Serial C1 Inhibitor Levels in Patients with Ventilator-Associated Pneumonia: A Prospective Observational Study

Gurhan TASKIN, Ali SELCUK, Serhat UYSAL

ABSTRACT

Objective: C1-inhibitor (C1-INH), an acute-phase protein, regulates the activation of the complement cascade and acts as a down-regulator of the inflammatory process. In experimental models, it was shown that pneumonia with mechanical ventilation is associated with an increase of complement activation in the lungs. The primary aim of this study was to evaluate the serial changes of C1-INH levels in patients with ventilator-associated pneumonia (VAP).

Methods: Twelve patients were included in this prospective and observational study conducted between June 2018 and February 2019. Blood samples for C1-INH levels were obtained at the time of VAP diagnosis and on the 2nd, 4th, and 6th days following diagnosis (total of 48 samplings). At the time of C1-INH sampling, patients were screened for clinical pulmonary infection score, arterial blood gas analysis, mechanical ventilation parameters, complete blood count, C-reactive protein, procalcitonin levels, and other routine laboratory tests.

Results: No differences were found between surviving (n=7) and non-surviving (n=5) patients in terms of C1-INH levels at any measurement time (days 0, 2, 4 and 6) (p=0.982, p=0.677, p=0.790, p=0.930, respectively). VAP patients with septic shock had higher C1-INH levels than patients without shock, on the days following the diagnosis. C1-INH levels significantly correlated with concurrently measured white blood cell (R²=0.095, p=0.030), lactate (R²=0.109, p=0.012), procalcitonin (R²=0.120, p=0.009), alanine aminotransferase (R²=0.179, p=0.002) levels, and PaO₂ / FiO₂ ratio (R²=0.091, p=0.022).

Conclusion: Serial monitoring of C1-INH levels may aid in prediction of prognosis in the early phase of VAP patients, especially those accompanied by septic shock.

Keywords: C1 inhibitor, ventilator-associated pneumonia, sepsis, septic shock, prognosis

Introduction

To date, some laboratory and clinical parameters have been studied as predictors of prognosis and indicators of treatment response in patients with ventilator-associated pneumonia (VAP) (1-4). But, the prognostic value of these parameters is still controversial. In order to predict the prognosis of VAP, biological markers that can be used, especially in the early stage of the disease, are still needed.

C1-inhibitor (C1-INH), an acute-phase protein, regulates the activation of the complement cascade by inhibiting the classical and lectin pathway, and acts as a down-regulator of the inflammatory process (5, 6). As the synthesis of C1-INH fails to meet the demand relatively during inflammation, complement activation may progress to an excessive response (7, 8). Therefore, increased complement activation in the lung may also cause additional lung damage in patients with VAP. To date, C1-INH has not been evaluated as a prognostic biomarker during a culture-proven VAP episode.

The main purpose of this prospective study was to evaluate the serial change of C1-INH levels in VAP prognosis.

Materials and Methods

Ethics approval and informed volunteer consent

This single-center, prospective and observational study was conducted in a 10-bed adult intensive care unit (ICU) of Trabzon Kanuni Training and Research Hospital, from June 2018 to February 2019. The study was conducted in accordance
with the Declaration of Helsinki, and ethical approval was obtained from the local Ethics Committee of Clinical Trials (09 May 2018, Approval No.: 2018-20). The legal representatives of patients deemed eligible to be included in the study, or first-degree relatives in the case of the absence of a legal representative, were fully informed about the study. Those who agreed to the patient’s participation completed the informed consent form before the patient was enrolled in the study.

**Diagnosis of VAP**

VAP refers to pneumonia that develops at least 2 days after endotracheal intubation (9, 10). In these patients, the following criteria were used for diagnosis: VAP was regarded as possible if new or progressive radiographic lung infiltrates with at least two of the three following features: fever ≥ 38°C or hypothermia <36°C, leukocytes ≥12,000/mm$^3$ or ≤4,000/mm$^3$, or new/increased purulent endotracheal secretions (>25 neutrophils and <10 squamous epithelial cells [x100]) (9, 10). Quantitative culture of deep endotracheal aspirate results with ≥10$^6$ colony forming units (CFU)/mL was used to confirm VAP diagnosis (10). Patients diagnosed with VAP in the first 4 days of mechanical ventilation (MV) were defined as early-onset VAP, and those diagnosed with VAP on the 5$^{th}$ day or later were defined as late-onset VAP (9, 10).

