SEVERE PULMONARY INFECTIONS

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Prevention and treatment of severe pulmonary infections is the subject of this issue's cover story. Lung infections are common in the ICU and have a number of challenges in prevention, diagnosis and treatment.

First, Dr. Matthieu Boisson and Prof. Olivier Mimoz outline measures for the prevention of ventilator-assisted pneumonia (VAP), which they think must be a priority in the management of critically ill patients. The incidence of VAP has been hard to measure in the absence of objective diagnostic criteria. Dr. David Pearson and colleagues discuss the need for objectivity for surveillance of patients treated by mechanical ventilation, in the context of the U.S. Centers for Disease Control and Prevention's Ventilator Associated Event diagnostic key. It is important that this new tool is validated, to provide objective validated criteria for the diagnosis of ventilator-associated events. Next, Prof. Michael Niederman describes recent findings in the use of aerosolised antibiotics in mechanically ventilated ICU patients, and argues that it may be time to reevaluate their use for therapy of lower respiratory tract infection.

In the final article in our Sepsis series, Prof. Martin Matejovic and colleagues look at the ongoing debate on the role of haemodynamic alterations in sepsis-related renal failure.

In the Matrix section, Prof. Samuel Tisherman reviews the role of therapeutic hypothermia in severe trauma, which may be of benefit for haemorrhagic shock, traumatic cardiac arrest, traumatic brain injury and spinal cord injury. Next, Prof. Terence Valenzuela looks at the potential of ischaemic conditioning, including preconditioning, preconditioning and postconditioning, for neuroprotection in stroke.

In the Management Section, Univ.-Prof. Gernot Marx and Mr. Rainer Beckers discuss the promise of tele-intensive care medicine in improving healthcare outcomes, workflow, efficiency and quality.

As we approach the 100th anniversary of World War I, it is salutary to be reminded of the advances in military medicine. Mobile critical care in combat, and the benefits flowing on for remote critical care and evacuation of civilians in natural disasters, is the subject of the article by Lieutenant Colonel Michael Reade. Next, Dr. Chris Subbe highlights the impact of rapid response teams on the ICU. Such teams improve referral to the ICU and affect rates of admissions. Further improvements may be gained through advances in technology.

Prof. Jan Bakker is well-known for his research on blood lactate. He is interviewed for this issue on this and other interests, which include ethics and end-of-life care.

Our Country Focus is Saudi Arabia. Dr. Mariam Alansari and Prof. A.H. Alzeer discuss the Kingdom of Saudi Arabia's healthcare framework for Haj, the annual mass gathering of pilgrims to Mecca, which brings unique challenges.

As always, if you would like to get in touch, please email **editorial@icu-management.org.**

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PREVENTION OF VENTILATOR-ASSOCIATED PNEUMONIA

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Introduction

Healthcare-associated infections have become a challenge in public health policy. In critically ill patients, ventilator-associated pneumonia (VAP) is the most frequent healthcare-associated infection. Depending on studies, 10% to 30% of ventilated patients will develop a VAP during their ICU stay (Chastre et al. 2002). VAPs account for heightened morbi-mortality, lengthened stays in intensive care and increased treatment costs. These infections also trigger a rise in the consumption of antibiotics, which favours the development of bacterial resistance. Therefore, decreasing VAP incidence must be a priority in the management of critically ill patients.

