Clinical pulmonary infection score and C-reactive protein in the prediction of early ventilator associated pneumonia

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Abstract  Introduction: The risk of ventilator-associated pneumonia (VAP) is highest early in the course of hospital stay. Most clinicians continue to rely on a clinical diagnosis of hospital-acquired pneumonia (HAP) because it is convenient. In an effort to improve the specificity of clinical diagnosis, the clinical pulmonary infection score (CPIS) was developed. Serum C-reactive protein (CRP) measurements in intensive care unit (ICU) patients enabled the early diagnosis of sepsis.

Aim of the work: The aim of this work was to evaluate the role of the clinical pulmonary infection score and C-reactive protein in the prediction of early ventilator associated pneumonia.

Patients and methods: Eighty patients recently were intubated and mechanically ventilated with no manifestations of infection; no infiltrates on chest X-ray for 48 h after intubation and had normal serum CRP at the first day of intubation. All patients were admitted to the intensive care unit in the Chest Department, Alexandria University Hospital and enrolled after obtaining informed consents. All patients were subjected to the following: full history taking, thorough clinical examination, laboratory investigations including total and differential white blood count, radiological evaluation, daily serum CRP assessment during the first 5 days of intubation and the calculation of CPIS at the onset of rising CRP.

Results: In this study, the age of all patients ranged from 34 years to 65 years with a mean age of 50.1 ± 8.7 years. There were 44 male patients representing (55%) and 36 female patients representing (45%) of the study population. Serum CRP ranged from 0.8 to 3 mg/l with a mean of 1.1 ± 0.4 mg/l on the first day of intubation and from 3.1 to 5 mg/l with a mean of 4.2 ± 0.4 mg/l on the second day of intubation for all patients. On the third day of intubation,
serum CRP ranged from 18 to 38 mg/l with a mean of $27.0 \pm 4.7$ mg/l in 11 patients while on the fourth day of intubation serum CRP ranged from 32 to 59 mg/l with a mean of $46.2 \pm 6.9$ mg/l in 12 patients. Lastly, serum CRP ranged from 50 to 66 mg/l with a mean of $60.7 \pm 2.6$ mg/l on the fifth day of intubation in 9 patients. Therefore, serum CRP increased in 32 patients. CPIS of the studied patients at the onset of rising serum CRP ranged from 7 to 10 in 24 patients. In the first 5 days of intubation, 32 patients out of 80 patients had high CRP, those were 40% of the study population and 24 patients of those 32 patients had high CPIS; those were 30% of the study population and 75% of patients had high CRP.

Conclusion: When the CPIS exceeded 6, there was an association with the presence of pneumonia which was confirmed by microbiological culture furthermore serum CRP is an easy, available and cheap test so daily serum CRP measurements to ICU patients enabled the early diagnosis of pneumonia and enhanced the value of the CPIS. Further studies of CPIS are needed with particular attention to how its variability might affect therapeutic choices.

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Introduction

Ventilator associated pneumonia (VAP) is an important form of hospital acquired pneumonia (HAP), specifically developing in a mechanically ventilated patient more than 48 h after tracheal intubation [1]. The overall or crude mortality associated with VAP ranges from 40% to 70% varying with underlying illness, the etiologic pathogen of lung infection, associated bacteremia, and the adequacy of the empiric antibiotic treatment [2–4]. However, the real impact of VAP is difficult to ascertain because risk factors for pneumonia such as underlying disease or the severity of illness also predispose patients to a greater mortality, and therefore these are potentially confounding variables. Therefore, whether patients die of or only with nosocomial pneumonia is probably one of the most difficult questions to answer [3].

Most clinicians continue to rely on a clinical diagnosis of HAP because it is convenient. The presence of pneumonia is defined by new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin. The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leucocytosis or leukopenia, and purulent secretions) represents the most accurate combination of criteria for starting empiric antibiotic therapy. Requiring all three clinical criteria is too insensitive and it will result in many patients with true pneumonia not receiving therapy [5].

In an effort to improve the specificity of clinical diagnosis, Pugin et al. developed the clinical pulmonary infection score (CPIS) [6]. In addition, it improved if a Gram stain of a deep respiratory tract culture was added to the evaluation (Table 1) [7]. When the CPIS exceeded 6, good correlation with the presence of pneumonia, as defined by quantitative cultures of bronchoscopic and non bronchoscopic BAL specimens, was found [8].