**Study design and data collection**

Patients under 18 years of age, patients with known hepatic disease or transaminase levels ≥3-fold higher than normal, patients with hereditary angioedema, patients with hypocomplementemia, and pregnant patients were excluded from the study. Two milliliters of venous blood samples were obtained from the included patients at the time of VAP diagnosis (day 0) and on the 2$^{nd}$, 4$^{th}$, and 6$^{th}$ days after diagnosis. After centrifugation at 1500 rpm for 15 minutes, serum was separated and stored at –20°C until the C1-INH level was studied. Quantitative levels of serum C1-INH were studied by a nephelometric method in Siemens BN Prospeck (Siemens Healthcare Diagnostics, Erlangen, Germany). At the same time as blood sampling for C1-INH measurement (days 0, 2, 4, and 6), complete blood count (CBC), C reactive protein (CRP), procalcitonin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine, erythrocyte sedimentation rate (ESR), arterial blood gas analysis (pH, lactate, partial arterial oxygen pressure [PaO$_2$]), MV parameters (fraction of inspired oxygen [FiO$_2$]), positive end-expiratory pressure [PEEP]), and clinical pulmonary infection score (CPIS) were recorded prospectively. Each patient’s age, sex, primary diagnosis at ICU admission, comorbid diseases, deep endotracheal aspirate culture results, length of ICU stay before VAP, duration of MV before VAP, mortality at 28$^{th}$ day following VAP diagnosis, and the date of death were recorded prospectively. Acute Physiology and Chronic Health Assessment II (APACHE II) scores calculated within the first 24 hours after ICU admission were recorded. The presence of sepsis and septic shock was investigated using the Sepsis-3 definitions during the study period (11). Bacteria found to be resistant to at least 1 antibiotic from 3 different antibiotic groups in a susceptibility test of deep endotracheal aspirate culture were identified as multidrug-resistant (MDR) bacteria (12).

**Statistical analysis**

The mean (standard deviation) was used to represent parametric continuous variables, and the median (minimum–maximum) was used to represent nonparametric variables. Kolmogorov–Smirnov test, skewness and kurtosis coefficients, and histogram graphs were used to differentiate parametric and nonparametric variables from continuous data of the patients. Ante-study analysis to reach 70% power calculated that at least 10 samples were needed; post-study power analysis was not applied. The Student’s t-test (independent t-test) was used for parametric variables and Mann–Whitney U-test was used for nonparametric variables. We performed simple linear regression analysis to assess correlations. $p < 0.05$ was considered statistically significant. The data analysis was done using Statistical Package for Social Sciences (SPSS) version 15.

**Results**

Between June 2018 and February 2019, a total of 12 VAP patients, 7 of whom were women, were included in the study. The mean age of the included patients was 73.6 ± 14.6 years. The median APACHE II score of the patients was 26 (min. 17–max. 35). Comorbidities observed were cerebrovascular disease (CVD) in 6 patients (50%), non-hematologic malignancy in 4 (33.3%), chronic obstructive pulmonary disease (COPD) in 4 (33.3%), diabetes mellitus (DM) in 3 (25%), congestive heart failure (CHF) in 3 (25%), and chronic renal failure (CRF) in 2 (16.7%). The median length of ICU stay before VAP was 15.5 days (min. 6–max. 65) and the median duration of MV before VAP was 10 days (min. 6–max. 51).

All included patients (100%) had late-onset VAP. Gram-negative bacilli (GNB) were dominant among the microorganisms found to be the causative pathogen. In seven patients (58.3%), the causative microorganism of VAP was MDR bacterium. The demographic, microbiologic, and clinical characteristics of VAP patients are shown in Table 1.

The 28-day mortality was seen in 5 patients (41.6%). No difference was found between surviving and non-surviving patients, in terms of C1-INH levels at any measurement time (days 0, 2, 4, and 6) ($p = 0.982$, $p = 0.677$, $p = 0.790$, $p = 0.930$, respectively) (Table 2). The curves of the serial values of C1-INH for all patients (survivors and non-survivors) showed at Figure 1. In the study period, all patients (100%) had sepsis, and 4 (33.3%) of them had septic shock concurrent with VAP. Patients with septic shock had higher C1-INH levels than those with not, especially on days after diagnosis (Figure 2). However, the difference was not statistically significant (days 0, 2, 4, and 6) ($p = 0.864$, $p = 0.798$, $p = 0.396$, $p = 0.734$, respectively). Three (75%) of VAP patients with concurrent septic shock died.