Physiopathology of VAP

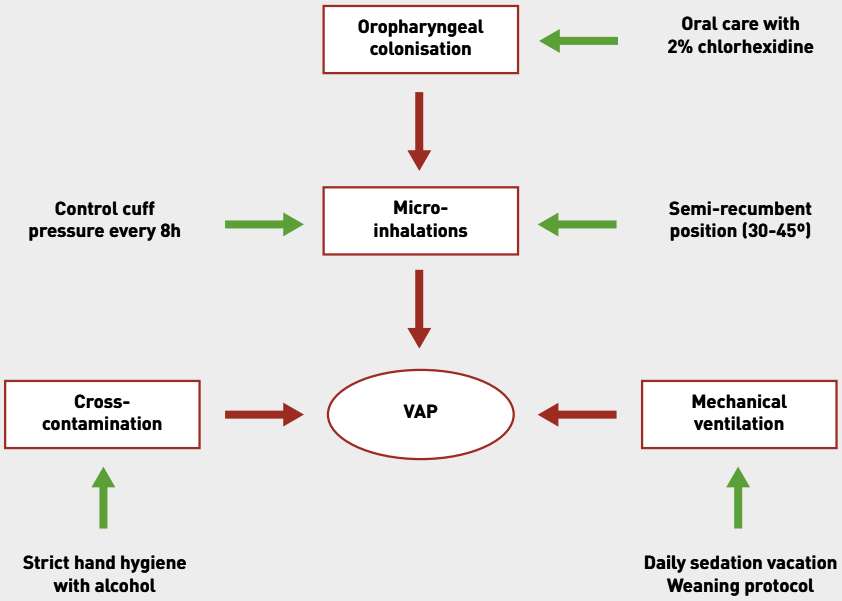
Enhanced knowledge of the complex physiopathology of VAP has led to the development of effective preventive strategies (see Figure 1). Colonisation of the upper and digestive airways by micro-organisms originating in the patient or coming from another patient through cross-transmission is the predominant mechanism of initiation. Fostered and favoured by the presence of a tracheal tube, it is at the origin of tracheal colonisation through the bacterial aspiration resulting from the passage, around the tube cuff, of oropharyngeal secretions in the vicinity of the trachea and the lower respiratory tract (Kollef 2004).

General Rules

Prevention measures are primarily based on the universal principles of standard hygiene. They are meant to prevent cross transmission of pathogens. These measures include basic hygiene: alcohol-based hand rubbing, wearing gloves for one patient - one activity. Screening for carriage of methicillin-resistant Staphylococcus aureus (MRSA) and other multi-drug resistant bacteria according to local ecology, and the use of contact precautions should be utilised to prevent cross-contamination (Siegel et al. 2007). Staff training with regard to these measures helps to ensure respect of their application.

More recently, universal decolonisation with intranasal mupirocin and daily bathing with chlorhexidine-impregnated cloths has been shown to be more effective than screening and isolation to prevent healthcare-associated infections (Huang et al. 2013). However, the lack of impact on the incidence of non-staphylococcus infections and the risk of the development of resistance to mupirocin and/or chlorhexidine with their wide use are limitations

Figure 1. Diagnostic Key for Ventilator-Associated Events



to the generalisation of this practice.

Avoiding Mechanical Ventilation Whenever Possible

While intubation and mechanical ventilation are major risk factors for VAP, recourse to non-invasive ventilation (NIV)is a safe and interesting alternative means of risk reduction. Indeed, its use is safe and effective to prevent VAP compared to the use of invasive mechanical ventilation (Hess 2005; Squadrone et al. 2005).

If intubation and duration of mechanical ventilation are among the most recognised risk factors for VAP, the first days of ventilation are the riskiest of all. As a result, early weaning from the ventilator and extubation should be considered as soon as the clinical situation allows for them. Excessive sedation/analgesia prolongs the duration of mechanical ventilation. Application of a sedation/analgesia algorithm integrating daily interruption of sedative drugs and daily spontaneous breathing trials is to be recommended (Girard et al. 2008). Conversely, failure of weaning leading to reintubation has been identified as a risk factor for VAP, of which incidence is heightened in the event of accidental extubation (de Lassance et al. 2002).