One prospective study evaluated 79 episodes of suspected VAP using the CPIS, and compared the findings with diagnosis established by BAL culture. A persistently low score < 6 for 3 days in patients with suspected nosocomial pneumonia makes the diagnosis unlikely and might guide the decision to stop treatment with antibiotics [6]. The original description of the CPIS required microbiologic data, and thus could not be used to screen for HAP. Singh et al. used a modified CPIS that did not rely on culture data to guide clinical management [9].

If a clinical strategy is used, reevaluation of the decision to use antibiotics based on serial clinical evaluations, by day 3 or sooner, is necessary, because patients who are improving will have signs of good clinical response by this time point [10]. Singh et al. have shown that some patients with a low clinical suspicion of VAP (CPIS of 6 or less) can have antibiotics safely discontinued after 3 days, if the subsequent course suggests that the probability of pneumonia is still low. This modified CPIS used by Singh et al. appears to be an objective measure to define patients who can receive a short duration of therapy [9].

C-reactive protein (CRP) is a plasma protein; an acute phase protein produced by the liver and adipocytes. It was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the C-polysaccharide of pneumococcus. Initially it was thought that CRP might be a pathogenic secretion, as it was elevated in people with a variety of illnesses, including carcinomas. Discovery of hepatic synthesis and secretion of CRP closed that debate. It is thought to bind to phosphocholine, thus initiating recognition and phagocytosis of damaged cells [11].

CRP is a member of the class of acute phase reactants as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6 which is produced by macrophages, endothelial cells and T-cells as well as adipocytes. CRP binds to phosphorylcholine on microbes. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages, which express a receptor for CRP. It is also believed to play an important role in innate immunity, as an early defense system against infections. The health care provider might use the CRP test to check for flare-ups of inflammatory diseases like rheumatoid arthritis, lupus, or vasculitis. The test might also be used to tell if anti-inflammatory medicine is working [12].

Aim of the work

The aim of this work was to evaluate the role of the clinical pulmonary infection score and C-reactive protein in the prediction of early ventilator associated pneumonia.
Materials and methods

Study population and subjects

Eighty patients recently were intubated and mechanically ventilated with no manifestations of infection; no infiltrates on chest X-ray for 48 h after intubation and had normal serum CRP at the first day of intubation. All patients were admitted to the intensive care unit in the Chest Department, Alexandria University Hospital and enrolled after obtaining informed consents.

Study measurements

All patients were subjected to the following:

- Full history taking including age, sex and history of other diseases.
- Thorough clinical examination including: general examination and local chest examination.
- Daily Laboratory investigations including total and differential white blood cells.
- Daily Radiological evaluation for new pulmonary infiltrates was carried out by:
  - Plain X-ray chest postero-anterior and lateral views.
  - Serum C-reactive protein (CRP) assessment daily during the first 5 days of intubation.
  - Calculation of the clinical pulmonary infection score (CPIS) at the onset of rising CRP.
  - Broncho-alveolar lavage (BAL) at the onset of rising CRP.

Statistical analysis

Statistical analysis will be performed with Sigma Stat 2.0 (Systat Software Inc., Point Richmond, Calif) and SPSS 14 (SPSS, Chicago, Ill) for Windows.

Results

In this study, eighty patients were mechanically ventilated with no manifestations of infection and had normal serum CRP at the first day of intubation. The age of all patients ranged from 34 to 65 years with the mean age of 50.1 ± 8.7 years. There were 44 male patients representing (55%) and 36 female patients representing (45%) of the study population. The duration of stay in the ICU ranged from 18 to 38 days with the mean duration of 27.1 ± 4.7 days. Serum CRP was measured for all patients. Serum CRP ranged from 0.8 to 3 mg/l with the mean of 1.1 ± 0.4 mg/l at the first day of intubation and from 3.1 to 5 mg/l with the mean of 4.2 ± 0.4 mg/l at the second day of intubation for all patients. At the third day of intubation, serum CRP ranged from 18 to 38 mg/l with the mean of 27.0 ± 4.7 mg/l in 11 patients while at the fourth day of intubation serum CRP ranged from 32 to 59 mg/l with the mean of 46.2 ± 6.9 mg/l in 12 patients. Lastly, serum CRP ranged from 50 to 66 mg/l with the mean of 60.7 ± 2.6 mg/l at the fifth day.

