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## ICU Volume 15 - Issue 1 - 2015 - Cover Story - The Lung

### Nosocomial Pneumonia



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This review discusses some of the key advances from the 2005 ATS / IDSA guidelines publication and emphasises future research for unsolved issues.

Ten years have passed since the publication of the American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) guidelines on nosocomial pneumonia (NP) (2005), which defined three different conditions regarding where or when the infection was developed. NP was defined as:

- a lower respiratory infection that develops in a hospitalised patient 48 hours or more after admission;
- and no evidence of presence or incubation of this was noticed at the time of admission.

Hospital-acquired pneumonia (HAP), ventilator associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP) were defined by expert opinion regarding clinical, image and laboratory findings. Recently, new data in respect to epidemiology, aetiology, diagnosis and treatment have been published. Some authors disagree on the definition of HCAP (Ewig et al. 2012). We believe that this group of patients represents a heterogenous population associated to specific comorbidities that should be taken into account.

NP increases costs, mechanical ventilation days (MVD) and hospital and ICU length of stay (LOS), so there should be no surprise that efforts from hospital administrations are aimed at preventing NP. In spite of these efforts, NP remains the second most common cause of nosocomial infection worldwide (Vincent et al. 2009).

#### Mechanisms of Disease

The lung gets infected via aspiration, inhalation or by haematogenous spread. The most common route of infection in NP is, by far, microaspiration from oropharyngeal and upper digestive tract secretions into the trachea. A dysregulation between normal host defences and the ability of microorganisms to colonise and invade the lower respiratory tract occurs. This becomes more evident in patients with an endotracheal tube that overcomes these defences, impairs mucociliary function, and accumulates secretions above the endotracheal cuff, favouring repeated microaspiration.

A depression of complement, cyclic adenosine monophosphate and calcium signalling pathways during preinfection phase were noticed in VAP patients when compared to ventilator-associated tracheobronchitis (VAT) patients (Martin-Loeches et al. 2012). Recently Rautanen et al. (2015) found some variants in the FER gene that were associated with a reduced risk of death from sepsis due to pneumonia. Further research should elucidate whether this is associated with NP.

#### Organisms

Microbiology on NP, as with any of the nosocomial infections, has evolved in the last years. Older patients and a global rise in multidrug resistant

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pathogens (MDR) have contributed to this. An international surveillance programme of NP in Europe, North and Latin America has identified the top six pathogens isolated: *Staphylococcus aureus* (28%) *Pseudomonas aeruginosa* (21.8%) *Klebsiella* species (9.8%) *E. coli* (6.9%) *Acinetobacter* species [6.8%], and *Enterobacter* species (6.3%) (Jones 2010). Four of the ESKAPE pathogens ( *Enterococcus faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. Aeruginosa* and *Enterobacter* species) constitute around 80% of ventilator-associated pneumonia (VAP) episodes (Sandiumenge et al. 2011; Koulenti et al. 2009; Eperatti et al. 2010; Kollef et al. 2005; Lee et al. 2013; Canadian Critical Care Trials Group 2006)

According to most guidelines NP should be empirically treated with broad-spectrum antibiotics trying to cover for MDR pathogens. Local high prevalence of potentially resistant microorganisms (PRM) and the presence of severe sepsis/ septic shock without the classical risk factors for PRM according to the 2005 ATS/IDSA guidelines have been associated as independent risk factors for PRM as the causative pathogen in HAP/VAP patients, reducing inappropriate therapy and improving outcome (Martin-Loeches et al. 2013).

The previous division based on time of onset of VAP can be improved, as recent studies reported that microorganisms involved in both early and late VAP were no different regarding time of onset (Gastmeier et al. 2009), nor even when MDR are involved (early-onset 27.8%, late-onset 32.3%,  $p=0.33$ ) (Restrepo et al. 2013). Even in immunosuppressed populations, such as lung transplant recipients, organisms causing VAP and VAT remain similar (Riera et al. 2014). This could lead to delay in the start of adequate treatment, which is associated with worse outcomes.

Some considerations must be taken into account regarding Methicillin-resistant *Staphylococcus aureus* (MRSA) VAP. Previous antibiotic exposure, extended admission to hospital, underlying chronic obstructive pulmonary disease and steroid use have been associated as risk factors. MRSA has been independently associated with an almost 50% higher likelihood of hospital death when compared with methicillinsusceptible strains (Hanberger et al. 2011), but local prevalence should be considered to initiate empirical treatment. American and European guidelines recommend vancomycin or linezolid for treatment of MRSA VAP, but which one to start with is still a dilemma. Linezolid has shown better clinical cure and survival (Kollef et al. 2004), but no differences in mortality (Wunderink et al. 2012). Vancomycin adverse events are an important reason to recommend linezolid in immunosuppressed patients, those receiving concomitant administration of nephrotoxic drugs, for severe sepsis and elderly patients (Rello et al. 2014).

