Recognition of Nosocomial Pneumonia in the Intensive Care Unit: Still a Confusing Issue

Pneumonia associated with mechanical ventilation in the intensive care unit (ICU) setting is one of the most common infections managed by intensivists. The current classification of nosocomial pneumonia includes hospital-acquired pneumonia, ventilator-associated pneumonia (VAP), and nursing home-associated pneumonia. Healthcare-associated pneumonia is the newest category of nosocomial pneumonia, and in many developed countries is probably the most common type of pneumonia requiring ICU care. Healthcare-associated pneumonia is a distinct type of nosocomial pneumonia—the others being hospital-acquired pneumonia and VAP—that is present at the time of hospital or ICU admission, where patients have specific underlying risk factors, including residence in a nursing-home or long-term care facility; recent hospitalization or treatment with antibiotics; having received home or hospital-based intravenous therapy, wound care, or dialysis; and immunosuppression.[1-3] In this issue of RESPIRATORY CARE, Shan et al report a meta-analysis in which they found the diagnostic performance of the clinical pulmonary infection score (CPIS) for VAP to be moderate, compared to a reference standard of lower respiratory tract quantitative cultures. However, they also concluded that the CPIS is simple and easy to perform, which makes it potentially useful in the diagnosis and clinical management of VAP.[4]

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Clinical criteria are non-specific for the diagnosis of nosocomial pneumonia, including VAP. Clinical findings such as fever, leukocytosis, and purulent secretions are known to complicate other non-infectious pulmonary conditions such as atelectasis and acute respiratory distress syndrome, and therefore lack specificity for the diagnosis of nosocomial pneumonia.[5-8] Similarly, chest radiograph can be non-specific for the diagnosis of nosocomial pneumonia. Wunderink et al found that no roentgenographic sign correlated well with the presence of pneumonia in mechanically ventilated patients.[9] The presence of air bronchograms was the only roentgenographic sign that correlated with autopsy-verified pneumonia, correctly predicting 64% of cases. The most frequently employed clinical diagnosis of VAP has traditionally required the presence of a new or progressive consolidation on chest radiology plus at least 2 of the following clinical criteria: fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions. This definition has been supported by several medical specialty groups,[3,10] despite the lack of specificity of these criteria.[6-9]

More recently, attempts were made to develop prediction models and scoring systems for nosocomial pneumonia. The Centers for Disease Control and Prevention's National Healthcare Safety Network established a clinical definition for probable nosocomial pneumonia.[11] Unfortunately, these diagnostic criteria have not been validated, and at least one study found that decision making using these criteria was less accurate, potentially resulting in the withholding of antibiotics in 16% of patients diagnosed with VAP via bronchoalveolar lavage (BAL).[12] Recently, we compared the observed rates of VAP with the National Healthcare Safety Network surveillance method versus the American College of Chest Physicians clinical criteria.[13] Over one year, 2,060 patients required mechanical ventilation for greater than 24 hours and were prospectively evaluated. Of these, 83 patients (4%) had VAP according to the American College of Chest Physicians criteria, as compared to 12 patients ($< 1\%$) according to the National Healthcare Safety Network surveillance method. The corresponding VAP rates were 8.5 versus 1.2 cases per 1,000 ventilator days, respectively. The agreement of the 2 sets of criteria was poor (kappa statistic 0.26). Cultures were positive in 88% of patients in the American College of Chest Physicians group, as compared to 92% in the National Healthcare Safety Network group.[13]

The CPIS is another diagnostic tool for nosocomial pneumonia. The CPIS is based on 6 variables: fever; leukocytosis; tracheal secretions; oxygenation; radiographic infiltrates; and semi-quantitative cultures of samples collected via suctioning, with Gram stain.[14] The original description showed a sensitivity of 93% and a specificity of 100%, but that study included only 28 patients, and the CPIS was compared to quantitative culture of BAL fluid, using a "bacterial index" defined as the sum of the logarithm of all bacterial species recovered, which is not considered an acceptable standard for the diagnosis of VAP.[14] Compared to pathology diagnosis, CPIS has demonstrated a moderate performance, with a sensitivity of 72–77% and a specific-

ity of 42–85%.[6,15] Similarly, CPIS has been found to be only moderately accurate compared to quantitative bacterial cultures of the lower respiratory tract for the diagnosis of VAP, with a sensitivity of 30–89% and a specificity of 17–80%.[16-20]

Several studies have evaluated the value of quantitative bacteriological data in establishing the diagnosis of VAP, compared to pathology and clinical criteria. Torres et al used quantitative cultures of respiratory specimens obtained via BAL, protected BAL, protected specimen brush, and samples collected via tracheobronchial suctioning, that were compared to histology of lung biopsy samples to establish the diagnosis of VAP.[21] The sensitivity for the diagnosis of VAP ranged from 16% to 37% when only histologic reference tests were used, whereas the specificity ranged from 50% to 77%. When lung histology of guided or blind specimens and microbiology of lung tissue were combined, all quantitative diagnostic techniques achieved higher, but still limited, diagnostic yields (sensitivity range 43–83%, specificity range 67–91%).[21] Other investigators found similar diagnostic accuracy employing histologic criteria as the reference standard.[22-28] Fàbregas et al also found that addition of the results of quantitative cultures to clinical criteria (CPIS) did not increase the accuracy of CPIS in diagnosing VAP.[6] More recently, Riaz et al compared nonquantitative and quantitative cultures for the diagnosis of VAP,[29] and found that nonquantitative culture of BAL was fairly good at ruling out VAP but was poor at establishing the presence of VAP, because of the low specificity of the test. The available evidence suggests that there is no one absolute accepted standard for the diagnosis of VAP.

