelectasis, formation of oxygen radicals, vasoconstriction, etc.) is neglectable.

Gunawardena et al. (1984) (114) found a significant increase in $paCO_2$ in nine hypercapnic COPD patients after 15 minutes of oxygen-driven nebulization, with a return to baseline values only 20 minutes after terminating nebulization. Various authors concluded that carbon dioxide levels increased after 15 minutes in patients with acute COPD exacerbation during nebulization using driving oxygen (112, 115).

Good practice:

Continuous monitoring ($SpO_2$, respiration rate, breathing pattern and pulse, mental state) is advisable during oxygen-driven nebulization drug therapy for patients at risk of hypercapnia (2).

Inhalation under high-flow oxygen therapy may result in changes in the aerosol, transport of particles to airways, and drug efficacy.

| WG3 | Recommendation (100% agreement) | |
|---|---|---|
| **3** | Oxygen shall be administered, monitored and controlled by staff trained in oxygen therapy. Patients shall be informed about the oxygen therapy.<br><br>Expert opinion | Expert consensus |

Our guideline search found an identical recommendation in the BTS guideline (2). The issue of staff training was not a key question for our literature search. The authors' own literature search did not identify useful studies. For lack of relevant studies, the recommendation provided in this guideline also relies on expert opinion. However, it is a strong recommendation, as the group of experts unanimously considers staff training and patient information to be indispensable elements of oxygen therapy.

Doctors, nurses, the members of emergency medical services, respiratory therapists who prescribe, administer, monitor, and/or manage oxygen therapy, shall be comprehensively trained. They shall be aware of the side effects and risks of hypoxemia and hyperoxemia and be able to identify the signs and symptoms of insufficient as well as excessive oxygen administration. Training shall cover the target saturation ranges, acting on one’s own responsibility, documentation, and patient observation. It is about understanding and being able to practically apply their knowledge of the core parameters of patient assessment in an emergency situation. In addition, they should be able to correctly read and document the readings and flow rates on the equipment and maintain a stable target saturation range (2).

Good practice:

Patient information about oxygen therapy by the medical staff (especially nurses and respiratory therapists) is helpful, as is the involvement of the patient's family members.

Their involvement and training can prevent an independent increase of oxygen due to dyspnea.

## 5.2 Oxygen delivery systems

| WG3 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **1** | Nasal prongs should be the primary choice for low $O_2$ flow rates (i.e. < 6 L/min), alternatively Venturi masks can be used with low oxygen flow rates.<br><br>Costello RW 1995 (116); Nolan KM 1993 (117), Eastwood GM 2008 (118), Stausholm 1995 (119), Ayhan 2009 (120) | **B** | |
| | | Moderate quality of evidence<br>⊕⊕⊕⊖ | Quality of life/adverse drug reactions |

With regard to key question 4, the evidence report identified 2 meta-analyses or systematic reviews and 1 randomized trial, none of which explored the question. Our guideline search found a recommendation on this issue in the BTS guideline (2). The recommendation is based on four cross-over studies (116, 117, 121, 122), and four randomized trials investigating the patient comfort of different oxygen delivery systems were identified in the context of our own research (96, 120, 123). Table 8 provides an overview of the studies.

Table 8: RCTs comparing different oxygen delivery systems. (96, 116–120, 123)

| Author, year | Type | n | Trial participants | Comparison | Patient comfort | Dislocation |
|---|---|---|---|---|---|---|
| Nolan et al. 1993 (117) | RCT | 30 | post-procedural | N, M | n.a. | M (67%) > N (6%) |
| Stausholm et al. 1995 (119) | cross-over | 25 | post-procedural | N. NS, M | VAS: N (85) > NS (72) > M (42); p 0,02 | n.a. |
| Eastwood et al. 2008 (118) | cross-over | 37 | inpatient | N. NS, M | VAS: N (66) = NS (63) > M (49); p < 0,001 | n.a. |
| Costello et al. 1995 (116) | cross-over | 99 | inpatient | N, VM | n.a. | VM (63%) > N (37%) |
| Ayhan et al. 2009 (120) | RCT | 106 | post-procedural | N, M | VAS: N (91) > VM (67); p 0,01 | M (76%) > N (4%) |
| Maggiore et al 2014 (123) | RCT | 105 | post extubation | VM, HFNC | VAS: VM (70)=HFNC (50) n.s. | VM (56%) > HFNC (32%) |
| Frat et al. 2015 (96) | RCT | 310 | respiratory insufficiency | RM, HFNC, | VAS: RM (60) < HFNC (71) > NIV (67) p 0.01. | n.a. |
| Rittayamai et al. 2014 (124) | cross-over | 17 | post extubation | RM, HFNC | RM (14)=HFNC (19) n.s. | n.a. |

RCT – randomized controlled trial; n – number of patients; N – nasal prongs; NC – nasal cannula; VAS – Visual Analogue Scale; RM – reservoir mask; HFNC – high-flow nasal cannula; NIV – NIV mask; VM – Venturi mask; n.s. – not significant; n.a. – not available

In conclusion, nasal prongs offered greater patient comfort and had lower dislocation rates than masks. Only one out of three RCTs indicated that high-flow nasal cannulae (HFNC) provided slightly superior comfort than masks. No randomized controlled studies with nasal

prongs as comparator were identified. Higher flow rates went along with more adverse effects (125) so that the differences in patient comfort between the delivery systems used in the studies may also be attributable to different flow rates.

Oxygen delivery systems consist of two components: the component providing the oxygen (e.g., in cylinders) and the component delivering the oxygen to the patient (e.g., nasal prongs or masks; Figure 5). The two components are selected based on clinical circumstances and patient needs (Table 9).

Table 9: Pros and cons of different oxygen delivery systems

| | Pros | Cons |
|---|---|---|
| Nasal prongs (N) | High patient comfort<br>Low cost | $FiO_2$ limited,<br>$FiO_2$ dependent on opening of the mouth and respiration rate |
| Nasal cannulae (NC) | Occupy only one opening of the nose<br>Low cost | Mucous membrane irritation |
| simple face masks (M) | $FiO_2$ independent of the opening of the mouth<br>Low cost | Low patient comfort<br>Risk of hypercapnia at flow rates < 5 L/min |
| Venturi masks (VM) | Reduced risk of hyperoxia and hypercapnia<br>Low aerosol formation | Noise |
| Reservoir masks (RM) | High $FiO_2$ | Low patient comfort, risk of hypercapnia at flows < 5 L/min |
| High-flow cannulae (HFNC) | High $FiO_2$<br>High patient comfort with good fit and humidification<br>Acceptable aerosol formation, secretolysis | More effort for staff, higher cost |
| Ventilation masks (NIV/CPAP) | High $FiO_2$<br>Low aerosol formation (2 tubes and/or filter) | Low patient comfort (e.g., pressure marks, claustrophobia)<br>more staff effort, higher cost |

CPAP – continuous positive airway pressure; NIV – non-invasive ventilation; $FiO_2$ – inspired oxygen concentration

Nasal prongs are suitable for administering low to moderate oxygen concentrations ($FiO_2$ 0.26–0.54) (116, 119, 122, 126). The inspired oxygen concentration depends on the opening of the mouth (126). For $O_2$ flow rates between 2 and 4 L/min, the $FiO_2$ delivered to the trachea can be calculated using the following formula: $FiO_2 = 0.21 + (O_2$ flow in L/min x 0.038) (17). Respiration rate, depth of breath, and mouth opening can affect the inspired oxygen concentration when using nasal prongs (2, 17, 126).

The inspired oxygen concentration for simple face masks is approx. 40–60% and highly dependent on the flow rate. $O_2$ flow rates below 5 L/min pose a risk of hypercapnic respiratory failure due to insufficient $CO_2$ washout (127).

Venturi masks use the Bernoulli's principle by introducing the oxygen through a tapered nozzle and swirling the air/oxygen mix entering at a high flow rate for inhalation. The resulting negative pressure draws in ambient air in accordance with the size of the opening, and mixes it with the oxygen at a fixed ratio, depending on the attachment used. If the $O_2$ flow through the nozzle is increased, the amount of fresh gas offered increases in line with the mixing ratio, but not the inspired oxygen concentration. Venturi masks have openings allowing excess air/oxygen mixture to escape. Venturi masks allow controlled oxygen delivery from 24–60%. Venturi masks shall be used with 24% and 28% attachments in patients at risk of hypercapnia (2). For patients with high respiration rates (> 30/min) the flow rate for Venturi masks shall be set above the minimum flow rates indicated in Table 10 (121). Oxygen delivery of 1–4 L/min via nasal prongs corresponds to $O_2$ delivery using a 24%, 28%, 31%, 35%, or 40% Venturi mask (122, 128). Unlike with nasal prongs, a Venturi mask does not increase the $FiO_2$ at higher flow rates.

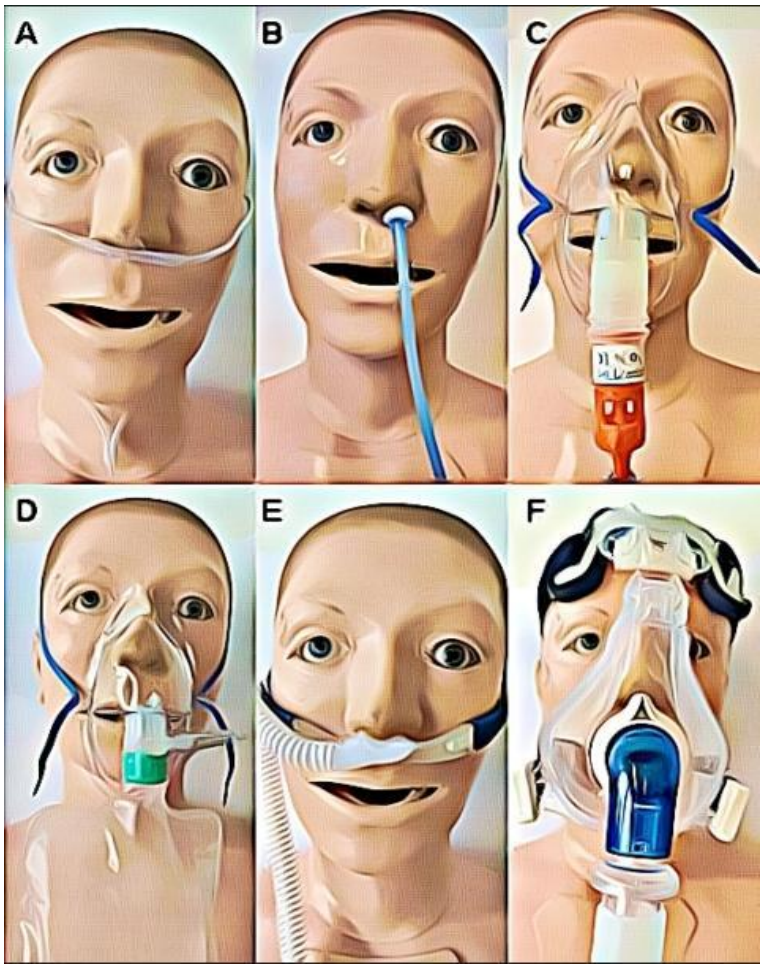
Table 10: Overview of Venturi masks and recommended flow rates

| Color of Venturi mask, $FiO_2$ | Oxygen flow in L/min (minimum flow rate*) |
|---|---|
| blue, 24% | 2 |
| white, 28% | 4 |
| orange, 31% | 6 |
| yellow, 35% | 8 |
| red, 40% | 10 |
| pink, 50% | 12 |
| green, 60% | 15 |

*Read the manufacturer's information; for respiration rates > 30/min, increase flow by 50%, as necessary (121). $FiO_2$ – inspired oxygen concentration

Significantly higher $FiO_2$ values can be achieved with a reservoir mask or HFNC while maintaining spontaneous breathing than with nasal cannulas/prongs or a simple mask. Reservoir masks are not indicated for patients at risk of hypercapnia (COPD, severe obesity with BMI > 40 $kg/m^2$, cystic fibrosis, chest wall deformities or neuromuscular disorders) (121).

Figure 5: Various oxygen delivery systems




A – nasal prongs; B – nasal cannula; C – Venturi mask; D – reservoir mask; E – HFNC (high-flow nasal cannula); F – NIV mask (non-invasive ventilation)

Good practice:

Nasal prongs/cannulae and Venturi masks are the preferred types of oxygen delivery in acute medicine.

The minimum $O_2$ flow rates as indicated by the manufacturer shall be observed when using Venturi masks.

Do not use simple face masks or reservoir masks in patients at risk of hypercapnia or with oxygen flow rates < 5 L/min.

## 5.3 Oxygen prescription

| WG 3 | Recommendation (100% agreement) | |
|---|---|---|
| **4** | Inpatient oxygen therapy shall be prescribed by a physician, specifying a target range of oxygen saturation.<br><br>Expert opinion | Expert consensus |

Our literature search could not identify relevant studies demonstrating that oxygen prescription is associated with the predefined clinically relevant aspects. The proportion of inpatients in which oxygen therapy is administered based on a prescription indicating a target range is suboptimal and ranges from 40–60% (1, 129). Medical oxygen was classified as medicine in Germany in 2005 and a prescription is required for supplemental oxygen administration. Prior to prescribing medical oxygen, clinicians shall evaluate the patient's clinical status to properly assess the guideline-compliant patient-specific target range of oxygen saturation, and consider it in their prescription. Oxygen therapy is to correct the hypoxemia and achieve the patient-specific oxygen saturation target range. The amount of oxygen to be administered depends on the patient's underlying condition. Based on the patient-specific prescription, trained nurses/respiratory therapists can independently monitor and control the therapy within the specified framework to achieve or maintain the desired target saturation range. Since nurses are those who spend the most time with the patient, they are able to detect changes without delay, and are in the best position to manage the delivery of oxygen.

Good practice:

In prescribing the delivery system (nasal cannula/prongs, mask, Venturi mask, reservoir mask, high-flow, etc.), consider $O_2$ requirement, breathing pattern (i.e., respiration rate, depth of breath), mouth opening, and risk of hypercapnia (17).

Oxygen therapy must be prescribed by a clinician. The prescription shall specify the type of delivery, amount of oxygen, target saturation ranges, and monitoring intervals. Figure 6 shows a sample prescription form as proposed by the guideline development group.

In an emergency situation, oxygen should be administered without a formal prescription (cf. 7.4) and documented in retrospect.

Figure 6: Sample oxygen prescription form

| **Oxygen ($O_2$) – Prescription** | | |
|---|---|---|
| **Target saturation range ($SpO_2$)**<br>**❑88-92%**<br>**❑92–96%**<br>**❑_____** | **Oxygen delivery**<br>❑Nasal cannula (NC)<br>❑Nasal prongs (N)<br>❑Mask (M, from 5 L/min)<br>❑Venturi mask (VM, observe minimum flow rate)<br>❑blue / 24%<br>❑white / 28%<br>❑orange / 31%<br>❑yellow / 35%<br>❑red / 40%<br>❑pink / 50%<br>❑green / 60%<br>❑Reservoir mask (RM, from 5 L/min)<br>❑High flow (HFNC, specify $FiO_2$% and L/min)<br>❑_____ | **Oxygen dosage**<br>Starting dose _____ L/min<br>Maximum _____ L/min*<br>Starting dose _____ %<br>Maximum _____ %*<br>*Reassess if $SpO_2$ remains below the target saturation range despite delivering the prescribed maximum oxygen dose. |
| Date:<br>Signature | | |

| WG3 | Recommendation (100% agreement) | |
|---|---|---|
| **5** | Each oxygen prescription should be based on a patient evaluation by clinicians or other specially trained healthcare professionals<br>Expert opinion | Expert consensus |

The guideline search did not identify any evidence-based recommendations in this regard in other guidelines. The authors' own and independent literature search did not find any randomized trials or meta-analyses (118, 120, 126).

