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MRSA Management: A Cost Efficiency Problem

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A recent meeting in Berlin gathered six experts in the field of ventilator associated pneumonia (VAP) to present an overview of the many aspects related to VAP that remain poorly defined. In part I of this report (ICU Management, March 2008), we highlighted the discussions surrounding the epidemiology and pathophysiology of VAP. In this second part, we will focus on controversies surrounding the diagnosis and management of VAP.

Agreement and Controversy in Diagnosis of VAP

General Agreement

There is general agreement that the diagnosis of VAP can be difficult! There is also agreement that an accurate diagnosis is crucial in enabling rapid initiation of antimicrobial therapy when needed and in avoiding unnecessary antimicrobials in patients who are not infected.

Ongoing Controversy

The best means of making a diagnosis is perhaps the most controversial area in the field of VAP. The main problem is that there is no gold standard against which other techniques can be compared.

There are two main approaches to the diagnosis of VAP: Non-invasive, based largely on clinical features and endotracheal aspirate cultures; and invasive, based on quantitative culture of secretions collected by invasive techniques.

Non-Invasive, Clinical Approach

Many of the standard diagnostic features of pneumonia, e.g., fever, leukocytosis, purulent sputum, are unreliable and nonspecific in the critically ill, mechanically ventilated patient. The chest X-ray, an important part of the non-invasive diagnostic approach, has reasonable sensitivity but specificity is low as several conditions can mimic or hide the chest X-ray features of VAP, including atelectasis, cardiogenic edema, acute respiratory distress syndrome, pulmonary embolus, pulmonary fibrosis. Combining chest Xray findings with other clinical features increases specificity, but reduces sensitivity. The Clinical Pulmonary Infection Score (CPIS), which includes five components - temperature, blood leukocyte count, tracheal secretions, oxygenation index, and chest X-ray - can also be used. In the original study, the diagnostic accuracy of the CPIS was quite good (Pugin et al, 1991); however, later studies did not confirm these results (Luyt et al, 2004). Sequential measures of biomarkers, like C-reactive protein (CRP) or procalcitonin (PCT), perhaps combined with the CPIS, may help improve the specificity of the clinical approach to diagnosis.

The clinical approach generally uses cultures of endotracheal secretions to aid diagnosis. Qualitative cultures of endotracheal aspirates are often not reliable enough to make a diagnosis of VAP as it is difficult to distinguish between colonising and pathogenic organisms, although a sterile culture in a patient without previous exposure to antibiotics suggests that VAP is unlikely. Quantitative cultures provide more reliable microbiological data but are not available everywhere as they are time-consuming and more costly.

The main advantages of the clinical approach are that it is non-invasive and requires no specialist equipment or skills.

Invasive Approach

The invasive approach replies more heavily on obtaining quantitative cultures of secretions by various techniques, including bronchoalveolar lavage (BAL) fluid culture, plugged telescoping catheter, and protected-specimen brush (PSB). The diagnostic accuracy of these techniques is generally good with high sensitivity and specificity although sensitivity depends on the cut-off thresholds chosen to distinguish between colonisation and infection. Importantly, diagnostic accuracy is dependent on several factors including appropriate selection of the sampling area and appropriate timing, ideally before introduction of new antimicrobial therapy, as accuracy decreases if performed after new antibiotics are introduced (Prats et al, 2002). Non-bronchoscopic, or mini-invasive, techniques have also been developed. These techniques have reasonable sensitivity and specificity, and seem to represent an attractive alternative to bronchoscopic techniques (Campbell, Jr., 2000). They are also associated with few complications, require fewer technical skills, and can be easily repeated at the bedside.

Advocates of the invasive approach argue that it enables a more accurate microbiological diagnosis to be made, thus assisting with antibiotic choices and reducing unnecessary antibiotic use. In addition, de-escalation may improve outcomes and invasive techniques may help in making de-escalation decisions (Giantsou et al, 2007). However, opponents argue that the invasive approach has several drawbacks, including that accuracy is strongly dependent on sampling time, results are not always reproducible and consistent, early forms of infection may be missed, specialised operator skills are required for bronchosopic techniques, microbiological collaboration is required, and there are few data that suggest that these strategies actually have any impact on outcomes.