Several studies have found that procalcitonin can help differentiate bacterial infection from other inflammatory conditions (eg, acute respiratory distress syndrome and autoimmune diseases) or nonbacterial infectious (ie, viral) diseases.[30-32] Therefore, procalcitonin monitoring may help limit overuse of antibiotics in patients with clinically suspected pneumonia.[32-34] A high procalcitonin level at admission and at day 3 appears to be a good predictor of treatment failure in patients with respiratory infection, whereas a low procalcitonin level supports a clinical response and suggests shortening or discontinuing antibiotics.[34,35] The use of procalcitonin to limit unnecessary antibiotics has been most extensively evaluated in patients with community-acquired pneumonia.[33,34] In a recent study, Briel et al randomized patients to either procalcitonin-guided antibiotic therapy or standard approach.[35] For patients randomized to procalcitonin-guided therapy, the use of antibiotics was discouraged based on levels (procalcitonin ≤ 0.1 μg/L or ≤ 0.25 μg/L, respectively) or encouraged (procalcitonin > 0.25 μg/L). With procalcitonin-guided therapy the antibiotic prescription rate was 72% lower (95% CI 66–78%) than with standard therapy. These types of investigations suggest that procalcitonin-guided therapy can reduce antibiotic use for respiratory tract infections in the out-patient setting without compromising patient outcomes.

Similar preliminary results have been observed for the use of procalcitonin in nosocomial pneumonia, although the findings have been mixed. Ramirez et al found that sequential procalcitonin measurement had the best sensitivity and specificity for VAP, compared to C-reactive protein and the CPIS.[36] However, Luyt et al found that procalcitonin level, and the rise in procalcitonin compared to baseline, had poor diagnostic value for VAP.[37] Although procalcitonin level may not be accurate for the diagnosis of VAP,[38] emerging data suggest that serial procalcitonin measurement may be used as a marker to terminate antimicrobial therapy and as a biomarker for sepsis.[39] The best support for procalcitonin's ability to limit unnecessary antibiotic therapy in patients with suspected lung infections, including VAP, comes from a recent trial that found an antibiotic duration reduction of almost 3 days compared to standard treatment.[40] However, in the control group the clinicians were allowed to determine when antibiotics should be discontinued, without having a rigorous protocol in place to guide antibiotic management.[41]

As none of the currently available diagnostic tests provides an absolutely accurate diagnosis of VAP when used alone, a strategy that combines diagnostic modalities may be advantageous. Patients with suspected VAP should undergo an evaluation that is supported by local expertise and should include imaging (chest radiograph and/or computed tomography), bacteria cultures from the lower respiratory tract, and possibly biomarkers. The results of this evaluation can be used to determine the likelihood of VAP and to guide therapy in a manner that attempts to optimize patient outcomes. Ensuring timely administration of appropriate antimicrobial therapy optimizes patient outcomes, and avoiding unnecessary antibiotic exposure minimizes the emergence of antimicrobial resistance. For unstable patients, delaying the initiation of appropriate antibiotic therapy should be avoided, because such delay is associated with higher mortality.[42] Therapy should not be postponed for the results of diagnostic studies. Alternatively, in stable patients, lower respiratory tract sampling via BAL or protected specimen brush reduces antibiotic use in patients with suspected VAP.[43-45]

A recent meta-analysis of 4 randomized studies, which included a total of 628 patients, found that invasive VAP diagnosis strategies did not alter mortality.[46] This finding was confirmed in a recent large randomized trial from Canada, which compared VAP diagnosis via a clinical approach to via BAL plus quantitative cultures.[47] There was no significant difference between the study arms in clinical outcomes or antibiotics use. Since invasive sampling for suspected VAP does not directly affect initial

antibiotic prescription, it is not surprising that it does not alter mortality.[48] The results of lower respiratory tract cultures are principally used to modify the initial antimicrobial regimen: de-escalation if the patient is improving, or escalation if the initial regimen was inappropriate for the offending pathogen.

In summary, the diagnosis of nosocomial pneumonia, and in particular VAP, can be confusing and problematic. However, clinicians should develop local strategies based on available resources, that attempt to balance the need to treat potentially serious infections in an appropriate and timely manner with the need to avoid unnecessary antibiotic exposure. Relatively simple protocols or guidelines can be developed at the local hospital level to accomplish these goals.[49,50]

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