Ventilator-Associated Pneumonia: The Clinical Pulmonary Infection Score as a Surrogate for Diagnostics and Outcome

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The Clinical Pulmonary Infection Score (CPIS) was developed to serve as a surrogate tool to facilitate the diagnosis of ventilator-associated pneumonia (VAP). The CPIS is calculated on the basis of points assigned for various signs and symptoms of pneumonia (eg, fever and extent of oxygenation impairment). Although some studies suggest that a CPIS >6 may correlate with VAP, most studies indicate that the CPIS has limited sensitivity and specificity. In addition, no well-done studies validate the CPIS in either acute lung injury or trauma. The interobserver variability in CPIS calculation remains substantial, suggesting that this cannot be routinely used across multiple centers to support the conduct of randomized clinical trials. Changes in the CPIS may correlate with outcomes in VAP, but it appears that the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen is a more important marker for outcomes than the CPIS. At present, the CPIS has a limited role both clinically and as a research tool.

Ventilator-associated pneumonia (VAP) has emerged as an important challenge in the intensive care unit (ICU). Representing >25% of all ICU-acquired infections, there are >100,000 cases annually in the United States alone [1]. VAP also accounts for more than one-half of all antibiotic use in the ICU [2]. Consequently, VAP is associated with substantial morbidity and costs [3, 4]. The estimated medical costs attributable to VAP are ~US $12,000 per case [4].

Despite being the ubiquitous focus of scientific investigations and quality initiatives, VAP continues to represent a conspicuous clinical conundrum. Although solid evidence indicates that this disease is preventable and that hospitals can decrease the rates of VAP, the struggle to develop an appropriate diagnostic strategy continues. The difficulty with diagnosis applies not only to clinical trials, but also at the beside in the care of critically ill patients. Needless to say, the diagnostic challenge has multiple implications for therapy.

The fundamental obstacle to the diagnosis of VAP is the absence of a uniform gold standard. Unlike for venous thromboembolism, for which there are clear gold standard tests and, as a result of these gold standards, validated surrogate tests for diagnosis, physicians treating persons suspected of having VAP have no one test, assay, or intervention that they can use to either make or exclude the diagnosis reliably. Beyond the impact of this challenge at the bedside, the absence of clearly established diagnostic criteria frustrates efforts to evaluate and compare across studies that focus on VAP. That is, definitional heterogeneity of VAP in different studies makes it difficult to ascertain whether these analyses are focusing on the same syndrome. Indeed, even the modes of obtaining secretions for objective microbiologic evaluation differ among studies, ranging from blind testing of endotracheal samples to quantitative cultures of bronchoscopically obtained lower airway secretions. Although the same scenario exists for community-acquired pneumonia, the issue is somewhat less pressing because of the limited costs and

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mortality associated with community-acquired pneumonia, compared with VAP.

Because of all these factors, it is apparent that a simple clinical tool for the diagnosis of VAP is urgently needed. The accuracy of a predictive instrument is quantified by its validity (ie, its presence represents the presence of the disease that it is intended to identify), reliability (ie, its evolution corresponds to the biologic evolution of the disease), and reproducibility (no major differences in its derivation either between different observers or by the same observer at different times). In addition to being valid, reliable, and reproducible, an ideal marker of VAP should (1) be noninvasive, (2) facilitate rapid diagnosis, (3) prompt earlier therapy, (4) help avoid excess antibiotic use, (5) identify patients early during the disease course who may experience treatment failure or who are not responding to treatment, and (6) assist in the conduct of clinical research.

To address these issues and the unmet need, Pugin et al [5] attempted to create a surrogate clinical marker for VAP. Of interest, the primary purpose of their study was to compare the clinical characteristics of diagnostic testing with blind endotracheal sampling to bronchoscopically obtained samples as the method for VAP diagnosis. In parallel, the investigators also defined the Clinical Pulmonary Infection Score (CPIS), a clinical score of 0–12 based on the following 6 variables: body temperature, leukocyte count, volume and character of tracheal secretions, arterial oxygenation, chest radiograph findings, Gram stain results, and results of culture of tracheal aspirate specimens (Table 1). In that study, 40 paired samples were obtained from 28 patients deemed to be at high risk of VAP by virtue of prolonged need for mechanical ventilation. The authors concluded that there was a good correlation between clinical score and quantitative bacteriology (r, 0.84 for bronchoscopic bronchoalveolar lavage [BAL]; r, 0.76 for nonbronchoscopic BAL; $P < .001$). They further noted that a CPIS threshold of 6 was a fairly accurate measure of the presence or absence of pulmonary infection, as signified by bacterial culture. Therefore, the CPIS was developed in a small convenience sample of mostly medically ill patients [5]. The elements of the score were included not on the basis of a rigorous review of evidence, but on the basis of expert opinion, and no validation of the score was undertaken by the authors at that time. Moreover, the authors made no effort to retrospectively evaluate the original data and adjust their score to better refine its accuracy on the basis of their observations.