Three randomised studies (Ruiz et al, 2000; Sanchez-Nieto et al, 1998; Sole et al, 2000) compared the use of invasive versus non-invasive techniques on outcomes and reported no differences in morbidity or mortality; however, these studies were limited by the small numbers of patients included, and by the fact that physicians did not adjust antibiotic therapy in many cases even when cultures were negative. In a study by Fagon et al (Fagon et al, 2000), organ failure rates and mortality rates were higher in patients managed according to a non-invasive protocol compared to those managed by an identical protocol but with invasive sampling. However, this study compared qualitative endotracheal aspirate culture with quantitative invasive cultures, thus limiting interpretation of the results. Finally, a recent prospective cohort study suggested no overall difference in mortality rates in patients managed with a clinical versus an invasive approach (Canadian Critical Care Trials Group, 2006). However, limitations in this study, including a high ratio of initially inappropriate therapy in the invasive group, exclusion of patients infected by MRSA or Pseudomonas, some of the most common but also most problematic pathogens in VAP, and poorly performed de-escalation therapy in the invasive group, again restrict the conclusions that can be drawn.

Currently, therefore, the jury is still out regarding the best approach to diagnosing VAP, despite recent American

Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines (2005) encouraging the use of quantitative lower respiratory tract cultures.

Agreement and Controversy in the Antimicrobial Treatment of VAP

General Agreement

All experts agree that the aim of antimicrobial therapy in VAP is to target the most likely causative organism with the most appropriate antibiotic(s) as early as possible. There is little doubt that correct choice of initial antimicrobial therapy is associated with better outcomes in patients with VAP. Importantly not only spectrum, but also dose, route, and timing, must be considered when selecting antibiotics, and collaboration between intensivists and microbiologists can facilitate these decisions. Multiple factors can affect antibiotic doses in ICU patients, including haemodilution, permeability alterations, hypoalbuminaemia, renal dysfunction, haemodialysis. It is possible that higher doses are needed in ICU patients than in other patient groups, and this warrants further study.

If broad-spectrum antibiotics are given empirically, the spectrum should be reduced as soon as culture results become available as prolonged antibiotic therapy may be harmful; nevertheless, doctors seem to be reluctant to change antibiotics even when they have results to suggest they should (Aarts et al, 2007)!

Importantly, antimicrobial therapy needs to be tailored to the particular locality as each unit has its own, unique pattern of colonisation and infection. General guidelines must be individualised by each unit as giving antibiotics to one patient can modify local microbiological patterns and hence affect treatment for other patients for the near future!

Ongoing Controversy

The first area of controversy in terms of antimicrobial therapy is whether to give one or more empiric antibiotics. Giving one effective drug may be adequate if the drug is indeed effective against the microorganism in question; however, if there is any uncertainty about likely microbes it is probably better to start with two drugs, and to simplify therapy when microbiological results are known. The ATS/IDSA guidelines (2005) recommend combination therapy in patients with resistant organisms but no data have actually shown any benefit of combination over monotherapy in this situation. The recently updated Surviving Sepsis Campaign guidelines (Dellinger et al, 2008) make a weak 2D recommendation in support of two agents in cases of sepsis associated with P. aeruginosa.

Duration of therapy is another area of controversy. The Surviving Sepsis Campaign Guidelines (Dellinger et al, 2008) suggest (1D) that 7-10 days is adequate for most but may need to be extended in patients who have a slow clinical response or associated deficiencies, including neutropenia. Duration probably needs to be assessed according to each patient's clinical course, but sequential sepsis marker values, e.g., CRP or PCT, may provide useful confirmation.

Summary

Despite considerable research in the field of VAP, many areas remain controversial. However, while, or perhaps by, focussing on the controversies of VAP, this summit also highlighted several key areas of overall agreement: First, VAP is an important complication of mechanically ventilated ICU patients and is associated with considerable morbidity and costs, and possibly excess mortality. Second, development of newer rapid tests and antibiograms (Bouza et al, 2007) is an important step forward in the diagnosis of VAP. Third, inadequate initial therapy of VAP is associated with higher mortality, length of stay, and costs. Fourth, antimicrobial therapy should be targeted at the likely pathogen, guided by local microbiological patterns, and adjusted based on susceptibility patterns and clinical resolution. Finally, despite progress in recent years, there is still much room for improvement in terms of diagnosis, therapy, and prevention of VAP.

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