

Clinical Practice Guideline

Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency

Falk Fichtner, Onnen Moerer, Felicitas Grundeis, Victoria Büniger, Sven Laudi, Michael Sander, on behalf of the Guideline Group on Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency*

Department of Anaesthesiology and Intensive Care, University of Leipzig Medical Center, Leipzig, Germany: Dr. med. Falk Fichtner, Dr. med. Felicitas Grundeis, PD Dr. med. Sven Laudi

Department of Anaesthesiology, University Medical Center Göttingen, Göttingen, Germany: Prof. Dr. med. Onnen Moerer

Charité – Berlin University of Medicine, Department of Anesthesiology and Intensive Care Medicine, Berlin, Germany: Dr. med. Victoria Büniger

Department of Anaesthesiology, Operative Intensive Care Medicine and Pain Therapy, Justus Liebig University of Giessen, Giessen, Germany: Prof. Dr. med. Michael Sander

*All mandate holders and other participants are listed in the eTable.

Summary

Background: Invasive ventilation saves lives but carries major risks, including ventilation-associated lung damage and long-term functional impairment. Data from recent studies compel reassessment of the evidence for every step of the clinical treatment pathway.

Methods: This updated clinical practice guideline is based on pertinent publications retrieved by a systematic search in Medline, Embase, and the Cochrane Library up to April 2023, supplemented by further high-quality studies published up to June 2024. The recommendations were developed in evidence-to-decision-frameworks (EtDF) according to GRADE, with the participation of intensive-care nurses and early career clinician-scientists.

Results: For patients in acute respiratory failure, it is suggested that noninvasive respiratory support techniques should be used so that intubation can be avoided. It is further suggested that spontaneous breathing should be enabled early on during invasive ventilation. For the first time, the use of various techniques for titrating the positive end-expiratory pressure (PEEP) is suggested for patients with moderate to severe acute respiratory distress syndrome (ARDS). In such patients, techniques aiming at a higher PEEP can lower mortality by 9% in absolute terms (95% confidence interval [1; 16]) compared to lower-PEEP strategies. Strong recommendations are given against the routine use of muscle relaxation or corticosteroid therapy in moderate to severe ARDS. For patients

with ARDS with a persistent, severe gas exchange disturbance after conservative options have been exhausted, veno-venous extracorporeal membrane oxygenation should be considered. VvECMO for patients with severe ARDS should be carried out at centers that are experienced in treating patients with severe ARDS and that fulfill specific structural requirements.

Conclusion: The goals of ventilator therapy should be to enable spontaneous breathing as soon as possible, keep respiratory parameters in the protective range, and adjust PEEP individually. Muscle relaxation or corticosteroids should not be part of the routine treatment of moderate to severe ARDS.

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Mechanical ventilation is an indispensable component of intensive care medicine for the treatment of acute respiratory insufficiency and many other critical conditions, but it is also an intervention associated with significant risks (1) and potential long-term sequelae (2). In Germany, just over 265 000 adults were mechanically ventilated in 2019 (3). Hospital mortality was 40.4% and rose markedly with age (18–59 years: 25.8% versus > 80 years: 55.8%). Total annual expenditure for ventilated adults was approximately 5.77 billion Euros (≈ 0.16 – 0.17% of gross domestic product [GDP]) (3).

Since the publication of the first version of the German clinical practice guideline “Mechanical ventilation and

extracorporeal membrane oxygenation in acute respiratory insufficiency” (4), numerous randomized controlled trials and meta-analyses on key questions regarding ventilation therapy have been published. These questions include, among others:

- Noninvasive ventilation (NIV) and high-flow nasal oxygen (HFNO) compared with invasive ventilation (5)
- Early spontaneous breathing in severe acute respiratory distress syndrome (ARDS) (6)
- Individualized PEEP settings (7)
- The use of corticosteroids (8).

Furthermore, in light of the first positive study results, other international guidelines are also attaching increasing importance to structured communication with critically ill patients and their relatives (9).

