Hyperoxemia as a risk factor for ventilator-associated pneumonia

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Abstract

Background: Consequences of hyperoxemia, such as acute lung injury, atelectasis, and reduced bacterial clearance, might promote ventilator-associated pneumonia (VAP). The aim of our study was to determine the relationship between hyperoxemia and VAP.

Methods: This retrospective observational study was performed in a 30-bed mixed ICU. All patients receiving invasive mechanical ventilation for more than 48 hours were eligible. VAP was defined using clinical, radiologic, and quantitative microbiological criteria. Hyperoxemia was defined as PaO$_2$ > 120 mmHg. All data, except those related to hyperoxemia, were prospectively collected. Risk factors for VAP were determined using univariate and multivariate analysis.

Results: VAP was diagnosed in 141 of the 503 enrolled patients (28 %). The incidence rate of VAP was 14.7 per 1000 ventilator days. Hyperoxemia at intensive care unit admission (67 % vs 53 %, OR = 1.8, 95 % CI (1.2, 2.9), p < 0.05) and number of days spent with hyperoxemia were significantly more frequent in patients with VAP, compared with those with no VAP. Multivariate analysis identified number of days spent with hyperoxemia (OR = 1.1, 95 % CI (1.04, 1.2) per day, p = 0.004), simplified acute physiology score (SAPS) II (OR = 1.01, 95 % CI (1.002, 1.024) per point, p < 0.05), red blood cell transfusion (OR = 1.8, 95 % CI (1.2, 2.7), p = 0.01), and proton pump inhibitor use (OR = 1.9, 95 % CI (1.03, 1.2), p < 0.05) as independent risk factors for VAP. Other multiple regression models also identified hyperoxemia at ICU admission (OR = 1.89, 95 % CI (1.23, 2.89), p = 0.004), and percentage of days with hyperoxemia (OR = 2.2, 95 % CI (1.08, 4.48), p = 0.029) as independent risk factors for VAP.

Conclusion: Hyperoxemia is independently associated with VAP. Further studies are required to confirm our results.

Keywords: Arterial oxygen tension, Ventilator-associated pneumonia, Critical care, Prevention, Outcome, Hyperoxemia, Hyperoxia
surfactant production are observed at high levels of inspired oxygen fraction (FiO\textsubscript{2}), promoting expiratory collapse and atelectasis [15, 16]. Hyperoxia also impairs mucociliary clearance and the antimicrobial action capacity of macrophages and immune cells [17]. Acute lung injury, atelectasis, and reduced bacterial clearance are well-known risk factors for VAP [18–20].

VAP is the most common ICU-acquired infection, and is associated with high mortality, duration of mechanical ventilation, and cost [21]. Therefore, prevention of VAP is a key issue in critically ill patients. Understanding the pathophysiology of VAP, and identification of risk factors are important in order to improve preventive strategies [22].

Previous animal studies strongly suggest a relationship between hyperoxemia and VAP. However, in spite of the obvious potential link between hyperoxemia and VAP, to our knowledge no study to date has evaluated the relationship between these two conditions. Therefore, we conducted this retrospective observational study to determine whether hyperoxemia is a risk factor for VAP.

Methods

Study characteristics

This retrospective observational study was performed in a 30-bed mixed ICU, located in the University Hospital of Lille, France. All data, except blood gases results, were collected prospectively during an 18-month period. Because of the observational design, and in accordance with French law, written informed consent was not required. The local institutional review board (Comité de Protection des Personnes Nord-Ouest IV) approved the study. All patients requiring invasive mechanical ventilation for more than 48 h, during an 18-month period, were eligible. The only exclusion criterion was duration of mechanical ventilation for \( \leq 48 \) h.

Definitions

VAP was defined as the presence of new or progressive pulmonary infiltrate, and at least two of the following criteria: (1) fever (body temperature \( \geq 38 \) °C) or hypothermia (<36 °C); (2) leukocytosis (>12 × 10\(^9\)/L leukocytes) or leukopenia (<3.5 × 10\(^9\)/L); and (3) purulent respiratory secretions. Microbiological confirmation was required in all patients (positive bronchoalveolar lavage \( \geq 10^5 \) colony-forming units (cfu)/mL, or positive tracheal aspirate \( \geq 10^5 \) cfu/mL) [23]. Only first episodes of VAP diagnosed \( >48 \) h after starting mechanical ventilation were taken into account. Early-onset episodes were defined as VAP diagnosed <5 days after starting mechanical ventilation, and late-onset episodes as VAP diagnosed \( \geq 5 \) days after mechanical ventilation. Hyperoxemia was defined as arterial oxygen tension (PaO\textsubscript{2}) \( >120 \) mmHg (\( >16 \) kPa) was considered as a day with hyperoxemia.