CPIS TEST CHARACTERISTICS

Since this original investigation, several studies have attempted to assess the usefulness of the score as a diagnostic tool. Multiple methods, both prospective and retrospective, have been used, and analyses have focused on broader cohorts and types of patients. For example, Papazian et al [6] used the CPIS in conjunction with 3 diagnostic techniques in a prospective postmortem study of 38 patients who died after ⩾72 h of mechanical ventilation; 18 of these patients had histological 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%) [6]. Because of the small sample size, the 95% confidence intervals (CIs) surrounding their point estimates of the screening characteristics of the CPIS were fairly wide. In another necropsy study, Fabregas et al [7] attempted to validate the CPIS by the presence of both histological and positive microbiologic evidence of pneumonia in patients receiving mechanical ventilation. The study involved 25 patients who had received mechanical ventilation for ⩾72 h and who died while receiving mechanical ventilation. Sputum samples were obtained immediately after death and before discontinuation of mechanical ventilation, followed by immediate postmortem lung biopsy of the areas with maximum infiltrates on a chest radiograph. Use of a CPIS >6 as the predictor of VAP, compared with microbiologic VAP criteria, resulted in a sensitivity of 77% and specificity of only 42%, and invasive testing was only marginally better [7]. For persons who had previously received antibiotics (the vast majority of patients at risk of VAP), the CPIS performed even more poorly.

SPECIFIC PATIENT POPULATIONS

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 nonmedical populations. This is of particular concern because (1) surgical patients account for more than one-half of cases of VAP in the United States and, (2) in trauma, blunt chest trauma and pulmonary contusion can mimic the signs and findings related to VAP. Emphasizing this point, Croce et al [8] 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 clinical suspicion of VAP. The prevalence of VAP with use of quantitative BAL culture was 42%, with the remainder representing inflammatory changes. The sensitivity of a CPIS >6 was

Table 1. Clinical Pulmonary Infection Score Calculation

Parameter	Points
Temperature, °C	
36.5–38.4	0
38.5–38.9	1
⩾39.0 and ⩽36.0	2
Blood leukocyte level, leukocytes/mm^{-3}	
4000–11,000	0
<4000 or >11000	1
Plus band forms ⩾500	2
Tracheal secretions	
<14+	0
⩾14+	1
Plus purulence	2
Oxygenation, PaO_2:FiO_2, mm Hg	
>240 or ARDS	0
⩽240 and no ARDS	2
Pulmonary radiograph finding	
No infiltrate	0
Diffuse or patchy infiltrate	1
Localized infiltrate	2
Culture of tracheal aspirate specimen (semiquantitative: 0–1, −2, or 3+)	
Pathogenic bacteria cultured ⩽1 or no growth	0
Pathogenic bacteria cultured >1+	1
Plus same pathogenic bacteria on Gram stain >1+	2

NOTE. ARDS, acute respiratory distress syndrome; PaO_2:FiO_2, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.

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 high a 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 [8]. Pham et al [9] 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 [9]. In an effort at retrospective validation of the CPIS, Luyt et al [10] relied on prospective data collected as part of a multicenter randomized trial of VAP diagnostic strategies in 201 patients. Consistent with the results of other studies, they found the CPIS to be an inadequate predictor of VAP. The investigators determined the CPIS on days 1 and 3 and dichotomized the day-3 score at the threshold of 6, by which a score >6 indicated the need for prolonged antimicrobial therapy. They found a low concordance with bronchoscopic diagnosis ($\kappa = 0.33$) and an unacceptably low specificity of 47%, precipitating potential overtreatment with antibiotics [10]. In the largest prospective study to date, the Canadian Critical Care Trials Group tested the discriminative power of the CPIS to detect VAP [11]. In this multicenter study involving 739 patients, the area under the receiver operating characteristic curve for the CPIS was low (0.47; 95% CI, 0.42–0.53), indicating no improved ability to predict VAP than that afforded by chance.

INTEROBSERVER VARIABILITY

Beyond issues with the sensitivity and specificity of the CPIS, interobserver variability remains a major concern. Although it seems that the calculation of the CPIS is straightforward and that multiple observers would concur about the actual score for a given patient, the current data do not support this belief. In a study by Schurink et al [12] involving a cohort of 99 consecutive patients receiving mechanical ventilation who were suspected of having VAP, a modified CPIS was compared with quantitative BAL fluid cultures as a VAP diagnostic tool. The microbiologic prevalence of VAP was 70%, and the sensitivity of a CPIS >5 as a diagnostic threshold was 83%, with a spec-

ificity of 17% (area under the receiver operating curve, 0.55). In addition to adding little certainty to the diagnosis of VAP beyond chance, the level of interrater agreement for the prospectively calculated CPIS at the threshold of 6 was extremely poor ($\kappa = 0.16$) [12]. This level of discordance indicates that 2 different physicians examining the same patient are highly unlikely to agree about the actual CPIS calculation. This point alone suggests that the CPIS can not be used to standardize practice or in the conduct and execution of clinical trials.

