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German S3 Guideline: Oxygen Therapy in the Acute Care of Adult Patients

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Abstract
Background: Oxygen (O_2) is a drug with specific biochemical and physiological properties, a range of effective doses and may have side effects. 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. Health care professionals are frequently uncertain about the relevance of hypoxemia and have low awareness about the risks of hyperoxemia. Numerous randomized controlled trials about targets of oxygen therapy have been published in recent years. A national guideline is urgently needed. ***Methods:*** A national S3 guideline was developed and published within the Program for National Disease Management Guidelines (AWMF) with participation of 10 medical associations. A literature search was performed until February 1, 2021, to answer 10 key questions. The Oxford Centre for Evidence-Based Medicine (CEBM) System ("The Oxford 2011 Levels of Evidence") was used to classify types of studies in terms of validity. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used for assessing the quality of evidence and for grading guideline recommendation, and a formal consensus-building pro-

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cess was performed. ***Results:*** The guideline includes 34 evidence-based recommendations about indications, prescription, monitoring and discontinuation of oxygen therapy in acute care. The main indication for O_2 therapy is hypoxemia. In acute care both hypoxemia and hyperoxemia should be avoided. Hyperoxemia also seems to be associated with increased mortality, especially in patients with hypercapnia. The guideline provides recommended target oxygen saturation for acute medicine without differentiating between diagnoses. Target ranges for oxygen saturation are based depending on ventilation status risk for hypercapnia. The guideline provides an overview of available oxygen delivery systems and includes recommendations for their selection based on patient safety and comfort. ***Conclusion:*** This is the first national guideline on the use of oxygen in acute care. It addresses health care professionals using oxygen in acute out-of-hospital and in-hospital settings.

Abbreviations used in this paper

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
CPR	Cardiopulmonary resuscitation
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
ICU	Intensive care unit
L/min	Liters per minute
NIV	Noninvasive 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
ROX	Respiratory rate-oxygenation
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

Contents

1 Introduction

Oxygen 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.

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 reversed after 2 days of oxygen supplementation, with the symptoms returning when the O_2 supply had been exhausted. After the therapy was resumed, the patient fully recovered over 4.5 days [1].

Cells use oxygen to get energy from the nutrients. 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.

The present guideline uses oxygen saturation as the key target parameter. 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 decided against recommending specifying target ranges for specific clinical conditions. This approach takes into account the increasing multimorbidity of patients and should help 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.

1.1 Physiology of Blood Gases

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:

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

where CaO_2 is O_2 content (in mL O_2/dL blood), Hb is hemoglobin concentration in blood (in g/dL), SO_2 is O_2 saturation, paO_2 is partial pressure of O_2 (in mm Hg), and 1.34 is Huefner'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 [2, 3].

paO_2 is a key parameter for assessing the pulmonary gas exchange and is obtained by blood gas analysis (BGA) which requires puncture which is painful for the patient and more time-consuming. Neither oxygen saturation nor the partial pressure of oxygen in arterial blood are suitable key parameters for determining the tissue oxygenation.

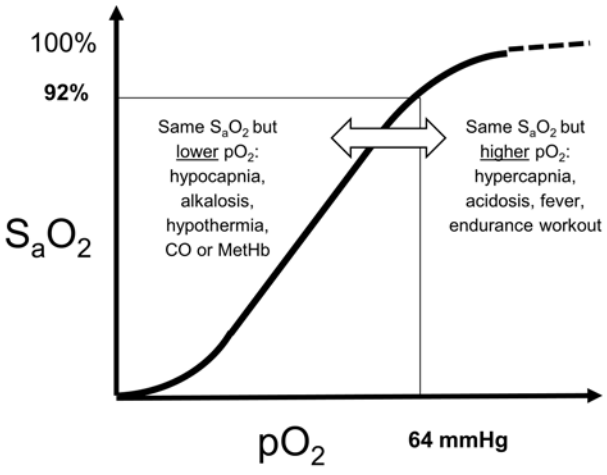
Hypoxemia, i.e. low blood oxygen levels, is often confused with hypoxia. Tissue oxygenation is essentially determined by hemoglobin levels and cardiac output and is only inadequately characterized by SaO_2 or paO_2. Nevertheless, much more attention is paid to hypoxemia in clinical practice than to these key parameters, which are not immediately available.

The oxygen binding curve (Fig. 1) characterizes the relationship between arterial oxygen saturation (SaO_2) as a function of the partial pressure of O_2 (paO_2).

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. The generally accepted normal $paCO_2$ range is 36–44 mm Hg. The normal pO_2 values when lying down and sitting vary depending on age [4, 5], with the latter being higher. In a large UK study on 37,000 patients, the median SpO_2 was 98% for adults aged 18–64 years, and 96% for the elderly.

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.

Fig. 1. Relationship between oxygen saturation and the partial pressure of oxygen.

Normal oxygen saturation in a population depends on altitude. A sample group of 3,812 people living in Tibet at an altitude of approximately 4,000 m, for example, had a mean SaO_2 of only 88% [6]. 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 (pO_2 <60 mm Hg) of 100% and a specificity of 86% [7]. 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 (SaO_2) of 90% [8]. 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% [9].

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 paO_2 <60 mm Hg and SaO_2 <90% [10]. There is currently no clear scientific evidence as to when and how much supplemental oxygen is needed to treat hypoxemia. The target ranges recommended in this guideline are based on current evidence which level of hypoxemia and hyperoxemia are likely to be harmful for patients and which target range can be safely used.

Tissue hypoxia may be hypoxemic, anemic, stagnant or histotoxic (e.g., in cyanide poisoning). Oxygen therapy usually serves to correct hypoxemic hypoxia.

Table 1. 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; $paCO_2$, partial pressure of carbon dioxide; ARDS, acute respiratory distress syndrome in adult patients.

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 1).

The alveolar-arterial partial pressure gradient (according to Helmholz [11]; the normal value at sea level is <(age/4) + 4 mm Hg) is calculated as

$$(FiO_2 \times 760) - (paCO_2/0.8) - paO_2,$$

where 760 is atmospheric pressure (760 mm Hg at sea level), and $FiO_2 = 0.21 + O_2$ flow in liters per minute (L/min) × 0.038 [12].

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) [13], to serve as indicators of increased mortality and the necessity of intensive medical care.

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 $paCO_2$ ≥45 mm Hg, potentially resulting in reduced SaO_2 and pO_2 levels. In chronic hypercapnia, e.g., in COPD, hyperoxemia may result in a dangerous increase in the $paCO_2$ as the pulmonary vasoconstriction of nonventilated areas is reversed in hyperoxemia. In addition, hypoxemia reduces the respiratory minute volume; in addition, oxygenated hemoglobin has decreased carbon dioxide carriage (Haldane effect) [14].

1.2 Permissive Hypoxemia

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 versus normoxemia in adults.

A 2014 meta-analysis did not identify any studies comparing permissive hypoxemia in ventilated patients versus a control group with normoxemia or mild hypoxemia [15]. Based on our own literature search, the only study investigating the concept of permissive hypoxemia in a randomized approach was the NeOProM collaboration [16], in which 4,965 preterm infants were randomized to receive oxygen therapy with a target SpO_2 of 85–89% or 91–95%. 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 acute respiratory distress syndrome (ARDS) patients, isolated mesenteric ischemia was also observed in 5% of patients with a target SpO_2 of 88–92% [17]. Hence, the range of hypoxemia that can be tolerated by critically ill patients in the medium term remains unclear.

An association of hypoxemia and increased mortality has repeatedly been described for large cohorts of hospitalized patients and emergency care [18, 19].

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 studied in prospective clinical trials. In a randomized controlled trial (RCT) on 838 patients, 82% of whom were ventilated, a liberal transfusion strategy (hemoglobin >10 g/dL) versus a con-

servative strategy (hemoglobin >7 g/dL) did not produce a significant difference in the 30-day survival rate [20]. To maintain tissue oxygenation 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 (CaO_2) and the cardiac output. The results of increasing the DO_2 in critically ill patients on survival, organ failure, length of hospitalization in RCTs were contradictory [21, 22]. A systematic review provided insufficient data to support a routine increase of DO_2 in critically ill patients [23]. The administration of inotropic agents to increase cardiac output may also produce side effects 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 approximately 70% [24]. This leads some authors to argue that even adult patients may be fully stable at an SpO_2 of 70%. There are definitely patients who are adapted to chronic hypoxemia (e.g., populations living at high altitudes or people with chronic hypoventilation) without reporting shortness of breath. Nevertheless, adjustment processes to chronic hypoxemia take several weeks and go along with an increase in hemoglobin levels, minute volume, and respiratory output. The experience that there are people who have adjusted to chronic hypoxemia cannot be transferred to patients with acute hypoxemia.

Acute altitude-induced hypoxemia above 6,700 m with saturation levels below 70% leads to loss of consciousness within a short period of time and is fatal after days even after acclimatization [25]. Even healthy subjects showed cognitive impairment in hypoxemia below 80% [26].