At the same time, observational data from the COVID-19 pandemic in the German healthcare system—albeit not fully transferable to the non-pandemic care setting—point to considerable heterogeneity in treatment standards in clinical practice and to a high mortality rate among patients receiving extracorporeal membrane oxygenation (ECMO) compared to other countries (10, 11).

This made it necessary to carry out a comprehensive, evidence-based update of the guideline (12), once again aimed at providing a consensus-based and practice-oriented basis for information and decision-making for all professional groups working in intensive care units in German-speaking clinical care settings.

Methods

The clinical practice guideline project was coordinated and financed by the German Society of Anaesthesiology and Intensive Care Medicine (*Gesellschaft für Anästhesiologie und Intensivmedizin*, DGAI). The interprofessional guideline group (*eTable*) comprised 101 mandate holders (28 specialists/societies/organizations).

A systematic literature search (up to April 2023) was conducted in Medline, Embase, the Cochrane Library, and international guideline databases. Additional high-quality studies were included up until the recommendations were voted on in June 2024. In total, seven working groups identified 37 057 hits, reviewed 3970 full texts, and ultimately based the recommendations on 280 evaluated publications (*eFigure*). Evidence was assessed according to the internationally established GRADE system (13). The certainty (quality) of the evidence was classified into four categories, from high (+++++) to very low (+), and an expert consensus (EC) was formulated if evidence was lacking.

The guideline group used, for the first time, the internationally established principle of the evidence-to-decision framework (EtDF) to develop the recommendations (14), in order to increase the clinical applicability and acceptability of the recommendations by additionally taking into account, among other things, the values and preferences of those affected, the availability of resources, and practical feasibility.

To improve implementation, particular emphasis was placed on involving intensive care nurses throughout the entire development process. Also for the first time, young scientists systematically participated in the process, with early-career scientists working in intensive care actively involved in the entire guideline development process.

Results and recommendations

In the following, key new or modified recommendations of the German clinical practice guideline are presented as examples, together with details of the underlying evidence, and arranged according to the sequence of a typical clinical treatment pathway.

Noninvasive respiratory support options

For the initial treatment of mild to moderate hypoxemic respiratory failure, the guideline group—based on new aggregated study data—proposes the initial use of noninvasive respiratory support methods (NIV, continuous positive airway pressure [CPAP] or HFNO) (weak recommendation, quality of evidence: moderate). The 2023 network meta-analysis on which this is based (5) showed that NIV and HFNO significantly reduced the intubation rate compared with standard oxygen therapy (SOT) (absolute risk reduction [ARR]: NIV versus SOT: ARR 14% (95% confidence interval: [5; 20], HFNO versus SOT: ARR 6% [0.9; 11.3]). In contrast, however, no significant effect on mortality was observed. Risks could lie primarily in delayed intubation, that is, if ineffective NIV is continued for too long. Data from COVID-19 cohorts (15) indicate that this may be associated with an increased mortality rate.

Enabling early spontaneous breathing rather than routine neuromuscular blockade

The question of whether patients with early-stage ARDS should be ventilated in a controlled manner and placed under neuromuscular blockade, or whether spontaneous breathing should be allowed early on, has long been the subject of research. Here, the guideline group formulated a strong recommendation against the use of muscle relaxants in moderate to severe early-stage ARDS (< 48 h) (quality of evidence: moderate), and instead proposes the early use of respiratory support methods that enable spontaneous breathing (weak recommendation, quality of evidence: very low).

The recommendation is based on the ROSE trial (16)—the largest randomized controlled trial on this topic—which showed that the routine use of muscle relaxation in the first 48 h was not associated with either a survival benefit or a reduction in ventilation duration, but with an increased rate of serious cardiovascular events in the intervention group (intervention: 14/501 versus control: 4/505).

