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LASTING LEGACY IN INTENSIVE CARE MEDICINE

Ventilator-associated pneumonia

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Ventilator-associated pneumonia (VAP) has been a known complication in the intensive care unit (ICU) since the late 1950s. Originally VAP was recognized as a cause of rising rates of Gram-negative, necrotizing pneumonia, which was uncommon at the time, and was attributed to ventilator and respiratory therapy equipment contaminating patients [1]. Subsequently, a number of studies demonstrated that critically ill patients had respiratory tract colonization, by their own Gram-negative flora, and these organisms often proliferated in endotracheal tube biofilm, and condensated in ventilator circuits, where they were often re-inoculated into patients during endotracheal suctioning and tubing circuit changes [2].

VAP was commonly reported in the 1980s where it occurred in up to 28% of mechanically ventilated patients, with the highest rates early in the course of intubation (3% per day risk up to day 5) [3]. These high rates were reported, in spite of controversies about overdiagnosis using clinical definitions, and whether bronchoscopic sampling was needed. VAP was not only the most common ICU-acquired infection, but had a mortality rate as high as 50%, with at least 25% of these deaths directly attributable to the infection, and not the underlying diseases [2, 3]. More recent studies have estimated a much lower attributable mortality for VAP [4].

Early and appropriate therapy has been consistently demonstrated to reduce mortality, and the efficacy of therapy has been challenged by the presence of multidrug-resistant Gram-negative and Gram-positive pathogens. In addition to endotracheal intubation itself, other risk factors for VAP include underlying serious illness (coma, acute lung injury, aspiration gastric colonization) and a variety of interventions (e.g., H2 blockers, reintubation, supine head position, low endotracheal tube cuff pressure). This information was used in the early part of this century to develop "ventilator bundles", which dramatically reduced the reported rates of VAP. In fact, at one point, it was presumed possible to have "zero VAP", and there was a belief that VAP was a medical error, fully preventable with simple interventions such as head of the bed elevation, daily awakening and weaning, and provision of oral care [5].

New classification

In the last several years, a new classification of pneumonias acquired during ICU stay has emerged and reflects the development of non-invasive ventilation and more commonly elderly and frail patients being admitted to the ICU. The new classification expanded hospital-acquired pneumonia (HAP) into ventilated and non-ventilated ICU-acquired pneumonias, while a new diagnosis emerged for ventilator-associated tracheobronchitis (VAT) [6–8]. Unlike VAP, patients with ventilated HAP were usually intubated after the onset of infection, and not with a preceding period of 48 h of ventilation. The definition of VAT shares the same criteria as VAP, except without the presence of new pulmonary infiltrates on portable chest radiograph [8]. The absence of lung infiltrates does not exclude the possibility that a percentage of VAT could be actual VAP, if a computed tomography scan is performed. It is thus possible that some reports of "zero VAP" were created artificially by reporting possible VAP as "ventilator-associated tracheobronchitis", or identifying intubated HAP patients that fulfil VAP criteria, as "ventilated HAP" and not VAP, among other potential explanations.

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Old and new challenges

A recurrent issue in VAP is making an accurate diagnosis in patients with a clinical suspicion of pneumonia [9]. In daily ICU practice, clinicians still use the presence of new radiographic infiltrates plus at least two of the classical clinical criteria for VAP diagnosis. Overall these criteria had 70% sensitivity and specificity in a postmortem study [9]. Recent developments in VAP diagnosis include the use of bedside lung ultrasound to detect pulmonary infiltrates compatible with pneumonia, and molecular point-of-care tests of respiratory secretions to identify potential pathogens. In skilled hands lung ultrasound has an important complementary role in VAP diagnosis [10]. The advantage of lung ultrasound is its non-invasive use at the bedside as both a diagnostic tool, and as a method to follow the response of VAP to treatment. The appropriate use of lung ultrasound in the diagnosis and management of VAP is still being defined in terms of patient-centered outcomes. Other unsolved topic in VAP is the use of invasive or non-invasive respiratory sampling for microbiological diagnosis. Potential new randomised controlled trials (RCTs) focusing on comparing each strategy associated with protocols for antibiotic stewardship, or applying molecular diagnostic methods could add to the field [11]. A main challenge still remains defining a gold-standard for VAP diagnosis.

Rapid and accurate microbial diagnosis of VAP is still a matter of debate. Recent advances in molecular tests provide promising tools for identifying pathogens and resistance profiles. A pilot RCT using the polymerase chain reaction (PCR) to detect methicillin-resistant *S. aureus* (MRSA) in the bronchoalveolar lavage (BAL) of mechanically ventilated patients has demonstrated better diagnostic performance and antibiotic management than with traditional methods [12]. Other multicenter studies show a very good sensitivity and good concordance of rapid molecular tests for both MRSA and Gram-negative bacilli with conventional cultures [13, 14].

In the last decade, the emergence of multi-drug and extensively drug-resistant (MDR and XDR) Gram-negative bacilli has presented a tremendous challenge for clinicians. Experts commissioned by the World Health Organisation (WHO) prioritized carbapenem-resistant Acinetobacter, ESBL-producing Enterobacterales, and carbapenem-resistant *Pseudomonas aeruginosa* as the major challenges for the future [15]. Importantly, there is a worldwide variability of the prevalence of these microorganisms and their different mechanism of resistance. In the last 5 years, several new antibiotics have been studied and approved for use in VAP [16]. Most of them include the combination of a beta-lactam or a carbapenem with a beta-lactamase inhibitor (ceftazidime–avibactam, ceftolozane-tazobactam, imipenem–relebactam, meropenem–vaborbactam) or beta-lactams with new mechanisms of action (e.g., cefiderocol), some of them with broad activity against almost all MDR/XDR microorganism [16]. Although timely and accurate treatment is fundamental for better outcome, empiric overtreatment is also frequent in VAP and necessitates an organized approach to antibiotic stewardship. Importantly, risk factors and scores for MDR have not been accurate enough so far to better target initial empiric treatment.