According to retrospective analyses, hypoxemia is a negative prognostic indicator in inpatients and emergency room patients (31, 32). Oxygen prescription therefore requires reassessing the patient to be able to detect clinical deterioration at an early stage and prevent

events such as CPR, transfer to ICU, or death. The reassessment intervals are determined by the severity of vital sign abnormalities and the extent of hypoxemia. In the UK, reassessment is recommended every 12 hours, even in patients with normal vital signs. For hospitalized patients, the UK recommends reassessments every 4–6 hours for patients with freshly started or ongoing oxygen therapy (130).

Based on expert opinion, the BTS guideline recommends 6-hour intervals for patients on oxygen therapy and continuous monitoring depending on where the oxygen therapy takes place (ICU/emergency room/regular ward, etc.) if multiple vital signs outside the normal range and patients have a NEWS2 score ≥ 7. Continuous monitoring is recommended in track and trigger systems when multiple vital signs are outside the normal range. No randomized controlled trials are available in this regard, but it is known, for example, that approximately 40% of in-patients on high-flow oxygen therapy are intubated (96, 97). Therefore, the amount of oxygen required to achieve the target oxygen saturation may be associated with the occurrence of a life-threatening deterioration in the patient's condition (131).

Good practice:

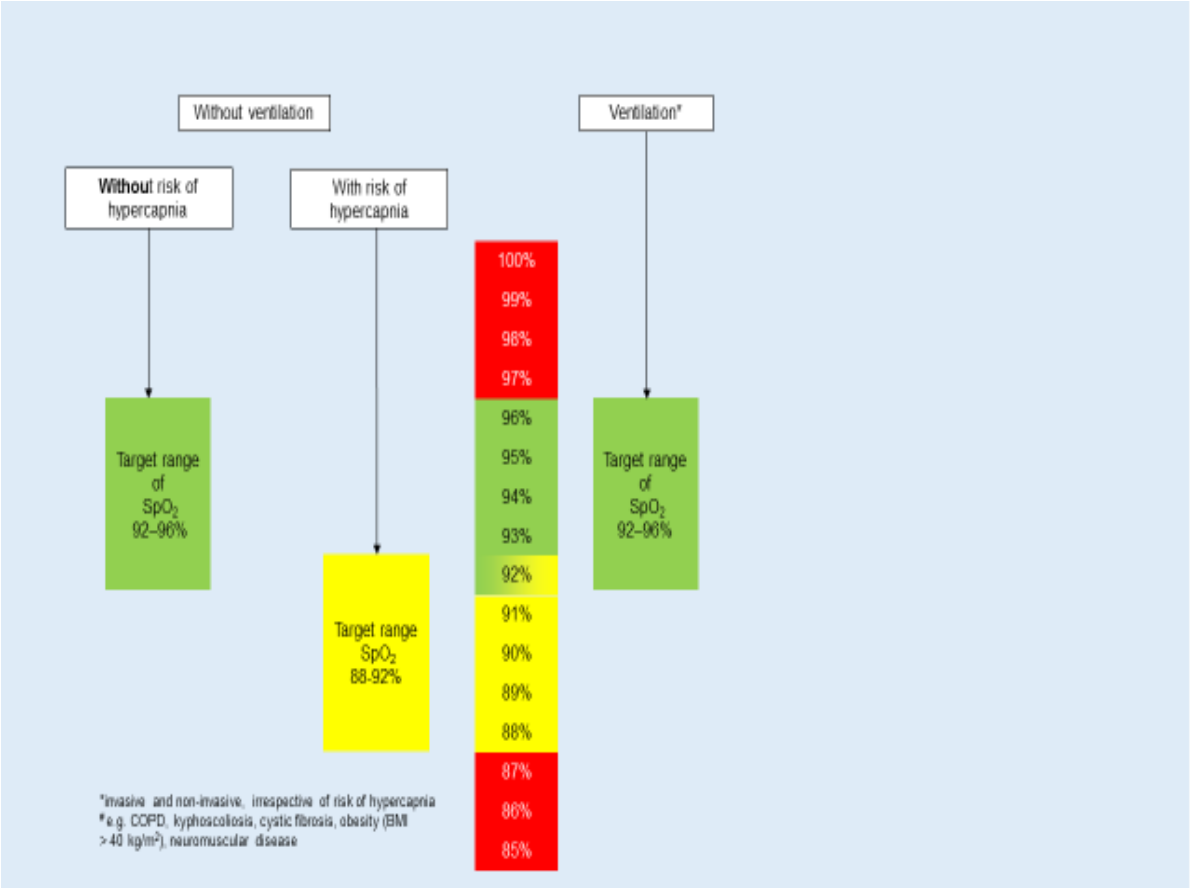
Vital signs shall be checked at least every 6 hours during oxygen therapy.

It is recommended to continuously monitor $SpO_2$, pulse, and respiration rate from flow rates above 6 L/min in patients under high-flow oxygen (HFNC), and to closely monitor the other vital signs (mental state, blood pressure, body temperature).

# 6 Application of oxygen

It is relevant for the target ranges of this guideline when hypoxemia and hyperoxemia are likely to be harmful for acutely ill patients and in which range oxygen therapy is not harmful and hence safe. Whether or not a patient is ventilated and whether or not a patient is at risk of hypercapnia plays a role in this context. The target oxygen therapy ranges listed in Figure 7 shall be used for these 3 patient groups.

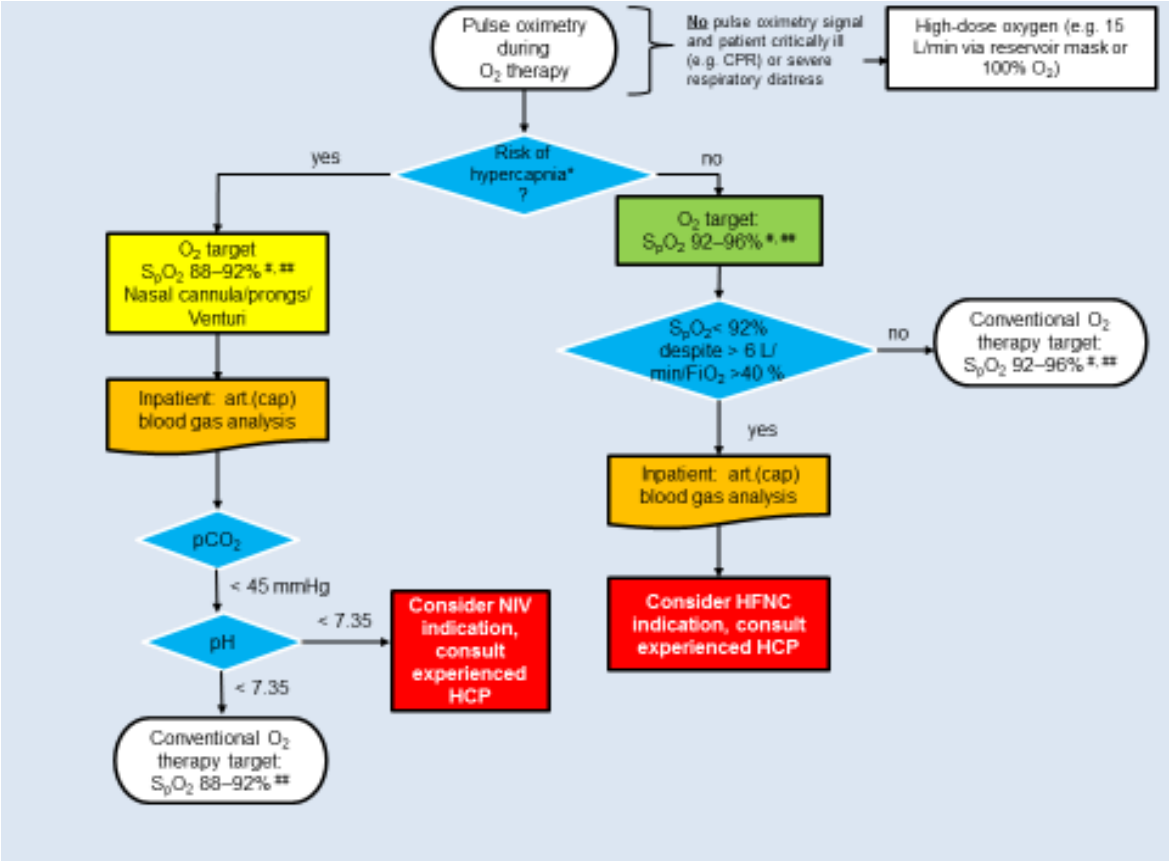
Figure 7: Target ranges of oxygen therapy for the different groups of patients




BMI – body mass index; $SpO_2$ – oxygen saturation measured by pulse oximetry; $SaO_2$ – arterial oxygen saturation

The recommended $O_2$ therapy for patients with spontaneous breathing is shown in Figure 8.

Figure 8: Oxygen therapy in non-ventilated patients




*e.g., COPD, BMI ≥ 40 kg/m2, cystic fibrosis, adults with neuromuscular or chest wall disorders.
[#] Do not start $O_2$ below $SpO_2$ 88% or 92%, respectively
[##] Stop or reduce $O_2$ above 92% or 96%, respectively
[O] HCP experienced in the diagnosis and treatment of patients with respiratory failure or critically ill patients
CPR – cardiopulmonary resuscitation; $SpO_2$ – oxygen saturation as measured by pulse oximetry; $O_2$ – oxygen; NIV – non-invasive ventilation, HFNC – high-flow oxygen, BMI – body mass index; art. – arterial; cap – capillary; $pCO_2$ – partial pressure of carbon dioxide

Good practice:

The oxygen dose initially selected in a hypoxemic patient depends on the severity of hypoxemia and the associated circumstances. The following approach has been tried and tested in real life situations (Table 11, modified based on (132)):

Table 11: Recommended starting dose of oxygen

| $O_2$ saturation without | $O_2$ starting dose |
|---|---|
| | No risk of hypercapnia |
| $SpO_2$ < 85% | $O_2$ > 5 L/min, Venturi mask ≥ 40% (red) |
| $SpO_2$ 85–91% | $O_2$ 2–4 L/min, Venturi mask 28% (white) or 35% |
| $SpO_2$ > 92% | No $O_2$ administration (exceptions: Chapters 7.3, 7.4, 7.8) |
| | Risk of hypercapnia |
| $SpO_2$ < 88% | $O_2$ 1–2 L/min, Venturi mask 24% (blue) or 28% (white) |
| $SpO_2$ > 88% | No $O_2$ administration (exceptions: Chapters 7.3, 7.4, 7.8) |

## 6.1 Oxygen saturation target ranges in acute conditions

| WG4 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **1** | The target saturation range of acute oxygen therapy for non-ventilated patients not at risk of hypercapnia shall be between 92% and 96% as measured by pulse oximetry. | **A** | |
| | | Moderate quality of evidence ⊕⊕⊕⊖ | Mortality |
| | Siemieniuk 2018 (3), Chu 2018 (43, 56), Wetterslev 2015(56) | Moderate quality of evidence ⊕⊕⊕⊖ | functional outcome |

The BTS guideline recommends that oxygen should be prescribed to achieve a target $SpO_2$ of 94–98%. The recommendation is supported by low-level evidence. However, several randomized studies and meta-analyses have been published on this topic since the publication of the guideline (2). Another evidence-based guideline provides a strong recommendation for maintaining an oxygen saturation of no more than 96% (upper limit) in acutely ill patients (3). The authors calculated that this corresponded to 11 fewer deaths (51 vs. 62) per 1,000 patients treated with conservative oxygen therapy. The recommendation on when oxygen therapy should be started in patients with acute cerebral and myocardial infarction included a weak recommendation for a lower limit < 90–92% and a strong recommendation for SpO2 < 93% (cf. Chapter 7.1). The latter groups of patients represented 90% of the patient population included in the meta-analysis (43).

Three meta-analyses and four randomized controlled trials on target oxygen ranges were identified by independent literature search (30, 43, 54, 133-135). The meta-analysis by Chu of 25 RCTs with 16,037 hospitalized patients demonstrated that liberal oxygen administration was associated with increased 30-day mortality (and at longest follow-up) (43). This meta-analysis included patients with sepsis, critical illness, stroke, trauma or emergency surgery, acute coronary syndrome, and cardiac arrest. Most randomized trials covered by the meta-analysis compared high-dose oxygen (with resulting hyperoxemia) in normoxemic patients against patients on ambient air or compressed air as placebo group. The authors reasoned that the increased mortality associated with hyperoxemia was attributable to proinflammatory effects, vasoconstriction, particularly in the myocardium and CNS, and increased oxidative stress. Thus, this meta-analysis not only failed to demonstrate superiority of hyperoxemia as a therapy approach for normoxemic patients, but also showed the risks across different conditions. Oxygen therapy has adverse effects on patients, e.g., drying of mucous membranes, nosebleeds, restriction of mobility, claustrophobia, difficulty communicating and eating/drinking (3). The upper limit of $SpO_2$ of 96% recommended in the meta-analysis by Chu is also based on the mean saturation at enrollment. A study (136) on 140 patients over 70 years of age provided a mean arterial oxygen saturation of 95%.

In the largest randomized trials on patients with stroke and acute myocardial infarction, the limit of $SpO_2$ below which oxygen was administered in any case ranged from 90–94% (133, 135, 137). Almost 38 000 patients with a median age of 69 years in 3 UK hospitals had a mean SpO2 on ambient air of 97% on admission (25% and 75% quartiles of 95% and 98%) (10).

Routine high-dose oxygen administration in the perioperative period (the inspiratory oxygen fraction ($FiO_2$) in most studies was 80%) provided contradictory results in randomized controlled trials in terms of a reduction of wound infections as well as postoperative nausea and vomiting vs. conservative dosing (mostly $FiO_2$ 30%). Based on a large meta-analysis (57) conducted for this indication, hyperoxemia is not reasonable during surgery.

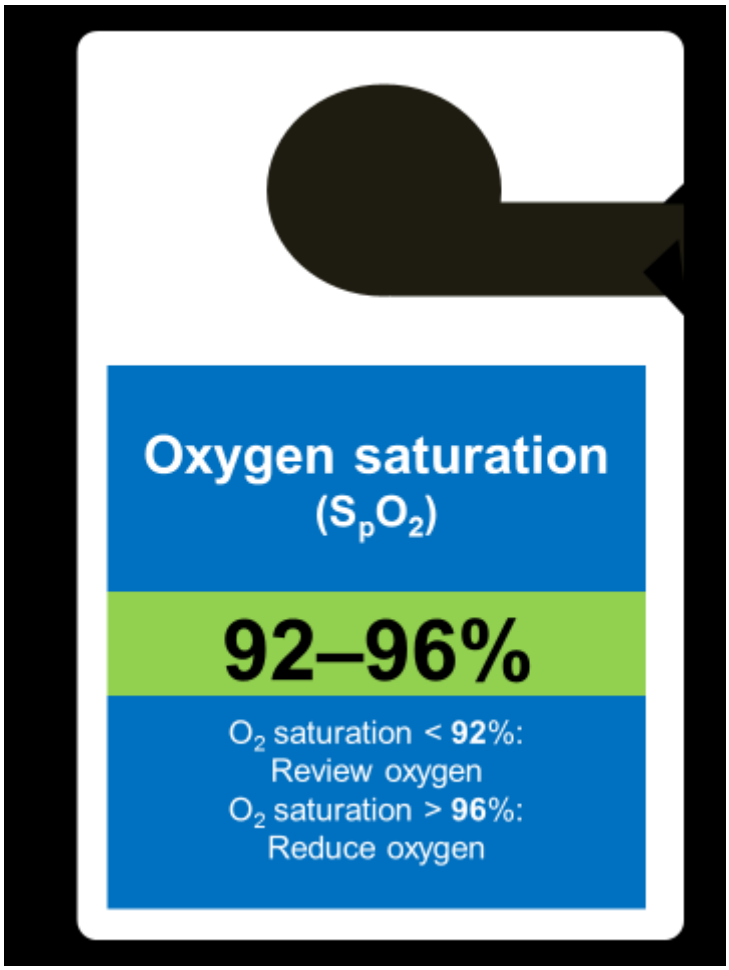
Good practice:

If oxygen saturation falls below 92%, starting or increasing oxygen therapy is reasonable in patients not at risk of hypercapnia. If the saturation exceeds 96%, it is indicated to discontinue or reduce the oxygen therapy.