*P. aeruginosa* is the second most isolated pathogen in VAP (PA-VAP), and patients at risk for *P. Aeruginosa* infection should receive combination treatment at onset to decrease probability of wrong initial treatment. Risk factors for MDR *P. aeruginosa* infection are prior antibiotic exposure, admission from chronic care facilities, old age, diabetes, long-term treatment in hospital, use of invasive devices, recent surgery, extended ICU stay, extended ventilation periods and higher illness severity scores (Rello et al. 2013a). Vasopressors on the day before PA-VAP, delay to treatment <12 days and susceptibility of pathogen have been associated with discharge without recurrence of VAP. Interestingly *Pseudomonas* resistance is not significantly associated with death or VAP recurrence, but delays ICU discharge (Planquette et al. 2013). Serotype of *P. aeruginosa* has been associated with mortality and clinical resolution. Outcomes tend to be worse in patients infected by serotype O1 or O11 and better in patients infected by serotypes O2, NT [not typeable] and O6 (Lu et al. 2014). This might be associated with distribution of virulence factors.

## Diagnosis

NP represents a daily challenge to clinicians, due to subjectivity and lack of a gold standard, particularly in patients with mechanical ventilation. Purulent secretions are a cornerstone in the diagnosis of lower respiratory tract infection – ventilator-associated respiratory infection (VARI). Some milestones have been proposed throughout the years (see Figure 1). Stevens and colleagues (2013) found almost no agreement among hospitals about the presence or absence of VAP in each case presented, suggesting that the previous Centers for Disease Control and Prevention (CDC) definition of VAP had the same precision as flipping a coin.

1985: BAL Intracellular organisms  
1990: Quantitative cultures  
1995: ATS/IDSA Guidelines  
1999: Consideration of local variability  
2003: The Tarragona Strategy  
2006: One versus two weeks of AB treatment  
2009: EUVAP Study  
2012: VAT paradigm  
NP=nosocomial pneumonia, BAL=bronchoalveolar lavage, ATS/IDSA=American Thoracic Society/Infectious Diseases Society of America, AB=Antibiotic, EUVAP=Pneumonia in Patients requiring mechanical ventilation in European Intensive Care Units, VAT=Ventilator-associated tracheobronchitis

**Figure 1.** Milestones in Management in NP

In recent years increasing concern has been directed to ventilator-associated tracheobronchitis (VAT). Patients with VAT must have clinical signs (fever, leukocytosis and purulent sputum), microbiologic findings, but no new opacities on the chest x-ray. It could be a precursor of VAP or present as a different entity, as shown by Dallas et al. (2011), reporting a median onset of VAT of 7.5 days after intubation and mechanical ventilation, compared to five days for the development of VAP. Antibiotic treatment directed to VAT has been associated with greater number of days free of mechanical ventilation (Nseir et al. 2008), and might prevent later VAP episodes (Nseir et al. 2014).

In an effort to improve accuracy and objectivity, the CDC has launched a new surveillance programme (Centers for Disease Control and Prevention 2015). It shifts the focus not only to pneumonia, but also towards a syndrome characterised by respiratory worsening while on mechanical ventilation. This approach provides three major advantages: it sidesteps the limited accuracy of VAP surveillance definitions,

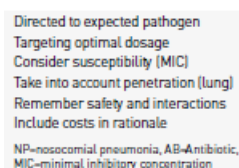
broadens the focus to include additional morbid events, beyond just pneumonia, and allows objective surveillance based on objective and measurable parameters. It ignores pathogens. Unfortunately, the correlation between new surveillance categories with the previous definition of VAP seems poor (Muscedere et al. 2013; Klein Klouwenberg et al. 2014), whereas the presence of these complications has been associated with a worse outcome. Whether these complications are preventable is yet to be assessed. A large multicentre validation is ongoing (European Society of Clinical Microbiology and Infectious Diseases 2014). Currently, this tool should be used only for surveillance.

Old techniques have erupted with new enthusiasm in pneumonia diagnosis, such as lung ultrasound: in community-acquired pneumonia (CAP) it showed a sensitivity of 93.4% and specificity of 97.7% in diagnosis (Reissig et al. 2012). A recent meta-analysis suggests that in expert hands it performs well in diagnosing pneumonia, and its use should be encouraged (Chavez et al. 2014). The newly proposed score, Chest Echography and Procalcitonin Pulmonary Infection Score (CEPPIS), combining clinical, oxygenation, microbiological, procalcitonin (PCT) levels and lung ultrasound to diagnose pneumonia showed promising results (sensitivity 80.5%, specificity 85.2%) when compared to Clinical Pulmonary Infection Score (CPIS) >6 (sensitivity 39.88% and specificity 83.3%) (Sinoff et al. 2013).