Limiting Micro-Inhalations

Intubation should preferably be orotracheal. Keeping a sufficient level of pressure in the tube cuff of the tracheal tube is of fundamental importance in limiting micro-aspirations. Ideally, pressure should be maintained between 20 cmH_2O (15 mmHg) and 30 cmH_2O (22 mmHg). If it is too low, there exists a risk of inhaling the subglottic secretions accumulated from the oropharynx, which is known to take on a preponderant role in VAP incidence. Regular monitoring of tube cuff pressure is consequently recommended, but its optimal frequency has yet to be clearly determined. To reduce these risks, automatic devices allowing for continuous regulation of tracheal tube cuff pressure have been developed. In a randomised study, the percentage of patients with a micro-inhalation of gastric contents was half lower in the group of patients where tube cuff pressure was maintained by a pneumatic system than in the control group where tracheal tube cuff was maintained by verification and adjustment 3 times a day with a manual manometer (Nseir et al. 2011). Moreover, the microbiologically confirmed VAP percentage had significantly diminished in the intervention group compared to the control group (9.8% vs. 26%; p = 0.032).

The interest of the semi-recumbent position has been assessed in several studies. The randomised and pioneering study by Drakulovic et al. compared the strictly supine rest position to the semi-recumbent position (objective 45°). Whether diagnosis was clinical or microbiological, the authors found a significant VAP reduction. Nevertheless, a recent multicentre prospective study compared the semi-recumbent position (objective 45°) to a position characterised as 'standard' (Van Nieuwenhoven et al. 2006). Notwithstanding monitoring more than once a day by a dedicated staff, the objective of 45° was reached in only 15% of the patients; mean angulation oscillated over the first week between 23° and 29°, while in standard position patients, its oscillation ranged from 10° to 15°. Given these clinical conditions, VAP incidence did not differ from one group to the other. It would consequently appear that even if the principle of a head-up position is accepted, the level of elevation to be reached remains undetermined; either an objective of 45°, which is difficult to attain, or else an objective ranging from 30° to 45°, which is more realistic, should be preferred.

Closed tracheal suction systems have been proposed to limit the risk of VAP. Unfortunately, threemeta-analyses have not found the closed system to be preferable in terms of lower VAP incidence, mortality or duration of stay in intensive care; as a result, it is not recommended(Subirana et al. 2007). The potential benefits of diminished crossed transmissions through this suction system have likewise failed to be demonstrated (Jongerden et al. 2007).

Subglottic secretion drainage is possible through use of a tracheal tube equipped with an orifice located above the cuff. Numerous studies have been conducted, and their findings have been summarised in a meta-analysis (Muscedere et al. 2011), showing that the use of subglottic aspiration is associated with a reduction of VAP risk. In parallel, duration of ventilation and stay in intensive care were significantly reduced, but without any effect on mortality and duration of hospital stay.

> *"Decreasing VAP incidence must be a priority in the management of critically ill patients"*

Limiting Oropharyngeal Colonisation

In intubated patients the modifications of saliva, with reduction of both its amount and the immune factors concentration, facilitates oropharyngeal microbial proliferation (Bonten et al. 1996). To limit this phenomenon, several ways have been proposed. Selective digestive decontamination (SDD), when associated with systemic antibiotic therapy, brings down VAP incidence (D'Amico et al. 1998) and mortality (Vandenbroucke-Grauls et al. 1991), while SDD alone reduces nothing other than the incidence of VAP. In spite of the interest of the aforementioned results, this preventive method is only marginally used and has not been included in the most recent recommendations. The probable reason for this reluctance resides in an ecological risk along with the potential emergence of multi-resistant bacteria(Daneman et al. 2013).

Oropharyngeal decontamination through local application of an antiseptic(chlorhexidine or povidone-iodine) for the purposes of limiting local flora represents another interesting method of VAP prevention. A meta-analysis involving 2481 patients showed some VAP diminution (Labeau et al. 2011). The benefits of chlorhexidine are more substantial in cardiothoracic surgery patients or when a high concentration (2%) is used.