The following microorganisms were defined as multidrug-resistant bacteria: ceftazidime or imipenem-resistant Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, \(-\)lactamase-producing Gram-negative bacilli and methicillin-resistant Staphylococcus aureus. Prior antibiotic use was defined as antimicrobial treatment during the 3 months preceding ICU admission. Immunosuppression was defined by the presence of neutropenia (neutrophils <500/µL), active solid or hematological malignancy, long-term corticosteroid therapy (\( \geq 1 \) mg/kg/d for >1 month), or HIV infection (CD4 < 50/µL during the previous 6 months).

Study patients

A VAP prevention strategy was routinely used during the study period. The ventilator circuit was not changed routinely. In all patients, a heat-moisture exchanger was positioned between the Y piece and the patient. These exchangers were changed every 48 h or more frequently if visibly soiled. Sedation and weaning were based on a written protocol. A minimal positive end-expiratory pressure of 5 cm H\textsubscript{2}O was used in all patients. Selective digestive decontamination and subglottic secretion drainage were not used. The oral cavity was cleaned with chlorhexidine three times daily. Cuff pressure was measured and adjusted (25 cm H\textsubscript{2}O) by nurses thrice a day. Tracheal suctioning was routinely performed by nurses, using an open tracheal suction system. Patients remained in the semi-recumbent position, and received enteral nutrition based on a written protocol.

Antibiotic treatment for patients with suspected VAP was based on American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines [23]. Antibiotic treatment for other infections was based on written local guidelines adapted from international and national guidelines. Stress ulcer prophylaxis was not routinely used.

Data collection

All data were prospectively recorded, except blood gases results. The following characteristics were recorded at ICU admission: age, male gender, severity of illness based on simplified acute physiology score (SAPS) II, logistic organ dysfunction (LOD) score, and McCabe score; comorbidities (diabetes, chronic obstructive pulmonary disease (COPD), chronic heart failure, cirrhosis, chronic renal failure requiring dialysis, or immunosuppression), location before ICU admission, admission category (medical or surgical), reason for ICU admission (acute exacerbation of COPD, acute respiratory distress syndrome, pneumonia, congestive heart failure,
neurologic failure, poisoning, shock [24], cellulitis, or infection), and prior antibiotic use.

During the ICU stay data were collected on tracheostomy, red blood cell transfusion, sedation, stress ulcer prophylaxis, use of neuromuscular-blocking agents, number of days with PaO2 > 120 mmHg, percentage of days with PaO2 > 120 mmHg, occurrence of VAP, duration of mechanical ventilation, and ICU mortality.

Statistical analysis
SPSS software (SPSS, Chicago, IL, USA) was used for data analysis. Categorical variables were described as frequency (%). The distribution of continuous variables was tested for normality. Normally distributed and skewed continuous variables were described as mean ± standard deviation (SD) or as median and interquartile range (IQR), respectively. All p values were two-tailed. Differences were considered significant if p values were <0.05.

In order to determine factors associated with VAP, patients with VAP were compared with those without VAP using bivariate and multivariate analyses. The chi-square (χ²) test or Fisher’s exact test was used to compare qualitative variables, as appropriate. Student’s t test or the Mann-Whitney U test was used to compare normally distributed, and skewed continuous variables, respectively. Potential interactions were tested, and the Hosmer-Lemeshow goodness-of-fit was calculated. The odds ratio (OR) and 95 % confidence interval (CI) were calculated for all significant variables in univariate analysis and in multivariate analysis. Exposure to potential risk factors for VAP was taken into account until the occurrence of VAP, or until ICU discharge in patients with and without VAP, respectively.

Because of obvious interaction between hyperoxemia at ICU admission, number of days with hyperoxemia, and percentage of days with hyperoxemia, three different models of multivariate analysis were used. Each of these models included all variables with p values <0.1 on univariate analysis, and hyperoxemia at ICU admission, number of days with hyperoxemia, or percentage of days with hyperoxemia. Further, univariable and multivariable Cox proportional hazard models were used to determine risk factors for VAP. All variables with p values <0.1 in the univariable model, and hyperoxemia at ICU admission, or percentage of days with hyperoxemia were included in the final multivariable models.