"VAP is back"

With the advent of the pandemic caused by the coronavirus disease 2019 (COVID-19) in 2020, much has changed and VAP returned, or always has been, as a main issue in ICUs worldwide [17]. Many series report high rates of VAP, in spite of modern prevention efforts, with reported rates over 40%, using bronchoscopic diagnosis [18]. Clearly VAP has not gone away, and this resurgence may be explained by the realization in high-income countries that it is now "politically acceptable" to accurately report this illness. Other factors that can explain the resurgence of high incidence rates of VAP during COVID-19 include the severity of COVID-19 illness per se and its associated treatments (e.g., deep sedation, prolonged mechanical ventilation, corticosteroid and anti-IL 6 treatments), along with a decrease in nurse-to-patient ratios, and less compliance with preventive measures [17].

Based on lessons from the past, we have learned the key management issues in VAP, a disease that is not going away. In the future, we need to develop new approaches and future investigations should focus on epidemiology, prevention, diagnosis and treatment of VAP (Table 1).

Table 1 Main challenges and lessons learned from the VAP legacy

Domain	Challenge	Learned	Future research
Epidemiology	Surveillance	Zero-VAP rates achieved by the usual active/passive surveillance are not reliable. There are alternatives for surveillance, such as ventilator-associated events. The impact of these alternatives on patient-centered outcomes and antibiotic consumption is not clear	• How can we accurately capture the VAP burden? • What will be the impact of new diagnostic molecular methods on VAP incidence? • How can we keep updated about representative VAP epidemiology? • Should we expect to have different VAP incidence rates for specific patients, such as burn, trauma, patients with ARDS?
Epidemiology	Data from low-and middle-income countries (LMIC)	There has been evidence that pathogens, burden, and attributable mortality of infections in LMIC are differently than in high-income countries. General descriptive, high-quality data on VAP epidemiology from LMIC is missing	• What is the incidence of VAP in ICUs in LMICs? • How to confirm microbiological diagnosis of VAP in ICUs at LMICs without a microbiological laboratory facility? • What are the pathogens and its antibiotic resistance patterns in VAP in ICUs in LMICs? • What is the attributable mortality of VAP in ICUs in LMICs?
Prevention	Pathophysiology of VAP	Gravity-driven microaspiration, associated with decreased performance of the mucociliary clearance, is the main determinant of VAP development	• What are the patient factors associated with the risk of VAP development? • What is the role of microbiome manipulation in controlling and preventing VAP? • Is the use of corticosteroids and antibiotics in specific populations (e.g., trauma) effective in tackling different pathways of VAP pathophysiology? • Should we treat VAT patients to prevent VAP development?
Prevention	Bundle implementation	The implementation science used in VAP prevention bundles was pioneered in ICU bundles and has been successful in preventing VAP	• What are the most cost-effective items of VAP prevention bundles? • How do we keep VAP prevention bundles working during increased workload and/or decreased nurse-to-patient ratio?
Diagnosis	Gold standard for diagnosis	Single signs or symptoms are not reliable for VAP diagnosis. Using validated diagnostic criteria is better than not using any criteria	• Which criteria should be used for clinical VAP diagnosis in the ICU? • Should we use different clinical VAP criteria for specific patients, such as burn, trauma, patients with ARDS? • What is the added value of incorporating biomarkers, lung ultrasound or tomography on VAP diagnosis?
Diagnosis	Microbiological diagnosis	It is difficult to separate colonization from infection and the use of semi-quantitative or quantitative evaluation increases the probability to diagnose infection. Usual culture medium-based studies of respiratory and other samples have delayed results for making a bedside decision. Ongoing antibiotic use upon VAP diagnosis decreases likelihood of achieving microbiological diagnosis of VAP	• What is the clinical impact on implementing bedside molecular diagnostic tools for patients with clinically suspected VAP? • When and how should we prioritize invasive respiratory sampling? • Is a multifaceted approach including high-quality Gram stain evaluation, invasive respiratory sampling and molecular diagnosis cost-effective for patient outcomes and reduction of antimicrobial resistance?

Table 1 (continued)

Domain	Challenge	Learned	Future research
Treatment	Appropriate and timely antibiotic treatment	The pathogens of VAP changes by unit, hospital, country and time of mechanical ventilation. Appropriate empiric antibiotic treatment decreases the probability of worse clinical evolution and prognosis	• How should we define unit-specific empiric antibiotic treatment guidance for VAP? • What is the role of new antimicrobial agents as either empiric or definitive therapy? • What is the ideal duration of antibiotic treatment for microbiological defined and non-defined VAP? • Is there still a place for the use of biomarker-guided antibiotic therapy on improving clinical outcomes and better antibiotic use for VAP compared with clinical bedside assessment?
Treatment	Multi-drug-resistant pathogens	The incidence of multi-drug-resistant pathogens in VAP can be high, but it has a multi-factorial causes. Initial clinical severity presentation is not associated with multi-drug resistance	• What is the role of aerosolized antibiotics in VAP caused by multi-drug-resistant pathogens? • Which target antibiotic treatment is better to treat multi-drug-resistant pathogen?

ARDS Acute Respiratory Distress Syndrome; *ICU* Intensive Care Unit; *VAP* Ventilator-associated Pneumonia; *VAT* Ventilator-associated Thracheobronchitis

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Declarations

Conflicts of interest
AT: Advisory board or lectures (Pfizer, MSD, Janssen, Menarini).

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