In contrast, the guideline group regards the indirect evidence from studies on the use of airway pressure release ventilation (APRV) and observational data from the LUNG SAFE trial (association between early spontaneous breathing and a reduction in ventilation days and a shorter intensive care unit stay) (6) as indicating a relevant patient benefit of early spontaneous breathing (< 48 h after intubation). A possible risk that has not yet been precisely quantified is patient self-inflicted lung injury (P-SILI) in cases of uncontrolled, forced spontaneous breathing (17). Based on the presented benefit–risk assessment and due to the very low quality of evidence, a weak recommendation is made here for the early use of assisted ventilation to enable spontaneous breathing in mechanically ventilated patients with acute respiratory insufficiency.

Advantages of methods supporting minute ventilation

The previous general classification of methods, in particular methods supporting spontaneous breathing, according to the respective interaction of spontaneous breathing and mechanical ventilation, remains unchanged:

Table

Proposed methods for adjusting PEEP individually in patients with moderate and severe ARDS

Methods of PEEP adjustment	Target parameters	Recommended approach to PEEP adjustment
FiO ₂ /PEEP table	Oxygenation (PaO ₂ /FiO ₂ ratio/ alternatively SpO ₂ /FiO ₂)	Initial adjustment according to the FiO ₂ /low-PEEP table; if the PaO ₂ /FiO ₂ ratio is < 200 mm Hg, switch to the FiO ₂ /high-PEEP table; if there is a clinical improvement (e.g., PaO ₂ /FiO ₂ increase > 25 mm Hg), maintain the high-PEEP strategy; otherwise, consider PEEP reduction
Quasi-static pressure–volume curve	Global compliance	Determination of volume-dependent compliance using a quasi-static pressure–volume curve (low-flow curve); ventilation in the region of best compliance (set PEEP 2 mbar above the “lower inflection point” of the inspiratory part of the low-flow curve)
Decremental PEEP trial	Global compliance	Gradual PEEP reduction (decremental PEEP trial), starting at 24 mbar (if hemodynamically tolerated) down to approximately 5 mbar while measuring global respiratory system compliance (CRS); stepwise reductions of 2–3 mbar (every 2–3 min), small VT and ΔP, PEEP adjustment in the region of best compliance (lowest PEEP that prevents a fall in CRS)
Decremental PEEP trial	Regional compliance changes, determined using electrical impedance tomography (EIT): overdistension (regional compliance loss at higher PEEP) versus alveolar collapse (regional compliance loss at lower PEEP)	Decremental PEEP trial under pressure-controlled ventilation with constantly low ΔP (e.g., 10–12 mbar) while monitoring with EIT, stepwise PEEP reductions of 2–3 mbar (every 2–3 min), evaluation of regional distension and alveolar collapse by means of regional compliance changes; select PEEP such that both overdistension and alveolar collapse are minimized, e.g., at the intersection of overdistension and collapse
Incremental PEEP trial	Global compliance	Starting at 5 mbar, increase PEEP in 2-mbar steps as long as compliance increases; adjust PEEP to the value with the highest global compliance
Esophageal pressure measurement	End-expiratory transpulmonary pressure	If the end-expiratory transpulmonary pressure (P _{TPE}) is negative, increase PEEP; if P _{TPE} is positive, reduce PEEP; target: P _{TPE} = 0 (± 2 mbar)
Lung ultrasound	Reaeration score	Total score from 12 lung regions (six per side of the chest); score: A-Profile = 0 points, > two isolated B-lines = 1 point, confluent B-lines = 2 points, consolidation = 3 points

ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure

- Ventilation methods that support tidal volume relieve each individual spontaneous inspiratory effort (e.g., pressure support ventilation [PSV]).
- Methods that support minute ventilation (MV) (for example, biphasic positive airway pressure [BIPAP] or APRV) enable spontaneous breathing, but ensure a minimal minute ventilation even in apnea through intermittent mechanical switching between pressure levels.
- Adaptive modes adjust the extent of mechanical support to the individual inspiratory efforts of the patient.

The strongest indications of a relevant patient benefit come from prospective studies on the minute ventilation-supporting mode APRV. In the original concept (18), spontaneous breathing was made possible during a long mechanical inspiratory phase—functionally during a “high CPAP”—after which the airway pressure was briefly reduced to ambient pressure before being increased again. Currently, due to the many different settings used for APRV in studies and the emergence of other MV-supporting modes (for example, BIPAP) in research and routine clinical practice, considerable heterogeneity has developed in the understanding of the nomenclature and characteristics of these methods (19). However, what all these methods have in common is the principle of pressure-controlled ventilation with the possibility of spontaneous breathing during the inspiratory and expiratory phases.

