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Jordi Rello
Jordi Riera
Ricardo Serrano

What's new in ventilator-associated pneumonia?

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J. Rello (✉) · J. Riera
Vall d'Hebron Institut of Research, CIBERES, Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain
e-mail: jrello@crips.es

R. Serrano
Department of Intensive Medicine, Hospital General Universitario de Alicante, Alicante, Spain

The classic paradigm of ventilator-associated pneumonia (VAP) assumes that the clinical presentation of this infection is similar to community-acquired pneumonia. Most randomized clinical trials even enclose cough or pleural pain as part of this presentation and presume a hypothetical sudden onset. However, lower respiratory infection in ventilated patients are presenting with progressive hypoxemia (and hypotension) that is in contrast with the sudden onset of rigor and temperature rise of bloodstream infections.

Diagnosis of pneumonia or tracheobronchitis

The definitions include many subjective components [such as chest X-ray (CXR), respiratory secretions assessment, even auscultation] and hence the interobserver variability for detecting VAP is high. A recent prospective survey reported that the agreement about classification of cases as VAP or not was nearly random, highlighting the limitations of the current definitions [1].

Again, in contrast with community-acquired pneumonia (CAP) episodes, respiratory infections in mechanically ventilated (MV) patients are heterogeneous. Poor comparison can be established when a patient with cardiac surgery is compared with another who underwent trauma. A particular challenge is the development of pneumonia in the postoperative period of lung transplantation because its presentation may overlap with acute rejection that requires the opposite therapeutic approach (increase versus decrease of immunosuppressors). Recently, Riera and colleagues [2] reported that pneumonia was related to increased in-hospital death (42.9 vs 11.5 %; $p = 0.01$), while tracheobronchitis was not related to increased mortality (14.0 vs 14.7 %; $p = 0.9$) but both prolonged the duration of MV by more than 1 week. Interestingly, tracheobronchitis doubled episodes of pneumonia in this subset of patients.

It is more important to focus on complications such as the impact of the respiratory infection on oxygenation [3] when taking management decisions. The US Centers for Disease Control and Prevention (CDC) current diagnosis of ventilator-associated tracheobronchitis (VAT) is based on the absence of CXR infiltrates and the presence of signs consistent with respiratory inflammation along with at least one microbiologic criterion. However the lack of objectivity and the inherent variability in the interpretation of CXR in MV patients make it difficult to take decisions based on CXR. Lung ultrasonographies may replace CXR in pneumonia diagnosis [4].

Surveillance

Klompas and Kalil [5] proposed a simple, objective surveillance definition for ventilator-associated complications (VAC) shifting the focus of surveillance from pneumonia alone to complications of MV. Some of these events may be unavoidable consequences of caring for the critically ill patients, so zero may no longer be a realistic goal [6].

The CDC adopted these newer definitions that deliberately broaden the focus from routine surveillance of pneumonia alone to outcomes and complications of mechanical ventilation. VAC has simplicity, objectivity, and is more consistently associated with adverse outcomes than VAP. However, the overlap between VAP and infection-related VACs (iVACs) has been reported to be lower than 30 %. Indeed, the majority of pneumonias that do not qualify as iVACs fail to qualify because of lack of increase in ventilator settings. In other words, these are pneumonias with little or no hypoxemia. One wonders about their clinical significance. Furthermore, the objectivity of VACs cannot be taken for granted, as there are potential sources of variability, including possible discrepancies between surveyors charged with manually finding and processing the daily minimum data and electronic systems that analyze ventilators' minute-by-minute settings. Potential drawbacks are that many patients were excluded, such as those with hypoxemia rescue therapy, prone position, or high frequency ventilation. In contrast to the large proportion of patients with VAP, VAT episodes are not identified. Therefore, iVAC is a surveillance concept that reflects decisions made by clinicians rather than a diagnosis concept meant to trigger antibiotics.

Therapy

Beta-lactam inhibitors (e.g., avibactam) act in combination with beta-lactams or carbapenems to increase treatment efficacy and spectrum [7]. Nebulized antibiotics with newer devices have emerged for adjuvant therapy of multidrug-resistant (MDR) organisms, but evidence-based guidelines are lacking [8]. Again, stratification by hypoxemia would help to identify potential benefits and complications. The recently reported differences in outcomes between different serotypes of *Pseudomonas aeruginosa* offer new perspectives of management [9]. Interestingly, alternative therapies other than antibiotics [10] are being developed as adjuvant therapies.