### Table 1

| Temperature (°C) | CPIS |
|------------------|------|
| 36.5 ≤ 38.4      | 0    |
| 38.4 ≤ 38.9      | 1    |
| < 36 or ≥ 39      | 2    |
| White blood count|      |
| ≥ 4000 ≤ 11,000  | 0    |
| < 4000 or > 11,000| 1    |
| Secretions       |      |
| ≤ small/day      | 0    |
| Moderate/large   | 1    |
| Purulent         | 2    |
| Chest radiograph |      |
| No infiltrate    | 0    |
| Diffuse/patchy infiltrate | 1 |
| Localized infiltrate | 2 |
| PaO2/FiO2 ratio  |      |
| > 240 without ARDS | 0 |
| < 240 without ARDS | 2 |
| Culture          |      |
| < 10,000 bacteria or no growth | 0 |
| > 10,000 bacteria | 1 |
| Positive Gram stain | 1 |

### Table 2

| Age (years) | 34–65 | 50.1 ± 8.7 |
| Sex         |      |
| Male        | 44(55%) |
| Female      | 36(45%) |
| Duration of Stay in ICU (days) | 18–38 | 27.1 ± 4.7 |
| CRP (mg/l)  |      |
| 1st day (in the 80 patients) | 0.8–3 |
| 2nd day (in the 80 patients) | 1.1 ± 0.4 |
| 3rd day (in 11 patients) | 3.1-5 |
| 4th day (in 12 patients) | 4.2 ± 0.4 |
| 5th day (in 9 patients) | 18–38 |
| PaO2/FiO2 ratio > 240 without ARDS | 27.0 ± 4.7 |
| < 240 without ARDS | 32–59 |
| Positive Gram stain | 46.2 ± 6.9 |
| Culture <10,000 bacteria or no growth | 0 |
| >10,000 bacteria | 2 |
| <10,000 bacteria | 3 |

### Table 3

| Temperature (°C) | 38–40 |
|------------------|-------|
| At onset of VAP (WBCs/mm³) | 39.04 ± 0.680 |
| Bronchoalveolar lavage (BAL) Gram stain (number of patients) | 12–23 |
| Gram negative | 17 |
| Gram positive | 7 |
| Secretions (number of patients) | 6 |
| ≤ Small/day | 4 |
| Moderate to large | 6 |
| Purulent | 14 |
| Chest radiograph (number of patients) | 5 |
| No infiltrate | 4 |
| Diffuse/patchy infiltrate | 6 |
| Localized infiltrate | 10 |
| PaO2/FiO2 ratio (number of patients) | 16 |
| < 240 without ARDS | 8 |
| ≥ 240 without ARDS | 7–10 |
| CPIS (in 24 patients) | 8.48 ± 1.031 |
of intubation in 9 patients (Table 2). Therefore, serum CRP increased in 32 patients.

Clinical Pulmonary Infection Score (CPIS) of the studied patients at the onset of rising CRP ranged from 7 to 10 (Table 3) in 24 patients.

At the first and second day of intubation, serum CRP was normal for all the eighty patients. At the third day of intubation serum CRP increased in 11 patients, 8 of them had high CPIS (ranged from 7 to 10) at the onset of rising serum CRP. At the fourth day of intubation serum CRP increased in 12 patients, 10 of them had high CPIS (ranged from 7 to 10) at the onset of rising serum CRP. At the fifth day of intubation serum CRP increased in 9 patients, 6 of them had high CPIS (ranged from 7 to 10) at the onset of rising serum CRP (Table 4).

Therefore in the first 5 days of intubation, 32 patients out of 80 patients had high serum CRP, those were 40% of the study population and 24 patients of those 32 patients had high CPIS; those were 30% of the study population and 75% of patients with high serum CRP.

Smith et al. [15] used CRP as a useful sensitive marker of bacterial infection in cases of pneumonia. There was marked elevation of serum level of CRP within a few hours of infection.