The exact range within which hypoxemia is tolerated in the medium term is unknown for lack of controlled trials. 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 min in healthy subjects at an arterial saturation rate of 78% [27], and myocardial lactate was released at a saturation of <75% [28] when exercising in a low-oxygen environment. In patients with coronary artery disease, myocardial lactate was produced at rest during moderate hypoxemia ($SaO_2 < 85\%$) [29]. An oxygen saturation of 85% is therefore frequently regarded 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. The recommended ranges of this guideline take into account the limitations of pulse oximetry, whose 95% confidence interval (CI) in terms of actual consistency with arterial saturation (SaO_2) ranges from 84 to 92% for an SpO_2 of 88%, for example.

1.3 Hyperoxemia

Hyperoxemia, like hypoxemia, is not precisely defined. The normal O_2 saturation at sea level is 96% [30]. 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 [31]. 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 negatively affects patient mobilization, food and fluid intake, and communication [32]. 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 [33]. A meta-analysis of 25 randomized controlled O_2 trials provided strong evidence of an increased relative risk of in-hospital mortality with hyperoxemia under liberal oxygen therapy [31]. The relative risk of 3-month mortality was 1.18 in ICU patients with a higher oxygen target range and a higher incidence of severe adverse events [34]. 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 [35, 36]. The increased free radical generation during hyperoxia can result in cell damage [37]. Hyperoxemia may result in falsely reassuring SpO_2 levels and delay the detection of a deterioration in hypoxemic patients in comparison to conservative O_2 therapy [6, 38]. In patients with COPD, prehospital hyperoxia was associated with greater in-hospital mortality and increased the risk of hypercapnic respiratory failure on admission [39]. Hyperoxemia leads to coronary vasoconstriction [40], and routine supplemental oxygen therapy does not improve the mortality after myocardial infarction [41]. In 21 studies on 7,597 patients, hyperoxia did not improve intra- and postoperative wound healing [42].

2 Methods

This is the official translation of the condensed version of the German version of the guideline [43]. The guideline was developed and published within the Program for National Disease Management Guidelines of the Association of the Scientific Medical Societies in Germany.

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

The guideline was published in June 2021 in its original German version and will be valid for 3 years until June 30, 2024. The following supplementary documents to this guideline are available online: disclosures of conflicts of interest, evidence report, report of existing guidelines and evaluation of evidence for recommendations.

This guideline addresses health care professionals using oxygen in acute out-of-hospital and in-hospital settings. The guideline is intended for out-of-hospital and in-hospital emergency settings and included recommendations for the treatment of critically ill patients including patients on invasive ventilation. Furthermore, the guideline is intended to include recommendations for supplemental oxygen therapy during procedures with conscious sedation, e.g. during endoscopy. 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 was out of scope of this guideline. The guideline also intends to inform other users of oxygen in prehospital and in-hospital settings, such as health care and nursing staff, members of the emergency rescue services, and physicians.

The following medical associations participated in this 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).

The German Rescue Service Association (DBRD) was a designated advisor on specific issues, and a member attended consensus meetings. A patient representative of the Federal Association of Organ Transplant Patients (BDO) was involved in the guideline development process and participated in the consensus meetings.

An independent review of evidence included an independent guideline and literature search on 10 key questions for the guideline in 2019 and led to 2 reports. 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 in 2019, additional relevant studies had been published in the meantime. An additional literature search and evidence report of the recommendations were made in 2021. The literature search was performed until February 1, 2021.

During development the following key questions were 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 under 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 (HFNC) therapy superior to conventional O_2 treatment?

This guideline used 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. Level 1 consists of systematic review of RCTs, level 2 of RCT or observational study with dramatic effect, level 3 nonrandomized cohort study, level 4 are case series, case-control studies or historically controlled studies and level 5 mechanism-based reasoning (case studies, anecdotes, and personal opinions).

A formal consensus-building process was performed. A total of 3 structured consensus conferences were held in accordance with the model described by the National Institutes of Health, with 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

Table 2. Grades of recommendation

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

and summarization of proposals, as necessary, voting on the original version and on the amendments and repeat discussion and voting if no consensus was reached.

A consensus was reached if endorsed by >75% of participants, and a strong consensus was defined if endorsed by >95% of participants. Consensus (n = 4) or strong consensus (n = 30) was reached for all 34 recommendations.

For all recommendations, the guideline indicated 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 2).

The grade of each recommendation resulted from the quality of the evidence and the rationale for the strength of recommendation. Thus, a strong recommendation could be issued even without a high degree of certainty, if the recommendation was based on clinical assessment/experience.

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) was used for assessing the quality of evidence and for grading guideline recommendations. The guideline group started by defining patient-relevant end points.

Critical end points were mortality and quality of life. Important (but not critical) end points were new ischemic cardiovascular events, relief of shortness of breath, correction of hypoxemia, costs, necessity of ventilation (safety), adverse effects – like immobility/disability, discomfort, claustrophobia, mucosal desiccation, hoarseness (safety) – and functional outcome (Rankin scale: http://www.neuroreha.at/assets/rankin-scale-deu.pdf).

After adjusting for confounders, the quality of evidence was considered as high ⊕⊕⊕⊕, moderate ⊕⊕⊕⊖, low ⊕⊕⊖⊖ or very low ⊕⊖⊖⊖ for each end point. The overall quality of the evidence for all end points was assessed based on the lowest quality of the critical end points.

Recommendations were 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.

"Practice points" included practice point recommendations the authors considered relevant for the users of oxygen therapy and were not subject to a consensus voting process. The recommendations are often based on case reports, isolated literature references, and include clinically significant observations.

As for independence and disclosure of potential conflicts of interest, the guideline was developed independently of the funding organization. All members of the guideline group submitted a written disclosure of conflicts of interest. The conflicts of interest were screened by the guideline coordinator and the AWMF representative for any relevant conflicts. 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 or expert activities for a company in the health care 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, 3 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. S.K. and C.K. had a potential conflict of interest with regard to extracorporeal membrane oxygenation, which were rated as moderate in both cases. This guideline does not give a recommendation on extracorporeal membrane oxygenation. T.V. had a possible moderate conflict of interest on the subject of humidification. He did not participate in voting on the recommendation 6.6. on this topic.

3 Recommendations

Recommendation 1.1 (100% agreement)	Grade of recommendation/GRADE	
The underlying causes of hypoxemia should be identified and treated. Oxygen should be given to treat hypoxemia, not dyspnea Uronis 2007 [44], Uronis 2011 [45], Cranston 2008 [46]	**A**	
	High quality of evidence ⊕⊕⊕⊕	Quality of life

Three meta-analyses involving mostly cancer patients and COPD patients with breathlessness (the majority had an SpO_2 ≥90%) demonstrated that either perceived dyspnea was not improved by oxygen versus compressed air therapy or 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 [44–46].

Practice Points:

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/m^2) when lying on their back [47].

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

In palliative care, nonpharmacological measures are initially used to manage dyspnea in nonhypoxemic 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 nonhypoxemic patients with dyspnea.

3.1 Patient Assessment

Recommendation 2.2 (100% agreement)	
The assessment of patients presenting with dyspnea shall include respiration rate, pulse rate, blood pressure, body temperature, mental state as well as oxygen saturation	Expert consensus

SpO_2 is only one of several physiological parameters – so-called vital signs – for the assessment of patients, which are easily obtainable at the bedside by nursing staff. More than 1 million vital signs were measured in 27,722 patients upon admission [18]. 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% [18]. The critical levels identified in this context were: systolic blood pressure <85 mm Hg, 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 and nasal flaring. Hypoxemia may influence vital signs and symptoms [48]. Relevant hypoxemia can, for example, result in impaired consciousness, pectoral angina, arrhythmia or hypotensive/hypertensive circulatory response [10]. However, arterial hypoxemia does not necessarily lead to changes in vital signs [49]. Studies indicate that vital signs are insufficient in terms of predicting arterial hypoxemia [50–52].

Changes in consciousness may already be seen in the early stages of hypoxemia [53, 54]. Warning signs are anxiety, restlessness, and agitation followed by confusion and loss of consciousness [10]. "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. The National Early Warning Score (NEWS2) 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 [13].

Practice Points:

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/min.

Patients are considered clinically stable when they have a NEWS2 score <5 and their vital signs are predominantly in the noncritical range [13].

Training oxygen users in how to measure their respiration rate is useful if no monitor is available [55].

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

Recommendation 2.1 (100% agreement)	Grade of recommendation/GRADE	
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 Pedersen 2014 [56]	**A**	
	Low quality of evidence ⊕⊕⊖⊖	Mortality
	Moderate quality of evidence ⊕⊕⊕⊖	Hypoxemia
	Moderate quality of evidence ⊕⊕⊕⊖	Cardiovascular events

Pulse oximetry is a simple, noninvasive 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 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 health care [57, 58]. Pulse oximetry is less accurate than measuring the O_2 saturation of arterial blood, especially in the range below 80% [59, 60]. In the clinically relevant range (oxygen saturation 80–100%), SaO_2 and SpO_2 have an acceptable correlation. In clinically stable COPD patients, an SpO_2 <92% has high sensitivity and specificity for detecting an arterial saturation <90%.

