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WHAT'S NEW IN INTENSIVE CARE

The research agenda in VAP/HAP: next steps

Michael S. Niederman[1*], Ignacio Martin-Loeches[2] and Antoni Torres[3]

In the coming decade, ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) will continue to be major infections in the intensive care unit (ICU). While prevention efforts may reduce the frequency of these infections, we do not believe that "zero VAP", which is a common goal in the USA, has or will be achieved, as evidenced by continued antibiotic use for nosocomial respiratory infections [1]. In Europe, the degree of preventable VAP has been estimated to be approximately 50%, so many episodes will still be present, in spite of the use of ventilator bundles [2]. In the coming decade, we anticipate the need for better epidemiologic and diagnostic tools that will inform us about the true incidence of these infections and the impact of specific prevention strategies. For epidemiologic purposes, the concept of ventilator-associated events (VAE), used by some in the USA, has not gained traction in Europe and it seems unlikely to become a valued concept [3]. Recently, a systematic review and meta-analysis examined 61,489 patients receiving mechanical ventilation in eight countries and found that the pooled sensitivity and positive predictive value of each VAE type for VAP detection did not exceed 50%, reflecting that VAE surveillance does not accurately detect cases of traditional VAP [3]. The clinical management and importance of the ventilator-associated lower respiratory tract infections (VA-LRTI) concept also need clarification. A multicentre, prospective, observational study found improved outcomes with the use of appropriate antibiotic treatment in VA-LRTI (including ventilator-associated tracheobronchitis, or VAT) [4]. Future studies are needed to see if VAT is an appropriate illness for routine antibiotic therapy, or whether only certain specific VAT needs antibiotic treatment. One area not covered by VA-LRTI is pneumonia in non-ventilated patients, and the topic of HAP requires more study to clarify its true incidence and bacteriology (possibly with quantitative culture methods) and to determine if the current assumptions, that the bacteriology parallels that of VAP, are in fact accurate.

Diagnosis and bacteriology

In the coming years, the most revolutionary advances are likely to come with new molecular diagnostic methods, and other tools that will rapidly identify the etiologic pathogens of VAP and HAP [5]. Both sensitivity and specificity need to be defined, but these methods can inform us about the presence of multi-drug resistant (MDR) pathogens in a matter of hours. One new method uses fluorescence in situ hybridization (FISH) technology and immobilized live microbial cells to rapidly detect organism susceptibility to any antibiotic, which could lead to accurate and appropriate initial antibiotic therapy, while potentially decreasing unnecessary antibiotic use [5]. Although rapid diagnostic methods may not always distinguish colonization from infection, the high sensitivity of these methods means that the absence of an organism, can be used to guide de-escalation of initial empiric antibiotic therapy. However, studies are needed to confirm the efficacy, safety and cost-effectiveness of using these tools for initial antibiotic selection in the ICU [6]. Defining the frequency of MDR pathogens in each ICU is essential, since patients being treated in an ICU with more than 25% MDR pathogens have an increased risk of MDR VAP, regardless of other risk factors [7]. We would also like to see methodology that rapidly detects the presence of Gram-negative resistance genes, similar to current methods that detect methicillin-resistant *Staphylococcus aureus* (MRSA). Other rapid diagnostic

*Correspondence: msn9004@med.cornell.edu
[1] Division of Pulmonary and Critical Care Medicine, New York Presbyterian/Weill Cornell Medical Center, 425 E. 61st St, 4th Floor, New York, NY 10065, USA
Full author information is available at the end of the article

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Table 1 Research agenda for VAP/HAP

Epidemiology
To define the true incidence of VAP in ICUs that use effective prevention strategies
To define the incidence and clinical impact of ventilator-associated tracheobronchitis (VAT) and its outcomes, with and without therapy
To evaluate the utility of the ventilator-associated events (VAE) concept in Europe
Diagnosis
To apply rapid molecular diagnostic methods to patients with VAP and demonstrate the ability of these methods to guide more accurate and focused initial antibiotic therapy
To use new diagnostic methods to define the bacteriology of each ICU and its frequency of MDR pathogens
To explore other rapid diagnostic methods, not using molecular probes, such as the "electronic nose"
To define the bacteriology of HAP in non-ventilated patients
Therapy
To study new antibiotic therapies for MDR Gram-negatives and MRSA
To determine the efficacy of therapies for severe VAP, using monoclonal antibodies to MRSA and *P. aeruginosa*
To define the optimal combination agent for beta-lactams in the therapy of MDR Gram-negative VAP, and the best duration of combination therapy
To determine whether nebulized antibiotics should be used as routine first-line therapy or only as second-line therapy for refractory infection with MDR pathogens
To define the role of biomarkers in guiding the duration of therapy for MDR VAP infections
To optimize antibiotic dosing regimens and determine when prolonged or continuous beta-lactam infusions are valuable