The specified target oxygen saturation applies at rest. In acutely ill patients, values below the target range can be tolerated for a short period of time during exertion or coughing, if the oxygen saturation subsequently quickly returns to the target range (as a rule within less than 1 minute).

Oxygen cards indicating the $SpO_2$ target range at the bedside are useful for all patients on oxygen therapy (Figures 9 & 11).

Figure 9: $O_2$ card for patients not at risk of hypercapnia



## 6.2 Target oxygen saturation ranges for patients at risk of hypercapnia

| WG4 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **3** | Oxygen shall be prescribed for acutely ill, non-ventilated patients at risk of hypercapnia (e.g., COPD) for a target saturation range of 88–92% as measured by pulse oximetry. Oxygen therapy shall not be delivered or shall be reduced in this situation if the saturation is above 92% and shall only be started again if the saturation drops below 88%.<br><br>Austin 2010 (52), Kopsaftis 2020 (138) | **A** | |
| | | Moderate quality of evidence ⊕⊕⊕⊖<br><br>Low quality of evidence ⊕⊕⊖⊖ | Mortality<br><br>Intubation |

Our guideline search found that the BTS guideline recommends prescribing a target $SpO_2$ range of 88–92% for patients at risk of hypercapnia (low level of evidence). The level of evidence supporting this recommendation was high for COPD patients and low for all other patients (2).

The authors' own literature search identified one meta-analysis in addition to the evidence report (138). This meta-analysis. However, is based on one RCT only (52). In this RCT (49), 403 patients with suspected COPD (the diagnosis was retrospectively confirmed in 214 patients) were treated by emergency staff with either high-dose oxygen (6–8 L/min by mask) or with cautious oxygen administration titrated to a target saturation between 88% and 92%. 9% of patients treated with high-dose oxygen vs. 3% of those treated with conservative oxygen therapy died while in hospital (treatment effect 0.05–0.91). The Cochrane analysis (138) included only the Austin study on $O_2$ therapy in COPD patients, which was conducted in a pre-hospital setting and had a mortality risk reduction (pre-hospital and in-hospital) of 0.22 (95% confidence interval 0.05–0.97) through titrated oxygen therapy (138). Intubation rates were not significantly increased under liberal oxygen therapy.

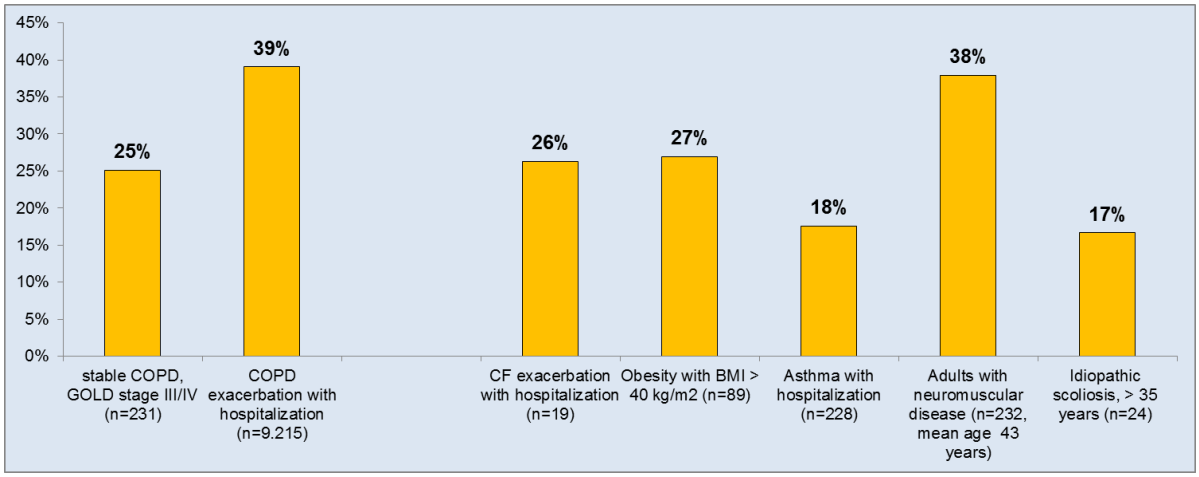
A study of 3524 blood gas samples in a single UK hospital found that 27% had a partial pressure of carbon dioxide of more than 45 mmHg (2). In a French randomized controlled trial on 187 hyperoxemic patients seen in the emergency department, 27% had a partial pressure of carbon dioxide of more than 45 mmHg (139). In a German analysis of 6,750 hospitalized patients, 2,710 of whom suffered from respiratory distress, 588 (22%) had a PaCO2 of 45 mmHg and more (140). Patients with COPD in particular, but also those with cystic fibrosis, thoracic deformities, neuromuscular disease, and obesity (BMI > 40 kg/m2) are at risk of hypercapnic respiratory failure in the context of ventilatory insufficiency ((141-147), Figure 10). In 22–34% of high-risk patients (including COPD and obesity), a significant increase in the transcutaneously measured partial pressure of carbon dioxide was observed

under high-dose oxygen therapy. Hence, the risk of hypercapnic respiratory failure was increased three- to fivefold vs. conservative oxygen therapy (112, 148-151).

In a prospective observational study on 2,645 COPD patients with in-hospital exacerbation in the UK, $SpO_2$ > 92% on admission was associated with increased in-hospital mortality (adjusted risk of death 1.98 (95% confidence interval (CI) 1.09–3.60) and 2.97 (95% CI 1.58–5.58), respectively, independent of the presence of hypercapnia (152).

In a before/after comparison at one of the study sites, a reduction of in-hospital mortality from 20% to 5% was observed among 186 patients with COPD exacerbation after a conservative oxygen strategy with oxygen titration was introduced in the pre-hospital setting (153).

Figure 10: Share of patients with hypercapnia across different conditions (141–147)



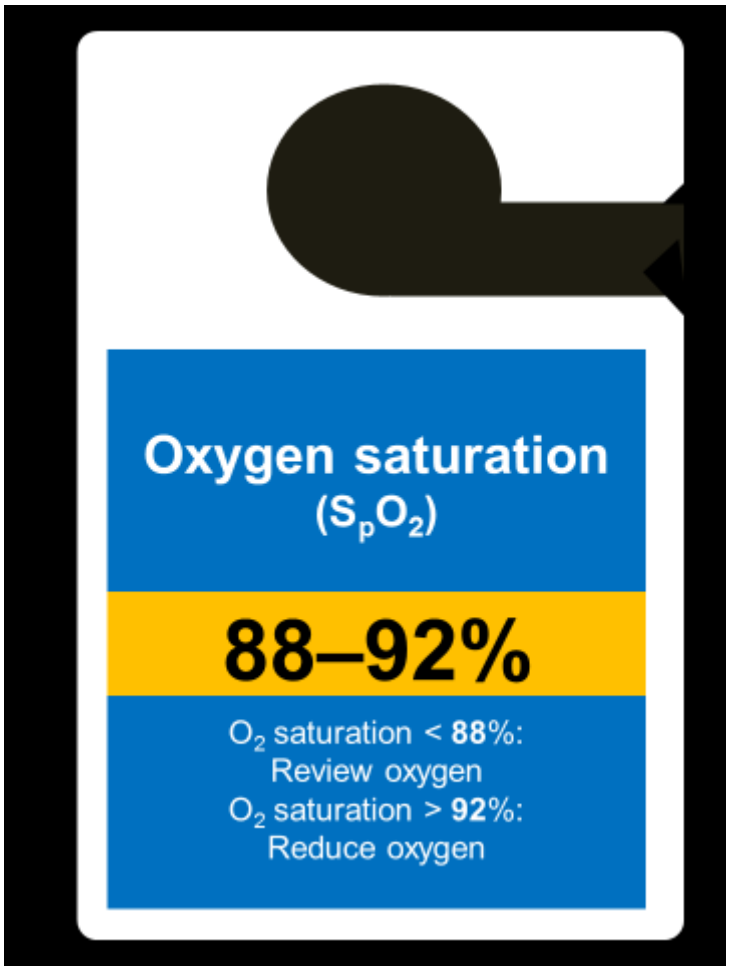

COPD – chronic obstructive pulmonary disease; GOLD – Global Initiative for Chronic Obstructive Lung Disease; CF –cystic fibrosis; BMI – body mass index

Good practice:

A lower oxygen saturation target range of 88–92% is advised for $O_2$ therapy in patients at risk of hypercapnia.

Dedicated $O_2$ cards (Figure 11) and emergency ID cards are useful for this group of patients.

Figure 10: $O_2$ card for patients at risk of hypercapnia




## 6.3 Target oxygen saturation ranges for ventilated patients

| WG4 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| 2 | The target arterial oxygen saturation range for ventilated patients shall be 92–96%. In addition to arterial blood gas analysis, oxygen saturation measurement by pulse oximetry shall be used to guide the oxygen delivery if compliance is acceptable (deviation of up to 2%) and in the pre-hospital setting.<br><br>Girardis 2016 (154); Panwar 2016 (155), Asfar 2016 (46), Barrot 2020 (30), Barbateskovic 2019, ICU-ROX (134) | **A** | |
| | | Moderate quality of evidence ⊕⊕⊕⊖<br><br>Low quality of evidence ⊕⊕⊖⊖ | Mortality<br><br>adverse events |

Our guideline search found that those of the identified guidelines that were rated high for their methodological quality exclude ventilated patients in their recommendations. The independent literature search identified one meta-analysis and two RCTs with ventilated patients (30, 43, 134). In addition, the authors were able to identify two additional meta-analyses and four additional RCTs in the context of their own literature search (45, 46, 154-157). Furthermore, large retrospective analyses of ICU patients (the vast majority of study subjects were ventilated) have been published (158-160).

Ventilated patients should be viewed separately, as they are usually continuously monitored in ICU and the risk of hypercapnic respiratory failure is lower under mechanical ventilation. Recent publications have shown harmful effects of hyperoxemia in intensive care patients, especially those who are ventilated.

Three large retrospective observational studies (36,307 patients (161), 19,515 patients (160), 152,680 patients (158) investigated the effect of hypoxemia and hyperoxemia on the in-hospital mortality of ICU patients. The Australian study by Eastwood demonstrated excess mortality in the first 24 hours only in hypoxemia, not in hyperoxemia ($paO_2$ > 120 mm Hg corresponding to a $SaO_2$ of 99%) (158-160). The UK study by Palmer demonstrated non-dose-dependent association of ICU mortality in the first 24 hours in patients with hyperoxemia ($paO_2$ > 100 mm Hg corresponding to a $SaO_2$ of 98%) (160). The analysis from the Netherlands showed an association between in-hospital mortality in the first 24 hours and hyperoxemia (defined as $paO_2$ > 123 mmHg, corresponding to a $SaO_2$ of approx. 99%) as well as hypoxemia ($paO_2$ < 67 mmHg corresponding to $SaO_2$ < 93%) (161).

In a meta-analysis of 10 randomized trials and 1,458 subjects, no association was found between 3-month mortality and hyperoxemia (target $SpO_2$ > 96%); however, hyperoxemia went along with a relative risk of 1.13 (1.04–1.23) of more adverse events such as infections, with very low level of evidence (45). For ARDS, a 2020 meta-analysis including a single study (26) indicated a conservative $SpO_2$ target range of 88–92% with a very low level of evidence (162). The authors of a 2017 meta-analysis (four studies with 372 patients) found conservative oxygen therapy to be associated with lower ICU mortality, 28-day mortality, in-hospital mortality, and non-respiratory organ failure than liberal $O_2$ therapy (156).

6 randomized trials (cf. Table 12) compared liberal vs. conservative oxygen therapy for mostly invasively ventilated ICU patients. Oxygen saturation target ranges were not consistent across studies, and the included patient populations were heterogeneous. About a quarter of the ventilation time was spent without supplemental oxygen administration under a conservative $O_2$ regime, without adverse effects being observed (134). The French study on 205 patients with acute respiratory distress syndrome (ARDS) was terminated prematurely due to safety concerns, as the conservative therapy group showed increased mortality vs. other studies with a particularly low target saturation range of 88–92%, and five patients in the conservative therapy group died of mesenteric ischemia. Mortality was also increased in the conservative therapy group in the Australian multicenter study (155) with the same $SpO_2$ target range, albeit not significantly.

Table 12: Randomized controlled trials in ICU patients using different oxygen target ranges

| Study, year | n | Mean age, years | Share, non-surgical | Maximum intervention time | $pO_2/FiO_2$ (invasive ventilation %) | Liberal target | Conservative target | Outside target<br>Liberal above / below | Outside target<br>Conservative above / below | Mortality, liberal vs. conservative |
|---|---|---|---|---|---|---|---|---|---|---|
| CLOSE, 2016(155) | 103 | 62 | 77% | 7 days | 248 (100) | $S_pO_2 \geq 96\%$ | $S_pO_2$ 88–92% | 3% | 14% | 90 days: 37 vs. 40%[+] |
| | | | | | | $pO_2$ > 90 mmHg* | $pO_2$ 55-64 mmHg* | | | |
| OXYGEN-ICU, 2016(154) | 434 | 64 | 62% | N/A | N/A (67) | $S_aO_2$ 97–100% | $S_aO_2$ 94–98% | n.a. | 28% / n.a. | ICU: 11.6 vs. 20.2% |
| | | | | | | minimum $FiO_2$ 0.4, $pO_2$ $\leq$ 150 mmHg | $pO_2$ 71-99 mmHg | | | |
| HYPER2S, 2017(46) | 442 | 68 | 70% | 24 hours | 224 (100) | $FiO_2$ 1.0 | $S_aO_2$ 88–100% | 53%[##] / n.a. | | 28 days: 42.8 vs. 35.5% |
| | | | | | | | $pO_2$ 55–75 mmHg* | | | |
| ICU-ROX, 2020(134) | 965 | 58 | 69% | 28 days | 252 (100) | $S_pO_2 \geq 91\%$ | $S_pO_2$ 91-96% | 52.2%[#] / 0.8% | 28.1% / 1.9% | 90 days 32.5 vs 34.7%[+] |
| | | | | | | $pO_2 \geq 61$ mmHg* | $pO_2$ 61–81 mmHg* | | | |
| $LOCO_2$, 2020(30) | 205 | 63 | N/A | 7 days (on ventilator) | 118 (100) | $S_pO_2 \geq 96\%$ | $S_pO_2$ 88–92% | n.a. | n.a. | 28 days: 26.5 vs. 34.3% |
| | | | | | | $pO_2$ 90–105 mmHg | $pO_2$ 55–70 mmHg | | | |
| HOT-ICU, 2021(157) | 2,928 | 70 | 85% | 90 days | 125 (58) | $S_aO_2$ 96–98%* | $S_aO_2$ 87–93%* | > 25%**/ n.a. | ~75%** / n.a. | 90 days: 42.9 vs. 42.4% |
| | | | | | | $pO_2$ 82,5–97,5 | $pO_2$ 52.5–67.5 mmHg | | | |

Primary target range marked grey: *Calculated (163) as $S_aO_2 = (23{,}400 * (pO_2^3 + 150 * pO_2)^{-1} + 1)^{-1}$ [#] $S_pO_2 \geq 97\%$ [##] $pO_2 > 120$ mmHg, [+] mortality no primary endpoint,** extrapolated

$S_pO_2$ – oxygen saturation measured by pulse oximetry; $S_aO_2$ – arterial oxygen saturation; $pO_2$ – partial pressure of oxygen; $FiO_2$ – inspired oxygen concentration; ICU – intensive care unit; n.a. – not available

HOT-ICU (157) was published after the consensus process had been completed. It is the largest RCT on oxygen target ranges in ICU patients to date. In this study, 2,928 patients with severe hypoxemia (median oxygenation index 125 mmHg, 58% with invasive ventilation at randomization) were randomized to a conservative oxygen target range ($paO_2$ 60 mmHg with a maximum tolerance of 7.5 mmHg, achieving a median SaO2 of 93%) and a liberal oxygen target range ($paO_2$ 90 mmHg with a maximum tolerance of 7.5 mmHg, achieving a median $SaO_2$ of 96%). The 90-day mortality (primary end point) was not different between the conservative and the liberal $O_2$ group, with 42% and 43%, respectively.