Novel microbiologic diagnosis

A point-of-care test able to identify quickly and accurately resistance genes should improve the correct initial therapy and outcomes. Molecular diagnostic tools, metabolomics, and proteomics using an "artificial nose" are areas of promising research [11]. Indeed, a "personalized approach" in management of patients with ventilator-associated respiratory infections is required [12]. Initial antibiotic therapy should be started on the basis not only of epidemiological factors (comorbidities, duration of hospitalization, and prior antibiotic exposure) or Gram stain, because Genexpert® should be implemented for quick microorganism identification [13], but also for early detection of resistance genes like *mecA* gene or extended spectrum beta-lactamases. Advances in matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry allow early microorganism identification and also early susceptibility

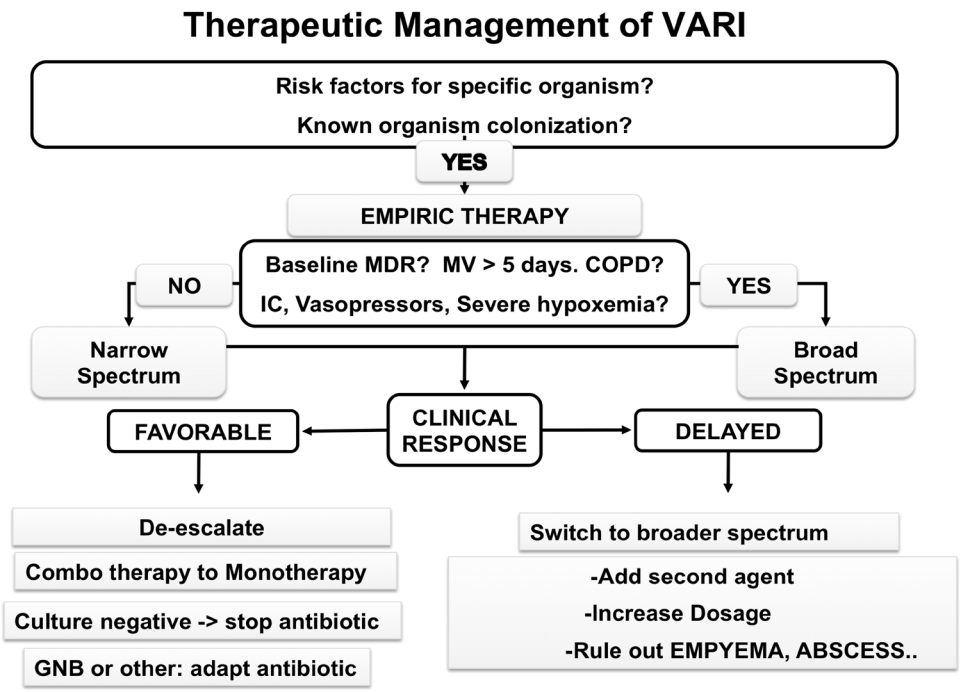

Fig. 1 Approach to the work-up of ventilator-associated pneumonia and tracheobronchitis (VARI)

testing with rapid detection of resistant isolates or carbapenemases from cultures [14].

Surrogates of outcome

Modification of therapy should be based on signs of clinical resolution (Fig. 1), which can be enhanced by adding some biomarkers. Esperatti et al. [15] validated a set of predictors of adverse outcomes in patients with ICU-acquired pneumonia in relation to clinically relevant assessment at 28 days. The lack of improvement of PaO2/FiO2 and Sequential Organ Failure Assessment score from day 1 to day 5 were independently associated with 28-day mortality and fewer ventilator-free days. Patients with predictors of adverse outcomes had higher serum inflammatory response accordingly to biomarkers evaluated.

Conclusions

Respiratory infections in MV patients develop as severe sepsis or septic shock in intubated patients. The onset is progressive. Purulent respiratory secretions are required for diagnosis, whereas the role of CXR and standard signs in community-acquired infections are secondary. Both pneumonia and tracheobronchitis are associated with prolonged MV period and ICU stay, providing a strong rationale for therapy. Hypoxemia is a hallmark sign of lower respiratory tract infections. Therefore, management should be based on a newer paradigm centered on hypoxemia.

Conflicts of interest JR served in speakers' bureau or/and advisory boards for Pfizer, Basilea, Navriba, Bayer, Tetraphase, LASCO, and AstraZeneca and received grant research support from Sanofi-Pasteur, Aridis, LASCO, and Cubist. The other authors declare no conflict of interest related to the current manuscript.

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