RESEARCH PROTOCOL

PRactice of VENTilation in Critically Ill PEDiatric Patients (PRoVENT–PED) – an international multicenter observational study

The PRoVENT–PED investigators

Correspondence
Relin van Vliet, MD
Department of Intensive Care
Amsterdam University Medical Centers, location 'AMC'
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands
Email: r.vanvliet@amsterdamumc.nl

PRactice of VENTilation in Critically Ill PEDiatric Patients (PRoVENT–PED) – an international multicenter observational study

Protocol ID	…
Short title	PRoVENT–PED
Version	1.0
Date	July 7, 2023
Coordinating investigator(s)	Relin van Vliet, MD Department of Intensive Care Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands Email: r.vanvliet@amsterdamumc.nl & Robert T.G. Blokpoel, MD UMC Groningen Hanzeplein 1 9713 GZ Groningen, The Netherlands Email: r.g.t.blokpoel@umcg.nl
Principal investigator(s)	David M. van Meenen, MD PhD Department of Intensive Care Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands E–mail: d.m.vanmeenen@amsterdamumc.nl & Martin C.J. Kneyber, MD PhD UMC Groningen Hanzeplein 1 9713 GZ Groningen, The Netherlands Email: m.c.j.kneyber@umcg.nl & Frederique Paulus, PhD Department of Intensive Care Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands E–mail: f.paulus@amsterdamumc.nl
Sponsor	Amsterdam UMC, location AMC Meibergdreef 9 1105 AZ Amsterdam, The Netherlands
Subsidizing party	N.A.
Independent expert(s)	…
Laboratory sites	N.A.
Pharmacy	N.A.

(CORE) STEERING COMMITTEE

Core Steering Committee	Steering Committee
Relin van Vliet, MD Amsterdam UMC, location AMC Amsterdam, the Netherlands	
David M.P. van Meenen, MD, PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	
Frederique Paulus, PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	
Robert Blokpoel, MD UMC Groningen 9713 GZ Groningen, The Netherlands	
Marcus J. Schultz, MD PhD Amsterdam UMC, location AMC Amsterdam, the Netherlands	
Martin C.J. Kneyber, MD PhD UMC Groningen 9713 GZ Groningen, The Netherlands	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABG	Arterial Blood Gas
AC	Assist Control
ARDS	Acute Respiratory Distress Syndrome
BiPAP	Bi-level Positive Airway Pressure
CBG	Capillary Blood Gas
CPAP	Continuous Positive Airway Pressure
Crs	Compliance
ΔP	Driving Pressure
ECMO	Extracorporeal membrane oxygenation
$EtCO_2$	End–tidal Carbon Dioxide
FiO_2	Fraction of Inspired Oxygen
GCP	Good Clinical Practice
HFNO	High–Flow Nasal Oxygen
HFOV	High-Frequency Oscillatory Ventilation
ICU	Intensive Care Unit
I:E	Inspiratory to Expiratory ratio
METC	(Dutch) Medical research ethics committee
NAVA	Neurally Adjusted Ventilatory Assist
NIV	Noninvasive Ventilation
NMBA	Neuromuscular Blocking Agents
PaO_2	Partial arterial Pressure of Oxygen
$PaCO_2$	Partial arterial Pressure of Carbon Dioxide
PALICC	Pediatric Acute Lung Injury Consensus Conference
PARDS	Pediatric Acute Respiratory Distress Syndrome
PCV	Pressure Controlled ventilation
PEEP	Positive End–Expiratory Pressure
PICU	Pediatric Intensive Care Unit
PIM	Pediatric Index of Mortality
PIP	Peak Inspiratory Pressure
Pmax	Maximum airway pressure
Ppeak	Peak pressure
Pplat	Plateau pressure
PRISM	Pediatric Risk of Mortality
PRVC	Pressure Regulated Volume Control
PS	Pressure Support
PSV	Pressure Support Ventilation
RR	Respiratory Rate
SaO_2	Saturation of Arterial Oxygen
(S)AE	(Serious) Adverse Event
SIMV	Synchronized Intermittent Mandatory Ventilation
SpO2	Saturation of Peripheral Oxygen
Sponsor	The party that commissions the organization or performance of research
VCV	Volume Controlled Ventilation
VILI	Ventilator Induced Lung Injury
VSV	Volume Support Ventilation
V_T	Tidal Volume
$V_T e$	Expiratory tidal volume
$V_T i$	Inspiratory Tidal Volume
WMO	(Dutch) Medical Research Involving Human Subjects Act