In numerous RCTs comparing non-invasive ventilation or CPAP therapy and supplemental oxygen therapy, the lower limit of oxygen saturation as measured by pulse oximetry at which the amount of oxygen was adjusted, was mostly between 90% and 92% (97, 164-166). The guideline authors therefore believe that the $SpO_2$ target range for oxygen therapy should be between 92–96%, even under non-invasive ventilation or CPAP.

In a prospective cohort study in the Netherlands (159) with data of more than 15,000 ICU patients, conservative oxygen therapy with a target $SpO_2$ range of 92–95% (alert from 97%) proved to be safe in comparison to a period of liberal oxygen therapy.

### 6.4 Compliance with oxygen therapy target ranges

In a large observational study in the Netherlands, 32% of measured partial pressures of oxygen were outside the target range of 55–86 mmHg in 3,007 ICU patients in whom $O_2$ delivery was manually adjusted based on blood gas analysis (BGA) results. 90% of oxygen readings were above the target range. Just under 27% of over 272,000 readings measured by pulse oximetry in the same study were within target range, which in this study was 92–100%. A large percentage of ($SpO_2$ or p $O_2$) readings were outside the target range, also in the randomized studies with ICU patients. In particular, between 14 and 75% of readings were above target range in the conservative oxygen therapy arms (cf. Table 8).

In 4 (randomized or cross-over) controlled trials with 16–187 patients on automatic oxygen titration, among them patients at risk of hypercapnic respiratory failure, 10–24% of the readings were above the target $SpO_2$ range under manual oxygen titration. The use of automated closed-loop $O_2$ titration systems resulted in significantly fewer (1–5%) readings above the target range (139, 167-169). Patient satisfaction with automated titration was assessed in a cross-over study including 19 patients (13 were available to be surveyed). 62% of patients reported high patient satisfaction. 77% of respondents reported limited mobility as a result of oxygen therapy (168). One out of 19 patients in this study experienced an adverse event because oxygen was not delivered due to battery failure of the automatic oxygen titration system.

Closed-loop systems (automatic titration) have been well studied for the treatment of preterm infants. A randomized trial with ventilated adults demonstrated that patients treated with closed-loop systems spend more time in the target oxygen saturation range (170).

Exceptions without a target oxygen saturation range are patients with cluster headache (Chapter 7.8), carbon monoxide poisoning (Chapter 7.3), and critically ill patients in whom pulse oximetry cannot be used (cf. Chapter 7.4).

It takes several weeks for a lung collapsed as a result of pneumothorax to resolve spontaneously, with a resorption rate of approx. 2% per day. In two small case series, the resorption of pneumothorax was accelerated by giving high-dose oxygen (up to 16 L/min via mask) (171, 172), without the method having found its way into any guidelines (173). In a RCT comparing treatment by drainage and conservative therapy in 316 patients with major spontaneous pneumothorax, spontaneous re-expansion was observed in 94% of patients in the conservative group at 8 weeks (174). High-dose oxygen therapy was not part of routine therapy in the group without drainage; patients were treated with oxygen only at a saturation rate < 92%. In secondary spontaneous pneumothorax, experts are concerned about hypercapnic respiratory failure under high-dose oxygen.

Good practice:

There is no recommendation for high-dose oxygen without a target $SpO_2$ range in spontaneous pneumothorax.

| **WG4** | **Recommendation (85 % agreement)** | |
|---|---|---|
| **4** | Patients with acute respiratory distress, increased respiration rate or drop in oxygen saturation > 3% from the baseline who have oxygen saturation levels ≥ 92% as measured by pulse oximetry should be subject to thorough clinical assessment, including blood gas analysis, as these may be signs of an acute illness.<br><br>Expert opinion | Expert consensus |

Our guideline search found an identical recommendation in the BTS guideline (2). Our literature search did not find randomized trials, meta-analyses, or systematic reviews on this topic. The recommendation is therefore based on expert opinion.

Breathlessness can have many causes and is not always accompanied by hypoxemia. Helpful tools in diagnosing patients with dyspnea without hypoxemia include their clinical history, vital signs, and blood gas analyses.

An increased respiration rate is associated with increased in-hospital mortality (31) and considered a warning signal, not only of pulmonary disease, but also of sepsis. The qSOFA (= quickSOFA) score was introduced in 2016 to identify patients at risk of sepsis outside the ICU setting. It is consists of three simple clinical criteria, i.e., respiration rate ≥ 22/min, altered mental state, and systolic blood pressure ≤ 100 mmHg. The risk is increased, if two or more of these criteria are met. The relevance of arterial blood gas analyses is outlined in Chapters 4 and 9. Tachypnea in normoxemic patients may be attributable to serious causes, but can also be the result of a harmless condition. Blood gas analysis, for example, may show metabolic disorders such as severe acidosis, whereas hyperventilation syndrome can usually be differentiated based on clinical findings.

## 6.5 Intractable hypoxemia

| WG4 | Recommendation (100% agreement) | |
|---|---|---|
| **7** | If an $SpO_2$ level of 92% is not achieved despite oxygen flow rates of more than 6 L/min, patients shall be assessed without delay by a physician experienced in the diagnosis and treatment of acute respiratory failure or critical illness<br><br>Expert opinion | Expert consensus |

Oxygen flow rates > 6 L/min frequently lead to the use of $O_2$ reservoir masks and high-flow oxygen therapy in clinical routine (cf. Chapter 5). In RCTs as well as in large cohort studies, the intubation rate of HFNC collectives was 35–40%. Patients with a severe gas exchange disorder are therefore a high-risk group and require immediate attention and, if possible, assessment by a healthcare professional experienced in critical care.

$SpO_2$ levels < 92% under > 6 L $O_2$/min correspond to an oxygenation index ($pO_2/FiO_2$ ratio) < 150 mmHg. Clinical experience shows that patients with persistent hypoxemia despite receiving 6 L/min of oxygen frequently require treatment in ICU. In the subgroup of ARDS patients treated with NIV, ICU mortality was increased below an oxygenation index of 150 (175). Persistent tachypnea above a respiration rate of 30/min after 1 hour of conventional oxygen therapy was associated with an increased intubation rate in the FLORALI trial (96).

The study by Austin (52), on the other hand, impressively demonstrated that high-dose oxygen with high risk of hypercapnic respiratory failure resulted in a significantly higher incidence of in-hospital deaths.. Patients with hypercapnic respiratory failure usually respond insufficiently to oxygen administration alone. In these patients, non-invasive ventilation is the primary line of treatment for hypoxemia and can be used either alone or in combination with oxygen to correct hypoxemia (cf. Section 6.5). Patients in the Austin study had a mean $SpO_2$ of 84–87% prior to randomization. The assessment of this patient population by experienced HCPs and the early use of NIV may therefore prevent intubation by avoiding the undiscerning administration of high-flow oxygen. In the clinical routine, $SpO_2$ values like these unfortunately often prompt an unreflected administration of high-dose oxygen. Liberal oxygen therapy is therefore usually contraindicated in patients with a relevant risk of hypercapnic respiratory failure.

If oxygenation in the target range cannot be achieved by nasal cannula or Venturi mask and hypercapnia is ruled out, alternative delivery systems shall be used. When using simple face masks or even reservoir masks, flow rates below 5 L/min should be avoided due to the increased risk of hypercapnia from carbon dioxide rebreathing (127, 176), cf. Chapter 5.2.

| WG4 | Recommendation (93 % agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **9** | Non-invasive ventilation shall primarily be used in the management of patients with hypercapnic respiratory failure with consecutive hypoxemia, especially those with COPD exacerbation and cardiogenic pulmonary edema and a pH < 7.35. Alternatively, HFNC can be used in hypoxemic and moderately hypercapnic patients.<br><br>Berbenetz 2019(177), Osadnik 2017(178) | **A** | |
| | | Moderate quality of evidence ⊕⊕⊕⊖ | Mortality |
| | | Moderate quality of evidence ⊕⊕⊕⊖ | Intubation |

The guideline search did not find a recommendation in this regard. The independent evidence search did not identify any useful studies. The authors' own literature search identified two Cochrane meta-analyses on the subject (177, 178).

The Cochrane meta-analyses for cardiogenic pulmonary edema (24 randomized trials, 2,664 patients) (177) and COPD exacerbation (17 randomized studies, 1.264 patients, (178) showed–with a moderate level of evidence—that both non-invasive ventilation and conventional oxygen therapy were associated with reduced in-hospital mortality and intubation rates. The meta-analysis found no increased risk of acute coronary events for cardiogenic pulmonary edema (177). This meta-analysis on pulmonary edema failed to establish superiority of NIV vs. CPAP, whereas NIV is superior to CPAP for the treatment of COPD. Non-invasive ventilation should also be considered for other hypercapnic and hypoxemic patients, e.g., those with neuromuscular disorders, class 3 obesity, cystic fibrosis, and thoracic deformities, when the partial pressure of carbon dioxide is > 45 mmHg and pH < 7.35. With the exception of individual cases, however, there are no randomized controlled studies in this regard (179, 180).

The S3 guideline on “Non-invasive ventilation in the treatment of acute respiratory failure”. (181) advocates non-invasive ventilation for hypercapnic patients with a pH of 7.3–7.35.

In recent years, high-flow nasal cannula (HFNC) oxygen therapy has been used as an alternative to NIV because it is easy to use and well accepted by patients.

In NIV, adjusting the mask (or helmet) and ventilation mode to an alert patient is a more complex process than using HFNC. In addition, the prolonged use of NIV often results in mask-induced pressure sores on the face, although these side effects can often be avoided by selecting a fitting mask and using padding.

There are seven randomized studies directly comparing HFNC vs. non-invasive ventilation in the acute management of 40–803 hypoxemic patients, and another study (165) comparing NIV and conventional oxygen therapy in addition. The five randomized trials, some of which included hypercapnic patients ($pCO_2$ 52–61 mmHg), demonstrated the non-inferiority of

HFNC vs. NIV in terms of intubation rate after 72 hours of use (182-186). In a randomized trial, the intubation rate of 204 emergency patients with all-cause respiratory failure (mean $pCO_2$ of 55 mmHg) was 13% under NIV and 7% under HFNC (182). The in-hospital mortality or 28-day-mortality in three studies with mainly freshly extubated patients ranged from 12–18% under NIV and from 15–20% under HFNC, and, hence, did not differ (184, 186-188). A crossover study in 24 stable COPD patients (189) showed that NIV reduced the transcutaneously measured partial pressure of carbon dioxide more significantly than HFNC (5.3 vs. 2.5 mmHg). In many HFNC studies, new-onset or progressive respiratory acidosis is a discontinuation criterion (98).

Good practice:

NIV is an important option for the acute treatment of markedly hypercapnic and hypoxemic patients with COPD exacerbation.

NIV, CPAP, and HFNC are reasonable treatment alternatives for patients with cardiogenic pulmonary edema and severe hypoxemia ($FiO_2$ > 0.4 or > 6 L/min) under conventional oxygen therapy.

HFNC does not seem to be inferior to NIV for patients with moderate hypercapnia.

| **WG4** | **Recommendation (100% agreement)** | **Grade of recommendation / GRADE** | |
|---|---|---|---|
| **11** | Non-invasive ventilation (NIV) may be considered in addition to oxygen administration for non-hypercapnic hypoxemic patients who are continuously monitored.<br><br>Ferreyro 2020(190), Zhang 2012(191) | **0** | |
| | | Low quality of evidence ⊕⊕⊖⊖ | Mortality |
| | | Low quality of evidence ⊕⊕⊖⊖ | Intubation |

None of the guidelines identified in the context of our guideline search provides a graded recommendation on this matter. The independent evidence report also did not identify any useful studies in this regard. The independent literature search on this recommendation identified two meta-analyses (190, 191).

The meta-analysis by Ferreyo analyzed 25 studies with a total of 3,804 patients comparing various types of respiratory support vs. standard oxygen administration in patients with acute hypoxemic pulmonary failure. Seven of these studies compared high-flow oxygen therapy, in part vs. non-invasive ventilation. The 90-day mortality in this meta-analysis was reduced for all types of support (HFNC, NIV, CPAP) vs. conventional oxygen therapy, with a relative risk of 0.83 (95% confidence interval 0.68–0.99) (190).

Another meta-analysis (191) looked at non-invasive ventilation vs. conventional oxygen therapy in nosocomial and community-acquired pneumonia. It included 3 randomized trials with a total of 151 patients. It was found—with a low level of evidence—that non-invasive ventilation reduces ICU mortality (odds ratio (OR) 0.28, 95% confidence interval (CI) 0.09–0.88) as well as the intubation rate (OR 0.26, 95% CI 0.11–0.61).

However, the share of patients with type 1 respiratory failure (i.e., those with isolated hypoxemia) and those with concomitant hypercapnia (type 2 respiratory failure) was not reported in these studies. In a study with 76 patients with acute respiratory failure, for example, 52% had a PaCO2 > 38 mmHg and a pH < 7.32 (192).

In conclusion, the role of non-invasive ventilation in patients with isolated hypoxemia is difficult to assess at present. It stands out from the randomized trials that some of the in-hospital mortality rates (15–81%) in these studies, especially for patients with acute respiratory failure under immunosuppressive therapy, as well as some of the intubation rates (10–77%) are very high (193-195). Considering the reduced intubation rate in these three studies as a result of using non-invasive ventilation or CPAP, the guideline authors believe that a treatment attempt is medically reasonable, at least in this subgroup. In the LUNGsafe study, however, a moderate to severe gas exchange disorder ($pO_2/FiO_2$ < 150 mmHg) was associated with failed NIV therapy in more than 41% of the 436 ARDS patients on NIV (175).

According to the S3 guideline on “Non-invasive ventilation in the treatment of acute respiratory failure”, CPAP or NIV, respectively, may be considered in order to avoid intubation in immunocompromised patients with AIDS, mild ARDS, and pneumonia, with due consideration of contraindications and discontinuation criteria (181).

# 7 Oxygen therapy in special groups of patients

## 7.1 Oxygen therapy in acute coronary syndrome

The authors' search found a national S3 guideline on cardiogenic shock (196). In addition, an international guideline on ST-elevation myocardial infarction including evidence assessment was identified in the context of the search (197). Randomized trials of oxygen therapy in patients with acute coronary syndrome generally excluded those at risk of hypercapnic respiratory failure (55, 133, 137). In the studies on these conditions (cf. Table 13), the lower limit of oxygen saturation as measured by pulse oximetry below which oxygen was administered in each case ranged from 85–94%.