No statistically significant difference was found between the surviving and non-surviving patients with respect to their age, sex, hospital stay before ICU admission, ICU stay and MV days before diagnosis, and comorbidities.

The correlation analysis between clinical parameters, laboratory findings and concurrently measured C1-INH levels in VAP
Table 1. Demographic, microbiologic and clinical characteristics of patients.

| Patient No. | Age (years) | Sex | APACHE II score | Diagnosis at ICU admission | Comorbidities | Length of ICU stay before VAP (days) | Length of MV before VAP (days) | Microorganisms identified as VAP causative pathogens | 28-day mortality |
|-------------|-------------|-----|-----------------|-----------------------------|---------------|------------------------------------|-------------------------------|------------------------------------------------|-----------------|
| 1           | 89          | F   | 33              | Sepsis, AKI                 | None          | 29                                 | 9                             | Acinetobacter iwoffii                        | Survive         |
| 2           | 76          | F   | 29              | Sepsis                      | DM, CVD       | 15                                 | 6                             | Escherichia coli                              | Survive         |
|             |             |     |                 |                              | Malignancy (Sarcoma) | 34                                 | 34                            | Pseudomonas aeruginosa                        | Survive         |
| 3           | 35          | M   | 29              | Sepsis, pneumonia           | CVD, COPD, Malignancy (Lung Cancer) | 7                   | 7                             | Klebsiella pneumoniae                        | Dead            |
|             |             |     |                 |                              |                |                                    |                               | Acinetobacter baumannii                      |                |
| 4           | 82          | M   | 24              | Pneumonia                   | CHF, COPD, Malignancy (Lung Cancer) | 9                   | 9                             | Pseudomonas aeruginosa                        | Survive         |
| 5           | 70          | M   | 35              | Cardiac arrest              | CHF, COPD, Malignancy (Lung Cancer) | 31                 | 31                            | Acinetobacter baumannii                      | Survive         |
| 6           | 64          | F   | 31              | Stroke                      | DM, COPD      | 65                                 | 15                            | Pseudomonas aeruginosa                        | Survive         |
| 7           | 84          | F   | 22              | Intracerebral hemorrhage    | HT, CVD       | 16                                 | 16                            | Pseudomonas aeruginosa                        | Dead            |
| 8           | 76          | M   | 20              | Sepsis, pneumonia, AKI      | CHF, malignancy (prostate carcinoma) | 51                 | 51                            | Acinetobacter baumannii                      | Dead            |
| 9           | 81          | F   | 23              | Acute pulmonary edema       | CHF, DM, CVD  | 6                                 | 6                             | Staphylococcus aureus                         | Survive         |
| 10          | 65          | M   | 17              | Pneumonia                   | COPD          | 11                                 | 11                            | Stenotrophomonas maltophilia                 | Survive         |
| 11          | 73          | F   | 28              | Sepsis, Pneumonia           | CRF, CVD      | 14                                 | 14                            | Pseudomonas aeruginosa                        | Survive         |
| 12          | 88          | F   | 19              | Pneumonia, AKI              | CRF, HT       | 16                                 | 9                             | Delftia acidovorans                          | Dead            |

VAP, ventilator-associated pneumonia; APACHE II, Acute Physiology and Chronic Health Evaluation II; F, female; M, male; ICU, intensive care unit; MV, mechanical ventilation; AKI, acute kidney injury; DM, diabetes mellitus; CVD, cerebrovascular disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; HT, hypertension; CRF, chronic renal failure.
patients is shown in Table 3. Despite $R^2$ values of correlations were not high, significant correlations were found between the concurrently measured C1-INH level and the levels of white blood cell (WBC) ($R^2=0.095$, $p=0.030$), lactate ($R^2=0.109$, $p=0.012$), procalcitonin ($R^2=0.120$, $p=0.009$), ALT ($R^2=0.179$, $p=0.002$), and PaO$_2$/FiO$_2$ ratio ($R^2=0.091$, $p=0.022$). A total of sixteen results of ESR measurements were excluded from the analysis due to the fact that they were obviously incorrect due to calibration problems occurring on different machines.