The evidence was assessed on the basis of meta-analyses of APRV (20, 21). This assessment was extrapolated to all MV-supporting methods involving pressure-controlled ventilation with the possibility of spontaneous breathing during the inspiratory and expiratory phases. The meta-analysis by Lim et al. (20) demonstrated a reduction in mortality among patients receiving APRV ventilation. With regard to the cumulative mortality in the control group, the absolute effect was approximately 10 fewer deaths per 100 patients (number needed to treat [NNT] ≈ 10; [6; 55]). As a further positive effect, the meta-analysis conducted by Carsetti et al. (21) demonstrated a reduction in cumulative intensive care unit length of stay of around 390 days per 100 patients. Subgroup analyses of ARDS patients showed consistent results, and no evidence of an increase in barotrauma compared to the control group was observed.

Taking into account the currently available evidence, the guideline group expanded the previous recommendation and, based on indirect evidence and a corresponding downgrade in the quality of evidence, now makes a weak recommendation in favor of the use of pressure-controlled ventilation with the option of spontaneous breathing during inspiration and expiration for the entire group of patients with acute hypoxemic respiratory failure (including ARDS) (quality of evidence: very low). At the same time, there is a possible risk of increased hyperinflation and greater work of breathing. This requires an individual benefit–risk assessment before and/or during use.

PEEP individualization and avoidance of prolonged recruitment maneuvers

Adjustment of positive end-expiratory pressure (PEEP) is a central element of mechanical ventilation. Here, both the type and severity of

the gas exchange disturbance need to be taken into account. In mild ARDS, the ARDS Network FiO₂/low-PEEP table is recommended (22), while in moderate to severe ARDS, the use of higher PEEP levels continues to be recommended (strong recommendation, quality of evidence: high). What is new for the latter group, however, is the proposal of a selection of methods that can be used as alternatives to the FiO₂/PEEP table for individualizing PEEP, taking into account technical availability and operator expertise (*Table*) (weak recommendation, very low quality of evidence). Also new is the now strong recommendation against prolonged recruitment maneuvers (>60-s duration).

The quality of evidence for the use of higher PEEP in moderate to severe ARDS is high. A network meta-analysis with over 4500 patients demonstrated that higher PEEP (7) in moderate to severe ARDS can reduce mortality (absolute reduction in mortality compared to a low-PEEP strategy: 9% ([1; 16])). Risks lie, in particular, in increased hemodynamic instability and the occurrence of barotrauma, explaining why individual titration remains an essential component. However, the low quality of evidence to date and the lack of indications pointing to the clear superiority of any single method with respect to patient-relevant outcome parameters ultimately permit only a weak general recommendation for methods of PEEP individualization (*Table*).

Corticosteroids: Avoiding overtreatment

For decades, the use of corticosteroids in ARDS has been the subject of controversy. The newly formulated recommendation is against the routine administration of corticosteroids in ARDS (quality of the evidence: very low). The background to this is the currently uncertain benefit–risk ratio of the treatment, which was thoroughly evaluated in the EtD framework, as well as the risk of overtreatment and potential harm perceived by the guideline group in the event of routine use.

Whereas the most recent large RCT of limited methodological quality (8) reported a reduction in the duration of mechanical ventilation, there are conflicting results from other RCTs on the question of whether corticosteroids reduce mortality (8, 23–25). At the same time, the risks of corticosteroid therapy have long been known, and current observational data—including those from the German healthcare system—suggest an association between corticosteroid treatment and increased mortality even in certain clinical courses of COVID-ARDS (26). The administration of corticosteroids can continue to be considered in mechanically ventilated patients with septic shock and persistent vasopressor requirements despite adequate fluid resuscitation (27).