SUMMARY

Rationale

Critically ill pediatric patients often need some form of ventilatory support. Remarkably, despite this worldwide use of mechanical ventilation, there is a lack of scientific evidence how these interventions can be applied most optimally. Much of the current clinical practice is based upon experience and data originating from critically ill adult patients. This probably explains the significant practice variability of ventilatory support. Following the introduction of new interventions, it is reasonable to assume that ventilatory support practices may have further changed and worldwide variances in ventilatory support could be substantial. We argue that it is imperative to understand how ventilatory support is currently being used to ascertain in which patient category existing or novel interventions may be considered to optimize ventilation strategies, and to support the development of clinical practice guidelines.

Objective

To a) describe the practice of ventilatory support in critically ill pediatric patients, b) to identify potentially modifiable ventilation setting and parameters that have independent associations with outcome including duration of ventilatory support, the number of days free from ventilatory support at day 28, length of ICU stay, and ICU mortality and c) to study the prevalence of the Pediatric Acute Respiratory Distress Syndrome (PARDS).

Study design

Investigator–initiated, prospective, international, multicenter observational cohort study over a 10-year period. Each year, data will be collected in two predefined 4-week periods, one in the winter season and one in the summer season. A third 4-week period will be in case of epi- or pandemics. Local investigators will capture data on demographics and baseline characteristics, ventilator settings and ventilation parameters, and outcomes in their hospital. Data collection is kept minimal to keep workloads associated with the study as low as possible.

Study population

Patients are eligible if (1) aged < 18 years; (2) admitted to an intensive care unit of a participating hospital; (3) for any (critical illness) necessitating ventilatory support for at least 12 hours. We exclude premature infants, i.e., patients with a postconceptional age corrected for gestational age < 37 weeks.

Main study endpoints

The primary endpoint is a set of key ventilation settings and ventilation parameters, including tidal volume (V_T), peak inspiratory pressure (PIP), plateau pressure (Pplat), positive end-expiratory pressure (PEEP), inspired fraction of oxygen (FiO_2), inspiration to expiration ratio (I:E), inspiration time, set respiratory rate, total respiratory rate, compliance (Crs), driving pressure (ΔP) and the mechanical power of ventilation (MP). Secondary endpoints include the incidence of PARDS, duration of ventilatory support, the number of days free from ventilatory support at day 28, length of ICU stay, and ICU mortality. We will also determine whether there are potentially modifiable factors that have an independent association with outcome.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Prospective collection of demographic data, ventilation settings and ventilation parameters, and outcomes means the risks are negligible and the burden is minimal.

1. INTRODUCTION AND RATIONALE

1.1. Practice of ventilatory support in children

Critically ill pediatric patients often need ventilatory support (1). Despite the worldwide use of this intervention and its lifesaving potential, studies on practice of ventilatory support in critically ill pediatric patients remain scarce. Various studies characterized practice of invasive ventilation in pediatric patients and reported significant variability (2, 3). However, these studies date back more than 10 years ago. Since new interventions have been introduced, it is likely that practice of ventilatory support have changed since then, and worldwide variances in ventilatory support could be substantial.

1.2. Practice of ventilatory support in adults

Much of the current practice is based upon experience and data originating from studies in critically ill adult patients. These adult studies have shown substantial variation in ventilator settings and ventilation parameters, between different patient categories and also between geo–economic regions (4). These studies also showed that certain ventilation settings and ventilation parameters have independent associations with outcome, including tidal volume (V_T), positive end expiratory pressure (PEEP), driving pressure (ΔP), mechanical power of ventilation (MP), and the fraction of inspired oxygen (FiO_2) (5-18).