Results
Patient characteristics
During the study period 503 patients received mechanical ventilation for >48 h, including 141 patients (28 %) who had at least one episode of VAP. The incidence rate of VAP was 14.7 per 1000 ventilator days. Early-onset and late-onset episodes occurred in 14 (10 %), and 127 (90 %) patients with VAP, respectively. The median (IQR) duration from starting mechanical ventilation to diagnosis of VAP was 14 (8, 23) days.

No significant difference was found in age (median (interquartile range) 60 (49, 73) vs 59 (47, 70), years, p = 0.265), SAPS II (48 (35, 61) vs 48 (36, 62), p = 0.772), LOD score (5 (2, 7) vs 5 (2, 9), p = 0.817), mortality rate (121 out of 289 (41.8 %) vs 82 out of 214 (38.3 %), p = 0.265), duration of mechanical ventilation (12 (6, 24) vs 13 (7, 26), p = 0.427), and ICU length of stay (15 (8, 29) vs 18 (10, 31), p = 0.243),

Table 1 Characteristics of study patients at ICU admission

| Variable                        | VAP                | P     |
|---------------------------------|--------------------|-------|
| Age, years                      | Yes 62 (51.5–74)   | 0.004 |
|                                 | No 57 (46–71)      |       |
| Male gender                     | Yes 102 (72)       | 0.339 |
|                                 | No 246 (67)        |       |
| SAPS II                         | Yes 53 (41–65)     | <0.001|
|                                 | No 45 (33–59)      |       |
| LOD score                       | Yes 6 (3–9)        | 0.241 |
|                                 | No 5 (2–7)         |       |
| McCabe score >2                | Yes 20 (14)        | 0.382 |
|                                 | No 37 (10)         |       |
| Transfer from other wards       | Yes 96 (68)        | 0.081 |
|                                 | No 216 (60)        |       |
| Chronic diseases                |                    |       |
| Diabetes                        | Yes 16 (11)        | 0.108 |
|                                 | No 62 (17)         |       |
| COPD                            | Yes 41 (29)        | 0.651 |
|                                 | No 98 (27)         |       |
| Cardiac failure                 | Yes 34 (24)        | 0.159 |
|                                 | No 67 (18)         |       |
| Cirrhosis                       | Yes 4 (3)          | 0.576 |
|                                 | No 14 (4)          |       |
| Chronic dialysis                | Yes 2 (1)          | 0.375 |
|                                 | No 10 (3)          |       |
| Immunosuppression               | Yes 38 (27)        | 0.196 |
|                                 | No 78 (22)         |       |
| Admission category              |                    | 0.499 |
| Medical                         | Yes 91 (65)        |       |
|                                 | No 245 (67)        |       |
| Surgical                        | Yes 48 (34)        |       |
|                                 | No 114 (31)        |       |
| Cause for ICU admission         |                    |       |
| Acute exacerbation of COPD      | Yes 16 (11)        | 0.677 |
|                                 | No 46 (12)         |       |
| ARDS                            | Yes 22 (15)        | 0.113 |
|                                 | No 38 (10)         |       |
| Pneumonia                       | Yes 40 (28)        | 0.458 |
|                                 | No 91 (25)         |       |
| Congestive heart failure        | Yes 5 (3)          | 0.516 |
|                                 | No 9 (2)           |       |
| Neurologic failure              | Yes 16 (11)        | 0.462 |
|                                 | No 50 (13)         |       |
| Poisoning                       | Yes 16 (11)        | 0.285 |
|                                 | No 30 (8)          |       |
| Shock                           | Yes 64 (45)        | 0.002 |
|                                 | No 111 (30)        |       |
| Cellulitis                      | Yes 10 (7)         | 0.052 |
|                                 | No 48 (13)         |       |
| Infection                       | Yes 97 (69)        | 0.856 |
|                                 | No 246 (67)        |       |
| Prior antimicrobial treatment   | Yes 70 (50)        | 0.924 |
|                                 | No 178 (49)        |       |
| PaO2 > 120 mmHg                 | Yes 95 (67)        | 0.004 |
|                                 | No 193 (53)        |       |

OR = 1.9, 95 % CI (1.3, 2.8); OR = 1.8, 95 % CI (1.2, 2.7). The results are expressed in number (%) for categorical variables and in median (IQR) for quantitative variables. ARDS acute respiratory distress syndrome, COPD, chronic obstructive pulmonary disease, CI confidence interval, ICU intensive care unit, LOD logistic organ dysfunction, MV mechanical ventilation, OR odds ratio, PaO2 arterial oxygen tension, SAPS simplified acute physiology score, VAP ventilated-associated pneumonia.
between patients with hyperoxemia and those with no hyperoxemia at ICU admission.