According to expert consensus, a target arterial saturation rate of 94–98% is recommended in cardiogenic shock due to myocardial infarction. The guideline references the meta-analysis by Chu (43) and the largest randomized DETO2X-AMI trial on patients with acute coronary syndrome, although only 1% of them had cardiogenic shock (133). In ST-elevation myocardial infarction, oxygen administration is recommended internationally only at a $SaO_2$ < 90% with a target saturation of 95% (moderate level of evidence). This recommendation is based on three randomized controlled trials and a Cochrane meta-analysis (55, 133, 198, 199). At a lower limit of 94%, approximately 25% of participants in the DETO2X-AMI trial already would have received $O_2$ at baseline. However, even in a subgroup analysis of patients with $O_2$ saturations between 90–94%, this approach was not associated with improved survival (200).

Two Cochrane meta-analyses found no evidence to support routine oxygen administration in acute myocardial infarction, and adverse effects were not excluded (198, 201). A meta-analysis of 8 studies with 7,998 patients also found no difference in the 30-day mortality between patients treated with compressed air/ambient air and those on routine oxygen therapy (3–8 L/min) (54).

Strong evidence speaks for an upper limit of 96% because it corresponds to the median level before randomization in myocardial infarction and stroke trials, it is the normal saturation in a population living at sea level, and higher levels under $O_2$ therapy were associated with increased mortality in the meta-analyses (3). Table 13 provides an overview of randomized trials with myocardial infarction patients (eight RCTs) comparing liberal vs. conservative oxygen therapy.

Table 13: Overview of randomized trials on myocardial infarction comparing liberal vs. conservative oxygen therapy

| Author, year, study acronym | Exclusion at $SpO_2$ | **n** | **Population** | $O_2$, liberal | $O_2$, conservative | Endpoint, liberal vs. conservative |
|---|---|---|---|---|---|---|
| Rawles 1976 (199) | n.a. | 200 | STEMI | 4 L $O_2$/min | No $O_2$ | In-hospital mortality 9% vs. 3% |
| Wilson 1997 (202) | n.a. | 42 | STEMI | 4 L $O_2$/min | Compressed air | Opioids: 73% vs. 96% |
| Ukholkina 2005 (203) | n.a. | 137 | STEMI | 3–6 L $O_2$/min | No $O_2$ | 10-day mortality 2% vs. 0% |
| Ranchord 2012, OPTMISE (137) | < 85% | 136 | STEMI | 6 L $O_2$/min | Target $S_pO_2$ 93–96% | 30-day mortality 2% vs. 3% |
| Stub 2015 (55), AVOID | < 94% | 441 | STEMI | 8 L $O_2$/min | No $O_2$ | 6-month mortality 4% vs. 6% |
| Koshnood 2018 (204), SOCCER | < 94% | 18 | STEMI | 10 L $O_2$/min | Compressed air | In-hospital mortality 4% vs. 4% |
| Heidari 2017 (205) | < 90% | 72 | NSTEMI | 4–6 L $O_2$/min | Compressed air | In-hospital mortality 0% vs. 3% |
| Hoffmann 2017 (133), DETO2X-AMI | < 90% | 6,629 | ACS | 6 L $O_2$/min | Target $S_PO_2$ $\geq$ 90% | 1-year mortality 5.0% vs. 5.1% |

vs. – versus; n.a. – not available; $O_2$ – oxygen; STEMI – ST-elevation myocardial infarction; NSTEMI – non-ST-elevation myocardial infarction; ACS – acute coronary syndrome; n –number of patients; $SpO_2$ – $O_2$ saturation as measured by pulse oximetry

The clinical practice guideline by Siemieniuk strongly recommends that patients with stroke and those with myocardial infarction should only be started on oxygen once their saturation drops below 93% (3). This recommendation was based on fewer coronary events and/or coronary revascularization procedures at 6 and 12 months in the meta-analysis. In conclusion, experts agree that the target ranges of oxygen therapy for patients with acute coronary syndrome are no different than those specified in Chapter 6.

An unblinded RCT including 50 patients with heart failure (excluding those requiring oxygen > 10 L/min) also showed no difference with regard to B-type natriuretic peptide levels, in-hospital mortality and re-hospitalization rates under conservative oxygen therapy (target $SpO_2$ 90–92%) vs. liberal $O_2$ therapy ($SpO_2$ > 96%) (206).

## 7.2 Oxygen therapy in neurological disorders

The authors' own research identified a national S3 guideline on stroke (207). There is also a 2019 international guideline for the management of cerebral infarction patients (208). The largest randomized trial on oxygen therapy for the management of stroke excluded patients with hypoxemia and hypercapnic respiratory failure (135). In the studies on these conditions, the oxygen saturation limit as measured by pulse oximetry below which oxygen was administered in each case ranged from 90–92% (cf. Table 14).

At a lower limit of 95%, as recommended in the guidelines on the management of patients with stroke, (207, 208) more than a quarter of the patients included in the largest randomized SOS trial would already have been treated with $O_2$ at baseline (135). However, the $O_2$ therapy was not associated with improved survival in this study, and no upper limit was defined.

There is strong evidence supporting an upper limit of 96% as it corresponds to the median level of subjects included in stroke trials before randomization, and to the normal level in a population living at sea level, and higher levels under $O_2$ therapy were associated with more deaths in the meta-analyses (3). Table 14 provides an overview of randomized trials (six RCTs) comparing liberal vs. conservative oxygen therapy for the management of cerebral infarction.

Table 14: Overview of randomized trials on stroke comparing liberal vs. conservative oxygen therapy.

| Author, year, study acronym | n | Exclusion at $SpO_2$ | $O_2$, liberal | $O_2$, conservative | Mortality, liberal vs. conservative | Functional outcome liberal vs. conservative |
|---|---|---|---|---|---|---|
| Ronning 1999 (209) | 560 | n.a. | 3 L $O_2$/min | No $O_2$ | 1-year mortality: 31% vs. 27% | 7 months: Stroke score 54 vs. 55 |
| Singhal 2005 (210) | 16 | > 3 L/min around 92% | 45 L $O_2$/min | SpO2 > 95% | 3-month mortality: 13% vs. 16% | 3 months: mRankin 3.2 vs. 4.1 |
| Padma 2010 (211) | 40 | > 3 L/min around 95% | 10 L $O_2$/min | 2 L compressed air/min | 3-month mortality: 0% vs. 10% | 3 months: mRankin 1.9 vs. 2.1 |
| Mazdeh 2015 (212) | 51 | n.a. | 8 L $O_2$/min | No $O_2$ | 6-month mortality: 19% vs. 12% | 3 months: mRankin 2.7 vs. 3.3 |
| Shi 2017 (213) | 16 | > 3 L/min around > 95% | 10 L $O_2$/min | No $O_2$ | n.a. | 7 days: NIHSS 5 vs. 7.5 |
| Roffe 2017 (135), SOS | 8,003 | < 90% | 2–3 L $O_2$/min | No $O_2$ | 3-month mortality: 10% vs. 10% | 3 months: mRankin 2.5 vs. 2.4 |

vs. – versus; n.a. – not available; $O_2$ – oxygen; mRankin – modified Rankin Scale (0–6); NIHSS – National Institutes of Health Stroke Scale (0–19); n – number of patients; $SpO_2$ – $O_2$saturation as measured by pulse oximetry

The clinical practice guideline by Siemieniuk strongly recommends that stroke patients should only be started on oxygen once the saturation drops below 93% (3). This recommendation was based on a meta-analysis, which found lower mortality from stroke under conservative $O_2$ therapy. The meta-analysis found no difference between liberal and conservative oxygen therapy with regard to functional outcomes after cerebral infarction (low level of evidence). This was also the conclusion of another meta-analysis of 11 RCTs on 6,366 patients with cerebral infarction (214).

In a large retrospective analysis of 3,420 patients with craniocerebral injury in the U.S., hyperoxemia was associated with increased in-hospital mortality (215). An Iranian RCT with 68 patients with craniocerebral injury found a slightly superior functional outcome at 6 months when 80% oxygen was administered during the first 6 hours of ventilation vs. 50% oxygen, with no $O_2$ saturation levels being reported. The authors of the BOOST-II study, in which 129 patients with craniocerebral injury were randomized to either conventional intracranial pressure monitoring or to a group in which brain tissue oxygenation was measured in addition, reported superior 6-month survival and functional outcomes for the group with additional measurement of the partial pressure of oxygen in brain tissue, without the study being primarily designed for these endpoints (216). In most patients in the intervention arm of this study, $FiO_2$ was increased to 60% or 100%, but, again, no systemic oxygen levels ($paO_2$, $SaO_2$, $SpO_2$) are reported. The national S3 guideline provides a weak recommendation to avoid

hypoxemia ($SaO_2$ < 90%) in patients with severe craniocerebral injury. The recommendation is based on retrospective analyses (217). The international guideline for the acute treatment of patients with brain injury recommends to avoid hyperoxemia and, based on expert opinion, advocates a $PaO_2$ target range of 80–120 mmHg (218).

Randomized controlled trials with patients after restoration of circulation following CPR also did not show a superiority of liberal oxygen administration (cf. Chapter 7.5, WG 5.1 recommendation).

Two large retrospective analyses including 252 and 936 invasively ventilated patients with subarachnoid hemorrhage showed higher in-hospital mortality and inferior functional outcome at 6 months in patients with hyperoxemia ($paO_2$ > 172 and 300 mmHg, respectively) (219, 220). No randomized controlled trials for this condition are available.

Cerebral vasoconstriction has been described under hypoxemia and neurotoxicity in the form of seizures has been described for hyperbaric oxygenation (44, 221). A meta-analysis found no beneficial effects of hyperbaric oxygen therapy (HBO) for the treatment of ischemic stroke ((222), cf. Chapter 7.4, Table 15). No RCTs are available on the treatment of brain abscess condition by HBO. In a retrospective case series in Sweden (20 patients treated with HBO and a control group of 20 patients treated without HBO), fewer treatment failures and lesser need for surgery were described for the HBO group as well as superior neurological outcomes. The latter, however, had already been superior in the HBO group prior to the therapy (223).

In conclusion, oxygen therapy target ranges for patients with neurological diseases do not differ from those specified in Chapter 6. In particular, hyperoxemia should be avoided in these patients.

## 7.3 Oxygen during pregnancy and childbirth

The guidelines recommend an oxygen saturation of 95% or more for managing asthma during pregnancy (224). However, no studies comparing various oxygen target ranges have yet been published. Five randomized controlled trials investigated the use of 2–10 L of oxygen/min vs. room air or without $O_2$ flow during childbirth in normoxemic pregnant women without asthma. Oxygen administration had no influence on the lactate or oxygen levels or on the pH in umbilical cord blood (225-227). In the randomized, single-center U.S. study of 99 pregnant women, the administration of 10 liters of oxygen per minute did not reduce the rate of cesarean or forceps deliveries and late decelerations as compared to the group on room air (228). Pregnant women with an initial saturation as measured by pulse oximetry of less than 97% were excluded from this study. The authors therefore conclude that the treatment of pregnant women, including those with asthma, should be based on the target oxygen levels considered adequate for other adult patient groups.

## 7.4 Oxygen therapy for the treatment of poisoning

| WG5 | Recommendation (100% agreement) | |
|---|---|---|
| **3** | Patients with carbon monoxide poisoning shall be given 100% oxygen or ventilated with 100% $O_2$ without delay and for a period of up to 6 hours, regardless of oxygen saturation ($SpO_2$). Hyperbaric oxygen therapy is an option in severe carbon monoxide poisoning (e.g., in patients with persistent altered mental state).<br><br>Expert opinion | Expert consensus |

The guideline search found the same recommendation in the BTS guideline (2). The independent evidence report did not identify any useful studies in this regard. The BTS guideline mentions two Cochrane meta-analyses on hyperbaric oxygenation (HBO) in carbon monoxide poisoning (229, 230). The independent literature search identified two additional meta-analyses on the role of HBO (231, 232). There are thus a total of four meta-analyses on this subject. All RCTs included in the 2018 meta-analysis by Lin and the 2019 meta-analysis by Wang have already been included in the most recent Cochrane analysis. The most recent meta-analysis by Wang reviews seven RCTs (2,023 patients) with hyperbaric $O_2$ therapy for the treatment of carbon monoxide poisoning in which 'neurological deficit' was an endpoint. It was the only analysis to show a benefit over normobaric therapy, albeit without evidence assessment. None of the meta-analyses established an association between HBO and reduced mortality.

Ordinary pulse oximeters are not suitable for differentiating between COHb and oxyhemoglobin, oxygen saturation measured by pulse oximetry can be misleading in carbon monoxide poisoning. Blood gas analyses are therefore indispensable. COHb levels > 3% are considered elevated. In smokers, COHb levels can be elevated by as much as 10% without causing symptoms. COHb levels correlate insufficiently with clinical symptoms. The treatment objective in carbon monoxide poisoning is the elimination of carbon monoxide (CO) from the organism to prevent acute damage (organ ischemia) as well as long-term sequelae (especially neurocognitive deficits). According to experts, high-dose oxygen can achieve hemoglobin saturation and shorten the elimination half-life of CO despite the superior affinity of carbon monoxide (233). Carbon monoxide poisoning shall therefore be immediately treated with the highest possible oxygen concentration, irrespective of oxygen saturation (SpO2).

The treatment shall be continued until the COHb has dropped to normal levels (< 3%) and the patient is no longer symptomatic. This is typically the cases after a maximum of five physiological COHb half-lives under 100% oxygen (approximately 375 minutes). Oxygen is

typically delivered via NIV/CPAP, reservoir masks and, in intubated patients, via the tube. Successful treatment of CO poisoning with high-flow oxygen therapy has also been described (234).

Conservative oxygen therapy has been recommended for the treatment of poisoning from paraquat (which is now banned) and bleomycin. Some historical studies recommend that oxygen should be administered only once saturation falls below 85%. The rationale is based on pathophysiology, i.e. the formation of free oxygen radicals (reactive oxygen species) when paraquat binds with molecular oxygen, which may be conducive to the development of pulmonary fibrosis. Oxygen administration has also been associated with increased pulmonary complications in bleomycin poisoning. However, no clear upper limit of oxygen saturation above which pulmonary toxicity increases in paraquat and bleomycin poisoning can be derived from the available literature.

The benefits and risks as well as the medical necessity of hyperbaric oxygen therapy have so far not been adequately demonstrated for any indication. HBO therapy for the treatment of carbon monoxide poisoning is based on plausible theories regarding the effectiveness of this method. The benefits of HBO have been evaluated for various indications in the context of numerous randomized clinical trials. The results of studies and meta-analyses on HBO are contradictory in part. There are several meta-analyses which failed to convincingly demonstrate the benefit of the therapy. It can therefore not be recommended for the treatment of carbon monoxide poisoning (cf. Table 15) in this guideline.