Discussion

In this study, it was shown that the serial change of C1-INH levels did not differ between survivor and non-survivor groups in VAP patients. In our study, patients with septic shock had higher C1-INH trends in days following the diagnosis than with not. Furthermore, C1-INH levels had correlations with still in use and noteworthy prognostic parameters such as levels of procalcitonin, lactate and PaO$_2$/FiO$_2$ ratio. To our knowledge, this is the first study reporting prognostic evaluation of C1-INH levels in patients with VAP. In addition, serial monitoring of C1-INH levels was performed for the first time in these patients. In animal models, it was shown that MV with pneumonia is associated with an

---

**Table 2.** Comparison of serial changes of C1-inhibitor levels between survivors and non-survivors in ventilator-associated pneumonia patients.

| C1-INH levels | Survivors (n=7 (58.3%)) | Non-survivors (n=5 (41.7%)) | p value |
|---------------|--------------------------|-----------------------------|---------|
| Day 0, μg/mL  | 417.1 ± 94.1             | 416.0 ± 62.6                | 0.982   |
| Day 2, μg/mL  | 400.0 ± 72.1             | 418.0 ± 71.2                | 0.677   |
| Day 4, μg/mL  | 417.1 ± 61.0             | 406.0 ± 80.8                | 0.790   |
| Day 6, μg/mL  | 415.7 ± 63.9             | 420.0 ± 102.7               | 0.930   |

C1-INH, C1 inhibitor.

**Table 3.** Correlation analysis between clinical and laboratory parameters and C1-inhibitor levels in ventilator-associated pneumonia patients.

| Variables          | Adjusted $R^2$ (square) | Standardized Coefficient | 95% Confidence interval for Beta | p value |
|--------------------|--------------------------|--------------------------|---------------------------------|---------|
| WBC, /mm$^3$       | 0.095                    | 0.344                    | 5.83x10$^{-7}$ to 106x10$^{-7}$ | .030*   |
| Lactate, mmol/L    | 0.109                    | 0.358                    | 5x10$^{-3}$ to 38x10$^{-3}$    | .012*   |
| Procalcitonin, ng/mL | 0.120                   | 0.372                    | 4.9x10$^{-4}$ to 32.76x10$^{-4}$ | .009*   |
| ALT, U/L           | 0.179                    | -0.443                   | -16x10$^{-4}$ to -4x10$^{-4}$  | .002*   |
| PaO$_2$/FiO$_2$ ratio | 0.091                   | -0.333                   | -63x10$^{-4}$ to -5x10$^{-4}$  | .022*   |
| CRP, mg/L          | -                        | -                        | -                               | .223    |
| ESR, mm/hr$^4$     | -                        | -                        | -                               | .392    |
| Albumin, g/dL      | -                        | -                        | -                               | .459    |
| pH                 | -                        | -                        | -                               | .693    |
| PEEP, cmH$_2$O     | -                        | -                        | -                               | .936    |
| AST, U/L           | -                        | -                        | -                               | .852    |
| Creatinine, mg/dL  | -                        | -                        | -                               | .688    |
| BUN, mg/dL         | -                        | -                        | -                               | .628    |
| APACHE II score    | -                        | -                        | -                               | .603    |
| CPIS               | -                        | -                        | -                               | .275    |

C1-INH, C1 inhibitor; WBC, white blood cell; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PEEP, positive end-expiratory pressure; AST, aspartate aminotransferase; PaO$_2$, partial pressure of arterial oxygen; FiO$_2$, fraction of inspired oxygen; BUN, blood urea nitrogen; APACHE II, acute physiology and chronic health evaluation II; VAP, ventilator-associated pneumonia; CPIS, clinic pulmonary infection score.

* A total of sixteen results of ESR measurements were excluded from the analysis due to the fact that they were obviously incorrect due to calibration problems occurring on different machines.