Veno-venous extracorporeal membrane oxygenation: strict indication and adherence to structural requirements

For establishing the indication for veno-venous extracorporeal membrane oxygenation (vv-ECMO), a new and now evidence-based recommendation has been formulated: The use of vv-ECMO in patients with severe ARDS should only be considered after all conservative therapeutic measures, including prone positioning, have been

exhausted and severe gas exchange disturbance persists (weak recommendation, quality of evidence: very low).

The EOLIA trial (28) failed to show a significant survival benefit for the routine use of vv-ECMO. At the same time, in the view of the guideline group, vv-ECMO therapy, as part of a comprehensive treatment concept, appears to reduce mortality in certain patients with severe ARDS. However, due to a lack of data, neither the exact subgroup nor the extent of the effect can be determined with greater precision at present.

To enable comprehensive treatment of ARDS and to minimize or optimally control its well-known serious complications (particularly bleeding, thrombosis, and vascular injury), the guideline group recommends that treatment be performed at centers experienced in the management of patients with severe ARDS, including vv-ECMO therapy, and has specified structural requirements to this end based on a systematic review of the literature (strong recommendations, expert consensus).

Weaning and WIND classification

For a more valid classification of the different clinical courses of weaning, the combined use of the WIND classification (29) and the subgroups of prolonged weaning as defined in the S2K guideline “Prolonged Weaning” (30) is recommended. Although the quality of evidence on this is low, initial investigations (31, 32) indicate that the WIND classification better reflects clinical outcomes in adults and children and represents clinical endpoints in a more nuanced manner than previously used classifications.

The need for patient and family information on long-term sequelae

In order to better deal with the long-term sequelae of mechanical ventilation, it is recommended that patients and their relatives be informed early on about the potential long-term effects (for example, on mental health) associated with mechanical ventilation (strong recommendation, expert consensus). The German DaCAPO study provides long-term data on survivors of ARDS (33). At 1 year post-discharge, a relevant proportion of patients still exhibited symptoms of posttraumatic stress disorder (32.6%), depression (8.9%), or an anxiety disorder (6.5%). At the same time, relevant gaps in the evidence regarding prevention, status assessment, and treatment of long-term sequelae of mechanical ventilation are evident.

The need for research to address gaps in the evidence

During the evidence analysis, several clinically relevant gaps were identified. These include, for example, the optimal balance between spontaneous breathing and mechanical ventilatory support in ARDS, the effectiveness of PEEP individualization methods in direct comparison, as well as the precise definition of ARDS patient subgroups who may still benefit from corticosteroids. Other relevant questions that remain open include the formulation and validation of more precise indication criteria for vv-ECMO treatment in severe ARDS, as well as the clinically valid assessment and quantification of long-term sequelae.

Box

Acute respiratory insufficiency: evidence-based treatment pathway*

Prerequisites:

Adult patient, systematic diagnostic evaluation (e.g., X-ray, ultrasound [heart–lung], bronchoscopy, computed tomography, pathogen diagnosis) and treatment of the treatable causes

1. Avoid invasive mechanical ventilation by using noninvasive ventilatory support (NIV or HFNO)

Exceptions: severe oxygenation impairment ($\text{PaO}_2/\text{FiO}_2 < 100$ mm Hg) or an unsecured airway: in these cases, early invasive mechanical ventilation.

Note: Recognize early signs of NIV failure

2. Enable spontaneous breathing during inspiratory and expiratory phases

Exceptions: right heart failure, increased ICP: in these cases, individual critical benefit–risk assessment

Note: Avoid forced spontaneous breathing

3. Consistent implementation of protective ventilation settings

SaO_2 92–96%, adequate PEEP (see PEEP setting), V_t 6–8 mL/kg (ARDS: V_t around 6 mL/kg), $P_{\text{plat}} \leq 30$ cm H₂O, $\Delta P \leq 14$ cm H₂O)

4. Progressive acute respiratory distress syndrome (ARDS): Prone positioning (from $\text{PaO}_2/\text{FiO}_2 < 150$ mm Hg), but no routine use of recruitment maneuvers, muscle relaxation, or corticosteroids