Table 15: Summary of meta-analyses of hyperbaric oxygen therapy

| Indication | Meta-analysis | RCT, n | Patients, n | Observation | Quality of study |
|---|---|---|---|---|---|
| Acute wounds | Eskes 2013 (235) | 4 | 229 | No evidence of accelerated wound healing (observation period 6–7 days). | Low |
| CO intoxication | Buckley 2011 (229) | 7 | 1,361 | No evidence of superior functional neurological outcome at 4–6 weeks. | Very low |
| Radiation damage | Bennett 2016 (236) | 14 | 753 | Improved wound healing after radiation proctitis, tooth extraction, mandibular resection | Moderate |
| Sudden hearing loss and tinnitus | Bennett 2012 (237) | 7 | 392 | Mild improvement of hearing in acute hearing loss, no effect in chronic hearing loss/tinnitus (after 6 months). | Low |
| Chronic wounds (incl. diabetes) | Kranke 2015 (238) | 12 | 557 | Wound healing improved in the short term (6 weeks), but not in the long term (1 year). No effect on amputations | Moderate |
| Ischemic cerebral infarction | Bennett 2014 (222) | 11 | 705 | No change in 6-month mortality, no consistent improvement of functional outcome (only in 4 out of 15 scales) | Moderate |
| Necrotizing infection | Thrane 2019 (239) | 0 | 1,155 | Four out of 17 case-control studies showed significantly lower mortality | Very low |

Good practice:

Blood gas analysis is useful for assessing carbon monoxide poisoning and determining the amount of carbon monoxide bound with hemoglobin (COHb). It is irrelevant in this case whether the blood sample is a venous, arterial or capillary sample.

It is reasonable to treat carbon monoxide poisoning with high-dose oxygen for up to 6 hours, regardless of oxygen saturation. In addition to the tube, high-dose $O_2$ therapy can also be delivered via NIV/CPAP, masks, or HFNC.

With the exception of carbon monoxide poisoning, the general target ranges of oxygen saturation (92–96% or 88–92% for patients at risk of hypercapnia) constitute reasonable oxygen ranges for the treatment of other intoxication conditions by oxygen therapy.

## 7.5 Pre-hospital oxygen therapy

| WG4 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **15** | In the pre-hospital setting, oxygen shall be administered with a target $SpO_2$ range of 92–96% (or 88–92% for patients at risk of hypercapnia). Only if $O_2$ saturation cannot be reliably established by pulse oximetry in an out-of-hospital setting and the patient is in a critical condition (e.g., CPR) shall high-dose oxygen (100% or 15 L/min) be administered.<br><br>Kopsaftis 2020(138), Austin 2010(52), Holmberg 2020(240) | **A** | |
| | | Moderate quality of evidence ⊕⊕⊕⊖<br><br>Very low quality of evidence ⊕⊖⊖⊖ | Mortality<br><br>Cardiovascular events |

Our guideline search found an identical recommendation in the BTS guideline (1). The independent evidence report did not identify any useful studies in this regard. A meta-analysis on the effect of hyperoxia on survival after cardiovascular arrest was considered in the development of the BTS guideline (241). Our own evidence search identified one international guideline including evidence assessment and one meta-analysis (240, 242), which can be applied to the subgroup of patients after pre-hospital cardiopulmonary resuscitation (CPR). The 2020 meta-analysis by Holmberg (240) reviewed seven RCTs, which predominantly included patients after pre-hospital CPR, with highly diverse patient groups. Due to the unacceptable bias of the study results, the authors were unable to provide a recommendation in favor of hyperoxemia or normoxemia.

In conclusion, the $SpO_2$ target ranges, which can be recommended for the pre-clinical setting, are no different than those recommended in Chapter 6 (Figure 7). The insights regarding the benefit of lower $SpO_2$ target ranges in the pre-hospital setting were gained especially for patients at risk of hypercapnia (COPD patients with exacerbation) (52, 138).

The pre-hospital setting is characterized by special conditions as blood gas analyzers are often not available and oxygen delivery systems (such as HFNC) and $O_2$ sources (usually compressed gas cylinders only) are available to a limited extent only. In the pre-hospital setting, oxygen may also be administered by non-medical staff in the context of first aid based on the defense of necessity. The latter allows the administration of some drugs, such as oxygen, by the members of emergency medical services with the patient's consent, when a physician is not available, and when absolutely necessary. According to the German Emergency Medical Services Act (Notfallsanitätergesetz, NotSanG), training for paramedics shall be based on the state of science and impart the skills necessary to independently provide emergency medical care to patients, to assist in the provision of such services, and to transport patients. To this end, specific tasks commonly performed by physicians can be delegated to EMS personnel in exceptional situations. As a result, specific instructions, lists of drugs and measures to train EMS personnel in this regard were developed at regional level (243). EMS personnel performing measures such as the administration of oxygen by delegation, bear the

responsibility for it. According to expert opinion, EMS personnel shall be trained in oxygen therapy at regular intervals.

High-dose oxygen administration is justifiable during CPR or when a reliable pulse oximetry signal cannot be obtained (e.g., patients with shock or centralization). Apart from these special situations, e.g., after return of spontaneous circulation (ROSC), it is recommended that the oxygen therapy target ranges be observed, also in the pre-hospital setting. So far, the concept of upper limits of oxygen saturation under $O_2$ therapy is not generally included in the instructions and treatment standards for EMS personnel.

Three randomized trials on the use of CPAP in patients with cardiogenic pulmonary edema and acute respiratory failure showed a reduction in the out-of-hospital intubation rate (244-246). Only in the study by Thompson was in-hospital mortality also significantly reduced vs. standard oxygen therapy when CPAP had been used in the pre-hospital setting. The study included 71 patients with acute respiratory failure (244).

Good practice:

If the $SpO_2$ signal is not reliable or not available, oxygen shall be administered as if no pulse oximeter was available.

With the exception of critical situations (e.g., during CPR), pulse oximetry is a meaningful tool for assessing a patient before initiating oxygen therapy, even in a pre-hospital setting.

In patients at risk of hypercapnia, drug nebulization with oxygen as a driving gas should be avoided in the pre-hospital setting or limited in time (Chapter 5.1).

It is recommended to have the following $O_2$ delivery devices available in the pre-hospital setting: $O_2$ reservoir mask (for high-concentration oxygen therapy); nasal prongs, Venturi mask, and $O_2$ delivery systems for patients after tracheostomy or laryngectomy, as applicable

A portable pulse oximeter device to assess patients with regard to the presence of hypoxemia and for initial assessment is an essential tool in the out-of-hospital setting, and a portable oxygen source is a useful part of emergency equipment for critically ill patients or those with respiratory distress,

Blood gas analyzers are usually not available outside of hospitals. It is therefore important to recognize the clinical symptoms of patients at risk of hypercapnia.

Emergency cards can help to identify and treat patients at risk of hypercapnia and those with a history of hypercapnia episodes (Figure 12).

Figure 11: Emergency card to be placed in the patient's emergency medical identification card for patients at risk of hypercapnia

| |
|---|
| Oxygen ($O_2$) emergency card: |
| Name: |
| ☐ Patient* suffers from chronic lung disease _____ and, during exacerbation, has increased blood carbon dioxide levels. |
| ❑Oxygen shall be used with caution in acute situations, with a target saturation range of ____ to ____%. |
| ❑Compressed air should be used for drug nebulization. If oxygen as driving gas for nebulization cannot be avoided, nebulization is to be limited to 6 minutes. |
| Date:<br><br>Signature: |

| WG5 | Recommendation (100% agreement) | Grade of recommendation / GRADE | |
|---|---|---|---|
| **1** | The highest possible oxygen flow shall be used during CPR. After return of spontaneous circulation and when the oxygen saturation can be reliably monitored, a target saturation range of 92–96% should be aimed for.<br><br>Holmberg 2020 (240), Wang 2014 (241) | **B** | |
| | | Low quality of evidence ⊕⊕⊖⊖ | Mortality |
| | | Low quality of evidence ⊕⊕⊖⊖ | functional outcome |

The guideline search showed that the BTS guideline (1) provides an identical recommendation on this matter. The independent evidence report did not explore the question. A meta-analysis on the effect of hyperoxia on survival after cardiovascular arrest was considered in the development of the BTS guideline (241). Our own evidence search identified one international guideline including evidence assessment and one meta-analysis (240, 242), that can be applied to the subgroup of patients after cardiovascular arrest in the pre-hospitalization phase.

Two smaller randomized trials with 35 and 61 patients, respectively, in whom circulation was restored after CPR demonstrated the non-inferiority of conservative oxygen therapy in the out-of-hospital setting (247, 248), while the study by Young (249), in the same clinical constellation, was discontinued early after 17 patients due to safety concerns regarding target saturation ranges of 90–94%. A single-center RCT (248) comparing the effectiveness of hyperoxygenation (target saturation 100%, n=17) vs. titrated oxygen (target saturation 94–98%, n=18) in the first hour after out-of-hospital CPR showed no improvement with regard to the 90-day survival rate (55% for conservative oxygen administration vs. 18% for hyperoxemia). Target saturation ranges of 90% and more were pursued in two Australian studies, without these studies having been designed for the mortality endpoint (247, 249). A 2019 meta-analysis by Holmberg & colleagues analyzed seven randomized trials and 36 observational studies. No conclusive result was obtained with regard to hyperoxemia vs. normoxemia after successful CPR. Six RCTs were analyzed in the context of the international guideline on $O_2$ therapy during and after CPR. It provides a weak recommendation to avoid hyperoxemia in post-cardiac arrest patients. Wang's meta-analysis covered 14 studies on oxygen therapy following CPR. Patients with hyperoxemia were found to have greater mortality. In this analysis, mortality was higher under hyperoxemia following CPR, however without a significantly inferior outcome for normoxemic patients. A recently published meta-analysis (7 RCTs of which 4 in the out-of-hospital setting) of 429 patients found lower mortality in patients on conservative vs. those on liberal $O_2$ therapy after return of spontaneous circulation (250).

Good practice:

Set $FiO_2$ to 1.0 during CPR.

## 7.6 Oxygen therapy in COVID-19 and other infectious lung diseases

<table>
<tr><th>WG5</th><th>Recommendation (100% agreement)</th><th colspan="2">Grade of recommendation / GRADE</th></tr>
<tr><td rowspan="3">5</td><td rowspan="3">The same principles and oxygen therapy target ranges that apply for other hypoxemic patients also apply for adults with infectious diseases transmissible by aerosols (e.g., SARS-CoV 2).<br><br>Alhazzani 2020(251)</td><td colspan="2">A</td></tr>
<tr><td>Moderate quality of evidence<br>⊕⊕⊕⊖</td><td>Mortality</td></tr>
<tr><td colspan="2"></td></tr>
</table>

Most COVID-19 patients without a history of pulmonary disease present with isolated hypoxemia on hospitalization. It has been observed that some COVID-19 patients have no symptoms of shortness of breath despite suffering from severe hypoxemia. This phenomenon is called “silent hypoxemia”. Given the unreliability of pulse oximetry in the lower SpO2 range and the shift of the oxygen dissociation curve in patients with fever, some authors advocate blood gas analysis for COVID-19 patients (252). Hospitalized COVID-19 patients must be closely monitored for vital signs (especially pulse oximetry) and respiration rate due to the dynamic deterioration process following hospitalization. Early warning systems such as NEWS2 have also been successfully used in COVID19 wards.

The evidence report provided no useful studies in this regard. The authors conducted their own search and found an evidence-based guideline published by the Surviving Sepsis Campaign. Based on their search result, no RCTs using different oxygen target ranges have yet been published.

The identified guideline recommends (with a low level of evidence) a lower limit of $SpO_2$ of 92% and (with a moderate level of evidence) an upper limit of 96% for COVID-19 patients treated with supplemental $O_2$ (251). The recommendation is based on two RCTs with ventilated subjects and one meta-analysis (30, 43, 134). None of these studies included COVID-19 patients. Based on theoretical considerations such as endothelitis, microthrombi, hypoxic vasoconstriction, and hypoxia-induced modulation of the ACE-2 receptor, lower target ranges are not recommended for the treatment of COVID-19 (253). The optimal $O_2$ target range for adults with COVID-19 is currently uncertain, and there is currently no evidence to suggest that the target oxygen saturation range for COVID-19 patients should differ from that for other conditions. Hyperoxemia (i.e. $SpO_2 > 96\%$ under supplemental $O_2$) was associated with increased in-hospital mortality in meta-analyses. In addition, hyperoxemia under $O_2$ therapy may lead to the delayed detection of respiratory failure, for example in COVID 19 patients (11). The Surviving Sepsis Campaign's evidence-based treatment guideline recommends a target oxygen saturation of range of 92–96% for COVID-

19 (251). The oxygen therapy algorithm outlined in Figure 7 should also be used in patients with viral respiratory tract infections.

The 2003 SARS-CoV-1 epidemic saw a relevant number of infections among hospital staff as a result of aerosol-generating medical procedures such as drug nebulization. In patients with SARS-Cov-2 and other RNA viruses such as influenza, respiratory syncytial virus, and rhinoviruses, viral RNA could be isolated from exhaled droplets (≤ 5 μm). Increased aerosol formation was observed at higher oxygen flow rates in conventional oxygen treatment via nasal cannula and face mask (extending up to 1 meter). Increased aerosol formation during exhalation is found under both high-flow oxygen therapy and NIV, depending on the depth of breaths (254).

For high-flow oxygen therapy, it has been demonstrated that expired air extends less than 20 cm from a patient—as long as the nasal cannula is properly placed—which is less than with conventional oxygen administration. This is attributed to the tighter fit of the high-flow cannula. Venturi masks also did not result in increased aerosol formation. Personal protective equipment, distancing, proper fit of HFNC or NIV mask, and the wearing of mouth–nose protection by patients on oxygen therapy appear to be appropriate measures to prevent infection of those in their vicinity. Insulated nose masks should be avoided in NIV, and instead, non-leaking masks and 2-tube systems should be preferred.

## 7.7 Patients with cluster headaches

<table>
<tr><th>WG5</th><th>Recommendation (100% agreement)</th><th colspan="2">Grade of recommendation / GRADE</th></tr>
<tr><td rowspan="3">4</td><td rowspan="3">For patients with cluster headache, oxygen shall be administered via a reservoir mask at a flow rate of at least 12 L/min for no less than 15 minutes.<br><br>Cohen 2009 (255), Bennett 2015 (256)</td><td colspan="2">A</td></tr>
<tr><td>High quality of evidence<br>⊕⊕⊕⊕</td><td>functional outcome</td></tr>
<tr><td colspan="2"></td></tr>
</table>

The guideline search found that the BTS guideline provides (1) the same recommendation, with a high level of evidence based on a randomized controlled trial (255). The independent evidence report did not explore the question as a key question. The authors' own literature search identified one meta-analysis (256).

Eleven studies with a total of 209 patients were evaluated in the 2015 Cochrane analysis. Low-quality evidence was found that acute migraine headaches and possibly cluster headaches are relieved by HBOT, and that NBOT may improve cluster headache (256). Oxygen administration at 7 L/min in a historical RCT with 52 patients with cluster headaches provided impressive symptom relief for 39 patients (75%). A second phase of the trial compared

ergotamine therapy vs. oxygen administration (7 L/min for 15 min) in 50 patients with cluster headache. Oxygen therapy resulted in a headache-related response in 82% of patients vs. 70% in the ergotamine group (257).

In another randomized placebo-controlled trial, 109 patients with cluster headache were treated with either 12 L/min $O_2$ for 15 min or 12 L/min of normal air (sham procedure) (255). The primary endpoint of freedom from pain after 15 min was achieved in 78% in the concentrated oxygen group vs. 20% in the control group ($p< 0.01$).

## 7.8 Oxygen use during procedures involving conscious sedation

| **WG4** | **Recommendation (93 % agreement)** | |
|---|---|---|
| **12** | In all procedures involving conscious sedation with the objective of maintaining spontaneous breathing, the patient's oxygen saturation shall be continuously monitored via pulse oximetry prior to and during the procedure, and in the recovery period.<br><br>Expert opinion | Expert consensus |

Hypoxemia is a frequent occurrence in procedures performed under sedation (commonly propofol) with the goal of preserving spontaneous breathing. Clinical monitoring via pulse oximetry is a requirement and stipulated, among others, in the quality assurance in colonoscopy agreement ("Qualitätssicherungsvereinbarung zur Koloskopie") pursuant to Section 135 of the German Social Code, Book V (SGB V)). (258). In gastrointestinal endoscopy, 8–57% of patients were found to have hypoxemia with $SpO_2$ levels < 90% in RCTs comparing midazolam vs. propofol.