**Risk factors for VAP by univariate analysis**
At ICU admission, age, SAPS II, LOD score, and percentage of patients with shock, or with PaO$_2$ > 120 mmHg were significantly higher in VAP patients, compared with those with no VAP (Table 1).

During the ICU stay, the percentage of patients with stress ulcer prophylaxis, red blood cell transfusion, or sedation was significantly higher in patients with VAP compared to patients without VAP. Number of days with hyperoxemia was also significantly higher in patients with VAP compared to patients without VAP (Table 2). The percentage of patients with VAP, based on the number of days with hyperoxemia is presented in Fig. 1.

**Microbiological results**
VAP was polymicrobial in 8 patients (6 %), and related to multidrug resistant (MDR) bacteria in 58 patients (41 %). Gram-negative bacteria represented 78 % of all bacteria, and were identified in 82 % of patients with VAP. *P. aeruginosa* (34 %), *S. aureus* (11 %), and *A. baumannii* (9 %) were the most common bacteria in patients with VAP. MDR bacteria represented 41 % of all bacteria (58 out of 149) (Table 3).

**Risk factors for VAP by multivariate analysis**
Because of significant ($p < 0.05$) interactions between hyperoxemia at ICU admission, number of days with hyperoxemia, and percentage of days with hyperoxemia, three different logistic regression models were used with only one of these factors in each model. No other significant ($p > 0.1$) interactions were found between other factors introduced in the multivariable models.

The results of the three logistic regression models are presented in Table 4. Number of days with hyperoxemia, hyperoxemia at ICU admission, and percentage of days with hyperoxemia were independently associated with VAP in models 1, 2, and 3, respectively.

**Risk factors for VAP by univariate and multivariate Cox proportional hazards models**
Hyperoxemia at ICU admission and percentage of days with hyperoxemia were independently associated with VAP, using two different Cox proportional hazards models (Table 5).

**Discussion**
Our results suggest that hyperoxemia is an independent risk factor for VAP. To our knowledge, our study is the first to evaluate the relationship between hyperoxemia and VAP. As discussed previously, this result could be explained by the occurrence of HALI, atelectasis, and

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### Table 2 Patient characteristics during the ICU stay

|                      | VAP          | No          | $p$  |
|----------------------|--------------|-------------|------|
| Stress ulcer prophylaxis |              |             |      |
| Proton-pump inhibitor | 122 (86)     | 279 (77)    | 0.002|
| Sucralfate           | 9 (6)        | 46 (13)     |      |
| No                   | 10 (7)       | 40 (11)     |      |
| Tracheostomy         | 24 (17)      | 47 (13)     | 0.243|
| Red blood cell transfusion | 86 (61) | 139 (38)    | <0.001$^a$ |
| Sedation             | 122 (86)     | 284 (78)    | 0.039$^b$ |
| Neuromuscular-blocking agent use | 10 (7) | 20 (6)      | 0.505|
| Mean number of ABG per day | 3 (1–6) | 2 (1–5)     | 0.261|
| Number of days with PaO$_2$ > 120 mmHg | 5 (2–7) | 3 (1–5) | <0.001 |
| Percentage of days with PaO$_2$ > 120 mmHg | 0.33 (0.19–0.58) | 0.33 (0.14–0.50) | 0.282 |
| Duration of MV prior to VAP, days | 14 (8–23) | 9 (5–17) | <0.001 |
| Total duration of MV, days | 30 (17–43) | 9 (5–17) | <0.001 |
| Length of ICU stay, days | 34 (19–45.5) | 12 (7–21) | <0.001 |
| ICU mortality         | 73 (52)      | 130 (35)    | 0.001$^c$ |