1.3. Need for a new study

Studies on practice of ventilatory support in critically ill pediatric patients remain scarce and much of the current practice is based upon data originating from critically ill adult patients. However, findings of studies in critically ill adult patients may not be translatable to critically ill pediatric patients due to different lung physiology and different immune responses. For example, lung compliance differs between different age groups, also the extend of ventilator induced lung injury (VILI) might be age–dependent (19) and pediatric patients are more susceptible to the adverse effects of oxygen toxicity than adults (20-22). Randomized clinical trials are needed to investigate the effectiveness of various ventilator settings to improve practice of ventilatory support. However, before we can design such studies, we first need to understand worldwide clinical practice in critically ill pediatric patients. The here proposed study will give capture detailed data on ventilatory support. This allows us to determine which potentially modifiable factors have independent associations with outcomes, including duration of ventilatory support, the number of days free from

ventilatory support at day 28, length of ICU stay, and ICU mortality. Since this study will run over a long period of time, and will include patients worldwide, we will be able to describe temporal changes and geo–economic differences.

2. OBJECTIVES & HYPOTHESES

2.1. Objectives

The aims of this study are to:

- describe the practice of ventilatory support;
- study temporal changes in practice of ventilatory support;
- study geo–economic differences in ventilatory support and outcomes in critically ill pediatric patients; and
- identify potentially modifiable factors that have independent associations with outcome including duration of ventilatory support, the number of days free from ventilatory support at day 28, length of ICU stay, and ICU mortality.

2.2. Hypotheses

We will test the following hypotheses:

- practice of ventilatory support varies substantially; and
- potentially modifiable factors related to ventilation have independent associations with outcome in critically ill pediatric patients, including duration of ventilatory support, the number of days free from ventilatory support at day 28, length of ICU stay, and ICU mortality.

3. STUDY DESIGN

Investigator–initiated, prospective, international, multicenter, observational study in critically ill pediatric patients. This study will start in 2024 and will run for a period of 10 years.

4. STUDY POPULATION

4.1. Population (base)

Critically ill pediatric patients receiving ventilatory support.

4.2. Inclusion criteria

Patients are eligible if:

- aged < 18 years;
- admitted to an intensive care unit (ICU) of a participating hospital during the period of data collection; and
- receiving ventilatory support > 12 hours.

4.3. Exclusion criteria

The following patients will be excluded:

- premature infants (i.e., postconceptional age corrected for gestational age < 37 weeks).

4.4. Sample size calculation

To investigate the association of a limited set of pre-specified confounders with mortality in critically ill pediatric patients receiving invasive ventilation using logistic regression we estimate to need 100 events using the 10 event per variable of thumb. We aim to add 10 covariates to the model. With a conservative estimate of overall PICU mortality of 3% (1, 23) 3300 patients are needed for this analysis. With a conservative estimate of 50 participating centers, including 30 patients per inclusion period, the first analyses can be performed after the first year of inclusions. To explore differences between age groups (< 1 month, 1-11 months, 1-2 years, 3-6 years, 7-12 years, 13-18 years) and to do the same analysis in these groups we need around 19.800 patients in total. Taking a dropout of participating centers of around 30% into account, we expect to reach this sample size after including patients for eight years. After the first year, we will also start to include patients receiving other types of ventilatory support (i.e., noninvasive ventilation (NIV), high–frequency oscillatory ventilation (HFOV), continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), and high–flow nasal oxygen (HFNO)). As some of these types, for example HFOV, are less frequently used and to be able to do the same analysis, we expect to need to include patients for approximately 10 years.

5. METHODS

5.1. Study endpoints

5.1.1. Main ventilator settings and parameters

The main study endpoint is a set of key ventilation settings and ventilation parameters, including tidal volume (V_T); peak inspiratory pressure (PIP); plateau pressure (Pplat); positive end-expiratory pressure (PEEP); fraction of inspired oxygen (FiO_2); inspiration to expiration ratio (I:E); inspiration time; set and total respiratory rate (RR); compliance (Crs); driving pressure (ΔP); and the mechanical power of ventilation (MP).