The authors identified a Cochrane analysis of pulse oximetry in postoperative monitoring [56]. With the use of pulse oximetry hypoxemic episodes were 1.5–3 times less likely with than without pulse oximetry monitoring with no significant differences in mortality or ICU admission. The use of pulse oximeters improved the detection of hypoxemia versus clinical monitoring alone, and this was demonstrated in various populations, and in the prehospital setting [7, 8, 50, 51, 61, 62]. We identified no high-level randomized trials to support this recommendation but it was supported by a systematic review in the field of emergency medicine [63].

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 [9].

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% [64] from the arterial saturation levels which was attributable to technical reasons.

In a large cohort study of almost 10,000 patients, occult hypoxemia was 3 times as high among African American patients versus Caucasians [65]. Overestimation of oxygen saturation by pulse oximetry has also been described in crisis situations of patients with sickle cell disease [66].

Practice Points:

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 under 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.

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 [67].

Recommendation 6.2 (92% agreement)	
Monitoring of oxygen by blood gas analyses should be performed in the following in-patient groups: – Critically ill patients, e.g., those suffering from shock or metabolic disorders – Ventilated patients – Patients with severe hypoxemia (>6 L O_2/min, or FiO_2 >0.4) – Patients at risk of hypercapnia (e.g., COPD, severe asthma, obesity with BMI >40 kg/m^2) – Patients where no reliable pulse oximetry signal can be obtained No routine blood gas measurements should be done in patients who are stable and do not fall into any of the above-mentioned patient groups	Expert consensus

Blood gases should be measured in emergency situations in critically ill [68] hypoxemic patients and are recommended for ventilated patients in the S3 guideline on ventilation [69]. 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 mm Hg corresponding to an oxygen flow rate >6 L/min or FiO_2 >0.4) [70–72] 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 BGA [63]. The downside of arterial puncture is the potential of complications and the fact that they are painful for the patients.

Practice Point:

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

Recommendation 2.3 (100% agreement)	Grade of recommendation/ GRADE	
Blood gas analysis of arterialized capillary blood from the earlobe can be used to assess non-ICU patients Zavorsky 2007 [73], Magnet 2017 [74], Ekkernkamp 2015 [75]	**0**	
	Low quality of evidence ⊕⊕⊖⊖	Hypoxemia
	Very low quality of evidence ⊕⊖⊖⊖	Quality of life

Due to the increased complication rate associated with arterial puncture, BGA (BGA) for non-ICU patients is often done using earlobe blood, which is arterialized by rendering it hyperemic (= capillary BGA) [76].

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 [63]. 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 [73]. In this analysis, the pO_2 from earlobe blood was found to be lower by 3.9 mm Hg on average, and from the fingertip by as much as 11.5 mm Hg.

Two other studies with 83 and 120 matched samples of stable long-term oxygen therapy patients showed the capillary pO_2 to be lower than the arterial pO_2 by 5.6 and 6.0 mm, respectively, on average [74, 75]. Major sources of error in capillary BGA include inadequate arterialization, 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) [74, 75]. According to expert opinion, capillary BGA can be used in stable patients outside the intensive care setting after thorough arterialization of the earlobe blood, but not in emergency situations when patients are unstable.

Practice Points:

Standard operation procedures should be established for capillary BGA. At least 5 min at a constant O_2 flow rate, at least 10 min of arterialization, and at least 15 min of rest are considered necessary preparatory steps for capillary BGA [76].

Both capillary BGA 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 BGA should be performed.

Recommendation 2.4 (100% agreement)	Grade of recommendation/ GRADE	
Venous blood gas analysis shall not be used to monitor oxygen therapy. Venous blood gas analyses are able to exclude hypercapnia only at a $pvCO_2$ <45 mm Hg Lim 2010 [77], Byrne 2014 [78], Bingheng 2019 [79], Bloom 2014 [80]	**A**	
	Moderate quality of evidence ⊕⊕⊕⊖	Hypoxemia

Blood gas measurements from venous blood samples have 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 mm Hg lower than in arterial blood. It is therefore not suitable for measuring oxygenation [77–79]. Venous BGAs are not suitable for monitoring oxygen therapy. There is also a difference of +3 to +6 mm Hg in the partial pressure of carbon dioxide compared to arterial measurements [77–80]. Three studies with used a cut-off of 30–46 mm Hg [81–84]. In three studies with matched arterial and venous BGAs, $pvCO_2$ was able to exclude arterial hypercapnia with a negative predictive value of 100% at a venous pCO_2 cutoff of <45 mm Hg (106–109).

3.2 Oxygen Prescription

Recommendation 3.4 (100% agreement)	
Inpatient oxygen therapy shall be prescribed by a physician, specifying a target range of oxygen saturation	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 with O_2 prescription ranges from 40 to 60% [85, 86]. Medical oxygen was classified as drug in Germany in 2005, and a prescription is required for supplemental oxygen administration.

Practice Points:

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 [12].

Oxygen therapy must be prescribed by a doctor. 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 (see 7.4) and documented in retrospect.

Recommendation 3.5 (100% agreement)	
Each oxygen prescription should be based on a patient evaluation by clinicians or other specially trained health care professionals 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 [87–89].

According to retrospective analyses, hypoxemia is a negative prognostic indicator in inpatients and emergency room patients [18, 19]. Oxygen prescription therefore requires reassessing the patient to be able to detect clinical deterioration at an early stage and prevent events such as cardiopulmonary resuscitation (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 h, even in patients with normal vital signs. For hospitalized patients, the UK recommends reassessments every 4–6 h for patients with freshly started or ongoing oxygen therapy [90].

Based on expert opinion, the BTS guideline recommends 6-h 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 are 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 RCTs are available in this regard, but it is known, for example, that approximately 40% of inpatients on high-flow oxygen therapy are intubated [70, 71]. 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 [91].

Practice Points:

Vital signs shall be checked at least every 6 h 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).

3.3 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. In Germany, medical O_2 in health care 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% [92]. 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 to 4, 2 to 16, and 4 to 32 L/min with a flow accuracy of +10% (+15% at the lowest setting). It must be ensured that medical staff is able 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 while others may provide it on the "equator").

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.

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 mixups. Oxygen outlets are hexagonal (Fig. 3). Nitrous oxide/oxygen mixtures (Livopan®) for analgesia shall not be used in patients at risk of hypercapnia.

Recommendation 3.2 (100% agreement)	
Oxygen shall not be used as driving gas or used for a short time only (generally less than 10 min, if compressed air is not available) for the nebulized administration of drugs in patients at risk of hypercapnia Expert opinion	Expert consensus

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. High-dose oxygen administration may result in hyperoxemia with acute hypercapnic respiratory failure [39].

In 1984, Gunawardena et al. [93] found a significant increase in $paCO_2$ in 9 hypercapnic COPD patients after 15 min of oxygen-driven nebulization, with a return to baseline values only 20 min after terminating nebulization. Two studies analyzed partial pressure of carbon dioxide during high-dose oxygen therapy versus compressed air in patients at risk for hypercapnia ADDIN EN.CITE. (The proportion of patients in whom the transcutaneously measured partial pressure of carbon dioxide ($PtCO_2$) had increased was higher in patients after nebulization with high-flow oxygen in comparison to compressed air-driven nebulization. This is important in emergency out-of-hospital situations where patients at risk of hypercapnia (e.g. COPD) 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 min to limit the increase in the partial pressure of carbon dioxide [93–95]. Compressed air-driven nebulizers or ultrasonic nebulizers shall be preferred in these patients.

Practice Points:

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 [63].

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.

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

Recommendation 3.3 (100% agreement)	
Oxygen shall be administered, monitored and controlled by staff trained in oxygen therapy. Patients shall be informed about the oxygen therapy Expert opinion	Expert consensus

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. 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 [63].

Practice Points:

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.

Patient involvement and training may prevent oxygen misuse.

3.4 Oxygen Delivery Systems

Recommendation 3.1 (100% agreement)	Grade of recommendation/ GRADE	
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 Costello 1995 [96]; Nolan 1993 [97], Eastwood 2008 [88], Stausholm 1995 [98], Ayhan 2009 [87]	**B**	
	Moderate quality of evidence ⊕⊕⊕⊖	Quality of life/ adverse drug reactions

This recommendation is based on 4 crossover studies [96, 97, 99, 100], and 3 randomized trials investigating the patient comfort of different oxygen delivery systems [70, 87, 101].

In conclusion, nasal prongs offered greater patient comfort and had lower dislocation rates than masks. Only 1 out of 3 RCTs indicated that HFNCs 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 [102] 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 are selected based on clinical circumstances and patient needs (Table 3).