Note: Contact a regional ARDS/ECMO center promptly

5. Aim for early mobilization

Begin no later than 72 h after admission

6. Implement a weaning protocol

Conduct *daily* spontaneous breathing trials and evaluate whether mechanical ventilation can be discontinued

7. Inform relatives and patients about the long-term sequelae of mechanical ventilation

PEEP setting:

Mild ARDS:

- FiO_2 /low-PEEP table (see below)

Moderate to severe ARDS: higher PEEP with individualized PEEP titration based on:

- Initial adjustment according to the FiO_2 /low-PEEP table; if $\text{PaO}_2/\text{FiO}_2 < 200$ mm Hg, switch to the FiO_2 /high-PEEP table (see below)
- Adjustment according to the best global compliance on a quasi-static pressure–volume curve or by a decremental or incremental PEEP trial
- Adjustment according to optimized end-expiratory transpulmonary pressure using esophageal pressure measurements
- Adjustment according to optimized regional compliance changes in EIT analysis
- Adjustment according to an optimized lung aeration score on lung ultrasound

Acute hypercapnic respiratory failure:

- Adjust the extrinsic PEEP to up to 85% of intrinsic PEEP

FiO_2 /low-PEEP table

FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP in cm H ₂ O	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24

FiO_2 /high-PEEP table

FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	1.0
PEEP in cm H ₂ O	5	8	10	12	14	14	16	16	18	20	22	22	22	24

*AWMF: S3 Clinical Practice Guideline on Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency (*Invasive Beatmung und Einsatz extrakorporaler Verfahren bei akuter respiratorischer Insuffizienz – Version 2.0*): long version dated 18.08.2025. AWMF Registry No. 001–021 2025; ICP, intracranial pressure; ECMO, extracorporeal membrane oxygenation; EIT, electrical impedance tomography; PEEP, positive end-expiratory pressure; P_{plat} , inspiratory plateau pressure; ΔP , airway driving pressure (inspiration/expiration)

Conclusion

The updated clinical practice guideline is intended to provide an evidence-based foundation, agreed upon through interdisciplinary and interprofessional consensus, for mechanical ventilation therapy and the use of vv-ECMO. The recommendations regarding the following aspects are particularly relevant for current clinical practice:

- The use of NIV and HFNO to avoid intubation
- Strategies to enable early spontaneous breathing and individualized PEEP adjustment
- A restrictive approach to corticosteroids in ARDS
- Strictly individualized indications for vv-ECMO in severe ARDS
- Early provision of information to patients and families regarding possible long-term sequelae of mechanical ventilation.

The updated evidence-based treatment pathway is presented in the *Box*.

Despite significant advances in knowledge as a result of new studies, important clinical questions—such as the selection and adjustment of ventilation parameters, the use of vv-ECMO therapy, and long-term sequelae—still need to be addressed scientifically in order to make the treatment and follow-up care of patients in acute respiratory failure in the intensive care unit even more patient-centered and, in an evidence-based manner, safer and more effective in the future.

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Conflict of interest statement

FF, FG, VB, and SL received reimbursement of travel expenses and congress fees from the DGAI.

OM received speaker's fees from CSL Behring (coagulation) and Advitos GmbH (treatment of multi-organ failure). His department held Getinge-supported workshops (hemodynamic monitoring). Onnen Moerer received support (reimbursement of travel expenses and congress fees, as well as speaker honoraria) from the DIVI and the DGAI in the context of his participation in their respective annual congresses. He is spokesperson for the "Lung Failure" section of the DIVI.

MiS received speaker honoraria and consultancy fees from Edwards Life Sciences/BD. He received support (reimbursement of travel expenses and congress fees, as well as speaker honoraria) from the DIVI and the DGAI in the context of his participation in their respective annual congresses.

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Clinical practice guidelines in the *Deutsches Ärzteblatt*, as in many other journals, are not subject to a peer review process, since clinical practice (S3 level) guidelines are texts which have already been evaluated, discussed, and broadly agreed upon multiple times by experts (peers).