* $= p<0.05$
increase of the classical and/or lectin complement activation in the lungs (13). Furthermore, in human studies, excessive activation of complement has been shown to related with progress in lung injury (14-16). So that, we hypothesized that serial monitoring of C1-INH levels may have a prognostic significance in VAP patients. Although, no statistically significant difference was found between surviving and non-surviving VAP patients, our study indicates some considerable findings about possible prognostic role of C1-INH levels in VAP patients. In our study, it was shown that increased complement activation via enhanced inflammation could cause remarkable changes in the C1-INH levels, especially in cases accompanied by septic shock. Activation of the complement system as part of the inflammatory response in patients with sepsis is a known mechanism (17). The complement system regulator C1-INH also increases in order to prevent excessive activation (18). In many experimental and animal studies, the treatment of C1-INH concentrates on sepsis has been reported to decrease vascular permeability, improve microcirculation, and even increase survival (19-21). On the other hand, Tapisiz et al. reported that functional C1-INH levels did not differ between septic newborns and controls. Additionally, they found no difference between newborns with sepsis and severe sepsis and septic shock in terms of C1-INH levels (22). In our study, although not shown statistical significance, shock patients’ C1-INH levels were higher than sepsis patients (430.0 ± 67.8 vs. 396.3 ± 71.3, 442.5 ± 66.0 vs. 397.5 ± 65.8, 432.5 ± 88.4 vs. 410.0 ± 77.4, on the 2nd, 4th and 6th days after diagnosis, respectively). That might be due to small sample size of our study, larger sample calculations would give more convincing results. About half of patients with VAP are accompanied by septic shock and septic shock is the one of the significant independent risk factors for mortality in VAP patients (23). Additionally, as confirming this relationship, in our study, a significant correlation was found between C1-INH and lactate levels, whose prognostic value for septic shock is well-known. Lactate is an important metabolic marker that shows tissue hypoperfusion and deterioration in microcirculation, and indicates morbidity and mortality in most of critically ill patients (24). Since high lactate levels are thought to reflect the presence and severity of organ dysfunction, it is considered as a sign of circulatory impairment and shock (24-26). The positive correlation between simultaneously measured C1-INH and lactate levels revealed in our study, suggests that C1-INH levels may be useful in predicting septic shock severity and consequently mortality in VAP patients.

To date, many studies have evaluated the potential of infection biomarker procalcitonin to improve the diagnostic efficacy of patients with sepsis or pneumonia and its impact on decisions regarding antibiotic therapy (27-30). Also, it has been showed to be associated with severity of pneumonia (31). Additionally, procalcitonin is thought to have substantial prognostic value in VAP patients. Previously, Luyt et al., evaluating procalcitonin kinetics in patients with VAP, reported that a procalcitonin value greater than 0.5 ng/mL on day 7 of diagnosis was the strongest independent prognostic marker that could predict death and VAP recurrence (4). In another study, Seligman et al. reported that procalcitonin levels on the 4th day of diagnosis had the highest positive and negative predictive value of VAP mortality (32). In addition, Hillas et al. reported that changes in procalcitonin levels were significantly correlated in predicting survival in VAP patients (33). In the current study, C1-INH levels shown to be correlated with two important infectious inflammatory markers—procalcitonin and WBC.

Crude mortality in critically ill patients with VAP has been reported as ranging from 25% to 70% (34-36). Due to an increase in the frequency of MDR pathogens related nosocomial infections, late-onset VAP has higher mortality rates than early-onset VAP (37). In this study, the 28-day mortality rate was 41.6% in critically ill patients with late-onset VAP, and more than half of them (58%) had MDR pathogen caused VAP. Therefore, it can be stated that the mortality rate observed in our study is consistent with the literature data.

Another noteworthy finding of this study is the significant negative correlation between C1-INH level and PaO2/FiO2 ratio, which are thought to be an objective indicator of oxygenation. The PaO2/FiO2 ratio in patients with VAP has been shown to be an important clinical parameter, in terms of clinical outcomes, in some studies (3, 4). A retrospective study by Esperatti et al. including 335 patients, reported that lack of improvement in PaO2/FiO2 ratios within 5 days following the diagnosis of VAP is a strong indicator of mortality (38). An increase in C1-INH levels may indicate an augmentation in the activation of the complement system and thus an exacerbation of inflammation and deterioration in oxygenation. We think these findings suggest that C1-INH levels have a prognostic role in VAP patients.