Venturi masks use 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. 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 4 [99]. 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 [100, 103]. Unlike with nasal prongs, a Venturi mask does not increase the FiO_2 at higher flow rates.

Practice Points:

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.

3.5 Application of Oxygen

Target ranges for oxygen saturation recommended in this guideline are chosen to prevent hypoxemia and hyperoxemia at levels which are likely to be harmful for acutely ill patients. 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 2 shall be used for these 3 patient groups.

Exceptions without a target oxygen saturation range are patients with cluster headache, carbon monoxide poisoning, and critically ill patients in whom pulse oximetry cannot be used.

The recommended O_2 therapy for patients with spontaneous breathing is shown in Figure 3.

3.6 Oxygen Saturation Target Ranges in Acute Conditions

Recommendation 4.1 (100% agreement)	Grade of recommendation/ GRADE	
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 Siemieniuk 2018 [32], Chu 2018 [31, 42], Wetterslev 2015 [42]	**A**	
	Moderate quality of evidence ⊕⊕⊕⊖	Mortality
	Moderate quality of evidence ⊕⊕⊕⊖	Functional outcome

Three meta-analyses and four RCTsrandomized controlled trials on target oxygen ranges were identified by independent literature search [17, 31, 41, 104–106]. The meta-analysis by Chu et al. [31] 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). This meta-analysis

Table 3. Pros and cons of different oxygen delivery systems

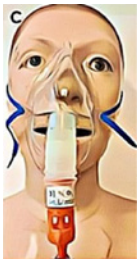
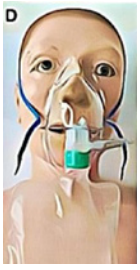
		Pros	Cons
Nasal prongs (FiO_2 0.26–0.54)		High patient comfort Low cost No interference with oral intake	FiO_2 limited and unreliable FiO_2 dependent on opening of the mouth and respiration rate
Nasal cannulae (FiO_2 0.2–0.4)		Occupy only one opening of the nose Low cost No interference with oral intake	Mucous membrane irritation
Simple face masks (FiO_2 0.35–0.60)	No figure	FiO_2 independent of the opening of the mouth Low cost	Low patient comfort Risk of hypercapnia at flow rates <5 L/min Prevents patient from eating and drinking
Venturi masks (FiO_2 0.24–0.60)		Reduced risk of hyperoxia and hypercapnia Low aerosol formation	Low patient comfort Prevents patient from eating and drinking Experienced personal necessary
Face tent (FiO_2 0.35–0.5)	No figure	Patient comfort High FiO_2 delivery	FiO_2 unreliable
Reservoir masks (FiO_2 0.6–0.9)		High FiO_2 Useful in emergency situations	Low patient comfort Risk of hypercapnia at flows <5 L/min Prevents patient from eating and drinking
High-flow cannulae (FiO_2 0.3–1.0)		High FiO_2 High patient comfort Good control of FiO_2 Acceptable aerosol formation if fitted correctly Provides modest PEEP Washout of CO_2 in dead space	More effort for staff Closer monitoring Higher cost

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Table 3 (continued)

		Pros	Cons
Ventilation masks (FiO_2 0.25–1.0)		High FiO_2 Low aerosol formation (if double tubing and/or filter)	Low patient comfort (e.g., pressure marks, claustrophobia) More staff effort, higher cost

FiO_2, inspired oxygen concentration; PEEP, positive end-expiratory pressure. From https://www.awmf.org/leitlinien/detail/ll/020-021.html.

Table 4. Overview of Venturi masks and recommended flow rates

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

[a] Read the manufacturer's information; for respiration rates >30/min, increase flow by 50%, as necessary [99]. FiO_2, inspired oxygen concentration.

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. Increased mortality associated with hyperoxemia may have been caused by proinflammatory effects, vasoconstriction, particularly in the myocardium and CNS, and increased oxidative stress. The upper limit of SpO_2 of 96% recommended in the meta-analysis by Chu et al. is also based on the mean saturation at enrollment.

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 to 94% [104, 106, 107]. Almost 38,000 patients with a median age of 69 years in 3 UK hospitals had a mean SpO_2 on ambient air of 97% on admission (25th and 75th quartiles of 95 and 98%) [30].

Routine high-dose oxygen administration in the perioperative period (the inspiratory oxygen fraction (FiO_2) based on a large meta-analysis [108] conducted for this indication, hyperoxemia is not reasonable during surgery.

Practice Point:

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 min).

Oxygen cards indicating the SpO_2 target range at the bedside are useful for all patients on oxygen therapy (Fig. 4, 5).

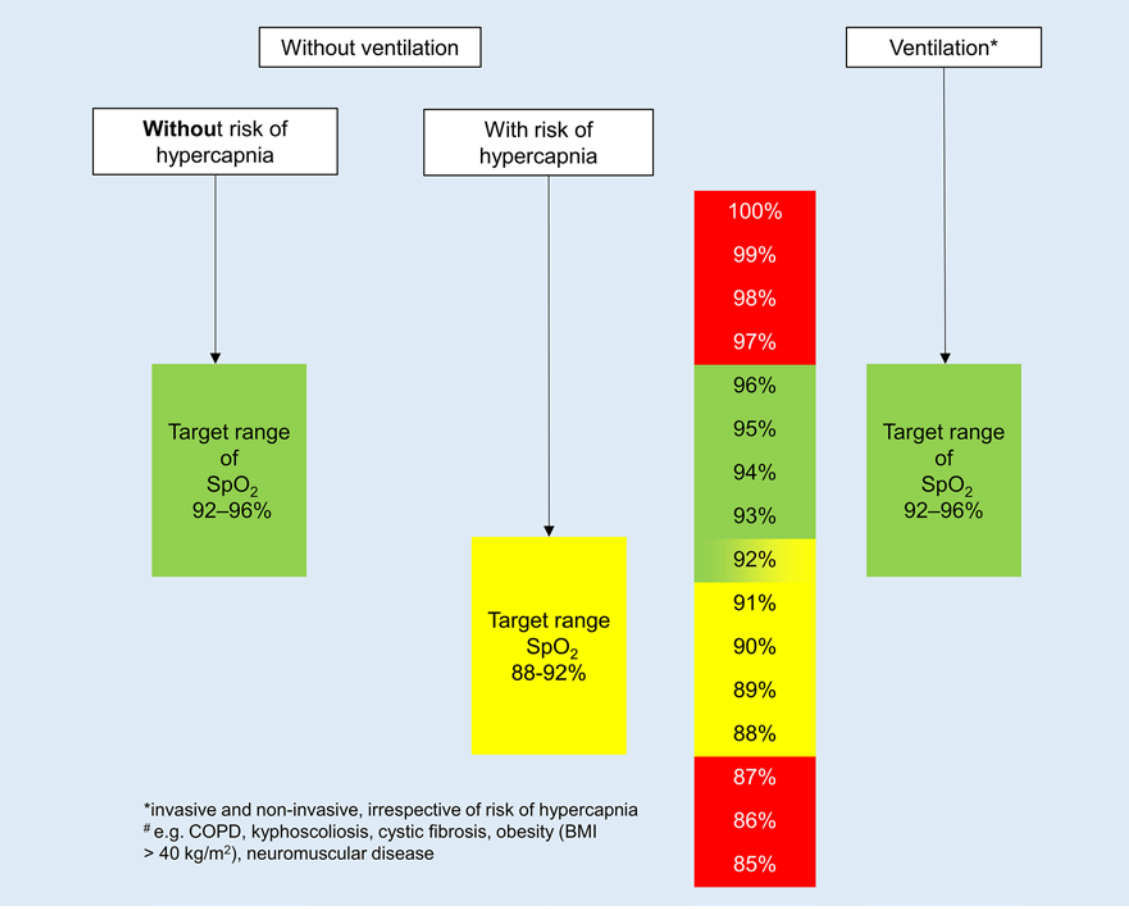

Fig. 2. Target ranges of oxygen therapy for the different groups of patients. BMI, body mass index; SpO_2, oxygen saturation measured by pulse oximetry; SaO_2, arterial oxygen saturation. From https://www.awmf.org/leitlinien/detail/ll/020–021.html.

3.7 Target Oxygen Saturation Ranges for Patients at Risk of Hypercapnia

Recommendation 4.3 (100% agreement)	Grade of recommendation/ GRADE	
Oxygen shall be prescribed for acutely ill, nonventilated 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% Austin 2010 [39], Kopsaftis 2020 [109]	**A**	
	Moderate quality of evidence ⊕⊕⊕⊖	Mortality
	Low quality of evidence ⊕⊕⊖⊖	Intubation

The authors' own literature search identified one meta-analysis in addition to the evidence report [109]. However, this meta-analysis is based on 1 RCT only [39]. 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 versus 3% of those treated with conservative oxygen therapy died while in hospital (treatment effect 0.05–0.91). Intubation rates were not significantly increased under liberal oxygen therapy.