5.1.2. Secondary ventilation settings and parameters

Secondary parameters are type of ventilatory support; type of airway management; type of ventilation mode; saturation of peripheral oxygen (SpO_2); end-tidal carbon dioxide ($EtCO_2$) and only if available blood gas analysis.

5.1.3. Clinical outcomes

The clinical outcomes involve the incidence of Pediatric Acute Respiratory Distress Syndrome (PARDS); number of ventilation-free days at day 28; duration of ICU stay; ICU mortality and cause of death.

5.2. Data to be collected

All data to be collected are part of standard clinical care.

5.2.1. Patient characteristics

- Age (weeks or months);
- Sex (male or female);
- Height (cm);
- Weight (kg); and
- Gestational age (weeks).

5.2.2. Medical status

- Comorbidities (pulmonary, cardiac, neuromuscular, syndrome/genetic abnormalities, oncologic, organ transplant, chronic ventilation, mental retardation);
- Reason of ventilatory support; and
- Pediatric Risk of Mortality (PRISM) or Pediatric Index of Mortality (PIM) score, depending on which scoring system is used in the Pediatric Intensive Care Unit (PICU).

5.2.3. Data collection at day of intubation

(note that this could also be the day of admission to a pediatric ICU if transferred from another hospital with mechanical ventilation)

- Date of ICU admission; and
- Date and time of intubation (if the patient is transferred from another hospital than day 0 is the day of admission).

5.2.4. Daily data collection

(this is for the first three full calendar days in the pediatric ICU)

At start of ventilation or at arrival when the patient has been intubated in another hospital, ventilation data will be collected directly and after 1 hour (name ‘day 0’). Thereafter, ventilation data will be collected daily at a time point in the morning representing a steady state overnight, e.g., before the first morning blood gas is drawn, up to day 3, or the day of extubation or death.

- Type of ventilatory support: invasive ventilation; noninvasive ventilation (NIV), high–frequency oscillatory ventilation (HFOV), continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), and high–flow nasal oxygen (HFNO);
- Type of airway management: intubation or tracheostomy (invasive); nasal/facial mask (non-invasive);
- Ventilation mode: volume controlled ventilation (VCV), assist-control (AC) or synchronized intermittent mandatory ventilation (SIMV); pressure controlled ventilation (PCV), AC or SIMV; volume support ventilation (VSV); pressure support ventilation (PSV); synchronized intermittent mandatory ventilation (SIMV) ± pressure support (PS); pressure regulated volume control (PRVC); neurally adjusted ventilatory assist (NAVA); NIV; HFOV; (n)CPAP; BIPAP; and HFNO;
- Ventilator settings: including but not restricted to: expiratory tidal volume (V_Te) (mL) or inspiratory tidal volume (V_{Ti}) (mL) (only in case V_Te is not available); PEEP (cm H_2O); PIP (cm H_2O) or Pplat (cm H_2O) (cm H_2O); level of pressure support above PEEP (cm H_2O); trigger (flow or pressure, if flow then rate set); FiO_2 (%); set and measured RR; I:E ratio; or inspiration time; SpO_2 (%); $EtCO_2$ (kPa);
- Arterial blood gas (ABG) analysis results or capillary blood gas (CBG) analysis results, only if available: pH; partial pressure of oxygen (PaO_2) (kPa or mmHg); partial pressure of carbon dioxide ($PaCO_2$) (kPa or mmHg);

- Imaging: X-ray (y/n). If yes, the first available X-ray after start of mechanical ventilation, will be assessed by the researcher (to prevent inter-observer variability) whether new opacities (unilateral or bilateral) consistent with acute pulmonary parenchymal disease are seen which are not due primarily to atelectasis or pleural effusion (y/n);
- Treatment: undergoing veno–venous, veno–arterial or arterio–venous extracorporeal membrane oxygenation (ECMO) (y/n); use of sedative (y/n) if yes: continue or bolus; use of neuromuscular blocking agents (NMBA) (y/n); if yes: continue or bolus; use of opiates (y/n); if yes: continue or bolus; use of vasoactive drugs (y/n); if yes: continue or bolus; and use of prone positioning.