Conclusion

Many specific preventive measures have been studied to reduce the incidence of VAP. The most important include oro-tracheal intubation, maintaining tube cuff pressure between 25 and 30 cmH_2O, use of a sedation-analgesia algorithm allowing for early weaning from ventilation, privileging use of non-invasive ventilation, the semi-recumbent position at 30-45°, and regular nasal and oro-pharyngeal decontamination with chlorhexidine. All these measures must be used in bundles. ■

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Kimberly-Clark

VAP, VAC, IVAC AND VENTILATOR-ASSOCIATED EVENTS:

THE NEED FOR OBJECTIVITY FOR SURVEILLANCE

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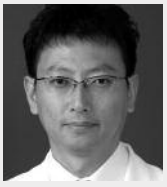

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The novel U.S. Centers for Disease Control and Prevention's Ventilator Associated Event (VAE) diagnostic key will enable sensitive tracking of all significant pulmonary complications of mechanical ventilation. The use of objective, validated criteria will provide more accurate and reliable data for local audit and interhospital benchmarking. We anticipate that it will replace VAP incidence as a quality assurance tool in critical care.

Background

The incidence of ventilator-associated pneumonias (VAPs) has long been considered the reference benchmark for guiding continuous quality improvement in mechanically ventilated patients. In recent times, however, its validity as a tool for such surveillance has been called into question. This article will discuss the evolution of ventilator-associated pneumonia into the ventilator-associated event (VAE) and the importance of now validating this tool for use in both internal and external quality assurance processes.

Ventilator-Associated Pneumonias

A VAP is diagnosed when a mechanically ventilated patient satisfies certain systemic, clinical and pulmonary criteria (Horan et al 2008). Within these diagnostic criteria scope for subjectivity exists, resulting in an algorithm favouring sensitivity over specificity for VAP diagnosis. As the treatment of VAPs is antibiotics, the knock-on implications for this lack of specificity, in terms of antimicrobial stewardship, are clear. There remains no gold standard for VAP diagnosis in vivo, and, as a consequence, VAP prevalence is very difficult to quantify accurately. Evidence from prevention-targeted randomised controlled trials would suggest that this figure lies somewhere between 16% and 21% (Lorente et al 2012; Rello et al 2002; Rello et al 2013; Barbier et al. 2013; Melsen et al. 2013). Compounding this baseline variation is a lack of objectivity within some of the diagnostic criteria, reflected both in a widespread inter-observer variability in VAP diagnosis (Klompas 2008), and in post-mortem studies revealing that as many as half of all cases are misdiagnosed (Tejerina et al. 2010). Mathematical modelling has also been able to demonstrate that the prevalence of other pulmonary conditions will affect the rate of VAP diagnosis, despite a constant, fixed VAP incidence (Klompas et al. 2008).

Several bodies have attempted to standardise and increase the specificity of diagnostic criteria (Lorente et al. 2012; Torres et al. 2009; Guidelines 2009), of which the Centers for Disease Control and Prevention (CDC)'s version is the most widely utilised. Studies performed at the CDC's prevention epicentres by Klompas and colleagues (Klompas et al, 2011) advanced this by replacing subjective criteria with objective, quantifiable data for pulmonary deterioration where possible. They then applied this modified VAP definition to retrospective data, and were able to demonstrate improved capacity to predict 'hard' outcomes of duration of mechanical ventilation, ICU length of stay and mortality when compared with their traditional VAP definition. Although clearly demonstrating an association between objective data and clinically relevant outcomes, this revised tool did not increase specificity for VAP diagnosis.