The results are expressed in number (%) for categorical variables and in median (IQR) for quantitative variables. Exposure to potential risk factors for VAP was taken into account until VAP occurrence, or until ICU discharge in patients with and without VAP, respectively. $^a$OR = 2.5 (1.7, 3.7); $^b$OR = 1.8 (1.02, 3.0); $^c$OR = 1.9 (1.3, 2.8)

VAP ventilator-associated pneumonia, CI confidence interval, ICU intensive care unit, OR odds ratio, ABG arterial blood gas, PaO$_2$ arterial oxygen tension, MV mechanical ventilation
reduced mucocilliary clearance in patients with hyperoxemia [25–28]. Previous studies reported high rates of VAP in patients with acute respiratory distress syndrome [18, 29]. Further, positive expiratory pressure was identified as a preventive measure against VAP [30], by reducing atelectasis in mechanically ventilated patients [31]. Excess oxygen administration could damage tissues through the production of reactive oxygen species (ROS). In excessive concentrations, ROS-mediated stress can lead to cellular necrosis and apoptosis [32]. Therefore, the process of oxidative stress might promote the development of multi-organ failure [33]. In addition, oxidative stress is responsible for direct damage to biological molecules (DNA oxidation, proteins, lipids and carbohydrates) and indirect injury through the release of cytotoxic products and mutagenic effects of lipid oxidation [16].

Recent animal studies support the role of hyperoxemia in the pathogenesis of VAP. Entezari and colleagues demonstrated that prolonged exposure to hyperoxia can compromise the ability of macrophages, an essential part of innate immunity, to phagocytose *P. aeruginosa* [34]. The same group of investigators reported that hyperoxia results in elevated concentrations of high mobility group box-1 (HMGB1), and mortality in mice infected with *P. aeruginosa* [17]. Treatment of these animals with a neutralizing anti-HMGB1 monoclonal antibody allowed a reduction in bacterial counts, injury, and numbers of neutrophils in the lungs, and an increase in leucocyte phagocytic activity compared with control animals. Another recent animal study suggests that hyperoxia increases mortality in mice with *A. baumannii* pneumonia, and that procysteine improves survival by increasing the phagocytic activity of alveolar macrophages [35].

The incidence of multidrug resistant bacteria was relatively high in patients with VAP. This could be explained by the high percentage of patients with late-onset VAP, prior antibiotic treatment, or COPD, and the high percentage of late-onset VAP.

### Table 3 Microorganisms isolated in patients with ventilator-associated pneumonia

| Microorganisms                        | Number (%) |
|---------------------------------------|------------|
| Gram-negative bacilli                 | 116 (82)   |
| *Pseudomonas aeruginosa*              | 48 (34)    |
| *Escherichia Coli*                    | 14 (10)    |
| *Acinetobacter baumannii*             | 13 (9)     |
| Enterobacter sp.                      | 13 (9)     |
| Klebsiella sp.                        | 8 (5)      |
| *Proteus mirabilis*                   | 6 (4)      |
| *Serratia sp.*                        | 5 (3.5)    |
| *Stenotrophomonas maltophilia*        | 4 (2.8)    |
| Others                                | 5 (3.5)    |
| Gram-positive cocci                   | 33 (23)    |
| Methicillin-resistant *S. aureus*     | 11 (7.8)   |
| *Staphylococcus epidermidis*          | 7 (5)      |
| Methicillin-sensitive *S. aureus*     | 5 (3.5)    |
| Enterococcus sp.                      | 5 (3.5)    |
| *Streptococcus pneumoniae*            | 5 (3.3)    |
severity of illness at ICU admission. All these factors were previously identified as independent risk factors for multidrug resistant bacteria [36–39].

Our study has several limitations. First, it was a retrospective study performed in a single center. Therefore, our results could not be generalized and further prospective multicenter studies are needed to confirm these findings. However, all data, except those related to hyperoxemia, were prospectively collected. Second, the cutoff used for hyperoxemia (>120 mmHg) was selected based on the current literature [12, 40, 41]. For example, normal PaO2 is defined by the British Thoracic Society as between 90 and 110 mmHg for patients under 70 years of age and according to the sea level [42]. However, other studies used a different cutoff (i.e., to PaO2 ≥ 300 mmHg) to define hyperoxemia [8, 43, 44]. Because a day with at least one PaO2 value >120 mmHg was considered as a day with hyperoxemia, our definition of hyperoxemia might have over-estimated the time period of hyperoxemia. Continuous control of pulse oximetry could be more appropriate to accurately determine time spent with hyperoxemia. Third, no information was collected on PaO2, FiO2, or positive end-expiratory (PEEP) values. Some risk factors, such as head-of-bed elevation and under-inflation of tracheal cuff, were not evaluated in this study. Finally, because of the retrospective design, exploratory investigations, such as measurement of ROS or evaluation of immune function could not be performed.