A study of 3,524 blood gas samples in a single UK hospital found that 27% had a partial pressure of carbon dioxide of more than 45 mm Hg [63]. In a German analysis of 6,750 hospitalized patients, 2,710 of whom suffered from respiratory distress, 588 (22%) had a $PaCO_2$ of 45

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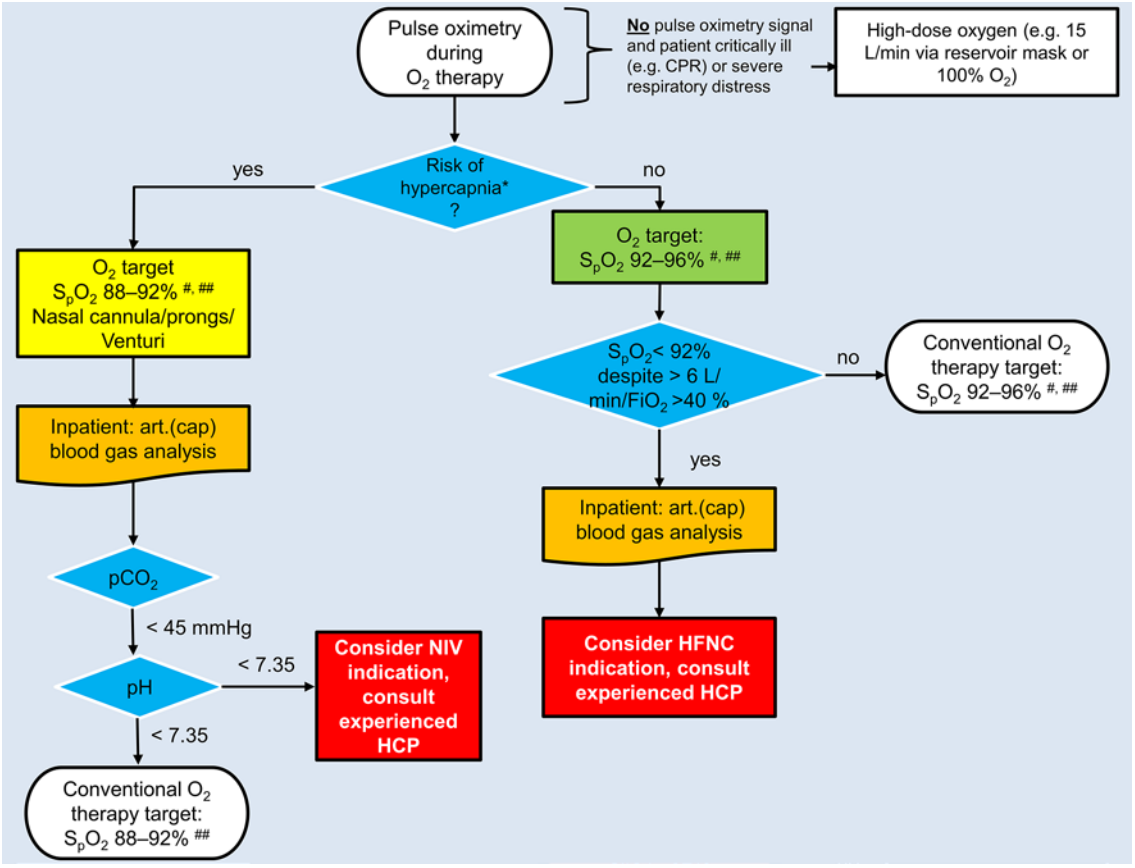


Fig. 3. Oxygen therapy in nonventilated patients. CPR, cardiopulmonary resuscitation; SpO_2, oxygen saturation as measured by pulse oximetry; O_2, oxygen; NIV, noninvasive ventilation; HFNC, high-flow oxygen; BMI, body mass index; art., arterial; cap., capillary; pCO_2, partial pressure of carbon dioxide; HCP, health care provider. * e.g., COPD, BMI ≥40 kg/m^2, 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.

mm Hg and more [110]. Patients with COPD in particular, but also those with cystic fibrosis, thoracic deformities, neuromuscular disease, and obesity (BMI >40 kg/m^2), are at risk of hypercapnic respiratory failure in the context of ventilatory insufficiency [111–117]. 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 versus conservative oxygen therapy [95, 118–121].

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% CI 1.09–3.60) and 2.97 (95% CI 1.58–5.58), respectively, independent of the presence of hypercapnia [122].

3.8 Target Oxygen Saturation Ranges for Ventilated Patients

Recommendation 4.2 (100% agreement)	Grade of recommendation/ GRADE	
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 prehospital setting Girardis 2016 [123], Panwar 2016 [124], Asfar 2016 [125], Barrot 2020 [17], Barbateskovic 2019, ICU-ROX [105]	**A**	
	Moderate quality of evidence ⊕⊕⊕⊖	Mortality
	Low quality of evidence ⊕⊕⊖⊖	Adverse events

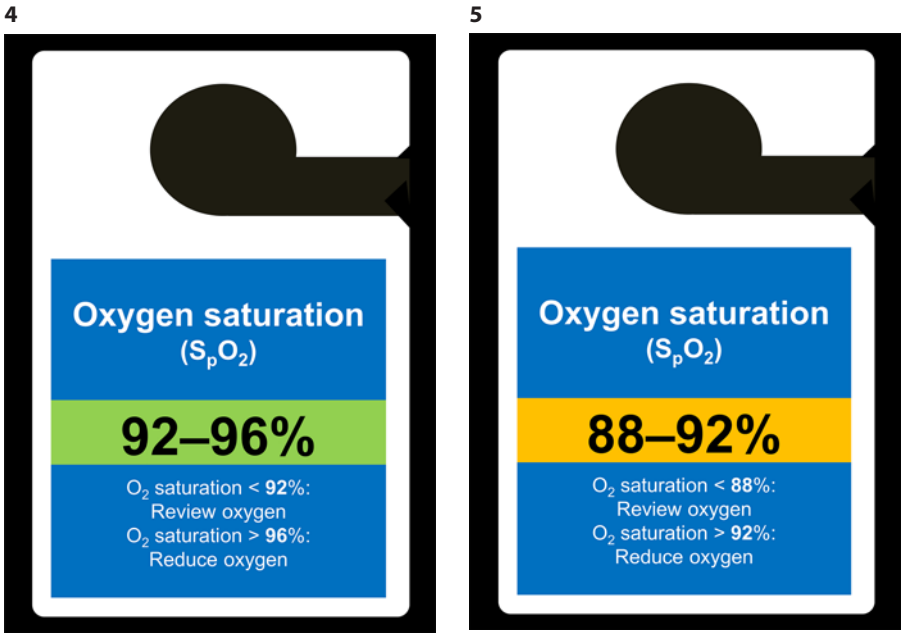


Fig. 4. O_2 card for patients not at risk of hypercapnia.
Fig. 5. O_2 card for patients at risk of hypercapnia.

Ventilated patients should be viewed separately, as they are usually continuously monitored in the 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 [126], 19,515 patients [127], 152,680 patients [128]) investigated the effect of hypoxemia and hyperoxemia on the in-hospital mortality of ICU patients.

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 a very low level of evidence [34]. 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 [129]. The authors of a 2017 meta-analysis (4 studies with 372 patients) found conservative oxygen therapy to be associated with lower ICU mortality, 28-day mortality, in-hospital mortality, and nonrespiratory organ failure than liberal O_2 therapy [130].

Six randomized trials compared liberal versus 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 [105]. The French study on 205 patients with ARDS was terminated prematurely due to safety concerns, as the conservative therapy group showed increased mortality versus other studies with a particularly low target saturation range of 88–92%, and 5 patients in the conservative therapy group died of mesenteric ischemia. Mortality was also increased in the conservative therapy group in the Australian multicenter study [124] with the same SpO_2 target range, albeit not significantly.

The HOT-ICU trial [131] 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 mm Hg, 58% with invasive ventilation at randomization) were randomized to a conservative oxygen target range (paO_2 60 mm Hg with a maximum tolerance of 7.5 mm Hg, achieving a median SaO_2 of 93%) and a liberal oxygen target range (paO_2 90 mm Hg with a maximum tolerance of 7.5 mm Hg, 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 noninvasive ventilation (NIV) or continuous positive airway pressure (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% [71, 132–134]. The guideline

authors therefore believe that the SpO_2 target range for oxygen therapy should be between 92 and 96%, even under NIV or CPAP.

3.9 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 mm Hg in 3,007 ICU patients in whom O_2 delivery was manually adjusted based on 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 92–96%. A large percentage of (SpO_2 or pO_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.

In 4 (randomized or crossover) 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 [135–138]. 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 [139].

In two small case series, the resorption of pneumothorax was accelerated by giving high-dose oxygen (up to 16 L/min via mask) [140, 141], without the method having found its way into any guidelines [142]. In an 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 [143]. 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.

Practice Point:

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

Recommendation 4.4 (85% agreement)	
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	Expert consensus

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 BGAs.