In five randomized controlled trials on the use of capnometry in the context of various procedures (bronchoscopy in 2 studies, endoscopic retrograde cholangiography-pancreaticography in 1 study, colonoscopy and various procedures in 1 study) with 132–1,386 participants, hypoxemia according to various definitions was found in 25–44% of study participants (259-263). Using capnometry to measure apnea or hypopnea, these conditions were recorded in 22–65% of study participants during the procedure, meaning that most hypoxemic episodes likely were caused by hypoventilation. In a RCT comparing HFNC vs. conventional oxygen therapy in two groups of 30 patients each during bronchoscopy, the difference in the proportion of patients experiencing desaturation ($SpO_2$ < 90%) (13%) vs. patients in the high-flow nasal oxygen group (33%) was non-significant (264).

In the light of this frequency, the authors see a clear indication for continuous monitoring via pulse oximetry before during and after such procedures. An indication for extended hypoxemia monitoring also applies during hypoventilation episodes.

| WG4 | Recommendation (100% agreement) | |
|---|---|---|
| **13** | In all procedures involving conscious sedation with the objective of maintaining spontaneous breathing, patients should be assessed for hypoventilation if hypoxemia is encountered ($SpO_2$ < 92%, or 88% for patients at risk of hypercapnic respiratory failure), and oxygen should be administered as part of a multimodal approach.<br><br>Expert opinion | Expert consensus |

In the absence of studies supported by high-level evidence, this recommendation is based on expert opinion.

The reported incidence of adverse cardiopulmonary events is 5% under benzodiazepines and 0.1% in propofol studies (265, 266), although the definitions of 'adverse cardiopulmonary events' are quite heterogeneous across these studies. Hypoxemia or desaturation during procedures involving conscious sedation such as endoscopy is a common occurrence. The majority of hypoxemia during procedures involving conscious sedation is the result of hypoventilation, in one study the rate was even as high as 100% (262). In clinical experience, a significant desaturation ($SpO_2$ < 90% or a prolonged (> 1 min) drop > 4% during endoscopy) usually cannot be corrected by supplemental oxygen alone. When oxygen is administered, a target oxygen saturation of range of 92–96% (or 88–92% for those at risk of hypercapnia) should be reached. Bronchoscopy procedures, and in particular interventional bronchoscopy, go along with an increased risk of hypoxemia, depending on the lung function (267, 268).

Oxygen administration via nasal cannula can significantly decrease the incidence of hypoxemic events. However, the prophylactic administration of oxygen before and during procedures involving conscious sedation, especially in patients at risk of hypercapnic respiratory failure, is controversial. In a randomized study on 389 patients undergoing gastrointestinal endoscopy, half were given prophylactic oxygen (2 L/min), while the other half were administered oxygen only upon desaturation (269). Desaturation events ($SpO_2$ < 95%) occurred in 21% in the $O_2$ group vs. 81% in the control group without prophylactic oxygen. 83% of desaturation events were mild ($SpO_2$ 90–94%). However, patients at risk of hypercapnia were excluded from this study, and no blood gas analyses to detect hypercapnia were performed. The same was true for the study by Wang, which excluded patients with prior cardiopulmonary disease. This study demonstrated the effectiveness of oxygen supplementation in the presence of hypoxemia, but called into question the merits of preventive oxygenation therapy (270). In another randomized trial, 50 patients undergoing endoscopic cholangiopancreatography under midazolam/fentanyl were divided into three groups: one group with oxygen delivery (2 L/min) via nasal cannula, another group with

oxygen delivery (2 L/min) via nasopharyngeal tube, and a group without prophylactic oxygen. The group without oxygen therapy had 47% desaturation events to levels below 90%, while the two oxygen groups had no such events (271). It is unclear whether patients at risk of hypercapnia were included in this study, and hypercapnic events were not investigated. Prophylactic oxygen therapy during endoscopy involving conscious sedation has been critically discussed by other authors (272). In hypoventilation and resulting hypoxemia, oxygen therapy is not a causal therapy, and but rather are methods such as inserting breathing devices (e.g., Guedel tube) or using assisted ventilation. The authors therefore are of the opinion that routine oxygen supplementation as a "safety buffer" cannot be generally recommended, especially not in patients at risk of hypercapnic respiratory failure (e.g., COPD, morbid obesity) during procedures involving conscious sedation with maintained spontaneous breathing.

Using capnometry to monitor ventilation during endoscopy allows to detect apnea/hypopnea episodes early. In a study on 132 patients, capnometry detected hypo-/apnea on average 60 seconds early (262). Using oximetry with ear sensor, however, also allowed to detect hypoxemia 30 seconds early in 104 bronchoscopy cases (83). Whether or not this translates to improved patient safety is unclear. The guidelines for sedation in gastroenterological endoscopy does not recommend routine monitoring by capnometry for endoscopy procedures performed under conscious sedation. The monitoring method could be useful in individual cases with extended procedural duration (258).

Five randomized controlled trials are available on the use of capnometry in procedures involving sedation with maintained spontaneous breathing, in which 121 to 1,386 patients were enrolled. Three studies had slightly fewer desaturation episodes in the capnometry group (25 vs. 42%, 18 vs. 32%, and 29 vs. 46%) (260, 262, 263). No significant difference was detected in two studies with 238 and 1386 patients (259, 261). In a 2011 meta-analysis of five studies on capnometry during procedural sedation with the objective of preserving spontaneous breathing, hypo- and apnea were recorded 17.6 times more (273). Three studies recorded slightly fewer desaturation episodes under capnometry monitoring: 25 vs. 42%, 18 vs. 32%, and 29 vs. 46% (260, 262, 263). In a 2020 meta-analysis of 14 trials, capnometry reduced the incidence of hypoxemia during procedural sedation, and apnea episodes were detected significantly earlier (274).

Using capnometry to monitor ventilation during procedural conscious sedation can help detect apnea/hypopnea episodes earlier. In a study on 132 patients, capnometry detected hypo-/apnea on average 60 seconds early (262).

Good practice:

Continuous monitoring by pulse oximetry is useful to detect hypoxemia, which is a common occurrence in all procedures involving conscious sedation.

Hypoxemia under conscious sedation is often caused by hypoventilation. The oxygen therapy in procedural sedation is oriented on the same target ranges ($SpO_2$ 92–96% or 88–92% in patients at risk of hypercapnia) as in other conditions. Oxygen administration alone is often not sufficiently effective in hypoxemia under procedural conscious sedation, and additional measures to correct hypoventilation are helpful.

An indicator of hypopnea is the transthoracic impedance, which is easily derived from ECG monitors. No randomized controlled trials are available to date, but the method is currently being studied in the context of a clinical trial (NCT04202029).

## 7.9 High-flow oxygen therapy

| **WG5** | **Recommendation (100% agreement)** | |
|---|---|---|
| **6** | In hospitalized patients with acute hypoxic pulmonary failure without hypercapnia, high-flow oxygen therapy should be initiated at a flow rate of 6 L $O_2$/min delivered via nasal cannula/mask if the oxygen saturation drops below 92%.<br><br>Expert opinion | Expert consensus |

The guideline search, the evidence report, and the authors' own literature search failed to identify relevant studies with a strong level of evidence on this question. The recommendation is therefore based on expert opinion.

In high-flow oxygen therapy, heated and humidified oxygen is delivered via nasal cannula at flow rates of 40–60 L/min. This seems to be well-tolerated by patients. High-flow oxygen therapy generates a low positive end-expiratory pressure and also reduces the breathing effort through $CO_2$ washout and the associated reduction of dead space.

A Cochrane meta-analysis by Corley reviewed 11 RCTs on high-flow oxygen vs. standard oxygen therapy via nasal cannula, face mask, and/or standard oxygen therapy in pulmonary failure or post-extubation (275). Due to a high risk of bias, the quality of the included studies

was insufficient to allow conclusive assessment. A systematic summary by Marjanovic (276) included five RCTs. While dyspnea and respiration rate were improved, there was no difference with regard to the endpoints of intubation, length of hospitalization, and mortality under high-flow therapy. Xiaofeng (277) conducted a systematic review on HFNC after extubation vs. standard oxygen therapy with the endpoint of reintubation. According to this review, the reintubation rate of critically ill patients was lower when HFNC was used. Wen conducted a systematic review of HFNC in immunosuppressed patients with acute pulmonary failure (259), evaluating eight RCTs. There was no difference in mortality under HFNC, but the intubation rate was lower and hospitalization shorter than with NIV.

In conclusion, HFNC is associated with lower intubation rates, at least in one meta-analysis, but the mortality was not significantly reduced vs. standard oxygen therapy.

| WG5 | Recommendation (100% agreement) | |
|---|---|---|
| 7 | Patients on high-flow oxygen should be closely reevaluated and HFNC discontinuation criteria defined.<br><br>Expert opinion | Expert consensus |

The guideline search, the evidence report, and the authors' own literature search failed to identify relevant studies with a strong level of evidence on this question. The recommendation is therefore based on expert opinion.

In a randomized controlled trial conducted in four ICUs in France, Lemiale examined the difference between high-flow oxygen by nasal cannula versus Venturi mask in 100 non-hypercapnic immunocompromised patients with hypoxic pulmonary failure (97). Upon enrollment, the oxygenation index ($PaO_2/FiO_2$) in the groups was 128 mmHg and 100 mmHg, respectively. After 24 h, 15% in the HFNC group and 8% in the Venturi group received invasive ventilation (p=0.36). In the overall course, 39% of participants were intubated. In the FLORALI study on 310 patients with respiratory failure comparing standard oxygen therapy, HFNC, and NIV, the mean oxygenation index ranged from 149–161 mmHg, with intubation rates ranging from 38%–51% (96). Mortality was only 12% in the HFNC arm of the study, while it was between 23% and 28% in the other two arms. In the absence of an immediate indication for intubation, closely monitored HFNC therefore appears to be a justified treatment approach.

In a 2018 trial on 778 immunosuppressed patients conducted by Azoulay, the oxygenation index ($PaO_2/FiO_2$) at enrollment was 117 mmHg and 108 mmHg, respectively (278). In this study, high-flow oxygen was not superior to conventional oxygen therapy (28-day mortality of 35.6% in the HFNC group vs. 36.1% in the standard oxygen group, p=0.94). Overall, 38.7% (HFNC) vs. 43.8% (conventional $O_2$ therapy) were intubated.

Another RCT on 322 emergency department patients with hypoxemic pulmonary failure (oxygenation index ($PaO_2/FiO_2$) 120–130 mmHg) without hypercapnia compared high-flow oxygen therapy vs. standard oxygen delivery (n=138) (279). The primary endpoint of 'escalation to NIV or intubation within 24 h' was 3.6% in the HFNC group vs. 7.2% in the conventional oxygen therapy group (p=0.16), 5.5% vs. 11.6% had invasive ventilation after 24 h, and, hence, was not significantly different. The 90-day mortality was 21.2% vs. 17.4% (p=0.16). Most patients with HFNC failure are not intubated initially, but only later during their hospitalization, which points to the necessity of continuous monitoring under this therapy.

Good practice:

The ROX index (cf. example in Table 16) is an additional index available at the bedside. It is calculated from $SpO_2$, $FiO_2$, and respiration rate, and a lower ROX value is associated with treatment failure as demonstrated in various patient populations.

In a prospective study, Roca and colleagues (98) examined the ROX index ($SpO_2/FiO_2$/respiration rate) to predict high-flow oxygen therapy failure in patients with community-acquired pneumonia (2, 6, 12, 18 and 24 hours after hospitalization). HFNC was used in patients with oxygen saturation < 92% and respiration rate > 25/min, with the oxygen being delivered through a face mask at 10 L/min or more. Treatment was initiated at a flow rate of 30 L/min with a target saturation > 92%. The flow rate was adjusted to the maximum tolerated by the patient. Treatment was discontinued and patients were intubated if they had a Glasgow coma score <12, needed vasopressors, had acidosis, or refractory hypoxemia. ROX values < 2.85, < 3.47, and < 3.85 at 2, 6, and 12 hours of HFNC initiation, respectively, were predictors of HFNC failure (specificity 99%, 99%, and 98%). A ROX index ≥ 4.88 was consistently associated with positive outcome.

Table 16: Example of ROX index

| | $SpO_2$ | $FiO_2$ | Respiration rate | ROX index |
|---|---|---|---|---|
| Patient 1 | 90% | 0.50 | 28/min | 6.4 |
| Patient 2 | 85% | 0.90 | 40/min | 2.3 |
| Patient 3 | 96% | 0.40 | 26/min | 9.2 |

$SpO_2$ – oxygen saturation as measured by pulse oximetry; $FiO_2$ – inspired oxygen concentration

The predictive power of the ROX index was confirmed in 289 COVID-19 patients after 6 hours of HFNC therapy (280).

According to expert opinion, patients on HFNC should be continuously monitored by pulse oximetry and for clinical symptoms, as 36% of pneumonia(280) and 37% of COVID-19 patients(98) treated with HFNC had to be intubated in the further course, which is consistent

with intubation rates of 38% and 39%, in the HFNC therapy groups in randomized trials (96, 97, 278).

HFNC systems are not available outside the hospital; reservoir masks and CPAP/NIV therapy are alternative options for the treatment of refractory hypoxemia in out-of-hospital settings.

# 8 Humidification of supplemental oxygen

<table>
<tr><th>WG6</th><th>Recommendation (100% agreement)</th><th colspan="2">Grade of recommendation / GRADE</th></tr>
<tr><td rowspan="2">6</td><td rowspan="2">Humidified oxygen shall not be used in low-flow oxygen therapy (via mask or nasal cannula) and also not for the short-term administration of high-flow oxygen.<br><br>Wen 2017(281), Poiroux 2018(282)</td><td colspan="2">A</td></tr>
<tr><td>Moderate quality of evidence<br>⊕⊕⊕⊖</td><td>Quality of life</td></tr>
</table>

The BTS guideline provides the same recommendation with regard to humidified oxygen based. It is supported by a meta-analysis. The authors of the BTS guideline (2) downgraded the meta-analysis to a moderate level of evidence due to study limitations, limited transferability, and inconsistencies (281). The meta-analysis is based on 25 RCTs with a total of 8,876 acutely ill adult patients and compared humidified vs. non-humidified oxygen. Most studies focused on a treatment duration of more than 24 h (range: 12 h to > 5 days) and distilled or sterile water was used for humidification. All studies described the use of low-flow $O_2$ (< 5 L/min). Relevant endpoints were quality of life and adverse effects. The use of non-humidified oxygen did not prove to have an impact on patient discomfort (dry nose or throat, cough, nosebleed, sensation of discomfort in the chest). However, bacterial contamination was more common in the group receiving humidified oxygen (OR 6.25; 95% CI 2.33–16.67), oxygen was administered 36 hours longer and the rate of subsequent respiratory infections was increased in these patients (OR 2.56; 95% CI 1.37–4.76).

Our own literature search found another RCT published in 2018. The study (282) on 354 subjects investigated the effect of dry vs. humidified oxygen on the quality of life of ICU patients. The study was rated as having a low level of evidence study to limitations and low accuracy. The study endpoint included 15 different symptoms, which were rated based on a scoring system between 6–24 hours after hospitalization. The study was not able to demonstrate that non-humidified oxygen was inferior to humidified oxygen in terms of patient comfort after 6–8 hours of oxygen therapy. An analysis of the data collected after 24 hours of oxygen therapy by subgroup suggests that non-humidified oxygen is not inferior to humidified oxygen in patients on low-flow oxygen (≤ 4 L/min), but may be associated with greater discomfort in patients on higher oxygen flow rates (> 4 L/min).