Prompt identification of the causative pathogen is an area of constant research. We believe that a point-of-care test able to identify quickly and accurately resistance genes should improve right initial treatment and outcome. This should be a priority area of research.

## Treatment for NP

Treatment of NP should never be delayed. Initiation according to the guidelines has been widely studied, favouring adequacy of treatment (Ferrer et al. 2010), clinical improvement, lower costs and better survival in the adherent group (Wilke et al. 2011). The Improving Medicine through Pathway Assessment of Critical Therapy in Hospital-Acquired Pneumonia (IMPACT-HAP) investigators showed that non-adherence to guidelines decreased 28-day mortality compared to guideline-compliant patients in 303 patients in four centres in the United States (Kett et al. 2011). Starting treatment of HCAP according to the presence of risk factors for MDR microorganisms demonstrated in 321 patients that only 53% received broad-spectrum antibiotic (AB) empiric therapy, yet 92.9% received appropriate therapy (Maruyama et al. 2013). We know that bacterial burden is high within the first hours of pneumonia onset, whereas persistent inflammatory response remains in spite of eradication of organisms. An effective AB prescribing bundle should be based on the right drug, at the right time, at the right dose and right duration (Rello 2013b) (See Figure 2).



Directed to expected pathogen  
Targeting optimal dosage  
Consider susceptibility (MIC)  
Take into account penetration (lung)  
Remember safety and interactions  
Include costs in rationale

NP=nosocomial pneumonia, AB=Antibiotic,  
MIC=minimal inhibitory concentration

**Figure 2.** Main Drivers to Prescribe AB in NP

Reports regarding VAT and its impact on outcome and LOS suggest the need to initiate treatment with the same criteria, but further studies are required to assess duration.

Most patients are underdosed, particularly young trauma patients after pneumonia onset. Therefore antibiotic dosage should be personalised in critically ill patients. Low therapeutic levels with standard doses of betalactams have been reported, and associated with worse outcomes (Roberts et al. 2014), especially with multiple organ dysfunction syndrome (Uldemolins et al. 2011).

Nebulised antibiotics are a promising approach, and they achieve high concentrations in lung tissue-minimising systemic absorption. High doses of colistin (5 millions of international units [mIU]/ 8 hours) are safe and effective in VAP caused by non-fermenter Gram-negative bacteria (Lu et al. 2012), whereas low doses (1 mIU/ 8 hours), effective for VAT or cystic fibrosis could be insufficient to treat it (Magretet al. 2010). A standardised administration protocol requiring vibrating mesh nebulisers might optimise outcomes. More evidence and guidelines are required before implementing this promising way to overcome MDR organisms. Adverse events, such as systemic penetration and restricted use in severe hypoxaemic patients are a limitation of implementation.

## Outcome

NP increases hospital LOS, mechanical ventilation days and ICU LOS. Mortality of NP is controversial. A prospective observational study in European ICUs reported mortality of 42.6% in patients without trauma and 17.2% when trauma was present (Lu et al. 2014). Another large study concluded that only 4.4% of deaths in the ICU on day 30 and 5.9% on day 60 could be attributable to VAP (Bekaert et al. 2011). However, a large meta-analysis reported an estimated attributable mortality of VAP around 13% (Melsen et al. 2013); high attributable rates were noticed in patients undergoing surgery and with an intermediate Acute Physiology and Chronic Health Evaluation II score (APACHE II) between 20 and 30. The lack of a gold standard method to diagnose VAP and variability in treatment can explain these results. Future studies to prevent VAP and therapeutic randomised control trials should incorporate this information in inclusion and exclusion criteria for enrolment.

## Prevention

VAP bundles have proved to lower VAP rates in ICUs where implemented (Rello et al. 2013c; Sinuff et al. 2013). Outcome parameters should be the endpoints. Elective *P. aeruginosa* vaccination or immunotherapy to block virulence in high-risk patients for PA-VAP is a potential approach

that requires further research. Genomics and new specific biomarkers should be investigated in order to improve initiation treatment and outcome.

## **Conclusion**

VAP management requires an individualised approach. Incorporation of biomarkers, molecular diagnosis techniques and echography might improve diagnosis. A new paradigm of ventilator-associated respiratory infections (VARI), incorporating tracheobronchitis is required. Preventive measures should focus on improving outcomes.

## **Acknowledgements**

Financial support: None.

The authors have no conflict of interest regarding this paper.

Published on : Fri, 13 Mar 2015