An increased respiration rate is associated with increased in-hospital mortality [18] and considered a warning signal, not only of pulmonary disease, but also of sepsis. Tachypnea in normoxemic patients may be attributable to serious causes but can also be the result of a harmless condition. BGA, for example, may show metabolic disorders such as severe acidosis, whereas hyperventilation syndrome can usually be differentiated based on clinical findings.

3.10 Intractable Hypoxemia

Recommendation 4.7 (100% agreement)	
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	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. 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 health care 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 mm Hg. Clinical experience shows that patients with persistent hypoxemia despite receiving 6 L/min of oxygen frequently require treatment in the ICU. In the subgroup of ARDS patients treated with NIV, ICU mortality was increased below an oxygenation index of 150 [144].

The study by Austin et al. [39], on the other hand, impressively demonstrated that high-dose oxygen with a 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, NIV is the primary line of treatment for hypoxemia and can be used either alone or in combination with oxygen to correct hypoxemia. Patients in the study of Austin et al. had a mean SpO_2 of 84–87% prior to randomization. The assessment of this patient population by experienced health care practitioners 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 [145, 146] (see chapter 5.2).

Recommendation 4.9 (93% agreement)	Grade of recommendation/ GRADE	
Noninvasive 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 Berbenetz 2019 [147], Osadnik 2017 [148]	**A**	
	Moderate quality of evidence ⊕⊕⊕⊖	Mortality
	Moderate quality of evidence ⊕⊕⊕⊖	Intubation

A Cochrane meta-analysis for cardiogenic pulmonary edema (24 randomized trials, 2,664 patients) [147] and COPD exacerbation (17 randomized studies, 1,264 patients) [148] showed – with a moderate level of evidence – that both NIV in comparison to standard of care was associated with reduced in-hospital mortality and intubation rates. A meta-analysis found no increased risk of acute coronary events for cardiogenic pulmonary edema [147]. This meta-analysis on pulmonary edema failed to establish superiority of NIV versus CPAP, whereas NIV is superior to CPAP for the treatment of COPD. NIV 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 mm Hg and pH <7.35. With the exception of individual cases, however, there are no randomized controlled studies on this topic [149, 150].

The S3 guideline on "Noninvasive ventilation in the treatment of acute respiratory failure" [151] advocates NIV for hypercapnic patients with a pH of 7.3–7.35.

There are 7 randomized studies directly comparing HFNC and NIV in the acute management of 40–803 hypoxemic patients, and another study [133] comparing NIV and conventional oxygen therapy in addition. The 5 randomized trials, some of which included hypercapnic patients (pCO_2 52–61 mm Hg), demonstrated the noninferiority of HFNC versus NIV in terms of intubation rate after 72 h of use [152–156]. In a randomized trial, the intubation rate of 204 emergency patients with all-cause respiratory failure (mean pCO_2 of 55 mm Hg) was 13% under NIV and 7% under HFNC [152]. The in-hospital mortality or 28-day-mortality in 3 studies with mainly patients early after extubation ranged from 12 to 18% under NIV and from 15–20% under HFNC and, hence, did not differ [154, 156–158]. A crossover study in 24 stable COPD patients [159] showed that NIV reduced the transcutaneously measured partial pressure of carbon dioxide more significantly than HFNC (5.3 vs. 2.5 mm Hg). In many HFNC studies, new-onset or progressive respiratory acidosis is a discontinuation criterion [72].

Practice Points:

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.

Recommendation 4.11 (100% agreement)	Grade of recommendation/ GRADE	
Noninvasive ventilation may be considered in addition to oxygen administration for nonhypercapnic hypoxemic patients who are continuously monitored Ferreyro 2020 [160], Zhang 2012 [161]	**0**	
	Low quality of evidence ⊕⊕⊖⊖	Mortality
	Low quality of evidence ⊕⊕⊖⊖	Intubation

The meta-analysis by Ferreyro et al. [160] analyzed 25 studies with a total of 3,804 patients comparing various types of respiratory support versus standard oxygen administration in patients with acute hypoxemic pulmonary failure. Seven of these studies compared high-flow oxygen therapy, in part versus NIV. The 90-day mortality in this meta-analysis was reduced for all types of support (HFNC, NIV, CPAP) versus conventional oxygen therapy, with a relative risk of 0.83 (95% CI 0.68–0.99) [160].

Another meta-analysis [161] studied NIV versus conventional oxygen therapy in nosocomial and community-acquired pneumonia and found – with a low level of evidence – that NIV 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 proportion 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 conclusion, the role of NIV in patients with isolated hypoxemia is difficult to assess at present. Hospital mortality rates (15–81%) in these patient groups, especially for patients with acute respiratory failure under immunosuppressive therapy, as well as intubation rates (10–77%) are very high [162–164]. The guideline authors believe that a treatment attempt is medically reasonable, at least in the latter subgroup. In the LUNGsafe study, however, a moderate to severe gas exchange disorder (pO_2/FiO_2 <150 mm Hg) was associated with failed NIV therapy in more than 41% of the 436 ARDS patients on NIV [144].

According to the National 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 [151].

3.11 Oxygen Therapy in Cardiovascular Diseases

Randomized trials of oxygen therapy in patients with acute coronary syndrome generally excluded those at risk of hypercapnic respiratory failure [104, 107, 165]. In these trials, the lower limit of oxygen saturation as measured by pulse oximetry below which oxygen was administered in each case ranged from 85 to 94%.

According to expert consensus, a target arterial saturation rate of 94–98% is recommended in cardiogenic shock due to myocardial infarction [166]. The guideline references the meta-analysis by Chu et al. [31] and the largest randomized DETO2X-AMI trial on patients with acute coronary syndrome, although only 1% of them had cardiogenic shock [104]. 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) [167]. This recommendation is based on three RCTsrandomized controlled trials and a Cochrane meta-analysis [104, 165, 168, 169]. At a lower limit of 94%, approximately 25% of participants in the DETO2X-AMI trial would already have received O_2 at baseline. However, even in a subgroup analysis of patients with O_2 saturations between 90 and 94%, this approach was not associated with improved survival [170].

Two Cochrane meta-analyses found no evidence to support routine oxygen administration in acute myocardial infarction [168, 171]. 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) [41].

Strong evidence speaks for an upper limit of 96% because it corresponds to the median level before randomization in trials involving patients with myocardial infarction and it is the normal saturation in a population living at sea level [32].

The clinical practice guideline by Siemieniuk et al. [32] strongly recommends that patients with stroke and those with myocardial infarction should only be started on oxygen once their saturation drops below 93%. 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 not different than for other patients.

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 rehospitalization

rates under conservative oxygen therapy (target SpO_2 90–92%) versus liberal O_2 therapy (SpO_2 >96%) [172].

3.12 Oxygen Therapy in Neurological Disorders

At a lower limit of 95%, as recommended in the guidelines on the management of patients with stroke [173, 174], more than a quarter of the patients included in the largest randomized SOS trial would already have been treated with O_2 at baseline [106]. 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 [32].

The clinical practice guideline by Siemieniuk et al. [32] strongly recommends that stroke patients should only be started on oxygen once the saturation drops below 93%. This recommendation was based on a meta-analysis, which found lower mortality from stroke under conservative O_2 therapy. This 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 [175].

In a large retrospective analysis of 3,420 patients with craniocerebral injury in the USA, hyperoxemia was associated with increased in-hospital mortality [176]. 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 [177]. 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 mm Hg [178].

RCTs with patients after restoration of circulation following CPR also did not show a superiority of liberal oxygen administration.

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 mm Hg, respectively) [179, 180]. No RCTs 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 [33, 181]. A meta-analysis found no beneficial effects of hyperbaric oxygen therapy (HBO) for the treatment of ischemic stroke [182].

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.

3.13 Oxygen during Pregnancy and Childbirth

Guidelines recommend an oxygen saturation of 95% or more for managing asthma during pregnancy [183]. However, no studies comparing various oxygen target ranges have yet been published. Five RCTs investigated the use of 2–10 liters of oxygen/min versus room air or without O_2 flow during delivery 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 [184–186]. In a randomized, single-center US study of 99 pregnant women, the administration of 10 liters of oxygen/min did not reduce the rate of cesarean or forceps deliveries and late decelerations as compared to the group on room air [187]. 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.

3.14 Oxygen Therapy for the Treatment of Poisoning

Recommendation 5.3 (100% agreement)	
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 h, 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)	Expert consensus

The BTS guideline [63] mentions 2 Cochrane meta-analyses on HBO in carbon monoxide poisoning [188, 189]. The independent literature search identified 2 additional meta-analyses on the role of HBO [190, 191]. There are thus a total of 4 meta-analyses on this subject. All RCTs included in these 2 recent 2018 meta-analyses have already been included in the most recent Cochrane analysis. Just the meta-analysis by Wang et al. [191] dem-

onstrated a benefit for HBO over normobaric therapy, albeit without evidence assessment. None of the meta-analyses established an association between HBO and reduced mortality.