methods are being evaluated, and one promising technology is the electronic nose, which can use gas chromatography to identify the presence of VAP and possibly specific pathogens, using real-time exhaled gas analysis from the ventilator, potentially leading to earlier and more accurate initial therapy [8]. It is also likely that we will see a number of new serum and lung lavage biomarkers that may be able to identify when to start and stop antibiotic therapy for VAP and HAP.

Therapy of VAP/HAP

We believe that in the coming decade, the greatest advances will be made in defining optimal therapy of VAP. New antibiotics are being developed for HAP/VAP including ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam, tedizolid, aztreonam/avibactam, carbavance, a siderophore cephalosporin and plazomicin [9]. These agents cover both Gram-negative and Gram-positive MDR pathogens and we anticipate studies demonstrating the efficacy of new agents that can combat our increasingly resistant infecting organisms. New non-antibiotic therapies are being developed, including monoclonal antibodies to specific pathogens, such as MRSA and *Pseudomonas aeruginosa*, and there are ongoing trials using these antibodies as either therapy or prevention of VAP [10].

Many therapeutic areas have poor data to guide management, as reflected by the lack of strong recommendations for specific therapy choices, in the latest American Thoracic Society/Infectious Diseases Society of America (ATS/ISDA) nosocomial pneumonia guidelines [11]. Unresolved areas include the need for combination therapy for Gram-negative infection, the optimal drug choice for MRSA pneumonia, and the correct duration of therapy for infection with these pathogens. Combination therapy for MDR Gram-negative infection is usually used to increase the likelihood of appropriate therapy, but the duration of combination therapy varies; however, 2–5 days is usually recommended. Combination therapy usually involves a broad-spectrum beta-lactam with either a fluoroquinolone (FQ) or aminoglycoside (AG), and the respective advantages of these drugs have been evaluated with conflicting results [12]. Studies are needed in patients with MDR Gram-negative VAP/HAP to define which drug should be part of a combination regimen.

Another new therapeutic area is the use of adjunctive therapy with nebulized antibiotics in VAP. This approach achieves high drug concentrations at the site of infection and may help reduce prolonged systemic antibiotic use by eradicating MDR Gram-negatives more rapidly and effectively than systemic therapy alone [13]. However, more information is needed about how to best deliver nebulized antibiotics and to demonstrate their value not only for VAP but possibly as the sole therapy for VAT. In VAT, appropriate antibiotic treatment (nebulized or systemic) is independently associated with reduced risk for transition from VAT to VAP, but therapy is not routinely recommended for all episodes of VAT [14]. Future studies will also clarify whether nebulized antibiotics have a role as first-line adjunctive therapy for VAP, or if they will be used only

as a second line rescue therapy for refractory infection due to MDR pathogens.

We anticipate other studies on VAP therapy that will clarify the role of biomarkers such as procalcitonin, to guide the duration of therapy, especially for patients with MDR pathogen infection. There will also be further exploration of optimized antibiotic pharmacokinetics and pharmacodynamics. The DALI study demonstrated the frequent ineffective dosing of antibiotics for critically ill ICU patients, and the studies of prolonged and continuous beta-lactam infusion have addressed this issue with varied success [15]. It seems likely that prolonged infusions will be more valuable when targeting highly resistant organisms, but not as a part of routine management; but more data are clearly needed along with implementing strategies of therapeutic drug monitoring (TDM). It is our belief that with future data that focus on VAP/HAP epidemiology, diagnostic methods, bacteriology and therapy, we will see further improvement in the outcomes of our patients (Table 1).

Author details
[1] Division of Pulmonary and Critical Care Medicine, New York Presbyterian/Weill Cornell Medical Center, 425 E. 61st St, 4th Floor, New York, NY 10065, USA. [2] Intensive Care Medicine, Department of Clinical Medicine, St. James's University Hospital, Trinity Centre for Health Sciences, Dublin, Ireland. [3] Pulmonary Intensive Care Unit, Respiratory Institute, Hospital Clinic de Barcelona, Universitat de Barcelona, Barcelona, Spain.

Compliance with ethical standards

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