In a review summarizing the poor diagnostic performance of the CPIS, Klompas concluded the following: "Routine bedside evaluation coupled with radiographic information provides suggestive but not definitive evidence that VAP is present or absent. Given the severity of VAP and the frequency of serious conditions that can mimic VAP, clinicians should be ready to consider additional tests that provide further evidence for VAP or that establish another diagnosis" [13, p 1592]. In contrast to these studies, in a retrospective study involving 58 patients with severe brain injuries, Pelosi et al [14] found the CPIS to increase from ICU entry to the day of VAP onset, providing a 97% sensitivity and 100% specificity for the VAP diagnosis. Despite that study, the weight of evidence suggests that the CPIS as a diagnostic tool for VAP has, to date, fallen short on both validity and accuracy.

CPIS AS A MARKER OF PROGNOSIS

Despite the limitations of the CPIS as a diagnostic tool, some researchers have proposed that it offers value as a marker of prognosis and, thus, might be useful as a surrogate end point in a clinical trial. In the initial research comparing serial changes in the CPIS with outcome, Luna et al [15] enrolled 427 consecutive patients receiving mechanical ventilation in a prospective observational cohort study at 6 critical care units in Argentina. Sixty-three patients were deemed to have VAP by both clinical and microbiologic criteria. The modified CPIS (microbiology data were excluded) was calculated both before and after the diagnosis of VAP. Although the CPIS increased consistently in all patients through the day of VAP diagnosis, it decreased significantly during the treatment phase in the survivors of VAP but remained elevated in the nonsurvivors. This observation revealed that the CPIS correlated well with eventual mortality. However, not all components of the CPIS contributed equally to explaining outcome. For example, these authors further determined that only measures of oxygenation (ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2:FiO_2]) and white blood cell count changes paralleled eventual mortality [15]. The other components of the CPIS added little to predicting survival. A similar result was reported in a secondary analysis of a subgroup with VAP in a large prospective randomized treatment trial [16]. In that study, the diagnosis of VAP was adjudicated as definite, probable, or possible on the basis of testing of endotracheal or lower airway samples. Of the 563 patients with VAP, 32% met prospectively defined criteria for clinical failure. In a logistic regression analysis of predictors of clinical failure, only failure of 1 CPIS component, the PaO_2:FiO_2, to improve between randomization and day 3 of the study was found to be an independent predictor of clinical failure (odds ratio, 1.71; 95% CI, 1.04–2.81) [16]. Failure of the PaO_2:FiO_2 to improve further segregated survivors not only from patients who experienced clinical failure but also from patients who eventually died. Therefore, these 2 large multicenter studies provide some evidence that, at the very least, the time-dependent changes in the PaO_2:FiO_2 early in VAP may provide some predictive power for VAP outcomes; however, the overall usefulness of the CPIS for this purpose remains in question.

CPIS AS A TOOL TO CONTROL ANTIBIOTIC USE

Because of concerns about emerging antimicrobial resistance, other researchers have explored the use of the CPIS as neither a diagnostic nor a prognostic tool, but rather as a means for preventing antibiotic overuse. Singh et al [17] randomized 81 patients with a CPIS ≤ 6 (ie, a low likelihood of pneumonia) to receive either standard treatment (10–21 days of antibiotics chosen by the attending physician) or 3 days of ciprofloxacin monotherapy. On day 3, patients were reevaluated. Antibiotics were discontinued if the CPIS remained ≤ 6. In patients for whom the CPIS increased to ≥ 6, ciprofloxacin therapy was continued or the medication was changed on the basis of the results of the microbiology data. The authors observed substantial differences between groups in the administration of antibiotics after day 3 (90% standard care vs 28% ciprofloxacin; $P < .001$). Similarly, patients in the ciprofloxacin arm whose CPIS remained at ≤ 6 were much less likely to continue antibiotic therapy after day 3 than were their counterparts in the standard care group (0% vs 96%). Of importance, although mortality and duration of ICU stay did not differ between the 2 groups, the rates of the development of antibiotic resistance, superinfection, or both were lower in the experimental arm than in standard care arm (15% vs 35%; $P = .017$) [17]. Of note, the CPIS on day 3 included a seventh parameter: radiographic progression of the infiltrates. Some might conclude from this study that the use of the CPIS successfully prevented excessive antibiotic use. However, it is unclear whether any of the patients with a low CPIS even required therapy. In other words, this analysis represents not a study of the CPIS as a management tool but a study of how the CPIS affected physician prescribing. A simple deescalation paradigm to antibiotic prescribing coupled with antibiotic stewardship should be studied for its ability to accomplish the same goal.

SUMMARY

The evidence to date does not support widespread use of the CPIS as a diagnostic, prognostic, or therapeutic decision tool, because it is not an adequate surrogate for the diagnosis of VAP. Its poor sensitivity and specificity in most studies preclude its use as an accurate noninvasive diagnostic device. 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 development of antimicrobial resistance. Despite these important findings, the CPIS is not and should not be used frequently in practice to guide therapeutic decisions or be used to facilitate the completion of clinical trials in VAP. Further study of CPIS use in this context is needed with particular attention to how its interrater variability might affect therapeutic choices. The advent of various biomarkers will either enhance the value of the CPIS or supplant it.

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