5.2.5. Follow–up

Outcome data will be collected at ICU discharge:

- PARDS (y/n), according to the 2023 Pediatric Acute Lung Injury Consensus Conference (PALICC) definition (24);
- Air leak during ICU stay;
- Intubated (y/n), and if not, extubation date;
- Successful extubation; defined as no reintubation within 48 hours after extubation (y/n), if not: reason of reintubation;
- Alive (y/n), and if not, date of death in ICU; cause of death;
- Number of ventilation-free days at day 28 (zero in case of death or start ECMO);
- Date of discharge from ICU; and
- Destination after ICU discharge (other ICU, ward or home).

5.3. Randomization, blinding and treatment allocation

To prevent that large centers, > 100 expected subjects per inclusion period, are overrepresented we will randomize eligible patients admitted to these centers for inclusion 1:1.

5.4. Study procedures

A physician from each participating country will be appointed as national coordinator. The researcher will enroll patients in the study. The participating centers will be visited by researchers to collect data of included patients. Before the start of data collection, a pilot study at the Amsterdam University Medical Center and the University Medical Center Groningen will be performed to detect and solve potential problems of the protocol.

5.5. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

5.6. Replacement of individual subjects after withdrawal

There will be no replacement of an individual subject after withdrawal.

5.7. Follow-up of subjects withdrawn from treatment

There will be no follow-up of a subject after withdrawal.

5.8. Premature termination of the study

There will be no reason for premature termination as no research related interventions will take place.

6. SAFETY REPORTING

6.1. Temporary halt for reasons of subject safety

N.A.

6.2. AEs, SAEs and SUSARs

N.A.

6.3. Data Safety Monitoring Board (DSMB) and Safety Committee

N.A.

7. STATISTICAL ANALYSIS

7.1. Descriptive statistics

Descriptive statistics will be used to describe baseline characteristics, ventilation settings and parameters. Categorical variables will be expressed as n (%). A p-value < 0.05 is considered statistically significant. Data will be analyzed with R (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org). No or minimal losses to follow–up for the primary and secondary outcomes are anticipated. In case of missing data, we will adjust complete–case analysis.

7.2. Visualization of endpoints

Data will be visualized using distribution graphs for ventilation settings, variables and parameters, and Kaplan–Meier curves for events like liberation from the ventilator, discharge and death.

7.3. Associations between ventilation settings, parameters and outcome

Propensity score matching will be used to adjust for confounding and univariate and multivariate analyses will be used to identify associations of predefined ventilation settings and parameters with outcome.

7.4. Planned analyses

This study will run for an estimated period of 10 years. If an adequate sample size is reached for a planned analysis, this analysis will be performed.

8. ETHICAL CONSIDERATIONS

8.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013), with Good Clinical Practice (GCP).

8.2. Recruitment and consent

The investigator will enroll patients in the study. All patients admitted to the pediatric ICU and receiving ventilatory support will be included. If needed, informed consent by the patient and/or parents will be obtained by the investigator.

8.3. Benefits and risks assessment, group relatedness

This study does not result in any risk or burdens to patients.

8.4. Compensation for injury

Since the study only collects data and no research related interventions will take place, participating in the study is without risk.

8.5. Incentives

There is no financial incentive for subjects to participate in this study.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1. Handling and storage of data and documents

Handling of personal data will comply with the General Data Protection Regulation. All collected data will be transcribed by investigators into a web-based electronic Case Report Form (Castor). Transcription will only take place in a secured environment. Directly identifying personal data will be separated from the research data and replaced by an assigned code. The directly identifying data will only be used to contact the patients and will only be available to the local investigators. Access to the assigned codes linked with personal data will be controlled with password protection. The passwords will only be given to directly involved investigators. Any data leaks will be reported to all parties within 1 working day after discovery of the leak.

9.2. Monitoring and Quality Assurance

In order to minimize the number of errors and missing data we will use standard operating procedures. Accuracy and consistency checks will be carried out by ad hoc checking by investigation coordinators.

9.3. Amendments

N.A.

9.4. Annual progress report

N.A.

9.5. Temporary halt and (prematurely) end of study report

N.A.