CRP test is considered as a general test, not a specific one. In other words, it can reveal that there is inflammation present

**Table 4** CRP and CPIS.

| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|-------|-------|-------|-------|-------|
| Positive CRP ($n = 32/80$) 40% of all patients | ($n = 0/80$) | ($n = 0/80$) | ($n = 11/80$) | ($n = 12/80$) | ($n = 9/80$) |
| High CPIS ($n = 24/32$) 75% of CRP +ve patients 30% of all patients | – | – | ($n = 8/11$) | ($n = 10/12$) | ($n = 6/9$) |

**Figure 1** Number of patients with positive CRP and high CPIS.

**Table 5** Bronchoalveolar lavage (BAL) of the studied patients.

| Bronchoalveolar lavage (BAL) (fungi) | Candida | Negative |
|-------------------------------------|---------|----------|
| 8                                   | 16       |

| Bronchoalveolar lavage (BAL) (microorganism) | Klebsiella pneumonia | MRSA | Pseudomonas aeruginosa | Streptococcus pneumoniae |
|---------------------------------------------|---------------------|------|-----------------------|------------------------|
| 7(29.17%)                                   | 4(16.67%)           | 10(41.66%) | 3(12.5%)             |

**Discussion**

The single greatest risk factor for VAP is related to the duration of mechanical ventilation. Early VAP occurs within the first 5 days of intubation. Late-onset VAP occurs after 5 days, is more commonly caused by multidrug resistant (MDR) pathogens, and carries higher morbidity and mortality [7,8]. The risk peaks at day 5 on the ventilator, plateaus after day 15, and then declines significantly, with the result that VAP is uncommon in patients on long-term mechanical ventilation [13]. The risk of VAP is highest early in the course of hospital stay, and is estimated to be three percent per day during the first five days of ventilation, two percent per day during days 5 to 10 of ventilation, and one percent per day after this [14].

In this study, all patients were assessed and they had normal serum CRP in the first and second day of intubation. Starting from the third to the fifth day of intubation, 32 patients out of 80 patients had high serum CRP, those were 40% of the study population and 24 patients of those 32 patients had high CPIS; those were 30% of the study population and 75% of patients with high serum CRP.

Smith et al. [15] used CRP as a useful sensitive marker of bacterial infection in cases of pneumonia. There was marked elevation of serum level of CRP within a few hours of infection.

CRP test is considered as a general test, not a specific one. In other words, it can reveal that there is inflammation present
in the body, but cannot tell you where it is. CRP levels rise in many conditions like urinary tract infection, bacterial meningitis, pelvic infection (PID), whole-body infection (sepsis), appendicitis, polymyalgia rheumatic, inflammatory bowel disease, temporal arteritis, rheumatoid arthritis, lupus, gout, Reiter’s syndrome, Crohn’s disease, acute pancreatitis, Hodgkin’s lymphoma, tuberculosis and burns. A special type of CRP test, the high-sensitivity CRP test (hs-CRP), may be done to evaluate the risk for having a sudden heart problem, such as a heart attack. However, the connection between high CRP levels and heart attack risk is not yet fully known [16].

Nonetheless, observations made in several studies suggested the usefulness of CRP to diagnose VAP. Povoa et al. [17] found that, for a threshold of 9.6 mg/l, CRP had 87% sensitivity and 88% specificity for VAP diagnosis. These same investigators also reported that daily CRP measurements in ICU patients enabled the early diagnosis of sepsis [18].

The investigators of numerous studies concluded that CRP contributes to diagnosing invasive bacterial infection, implying that it might have a role in the emergency department or ICU. However, CRP use for diagnostic purposes has yielded widely conflicting data. Some argue that because CRP is, by definition, a nonspecific indicator of inflammation, it cannot accurately differentiate among the many sources of potential tissue destruction [19–22].

In the present study, CPIS ranged from 7 to 10 in 24-patients from 32-patients at the onset of rising CRP, they represented (75%) of patients with high serum CRP and early microbiological evaluation of a deep respiratory tract culture was done at the onset of rising CRP. The most common organism was \textit{P. aeruginosa} followed by *Klebsiella pneumonia* then MRSA and \textit{S. pneumoniae} in the 24 patients with high CPIS.

Because there are other potential causes of fever, leukocytosis, and pulmonary infiltrates, clinical diagnostic criteria are overly sensitive in the diagnosis of VAP. So the CPIS combines clinical, radiographic, physiological (PaO2/FiO2), and microbiologic data into a single numerical result. In recent years, the CPIS has been used both for the early diagnosis of VAP and as a clinical indicator of the outcome of the infection [23].

Schurink et al. [24] found that ventilator-associated pneumonia was diagnosed in (69.6%) of patients. When using a CPIS > 5 as diagnostic cutoff, the sensitivity of the score was 83%. Although quantitative microbiological cultures of samples obtained by bronchoscopy are considered the most specific tool for diagnosing ventilator-associated pneumonia, this labor-intensive invasive technique is not widely used.