Two recent small studies [2, 5], one before-after and one randomized controlled study, suggested that a conservative oxygenation strategy might be safe in intubated critically ill patients, compared with a liberal strategy. However, none of these studies evaluated the impact of oxygenation strategy on VAP incidence. Further large randomized controlled trials are required to confirm these data, and to determine the impact of oxygenation strategy on VAP incidence.

Table 5 Risk factors for ventilator-associated pneumonia by Cox proportional hazards model

| Variable | Univariate analysis | Multivariate analysis (model 1) | Multivariate analysis (model 2) |
|----------|---------------------|-------------------------------|-------------------------------|
|          | HR (95% CI)         | P                             | HR (95% CI)           | P                             | HR (95% CI)           | P                             |
| At ICU admission |                    |                               |                               |                               |                               |                               |
| LOD score | 1.04 (1.01, 1.09)   | 0.044                         | -                             | 0.922                         | -                             | 0.138                         |
| Transfer from other wards | 0.65 (0.45, 0.93)   | 0.018                         | -                             | 0.356                         | -                             | 0.952                         |
| Prior antibiotic treatment | 0.67 (0.48, 0.94)   | 0.021                         | -                             | 0.483                         | -                             | 0.184                         |
| Neurologic failure | 1.82 (1.07, 3.09)   | 0.027                         | -                             | 0.111                         | -                             | 0.197                         |
| Poisioning | 3.24 (1.9, 5.51)    | <0.001                        | 2.49 (1.31, 4.72)             | 0.005                         | 2.16 (1.14, 4.09)             | 0.018                         |
| COPD | 0.55 (0.37, 0.89)   | 0.003                         | -                             | 0.063                         | -                             | 0.065                         |
| McCabe score >2 | 0.76 (0.59, 0.99)   | 0.042                         | -                             | 0.169                         | -                             | 0.726                         |
| PaO2 > 120 mmHg | 1.58 (1.11, 2.25)   | 0.011                         | NA                            | NA                            | 1.68 (1.16, 2.42)             | 0.006                         |
| During ICU stay |                    |                               |                               |                               |                               |                               |
| Percentage of days with PaO2 > 120 mmHg | 5.67 (3.15, 10.20) | <0.001                        | 6.23 (3.26, 11.9)            | <0.001                        | NA                            | NA                            |

HR hazard ratio, LOD logistic organ dysfunction, COPD chronic obstructive pulmonary disease, NA not applicable. P > 0.1 by univariate analysis for: age, male gender, simplified acute physiology score II, diabetes, cardiac failure, cirrhosis, chronic dialysis, immunosuppression, all causes of ICU admission except neurologic failure, stress ulcer prophylaxis, tracheostomy, red blood cell transfusion, sedation, and neuromuscular-blocking agent use.
Conclusion
Our results suggest a link between hyperoxemia and VAP. However, further large prospective studies are required to confirm these findings and to evaluate the impact of a conservative oxygen strategy vs a conventional strategy, on the incidence of VAP.

Key messages
- Hyperoxemia is independently associated with ventilator-associated pneumonia
- This association could be explained by the consequences of hyperoxemia, including acute lung injury, atelectasis, and reduced bacterial clearance
- Further large multicenter studies are required to confirm our results

Abbreviations
ARDS, acute respiratory distress syndrome; cfu, colony-forming units; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FiO2, inspired oxygen fraction; HALI, hyperoxic acute lung injury; ICU, intensive care unit; LOD, logistic organ dysfunction; MDR, multidrug resistant; OR, odds ratio; PaO2, arterial oxygen tension; ROS, reactive oxygen species; SAPS, simplified acute physiology score; VAP, ventilator-associated pneumonia

Authors’ contributions
SN, SS, KJ, and FW designed the study. SS, KJ, GL, and EJ collected the data. SS, KJ, and SN wrote the manuscript. All authors made substantial contributions. All authors read and approved the final version of the manuscript.

Competing interests
SN is involved with Bayer, Basilea, and Medtrocic (advisory board, and lecture); all other authors have no competing interests.

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