9.6. Public disclosure and publication policy

The study protocol will be registered on Clinicaltrials.gov before start of the study. The results of the study will be published in (inter–) national scientific journals and guidelines. The project leader will have final responsibility for the decision to submit for publication.

10. STRUCTURED RISK ANALYSIS

N.A.

11. REFERENCES

1. Heneghan JA, Rogerson C, Goodman DM, Hall M, Kohne JG, Kane JM. Epidemiology of Pediatric Critical Care Admissions in 43 United States Children's Hospitals, 2014-2019. Pediatr Crit Care Med. 2022;23(7):484-92.

2. Farias JA, Fernández A, Monteverde E, Flores JC, Baltodano A, Menchaca A, et al. Mechanical ventilation in pediatric intensive care units during the season for acute lower respiratory infection: a multicenter study. Pediatr Crit Care Med. 2012;13(2):158-64.

3. Farias JA, Frutos F, Esteban A, Flores JC, Retta A, Baltodano A, et al. What is the daily practice of mechanical ventilation in pediatric intensive care units? A multicenter study. Intensive Care Med. 2004;30(5):918-25.

4. Pisani L, Algera AG, Neto AS, Azevedo L, Pham T, Paulus F, et al. Geoeconomic variations in epidemiology, ventilation management, and outcomes in invasively ventilated intensive care unit patients without acute respiratory distress syndrome: a pooled analysis of four observational studies. Lancet Glob Health. 2022;10(2):e227-e35.

5. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-8.

6. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med. 2006;34(5):1311-8.

7. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. Jama. 2010;303(9):865-73.

8. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347-54.

9. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747-55.

10. Sahetya SK, Mallow C, Sevransky JE, Martin GS, Girard TD, Brower RG, et al. Association between hospital mortality and inspiratory airway pressures in mechanically ventilated patients without acute respiratory distress syndrome: a prospective cohort study. Crit Care. 2019;23(1):367.
11. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. Jama. 2016;316(15):1583-9.
12. Helmerhorst HJ, Arts DL, Schultz MJ, van der Voort PH, Abu-Hanna A, de Jonge E, et al. Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care. Crit Care Med. 2017;45(2):187-95.
13. Schjørring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, et al. Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. N Engl J Med. 2021;384(14):1301-11.
14. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020;382(11):989-98.
15. Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, et al. Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. N Engl J Med. 2020;382(11):999-1008.
16. Costa ELV, Slutsky AS, Brochard LJ, Brower R, Serpa-Neto A, Cavalcanti AB, et al. Ventilatory Variables and Mechanical Power in Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2021;204(3):303-11.
17. van Meenen DMP, Algera AG, Schuijt MTU, Simonis FD, van der Hoeven SM, Neto AS, et al. Effect of mechanical power on mortality in invasively ventilated ICU patients without the acute respiratory distress syndrome: An analysis of three randomised clinical trials. Eur J Anaesthesiol. 2023;40(1):21-8.
18. Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to-bedside review: the effects of hyperoxia during critical illness. Crit Care. 2015;19(1):284.
19. Kneyber MC, Zhang H, Slutsky AS. Ventilator-induced lung injury. Similarity and differences between children and adults. Am J Respir Crit Care Med. 2014;190(3):258-65.

20. Lilien TA, Groeneveld NS, van Etten-Jamaludin F, Peters MJ, Buysse CMP, Ralston SL, et al. Association of Arterial Hyperoxia With Outcomes in Critically Ill Children: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(1):e2142105.
21. Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, et al. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362(21):1959-69.
22. Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, et al. Oxygen saturation and outcomes in preterm infants. N Engl J Med. 2013;368(22):2094-104.
23. Arias Y, Taylor DS, Marcin JP. Association between evening admissions and higher mortality rates in the pediatric intensive care unit. Pediatrics. 2004;113(6):e530-4.
24. Yehya N, Smith L, Thomas NJ, Steffen KM, Zimmerman J, Lee JH, et al. Definition, Incidence, and Epidemiology of Pediatric Acute Respiratory Distress Syndrome: From the Second Pediatric Acute Lung Injury Consensus Conference. Pediatr Crit Care Med. 2023;24(12 Suppl 2):S87-s98.