The BTS guideline, based on expert opinion, recommends warming and humidifying oxygen in tracheotomized patients (T-piece or mask system), as the tracheostomy tube bypasses the patient's natural mechanisms for warming and moisturizing inspired gases. This can

contribute to reducing the build-up of secretions, maintaining a patent tracheostomy tube and minimizing subjective discomfort (2).

# 9 Monitoring and documentation of oxygen therapy

| WG6 | Recommendation (100% agreement) | |
|---|---|---|
| **3** | Repeat blood gas analysis should be performed approximately 30–60 minutes after a change in oxygen therapy in patients at risk of hypercapnia or with other BGA indications (cf. Chapter 4.4) in order to monitor pH and $pCO_2$.<br><br>Expert opinion | Expert consensus |

According to our literature search, the statements regarding patient selection and indication for blood gas analysis are based on expert opinion. Only one cohort study of 89 patients with acute severe asthma found that an oxygen saturation > 92% as measured by pulse oximetry suggests that respiratory failure is unlikely (> 5% of cases) and therefore arterial blood gas measurement is unnecessary (93).

Whether blood gas measurements should be repeated depends on the clinical condition of the patient and the time to the next blood gas analysis. Only a few systematic studies are available on the time to equilibration after an adjustment in supplemental $O_2$. In general, the oxygen saturation in blood gas samples equilibrates within a few minutes of increasing oxygen delivery (283, 284). Only indirect indicators are available with regard to $CO_2$. It takes approx. 30–60 minutes to reach equilibrium. The few clinical data were able to demonstrate at least a change in $PaCO_2$ for up to 20 minutes during and after bronchodilator inhalation in the selected patient population (COPD) (114, 285). The increase in oxygen saturation can also be monitored by pulse oximeter; pH and $pCO_2$ levels shall be verified by blood gas analysis, however, no earlier than after 30 minutes.

| WG 6 | Recommendation (100% agreement) | |
|---|---|---|
| **4** | Patients should be monitored for clinical symptoms and oxygen saturation pulse oximetry for 5 minutes after starting, adjusting or stopping oxygen therapy.<br><br>Expert opinion | Expert consensus |

This recommendation is consistent with the recommendation in the BTS guideline and based on systematic evidence assessment (2). These recommendations are based on expert opinion in the BTS guideline. Our literature search did not find any RCTs, meta-analyses, or systematic reviews suitable for answering the key question. This recommendation is therefore also based on expert opinion. Several small observational studies addressed blood oxygen equilibration times (286-289). The time to equilibration of $O_2$ saturation was four and a half minutes in spontaneously breathing patients (286), six minutes in ventilated patients, and seven minutes in ventilated COPD patients (290).

Patients should be monitored for clinical symptoms and oxygen saturation pulse oximetry for 5 minutes after starting, adjusting or stopping oxygen therapy. After this period, changes in oxygen saturation are usually reliably detected by pulse oximetry. However, special consideration should be given to the longer equilibration times in oxygen titration via reservoir systems. Clinical experience has shown that five minutes are not sufficient in this case.

Changes in cardiac output, microcirculation, hypoxemia, vasoconstriction, or vasodilation may increase the time to equilibration of $O_2$ saturation (81, 286, 287, 291).

Good practice:

Oxygen therapy must generally be documented in writing (template in Figure 13).

The documentation needs to indicate the delivery system and the amount of oxygen.

The oxygen dose administered shall be indicated each time oxygen saturation is recorded.

All vital signs shall be recorded and documented at pre-defined intervals during the oxygen therapy (cf. Chapter 4.1).

Figure 12: Sample template for the documentation of oxygen therapy

| Date | 1/07/2020 | 1/07/2020 | 1/07/2020 | 1/07/2020 |
|---|---|---|---|---|
| Time | 8:05 | 11:45 | 16:32 | 23:15 |
| $O_2$ L/min % | 1 | - | 28% | 6 |
| $O_2$ art | N | | VM | RM |
| $SpO_2$ % | 92 | 88 | 91 | 92 |
| Respiration rate/min | 22 | 28 | 30 | 28 |
| Mental state | A | A | A | C |

N – nasal prongs; VM – Venturi mask; RM – reservoir mask; A – alertness; C – confusion

According to decisions of the arbitration committee pursuant to Section 19 of the German Hospital Financing Act (Krankenhausfinanzierungsgesetz, KHG), respiratory insufficiency should be coded as follows when the documented saturation ($SpO_2$) is < 92% and oxygen is delivered: without hypercapnia as J96.00, with $paCO_2$ > 45 mmHg as J96.01, and with ventilation as J96.11. The guideline authors recommend the future classification of oxygen therapy, and of HFNC in particular, as a procedure.

# 10 Discontinuation of oxygen therapy

| WG7 | Recommendation (100% agreement) | |
|---|---|---|
| **1** | Oxygen delivery should be reduced when a patient is clinically stable and oxygen saturation is above the target range or has been within target range for several hours.<br><br>Expert opinion | Expert consensus |

Our literature search did not find randomized trials, meta-analyses, or systematic reviews on this topic. The recommendation is therefore based on expert opinion.

In most acutely ill patients, oxygen therapy is gradually reduced as the patient recovers. Oxygen therapy can be discontinued when a stable patient is able to stay in the target saturation range under low-dose oxygen. Signs of clinical stability include a normal respiration rate and other vital signs within the normal range. The oxygen saturation levels of recovering patients under low-dose oxygen therapy typically are in the upper range of their target corridor.

Some patients experience transient hypoxemia while recovering from an acute condition, e.g., due to the build-up of secretion. Some have acceptable oxygen saturations at rest during recovery, but experience exercise-induced desaturation. However, this is often not a reason for resuming oxygen therapy. By continuing to prescribe a target saturation range, it can be ensured that patients will promptly receive supplemental oxygen after an oxygen therapy has been stopped, should their saturation deteriorate again.

| WG7 | Recommendation (100% agreement) | |
|---|---|---|
| **2** | Oxygen therapy should be discontinued in patients not at risk of hypercapnia who have been clinically stable and within the target range for several hours under 2 L $O_2$/min. The lowest volume administered before stopping oxygen therapy in patients at risk of hypercapnic respiratory failure should be 1 L/min (or 0.5 L/min, as necessary).<br><br>Expert opinion | Expert consensus |

Our literature search did not find any randomized trials, meta-analyses, or systematic reviews on this topic. The recommendation is therefore based on expert opinion. However, there are a few case series highlighting the potential problem for some patients.

Especially for patients who experienced hypercapnic respiratory failure after high-dose oxygen therapy, there is a risk of rebound hypoxemia if oxygen is suddenly withdrawn. A step-by-step reduction of oxygen therapy and continuous monitoring of oxygen saturation levels is therefore recommended, especially in patients at risk of hypercapnia. Rebound hypoxemia can be explained using the alveolar gas equation (292). Carbon dioxide competes with oxygen in the alveoli. However, the body's capacity to store oxygen is limited, while large amounts of carbon dioxide can be stored due to its high solubility in tissues, extracellular fluid, and blood. The discontinuation of oxygen therapy in these patients results in a faster drop in the partial pressure of arterial oxygen than arterial carbon-dioxide due to high alveolar carbon dioxide, as the ability to increase ventilation is limited in these patients. Rebound hypoxemia can be substantial (saturation drop of up to 16% in a group of 10 COPD patients (293). Our own literature search identified two randomized trials comparing HFNC vs. standard oxygen therapy that were unable to demonstrate the phenomenon of rebound hypoxemia after extubation (187, 294).

According to case reports, a dramatic drop in oxygen can occur in hypercapnic patients after discontinuing high-dose oxygen therapy. The drop is greatest in the first 5 minutes of stopping the oxygen therapy, but the lowest point is only reached after 30–45 minutes. (293). The same phenomenon was also observed in eight patients with asthma in this study, albeit to a lesser extent. A feasibility study on 162 emergency room patients (295), the Guideline for Long-Term Oxygen Therapy (296) and the guideline on organ transplantation pursuant to Section 16 of the German Transplantation Act (102) recommend an observation period of five minutes to ensure oxygen equilibrium is reached.

| WG7 | Recommendation (100% agreement) | |
|---|---|---|
| **4** | $O_2$ delivery should not be adjusted if a patient experiences a transient (less than 1 minute) asymptomatic drop in oxygen saturation below target range after oxygen therapy has been stopped.<br><br>Expert opinion | Expert consensus |

Our literature search did not find any randomized trials, meta-analyses, or systematic reviews on this topic. The recommendation is therefore based on expert opinion. The recommendation is also supported by considerations and experiences derived from other situations.

Patients may occasionally experience transient hypoxemia after oxygen therapy has been stopped, for example in connection with low-level exercise or due to obstruction by mucus. Transient drops in oxygen saturation are also common in sleep-related breathing disorders (297). The decisive criterion for initiating oxygen therapy is hypoxemia at rest. In COPD patients on oxygen, isolated exercise-induced hypoxemia was not associated with reduced mortality or increased hospitalization (298).

In a retrospective single-center analysis of 71,025 patients after surgery, Rostin et al. found (299) that desaturation episodes below an $SpO_2$ of 90% (4.6% of patients) of more than one minute were associated with higher pulmonary complication rates in the first 10 minutes of extubation (OR 1.68; 100% CI 1.50–1.88) and intensive medical care.

Good practice:

In patients at risk of hypercapnia or with known hypercapnia, stopping oxygen therapy is only advisable after first reducing the flow rate to 0.5–1 L/min. In all other patients, reduce to 2 L/min before stopping oxygen therapy.

Oxygen therapy can be stopped immediately in patients not at risk of hypercapnia who have an oxygen saturation > 96% under 2 L/min of oxygen or less for at least 5 minutes.

If $O_2$ saturation drops below the desired target range after oxygen therapy has been stopped, the lowest $O_2$ flow rate that kept the patient in the target range is recommended to be resumed.

| WG7 | Recommendation (100% agreement) | |
|---|---|---|
| **5** | If a patient cannot be weaned from oxygen, $O_2$ therapy should be continued even after discharge. These patients should be reevaluated a few weeks after initiation of the oxygen therapy to review the indication for long-term oxygen therapy.<br><br>Expert opinion | Expert consensus |

Some patients with chronic pulmonary disease already are on long-term oxygen therapy. In this patient group, oxygen therapy should be slowly reduced to their previously used flow rate. A small number of patients who had severe respiratory or cardiac conditions may require home oxygen to be safe after being discharged from the hospital. This is particularly common in patients with COPD exacerbation. Cohort studies in these patients showed, however, that 21–33% of oxygen prescriptions no longer met the criteria for long-term oxygen therapy at reevaluation. In Germany, and also in other countries, oxygen therapy initiated in hospitalized patients is often not followed up upon (300-303). The authors recommend to educate patients with regard to oxygen therapy prior to discharge to improve adherence.

Decisions concerning an indication for long-term oxygen therapy should not be made on the basis of blood gas measurements taken during an acute illness. The Guideline for Long-Term Oxygen Therapy recommends following up on oxygen therapy within 12 weeks of starting oxygen therapy, and also as part of the re-evaluation of stable patients (296).

# 11 Conclusion

Oxygen is a drug and shall be prescribed by a healthcare professional if the indication is met (usually hypoxemia) (recommendation 3.4). The indication for $O_2$ therapy is hypoxemia (1.1). Medical staff and patients shall be trained in oxygen therapy (3.3). Oxygen therapy shall be documented in writing, regularly monitored and re-assessed (2.2, 3.5, 2.1, 6.2). Acute medicine needs to avoid both hypoxemia and hyperoxemia. Hyperoxemia also seems to be associated with increased in-hospital mortality, especially in patients with hypercapnia. More than a quarter of hospitalized acute care patients with hypoxemia also have hypercapnia, as demonstrated by blood gas analyses. This guideline provides recommended target oxygen saturation for acute medicine. Oxygen saturation target ranges should be defined for each acutely ill patient. With few exceptions (CO poisoning 5.3, CPR 5.1, cluster headache 5.4), the target ranges apply to all adult patients. They do not differ between diagnoses. The $O_2$ target ranges recommended in this guideline were chosen so that—based on the current state of science–they are not harmful for patients and can be used with confidence in the clinical routine. The target oxygen saturation ranges depend on the risk of hypercapnia and the ventilation status. Oxygen saturation target ranges (Figure 7) differ between spontaneously breathing patients not at risk of hypercapnia (target $SpO_2$ 92–96%, 4.2) and those at risk of hypercapnia (target $SpO_2$ 88–92%, 4.3). The recommended arterial oxygen saturation for ventilated patients is 92–96% (4.2).

The guideline provides an overview of available oxygen delivery systems (Figure 5) and includes recommendations for their selection (Table 9) based on patient safety and comfort (3.1). High-flow oxygen is proposed for patients requiring more than 6 L of $O_2$ per minute to reach the target range (5.6). Patients on high-flow oxygen should be continuously monitored (5.7).

Humidification is not necessary for short-term and low-dose oxygen therapy (6.6). Risk of hypercapnia plays a role when oxygen therapy is discontinued. This is due to the potential of rebound hypoxemia (7.2). It is recommended to re-asses patients who were weaned from oxygen while hospitalized and who were prescribed $O_2$ for home oxygen therapy within a few weeks of discharge. In this context, it needs to be reviewed whether the indication for long-term supplemental oxygen therapy continues to apply (7.5).

# 12 Appendices

- Disclosures of conflicts of interests 
- Evidence reports
  - Guideline-based evidence 
  - Evidence search 
  - Evaluation of evidence for the recommendations 

# 13 Statements by the medical societies.

The guideline was submitted for approval to the boards of the medical societies involved. The following feedback was received:

The German Respiratory Society (DGP), as the lead society, agreed and recommended to include a supplementary summary, which was added in Chapter 11.

The guideline was approved without reservation by the boards of the following medical societies: German Society of Medical Intensive Care Medicine and Acute Medicine (DGIIN), German Society of Internal Medicine (DGIM), German Neurological Society (DGN), Federal Association of Organ Transplant Patients (BDO), and German Cardiac Society (DGK).

The board of the German Interdisciplinary Association for Intensive and Emergency Medicine (DIVI) approved the guideline without reservation.

The German Society of Anesthesiology and Intensive Care Medicine (DGAI) contributed editorial corrections and recommended to also include the S3 Guideline for the Management of Patients with Serious Injuries/Trauma (reference # (217)) in the considerations. Furthermore, another recently published meta-analysis on oxygen therapy after cardiovascular arrest was included in the references (250) at the recommendation of the DGAI, as well as a single-center retrospective analysis of conservative oxygen therapy in patients with COPD exacerbations (153). Both studies were discussed in the background texts of the respective chapters (Chapters 6.2 and 7.4). Following the revision, the guideline was approved by the DGAI board.

The German Society of Neurocritical Care and Acute Medicine (DGNI) recommended that special consideration be given to neurological patients based on evidence-based guidelines of the European Society of Intensive Care Medicine (ESICM) and the American Heart Association (AHA). Both guidelines (208, 218) were discussed in the background text. The final version presents neurological patients in a separate chapter (Chapter 7.2) with special consideration of the recommended literature (BOOST-II study) (216), the description of the neurotoxicity of O2 and increased mortality under hyperoxemia in patients with cerebral infarction and subarachnoid hemorrhage (219, 220). Furthermore, the data available on

hyperbaric oxygen therapy (HBO) were revised in Chapter 7.4 at the recommendation of the DGNI and the relevant meta-analyses were mentioned.

# 14 List of figures



# 15 List of tables

# 16 References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