Alternative infectious sources, such as urinary tract, skin and soft-tissue infections, and device-related infections (i.e., central venous catheters) are common in hospitalized patients and should be ruled out before diagnosing VAP [25]. This is why in this study 25% of patients with high CRP levels had a CPIS of less than 6 and no evidence of VAP.

Chastre et al. [26] used the CPIS for the early diagnosis of pneumonia in patients at higher risk to have VAP. In a retrospective study involving 58 patients with severe brain injuries, Pelosi et al. [27] found the CPIS to increase from ICU entry to the day of VAP onset, providing 97% sensitivity and 100% specificity for the VAP diagnosis.

Papazian et al. [28] used the CPIS in a prospective post-mortem study of 38 patients who died after 72 h of mechanical ventilation; 18 of these patients had histologic evidence of pneumonia. The strength of this analysis was that histologic examination of tissue samples served as the gold standard for diagnosis. The authors’ findings indicated that, at the threshold of 6 points, the CPIS achieved a sensitivity of 72%, a specificity of 85%, and an overall accuracy of 79% for the presence of VAP; combining it with quantitative culture resulted in a slight increase in specificity (95%) at the expense of diminished sensitivity (67%).

One limitation of the earlier studies attempting to validate the CPIS is that none examined the CPIS in selected cohorts of patients for whom the diagnosis of VAP may have been particularly challenging. For example, in patients with acute lung injury, it is often difficult to determine whether a radiograph shows a new or changing infiltrate. Unfortunately, no studies have specifically addressed the CPIS in persons with acute respiratory distress syndrome, despite the fact that these persons are at exceedingly high risk of VAP. Moreover, few studies have explored the CPIS in non-medical populations. This is of particular concern because surgical patients account for more than one-half of cases of VAP in the United States and, in trauma, blunt chest trauma and pulmonary contusion can mimic the signs and findings related to VAP.

Emphasizing this point, Croce et al. [29] evaluated the use of CPIS in critically injured patients. In this retrospective study, the investigators reviewed 158 polytrauma patients who had 285 cultures of BAL fluid specimens performed because of a clinical suspicion of VAP. The prevalence of VAP with the use of quantitative BAL culture was 42%, with the remainder representing inflammatory changes. The sensitivity of a CPIS was only 61%, and its specificity for VAP was only 43%. In addition, there was no pattern to the over- or under-diagnosis of VAP based on the CPIS in trauma patients. In patients with a low CPIS, VAP was often found, and many patients with a high CPIS had negative quantitative culture results. The authors concluded that, in a trauma population, the CPIS is not an adequate means for differentiating VAP from noninfectious causes of lung injury.

Pham et al. [30] reached a similar conclusion in their assessment of CPIS in the treatment of burn patients. These investigators retrospectively calculated the CPIS for 28 patients who had 46 quantitative cultures performed to diagnose VAP and tested the characteristics of a CPIS threshold of 6 for the diagnosis of VAP. They found that the CPIS had poor discrimination; patients with positive and negative culture results had a similar CPIS (the mean CPIS was 5.7 and 5.5, respectively), and the sensitivity and specificity of the CPIS was 30% and 80%, respectively.

Early-onset VAP, usually carry a better prognosis, and are more likely to be caused by antibiotic-sensitive bacteria. However, patients with early-onset HAP who have received prior antibiotics or who have had prior hospitalization within the past 90 days are at greater risk for colonization and infection with MDR pathogens and should be treated similar to patients with late-onset VAP [8]. Ventilator-associated pneumonia is an important cause of morbidity and mortality in critically ill patients. Evidence-based clinical practice guidelines for the prevention, diagnosis, and treatment of ventilator-associated pneumonia may improve outcomes [31].

Of all the components of the CPIS, the measure of oxygenation provides the most information as a time-dependent factor during early VAP for predicting its outcome in response to treatment, and deriving a complex score appears to be superfluous for this purpose. The CPIS has been most
successfully used in guiding treatment decisions for patients with a low likelihood of VAP, for whom CPIS-guided therapy has resulted in lower costs and reduced the development of antimicrobial resistance [8].

In conclusion, when the CPIS exceeded 6, there was an association with the presence of pneumonia which was confirmed by microbiological culture furthermore serum CRP is an easy, available and cheap test so daily serum CRP measurements to ICU patients enabled the early diagnosis of pneumonia and enhanced the value of the CPIS. Further studies of CPIS are needed with particular attention to how its variability might affect therapeutic choices.

Conflict of interest

None declared.

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