Although in vivo and in vitro studies have shown synthesis in many different cell types, hepatocytes are the major source for C1-INH synthesis (39). ALT is a proven biomarker of hepatocellular injury and is also used for follow-up (40). In our study, a negative correlation was found between C1-INH and ALT levels. This result may suggest that C1-INH levels have a linear relationship with hepatocyte functions.

We acknowledge that certain limitations of this study should be underlined. Firstly, our study population is relatively small; these results need to be confirmed in a larger study group. Secondly, in our study, included patients had relatively high APACHE II scores, prolonged ICU stay, and long-term MV requirement than previous studies in this field, and all patients had sepsis during VAP. Therefore, there may have been other factors we could not evaluate and that may have influenced the results.

Conclusions
In this study, it was shown that the serial change of C1-INH did not differ between survivor and non-survivor groups. But our study provides useful information about VAP prognosis. In subgroup analysis, patients with septic shock had higher C1-INH trends in days following the diagnosis than with not. Furthermore, C1-INH levels had significant correlations with still in use and noteworthy prognostic parameters such as levels of procalcitonin, lactate and PaO2/FiO2 ratio. We think that, further studies of the serial change of C1-INH levels in VAP patients with larger populations may lead to new topics in the prediction of prognosis and assessment of treatment response.

Acknowledgements
We are grateful to the patient relatives who accepted their patient to participate in this study.
REFERENCES

1. Kiae BA, Ghiasi F, Moradi D. Preactinin and C-reactive protein as markers in response to antibiotic treatment in ventilator associated pneumonia in intensive care unit-hospitalized patients. Adv Biomed Res 2015;4:240. [CrossRef]

2. Wongsurakiat P, Tulamakitt S. Clinical infection score and a spot serum procalcitonin level to guide discontinuation of antibiotics in ventilator-associated pneumonia: a study in a single institution with high prevalence of nonfermentative gram-negative bacilli infection. Ther Adv Respir Dis 2018;12:175346618760134. [CrossRef]

3. Luna CM, Blanzaco D, Niederman MS, et al. Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med 2003;31:676–82. [CrossRef]

4. Luyt CE, Guérin V, Combès A, et al. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. Am J Respir Crit Care Med 2005;171:48–53. [CrossRef]

5. Cai S, Dole VS, Bergmeier W, et al. A direct role for C1 inhibitor in regulation of leukocyte adhesion. J Immunol 2005;174:6462–6. [CrossRef]

6. Reinholt L, Hartmann V, Döblo J, et al. C1 inhibitor serpin domain structure reveals the likely mechanism of heparin potentiation and conformational disease. J Biol Chem 2007;282:21100–9. [CrossRef]

7. Igonin AA, Protsenko DN, Galstasyan GM, et al. C1-esterase inhibitor infusion increases survival rates for patients with sepsis*. Crit Care Med 2012;40:770–7. [CrossRef]

8. Nuijens JH, Abbink JJ, Wachtfogel YT, et al. Plasma elastase alpha 1-antitrypsin and lactoferrin in sepsis: Evidence for neutrophils as mediators in fatal sepsis. J Lab Clin Med 1992;119:159–68. [CrossRef]

9. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416. [CrossRef]

10. Kald AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia:2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:861–111. [CrossRef]

11. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:810–10. [CrossRef]

12. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81. [CrossRef]

13. de Beer FM, Aslam H, Hoekstra J, et al. Plasma-derived human C1-esterase inhibitor does not prevent mechanical ventilation-induced pulmonary complement activation in a rat model of Streptococcus pneumoniae pneumonia. Cell Biochem Biophys 2014;70:795–803. [CrossRef]

14. Donnelly TJ, Meade P, Jagels M, et al. Cytokine, complement, and endotoxin profiles associated with the development of the adult respiratory distress syndrome after severe injury. Crit Care Med 1994;22:768–76. [CrossRef]

15. Meade P, Shoemaker WC, Donnelly TJ, et al. Temporal patterns of hemodynamics, oxygen transport, cytokine activity, and complement activity in the development of adult respiratory distress syndrome after severe injury. J Trauma 1994;36:651–7. [CrossRef]

16. Zilow G, Joka T, Obertacke U. Generation of anaphylatoxin C3a in plasma and bronchoalveolar lavage fluid in trauma patients at risk for the adult respiratory distress syndrome. Crit Care Med 1992;20:468–73. [CrossRef]