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Corresponding author

Dr. med. Falk Fichtner
falk.fichtner@medizin.uni-leipzig.de

Supplementary material

Complete list of full references, eTable, eFigure:
www.aerzteblatt-international.de/m2025.0225

Supplementary material to accompany the Clinical Practice Guideline

Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency

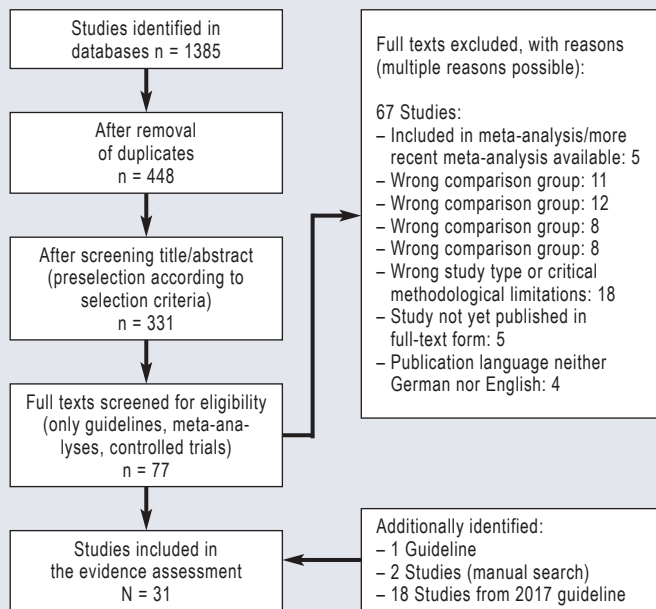
by Falk Fichtner, Onnen Moerer, Felicitas Grundeis, Victoria Büniger, Sven Laudi, and Michael Sander, on behalf of the Guideline Group on Mechanical Ventilation and Extracorporeal Membrane Oxygenation in Acute Respiratory Insufficiency

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eFigure



Example flow chart of the literature search and selection from Chap. 3.3 of the long version of the guideline on ventilation modes enabling spontaneous breathing (*"Spontanatmung-ermöglichende Beatmungsverfahren"*) (12)