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 [192]. Carbon monoxide poisoning shall therefore be immediately treated with the highest possible oxygen concentration, irrespective of oxygen saturation (SpO_2).

The treatment shall be continued until the carbon monoxide bound with hemoglobin (COHb) has dropped to normal levels (<3%) and the patient is no longer symptomatic. This is typically the case after a maximum of 5 physiological COHb half-lives under 100% oxygen (approx. 375 min). 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 [193].

Conservative oxygen therapy has been recommended for the treatment of poisoning from paraquat (which has been taken off the market) 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 in this guideline [182, 188, 194–197].

Practice Points:

BGA is useful for assessing carbon monoxide poisoning and determining the amount of 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 h, 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.

3.15 Prehospital Oxygen Therapy

<table>
<tr><td>Recommendation 4.15
(100% agreement)</td><td colspan="2">Grade of recommendation/
GRADE</td></tr>
<tr><td rowspan="3">In the prehospital 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
Kopsaftis 2020 [109], Austin 2010 [39], Holmberg 2020 [198]</td><td colspan="2">**A**</td></tr>
<tr><td>Moderate quality of evidence
⊕⊕⊕⊖</td><td>Mortality</td></tr>
<tr><td>Very low quality of evidence
⊕⊖⊖⊖</td><td>Cardiovascular events</td></tr>
</table>

A meta-analysis on the effect of hyperoxia on survival after cardiovascular arrest was considered in the development of the BTS guideline [199]. Our own evidence search identified a international guideline including evidence assessment and one meta-analysis [198, 200], which can be applied to the subgroup of patients after prehospital CPR. The 2020 meta-analysis by Holmberg et al. [198] reviewed 7 RCTs, which predominantly included patients after prehospital 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.

SpO_2 target ranges in the preclinical setting are not different from those recommended in Figure 2. The insights regarding the benefit of lower SpO_2 target ranges in the prehospital setting were gained especially for patients at risk of hypercapnia (COPD patients with exacerbation) [39, 109].

The prehospital 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 prehospital setting, oxygen may also be administered by nonmedical staff in the context of first aid based on the defense of necessity. According to expert opinion, emergency medical service 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, it is recommended that the oxygen therapy target ranges be observed, also in the prehospital setting.

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 [201–203]. Only in the study by Thompson et al. [201] was in-hospital mortality also significantly reduced versus standard oxygen therapy when CPAP had been used in the prehospital setting.

Practice Points:

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

It is recommended to have the following O_2 delivery devices available in the prehospital 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.

Recommendation 5.1 (100% agreement)	Grade of recommendation/ GRADE	
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 saturation range of 92–96% should be targeted Holmberg 2020 [198], Wang 2014 [199]	**B**	
	Low quality of evidence ⊕⊕⊖⊖	Mortality
	Low quality of evidence ⊕⊕⊖⊖	Functional outcome

The meta-analysis of Wang et al. [199] 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.

Two smaller randomized trials with 35 and 61 patients, respectively, in whom circulation was restored after CPR demonstrated the noninferiority of conservative oxygen therapy in the out-of-hospital setting [204, 205], while the study by Young et al. [206], 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 [205] comparing the effectiveness of hyperoxygenation (target saturation 100%, $n = 17$) versus 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 2 Australian studies, without these studies having been designed for the mortality end point [204, 206]. A 2019 meta-analysis by Holmberg et al. [198] analyzed 7 randomized trials and 36 observational studies. No conclusive result was obtained with regard to hyperoxemia versus normoxemia after successful CPR. A recently published meta-analysis [207] of 429 patients found lower mortality in patients on conservative versus those on liberal O_2 therapy after return of spontaneous circulation.

Practice Point:

Set FiO_2 to 1.0 during CPR.

3.16 Oxygen Therapy in COVID-19 and Other Infectious Lung Diseases

Recommendation 5.5 (100% agreement)	Grade of recommendation/ GRADE	
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) Alhazzani 2020 [208]	**A**	
	Moderate quality of evidence ⊕⊕⊕⊖	Mortality

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 SpO_2 range and the shift of the oxygen dissociation curve in patients with fever, some authors advocate BGA for COVID-19 patients [209]. 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 COVID-19 wards.

An 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 [208]. The recommendation is based on 2 RCTs with ventilated subjects and 1 meta-analysis [17, 31, 105]. 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 [210]. 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. In addition, hyperoxemia under O_2 therapy may lead to the delayed detection of respiratory failure, for example in COVID-19 patients [6]. The oxygen therapy algorithm outlined in Figure 3 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 m). Increased aerosol formation during exhalation is found under both high-flow oxygen therapy and NIV, depending on the depth of breaths [211].

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 under 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, nonleaking masks and 2-tube systems should be preferred.

3.17 Patients with Cluster Headaches

Recommendation 5.4 (100% agreement)	Grade of recommendation/GRADE	
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 min Cohen 2009 [212], Bennett 2015 [213]	**A**	
	High quality of evidence ⊕⊕⊕⊕	Functional outcome

Eleven studies with a total of 209 patients were evaluated in the 2015 Cochrane analysis. 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 versus 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 versus 70% in the ergotamine group [214].

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) [212]. The primary end point of freedom from pain after 15 min was achieved in 78% in the concentrated oxygen group versus 20% in the control group ($p < 0.01$).

3.18 Oxygen Use during Procedures Involving Conscious Sedation

Recommendation 4.12 (93% agreement)	
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	Expert consensus

Hypoxemia is a frequent occurrence in procedures performed 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) [215]. In gastrointestinal endoscopy, 8–57% of patients were found to have hypoxemia with SpO_2 levels <90% in RCTs comparing midazolam versus propofol.

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 to assess for hypoventilation episodes.

Recommendation 4.13 (100% agreement)	
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	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 [216, 217], although the definitions of "adverse cardiopulmonary events" are quite heterogeneous across these studies. 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 in a range of 92–96% (or 88–92% for those at risk of hypercapnia) should be set. Bronchoscopy procedures, and in particular interventional bronchoscopy, have an increased risk of hypoxemia, depending on the lung function [218, 219].

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 [220]. Desaturation events (SpO_2 <95%) occurred in 21% in the O_2 group versus 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 BGAs to detect hypercapnia were performed. In hypoventilation and resulting hypoxemia, oxygen therapy is not a causal therapy, but rather there are methods such as inserting breathing devices (e.g., Guedel tube) or using assisted ventilation. 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 s early [221]. In 5 RCTs 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 [221–225]. Using capnometry, events of apnea or hypopnea were recorded in 22–65% of study participants during the procedure, thus most hypoxemic episodes were likely caused by hypoventilation.

Practice Points:

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.

Another monitoring tool for ventilation is transthoracic impedance, which is easily derived from ECG monitors. No RCTs are available to date, but the method is currently being studied in the context of a clinical trial during endoscopy (NCT04202029).

4.1 High-Flow Oxygen Therapy

Recommendation 5.6 (100% agreement)	
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%	Expert consensus

In high-flow oxygen therapy, heated and humidified oxygen is delivered via nasal cannula at flow rates of 40–60 L/min. This is usually 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 et al. [226] reviewed 11 RCTs on high-flow oxygen versus standard oxygen therapy via nasal cannula, face mask, and/or standard oxygen therapy in pulmonary failure or after extubation. Due to a high risk of bias, the quality of the included studies was insufficient to allow a conclusive assessment. A systematic summary by Marjanovic et al. [227] included 5 RCTs. While dyspnea and respiration rate were improved, there was no difference with regard to the end points of intubation, length of hospitalization, and mortality under high-flow therapy. Ou et al. [228] conducted a systematic review on HFNC after extubation versus standard oxygen therapy with the end point of reintubation. According to this review, the reintubation rate of critically ill patients was lower when HFNC was used. Wen et al. [229] conducted a systematic review of HFNC in immunosuppressed patients with acute pulmonary failure (259), evaluating 8 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 1 meta-analysis, but the mortality was not significantly reduced versus standard oxygen therapy.

Recommendation 5.7 (100% agreement)	
Patients on high-flow oxygen should be closely re-evaluated and HFNC discontinuation criteria defined	Expert consensus

The literature search failed to identify relevant studies with a strong level of evidence on this question.

In an RCT with HFNC in patients with an oxygenation index (paO_2/FiO_2) 108–161 mm Hg, 39–51% of participants were intubated [71].

Practice Point:

The respiratory rate-oxygenation (ROX) index 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 et al. [72] examined the ROX index (SpO_2/FiO_2/respiration rate) to predict high-flow oxygen therapy failure in patients with community-acquired pneumonia. ROX values <2.85, <3.47, and <3.85 at 2, 6, and 12 h of HFNC initiation, respectively, were predictors of HFNC failure. A ROX index ≥4.88 was consistently associated with positive outcome. The predictive power of the ROX index was confirmed in 289 COVID-19 patients after 6 h of HFNC therapy [230].