Importance of VAP

For the very reasons outlined above, ascribing accurate attributable mortality to VAP is fraught with confounding issues. A recent meta-analysis concluded that the overall attributable mortality of VAP is 13% (Melsen et al 2013). Original patient data were taken from 24 randomised controlled trials assessing a broad range of VAP prevention techniques. VAP incidence was most commonly the primary outcome rather than mortality. Acknowledging that no gold standard exists for VAP diagnosis, the authors grouped included studies into categories, depending upon whether invasive specimens were required as part of the diagnostic key or not, thus allowing for regional variation in practice. Noteworthy here is an Australian-wide study showing little if any use of bronchoalveolar lavage in the diagnosis of VAP (Boots et al. 2005). As suspected, there was a variation between subgroups with higher rates for surgical patients and patients with mid-range severity as expressed by acute physiology and chronic health evaluation (APACHE) and simplified acute physiology score (SAPS) at admission (Melsen et al. 2013). The authors of the meta-analysis concluded that

the predominant cause of this increased risk of dying was the prolonged exposure to intensive care therapies (Melsen et al. 2013).

Quality Assurance

Any quality assurance marker must be evidence-based, clinically relevant and have optimal sensitivity and specificity. In addition, when used as a surveillance tool, it must be sufficiently common and preventable to have a demonstrable impact upon morbidity and mortality. As a subdivision of nosocomial infection, VAPs fulfill some of these criteria, but what is not often reported is the non-modifiable contribution to their aetiology. As an example, it would be hard to believe that an elective post surgical patient has the same baseline risk profile as a complicated medical patient; so it would not be fair to draw conclusions on standards of underlying care based solely on VAP incidence. Further emphasising the unreliability of this data was a study by Klouwenberg and colleagues (2013), who were able to demonstrate concordance in diagnosis of just 35%, for the same patient cohort, between different personnel responsible for surveillance reporting. As a tool for internal audit, if confounders of personnel and diagnostic criteria can be controlled for, then VAP surveillance may be of use, but when the generated data is used for external inter-ICU comparison then the impact of confounding bias is too great. Many interventions and 'bundles' have targeted VAP prevention (Melsen et al. 2013; Bouadma et al. 2012), with subsequent falls in VAP rates. However, a failure to reliably improve upon 'hard' clinical outcomes such as length of stay and mortality would suggest that in addition to the intervention, surveillance artifact may be present. Although this discordance between VAP rate lowering and static mortality rates may just relate to a failure to power for these outcomes, a more sinister aetiology may be true: in an era where financial disincentives are applied to perceived poor clinical performance, some hospital administrators have been accused of 'playing' the system to avoid penalty (Magill and Fridkin 2012). In the UK, the NHS has placed the responsibility for data integrity firmly at the feet of clinicians, advocating for firm clinician engagement in developing quality assurance tools. In turn, this has led to some campaigning for the abandonment of VAP incidence as a quality assurance tool in favour of newer markers (Shorr and Zilberberg 2012).

In regards to ventilator-associated events, whilst VAPs may be the most frequently documented they are far from the only complication of mechanical ventilation. Barotrauma, atelectasis and pulmonary oedema could all be considered to be common, preventable complications independently associated with poor clinical outcomes. For this reason, their incidence should have a role to play in benchmarking and subsequent quality improvement.

Thus, criticism can be grouped into three broad categories: i) the poor specificity for VAP of commonly used diagnostic tools ii) a multi-factorial lack of concordance in diagnosis between surveillance personnel, and iii) the lack of importance placed upon other, highly morbid, complications of mechanical ventilation in quality control initiatives.

> *"Objective, commonly captured data for all patients on ventilators is a more logical way forward"*

Ventilator-Associated Events and Ventilator-Associated Conditions

Klompas et al. explored the feasibility of purely objective diagnostic surveillance criteria for VAP (Klompas et al. 2012). Thirty-two different candidate definitions were created, composed of different combinations of the following signs: i) three thresholds for respiratory deterioration defined by sustained increases in daily minimum positive end-expiratory pressure or FiO_2 after either 2 or 3 days of stable or decreasing ventilator settings, ii) abnormal temperature iii) white blood cell counts iv) purulent pulmonary secretions defined by neutrophils on Gram stain, and v) positive cultures for pathogenic organisms. They concluded that only definitions requiring objective evidence of respiratory deterioration, detected through documentation of alterations in respiratory support, were significantly associated with increased hospital mortality. Crucially, placing these alterations on the first level of a novel diagnostic key would enable tracking of not only VAPs but also clinically significant non-VAP complications of mechanical ventilation. Collectively, these complications would be termed Ventilator-Associated Events (VAEs). As a surveillance tool, previously privileged pathologies would now be trapped and available for quality control.