eTable

Mandate holders and other participants

Specialist society/organization	Authors
Lead specialist society – Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI)	M. Adamzik ^{*1} , J. Ajouri ^{*1*2} , T. Becher ^{*1*2} , V. Bünger ^{*1*2} , M. Deja ^{*1} , R. Dembinski ^{*1} , F. Fichtner ^{*1} , F. Grundeis ^{*1*2} , M. Grupp ^{*1*2} , M. Habicher ^{*1*2} , S. Henkel ^{*1*2} , F. Hohmann ^{*1*2} , S. Kreyer ^{*1*2} , S. Laudi ^{*1} , C. Lotz ^{*1*2} , O. Moerer ^{*1} , T. Muders ^{*1*2} , R. Muellenbach ^{*1} , P. Neumann ^{*1} , C. Putensen ^{*1} , M. Ragaller ^{*1} , T. Rahmel ^{*1*2} , A. Sachkova ^{*1*2} , M. Sander ^{*1} , D. Schädler ^{*1} , S. Schaller ^{*1} , I. Schroeder ^{*1} , C. Seeber ^{*1} , S. Weber-Carstens ^{*1} , B. Weiß ^{*1} , S. Westfichtel ^{*1*2} , A. Wolf ^{*1*2} , H. Wrigge ^{*1} , M. Zimmer ^{*1*2}
Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)	A. Schäfer ^{*1} , F. Trudzinski ^{*1}
Schweizerische Gesellschaft für Intensivmedizin (SGI)	D. Berger ^{*1}
Österreichische Gesellschaft für Anästhesiologie, Reanimation und Intensivmedizin (ÖGARI)	J. Gratz ^{*1*2} , C. Krenn ^{*1} , D. Traxler ^{*1} , R. Ullrich ^{*1}
Verband der intensivmedizinischen Gesellschaften Österreichs (FASIM)	T. Staudinger ^{*1} , E. Grasmuk-Siegl ^{*1} , M. Urban ^{*1} , C. Schermann-Patz ^{*1} , O. Schindler ^{*1}
Deutsche Gesellschaft für Innere Medizin (DGIM)	P. Lepper ^{*1*2} , M. Pfeifer ^{*1}
Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP)	C. Fisser ^{*1*2} , T. Müller ^{*1} , B. Neetz ^{*1} , C. Rokus ^{*1} , B. Schönhofer ^{*1} , K. Warneke ^{*1}
Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung (DGK)	J. Dutzmann ^{*1*2} , U. Janssens ^{*1} , J. Pöss ^{*1}
Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN)	C. Karagiannidis ^{*1} , S. Kluge ^{*1}
Deutsche Gesellschaft für Chirurgie (DGCH)	D. Schreiter ^{*1}
Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie (DGTHG)	E. Dominik ^{*1*2} , C. Starck ^{*1} , G. Trummer ^{*1}
Deutsche Gesellschaft für Orthopädie und Unfallchirurgie (DGOU)	C. Kleber ^{*1}
Deutsche Gesellschaft für Thoraxchirurgie	No mandate holder appointed for the update; executive board participated in the confirmation process
Deutsche Gesellschaft für Hals-Nasen-Ohrenheilkunde, Kopf- und Halschirurgie (DGHNO-KHC)	A. Müller ^{*1} , Th. Hoffmann ^{*1}
Deutsche Gesellschaft für Neurochirurgie (DGNC)	P. Czorlich ^{*1} , J.-O. Neumann ^{*1}
Deutsche Gesellschaft für Neurologie (DGN)	P. Schramm ^{*1}
Deutsche Gesellschaft für Neurointensiv- und Notfallmedizin (DGNi)	H. Huttner ^{*1} , P. Schramm ^{*1}
Deutsche Gesellschaft für Kinder- und Jugendmedizin (DGKJ)	M. Olivieri ^{*1}
Deutsche Gesellschaft für Neonatologie und pädiatrische Intensivmedizin (DGNPI)	N. Bruns ^{*1*2} , Th. Schaible ^{*1}
Deutsche Gesellschaft für Geriatrie (DGG)	H. Frohnhofen ^{*1}
Deutsche Gesellschaft für Palliativmedizin (DGP)	S. Delis ^{*1} , S. Feit ^{*1*1}
Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM)	N. Hübner ^{*1} , M. Krone ^{*1*2} , F. Mattner ^{*1} , I. Wagenhäuser ^{*1*2}
Deutsche Gesellschaft für Fachkrankenpflege und Funktionsdienste e.V. (DGF)	E. Bock, R. Dubb ^{*1}
Deutsche Gesellschaft für Pflegewissenschaften	C. Papacek-Zimmermann ^{*1}
Physio Deutschland	P. Fischer ^{*1} , A. Fründ ^{*1}
Deutsche Gesellschaft für Perfusionstechnik und Technische Medizin	M. Baumgärtner, D. Buchwald ^{*1} , S. Maier ^{*1}
Deutsche Sepsis-Hilfe	No mandate holder appointed for the update; executive board participated in the confirmation process
Bundesverband der Organtransplantanten (BDO)	M. Veit ^{*1} , W. Veit ^{*1}
External expert group on intensive care nursing	S. Köppen ^{*1} , P. Dahlinger, A. Dobbermann, B. Heinze, T. Kempff, S. Krotsetis, P. Nydahl ^{*1} , S. Patterson, C. Thiele ^{*1}
Information science experts, Leipzig University Library, Medical and Science Library	Astrid Vieler ^{*1} , Maria Grzeschniok ^{*1} , Anna Seidel ^{*1}
Methodological support, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)	Methodological advice and support for the overall project: Dr. med. Monika Nothacker ^{*1} Implementation and moderation of the 3rd consensus conference: PD Dr. rer. nat. Helmuth Sitter ^{*1}

^{*1}Collaborators in guideline development; ^{*2}Representatives of early-career clinician-scientists (early-career mandate holders)