17. Bellinger D, Mardini B, Geng G. Cogulation and complement system in critically ill patients. Clin Hemorheol Microcirc 2015;61:185–93. [CrossRef]

18. Zeerleder S. C1-inhibitor: more than a serine protease inhibitor. Semin Thromb Hemost 2009;37:362–74. [CrossRef]

19. Schmidt W, Stenzel K, Gebhardt MM, et al. C1-esterase inhibitor and its effects on endotoxin-induced leukocyte adherence and plasma extravasation in postcapillary venules. Surgery 1999;125:280–7. [CrossRef]

20. Liu D, Zhang D, Scadidi J, et al. C1 inhibitor prevents Gram-negative bacterial lipopolysaccharide-induced vascular permeability. Blood 2005;105:2350–5. [CrossRef]

21. Liu D, Lu F, Qin G, et al. C1 inhibitor-mediated protection from sepsis. J Immunol 2007;179:3966–72. [CrossRef]

22. Tapisiz A, Ergenekon E, Oktay M, et al. C1 inhibitor level on neonatal sepsis and its relations with clinical findings. J Paediatr Child Health 2010;46:121–4. [CrossRef]

23. Valles J, Mesalles E, Mariscal D, et al. A 7-year study of severe hospital-acquired pneumonia requiring ICU admission. Intensive Care Med 2003;29:1981–8. [CrossRef]

24. Bakker J, Postelnicu R, Mukherjee V. Lactate: Where Are We Now? Crit Care Clin 2020;36:115–24. [CrossRef]

25. Bakker J, Gris P, Coiffins M, et al. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg 1996;171:221–6. [CrossRef]

26. Jansen TC, van Bommel J, Woodward R, et al. Association between blood lactate levels, Sequential Organ Failure Assessment subscores, and 28-day mortality during early and late intensive care unit stay: a retrospective observational study. Crit Care Med 2009;37:2369–74. [CrossRef]

27. Dusemund F, Bucher B, Meyer S, et al. Influence of procalcitonin on decision to start antibiotic treatment in patients with a lower respiratory tract infection: insight from the observational multicentric ProREAL surveillance. Eur J Clin Microbiol Infect Dis 2013;32:51–60. [CrossRef]

28. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study*. Crit Care Med 2006;34:44–53. [CrossRef]
29. Balk RA, Kadri SS, Cao Z, et al. Effect of procalcitonin testing on healthcare utilization and costs in critically ill patients in the United States. Chest 2017;151:23–33. [CrossRef]

30. de Jong E, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819–27. [CrossRef]

31. Liu D, Su LX, Guan W, et al. Prognostic value of procalcitonin in pneumonia: A systematic review and meta-analysis. Respirology 2016;21:280–8. [CrossRef]

32. Seligman R, Seligman BGS, Teixeira PJZ. Comparing the accuracy of predictors of mortality in ventilator-associated pneumonia. J Bras Pneumol 2011;37:495–503. [CrossRef]

33. Hillas G, Vassilakopoulos T, Plantza P, et al. C-reactive protein and procalcitonin as predictors of survival and septic shock in ventilator-associated pneumonia. Eur Respir J 2010;35:805–11. [CrossRef]

34. Chastre J, Fagon JY. Ventilator-associated pneumonia. Am J Respir Crit Care Med 2002;165:867–903. [CrossRef]

35. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. Chest 2002;122:2115–21. [CrossRef]

36. Katherson SG, Naing L, Jaalam K, et al. Ventilator-associated nosocomial pneumonia in intensive care units in Malaysia. J Infect Dev Ctries 2009;3:704–10. [CrossRef]

37. Timsit JF, Esaied W, Neuville M, et al. Update on ventilator-associated pneumonia. F1000Res 2017;6:2061. [CrossRef]

38. Esperatti M, Ferrer M, Giunta V, et al. Validation of predictors of adverse outcomes in hospital-acquired pneumonia in the ICU. Crit Care Med 2013;41:2151–61. [CrossRef]

39. Prada AE, Zahedi K, Davis AE 3rd. Regulation of C1 inhibitor synthesis. Immunobiology 1998;199:199:377–88. [CrossRef]

40. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000;342:1266–71. [CrossRef]