According to expert opinion, patients on HFNC should be continuously monitored by pulse oximetry and for clinical symptoms, as 36% of pneumonia [230] and 37% of COVID-19 patients [72] treated with HFNC had to be intubated in the further course, which is consistent with intubation rates of around 40%, in the HFNC therapy groups in randomized trials [70, 71, 231].

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.

4.2 Humidification of Supplemental Oxygen

Recommendation 6.6 (100% agreement)	Grade of recommendation/ GRADE	
Humidified oxygen shall not be used in low-flow oxygen therapy (via mask or nasal cannula) and not for the short-term administration of high-flow oxygen either Wen 2017 [231], Poiroux 2018 [232]	**A**	
	Moderate quality of evidence ⊕⊕⊕⊖	Quality of life

A meta-analysis based on 25 RCTs with a total of 8,876 acutely ill adult patients compared humidified versus nonhumidified oxygen. Most studies focused on a treatment duration of more than 24 h (range: 12 h to >5 days). All studies described the use of low-flow O_2 (<5 L/min). The use of nonhumidified oxygen did not prove to have an impact on patient discomfort. However, bacterial contamination was more common in the group receiving humidified oxygen (OR 6.25; 95% CI 2.33–16.67). The authors of the BTS guideline [63] downgraded the meta-analysis to a moderate level of evidence due to study limitations, limited transferability, and inconsistencies [229]. Oxygen was administered 36 h 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 [232] on 354 subjects investigated the effect of dry versus humidified oxygen on the quality of life of ICU patients. The study was rated as having a low level of evidence due to limitations and low accuracy. The study was not able to demonstrate that nonhumidified oxygen was inferior to humidified oxygen in terms of patient comfort after 6–8 h of oxygen therapy.

4.3 Monitoring and Documentation of Oxygen Therapy

Recommendation 6.3 (100% agreement)	
Repeat blood gas analysis should be performed approximately 30–60 min after a change in oxygen therapy in patients at risk of hypercapnia or with other BGA indications in order to monitor pH and pCO_2	Expert consensus

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 [233, 234]. Only indirect indicators are available with regard to CO_2. It takes up to 30–60 min to reach equilibrium. The few clinical data were able to demonstrate at least a change in $paCO_2$ for up to 20 min during and after bronchodilator inhalation in the selected patient population (COPD) [93, 235].

Recommendation 6.4 (100% agreement)	
Patients should be monitored for clinical symptoms and oxygen saturation pulse oximetry for 5 min after starting, adjusting or stopping oxygen therapy	Expert consensus

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 [236–239]. The time to equilibration of O_2 saturation was 4.5 min in spontaneously breathing patients [236], 6 min in ventilated patients, and 7 min in ventilated COPD patients [240].

Changes in cardiac output, microcirculation, hypoxemia, vasoconstriction, or vasodilation may increase the time to equilibration of O_2 saturation [61, 236, 237, 241].

Practice Point:

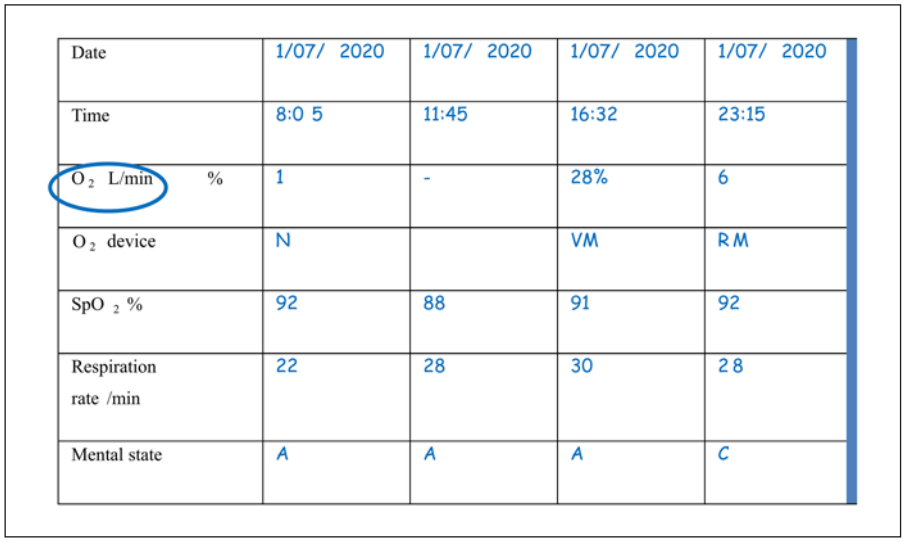
Oxygen therapy must be documented in written form (template in Fig. 6).

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 predefined intervals during the oxygen therapy (see recommendation 2.2).

According to decisions of the arbitration committee pursuant to section 19 of the German Hospital Financing Act (Krankenhausfinanzierungsgesetz), respiratory failure, the following procedure codes should be used depending on SpO_2, ventilation and presence of hypercapnia: J96.00 if SpO_2 is <92% without hypercapnia and if oxygen is delivered, J96.01 if $paCO_2$ is >45 mm Hg, and J96.11 if ventilation is applied. The guideline au-



Date	1/07/ 2020	1/07/ 2020	1/07/ 2020	1/07/ 2020
Time	8:0 5	11:45	16:32	23:15
O_2 L/min %	1	-	28%	6
O_2 device	N		VM	RM
SpO_2 %	92	88	91	92
Respiration rate /min	22	28	30	28
Mental state	A	A	A	C

Fig. 6. Sample template for the documentation of oxygen therapy. N, nasal prongs; VM, Venturi mask; RM, reservoir mask; A, alertness; C, confusion.

thors recommend updating the coding of oxygen therapy, and of HFNC in particular, as a procedure in the near future.

4.4 Discontinuation of Oxygen Therapy

Recommendation 7.1 (100% agreement)	
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	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. 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.

Recommendation 7.2 (100% agreement)	
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 liters 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)	Expert consensus

For patients who experienced hypercapnic respiratory failure after high-dose oxygen therapy, there is a risk of rebound hypoxemia if oxygen is suddenly withdrawn. Rebound hypoxemia can be explained using the alveolar gas equation [242]. Carbon dioxide competes with oxygen in the alveoli. While the body's capacity to store oxygen is limited, large amounts of carbon dioxide can be stored due to its high solubility. The discontinuation of oxygen therapy in this subgroup of 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). The drop is greatest in the first 5 min of stopping the oxygen therapy, but the lowest point is only reached after 30–45 min [243]. Two randomized trials comparing HFNC versus standard oxygen therapy were unable to demonstrate the phenomenon of rebound hypoxemia after extubation [157, 244].

Practice Points:

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 min.

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.

Recommendation 7.4 (100% agreement)	
O_2 delivery should not be adjusted if a patient experiences a transient (less than 1 min) asymptomatic drop in oxygen saturation below target range after oxygen therapy has been stopped	Expert consensus

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 [245]. 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 [246].

In a retrospective single-center analysis of 71,025 patients after surgery, Rostin et al. [247] found that desaturation episodes below an SpO_2 of 90% (4.6% of patients) of more than 1 min were associated with higher pulmonary complication rates in the first 10 min of extubation (OR 1.68; 100% CI 1.50–1.88) and intensive medical care.

Recommendation 7.5 (100% agreement)	
If a patient cannot be weaned from oxygen, O_2 therapy should be continued even after discharge. These patients should be re-evaluated a few weeks after initiation of the oxygen therapy to review the indication for long-term oxygen therapy	Expert consensus

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 re-evaluation. In Germany, and also in other countries, oxygen therapy initiated in hospitalized patients there is no universal follow-up after discharge [248–251]. 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 [252].

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Conflict of Interest Statement

The following conflicts of interests were revealed by independent review: T.V. reported a research grant by Pall (moderate conflict of interest on the subject of humidification). S.K. reported a moderate conflict of interest on the subject of extracorporeal membrane oxygenation to Xenios/Novalung (advisory, speaker fees and research grant). C.K. reported a moderate conflict of interest on the subject of extracorporeal membrane oxygenation to Maquet (speaker fees and research grant). All other authors have no relevant conflicts of interest to declare.

A detailed declaration of interests for individual authors with independent review can be found under https://www.awmf.org/fileadmin/user_upload/Leitlinien/020_D_Ges_fuer_Pneumologie/020–021i_S3_Sauerstoff-in-der-Akuttherapie-beim-Erwachsenen_2021–06.pdf.

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Author Contributions

J.G. wrote the application to develop the guideline and designed scope and outline of the guideline. J.G., P.C., U.H., U.J., C.K., S.K., M.N., S.R., T.V., H.W., and T.F. performed additional literature search. J.G., P.C., U.H., U.J., C.K., S.K., M.N., S.R., T.V., H.W., and T.F. phrased recommendations, background texts and graded evidence. J.G., P.C., U.H., U.J., C.K., S.K., M.N., S.R., T.V., H.W., and T.F. participated in the consensus process. J.G., H.W., and T.F. contributed to the draft of the manuscript. All authors critically reviewed and approved the final German version of the guideline.

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