Accordingly, in 2013 the CDC National Healthcare Safety Network (NHSN) introduced VAE surveillance, a novel tool for monitoring mechanically ventilated patients. Designed to replace VAP surveillance, VAE monitoring would provide objective, reproducible data tracking all complications of mechanical ventilation leading to an alteration in ventilator settings and an increase in respiratory support. This restratification comprises a three tiered mode (see Figure 1). Entrance into the VAE surveillance tool is through detection of an increase in daily minimum PEEP or FiO_2, objective data that can be reliably trapped by clinical information systems. In this way, all patients with clinically significant pulmonary complications are identified and their data recorded, irrespective of whether a VAP or non-VAP is causative. At this level they are referred to as Ventilator-Associated Conditions (VACs). The second tier, infection-related ventilator-associated complications (IVAC), is reached when VAC criteria are complemented by: i) traditional SIRS (systemic inflammatory response syndrome) signs of leucocytosis and abnormal temperature, and ii) the commencement of antimicrobials. Progression to the third tier occurs when evidence exists of a pulmonary source of infection, a 'possible' pneumonia being differentiated from 'probable' pneumonia on the basis of at least semi-quantitative pathogenic organism culture in the latter.

According to CDC NHSN, the uppermost two tiers, namely VAC and IVAC, are designed to be suitable for use in potential future public health reporting, inter-facility comparisons and pay-for-performance programmes. Requiring only objective data confers adequate external validity for this purpose and will also enable patterns of antimicrobial prescribing to be compared more reliably. Possible and probable VAP diagnosis would be utilised within internal quality control systems to allow for the variation in practice in obtaining the necessary respiratory specimens to confirm diagnosis.

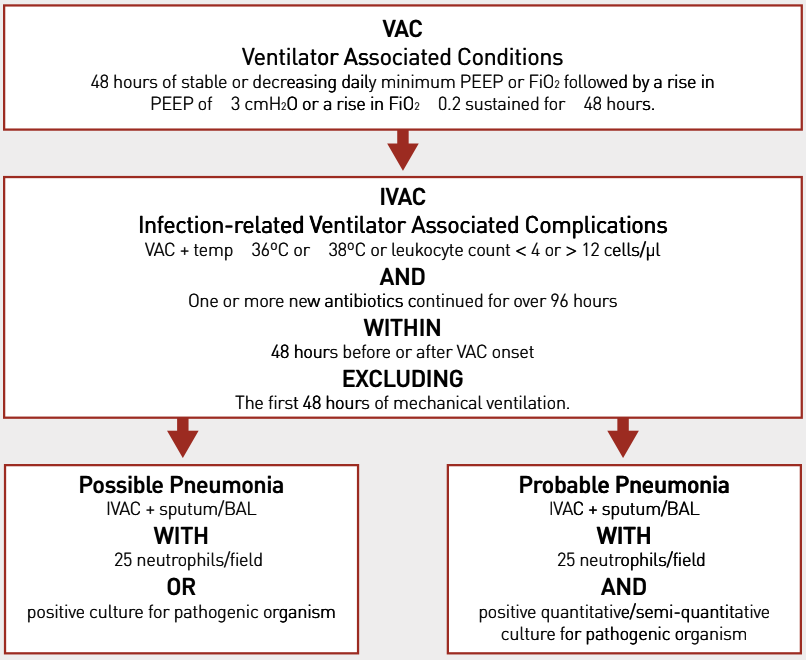
Validation

Hayashi and colleagues performed a retrospective evaluation of VAC (Hayashi et al. 2013). One of the aims of the study was to capture commonly recorded prospectively documented objective data (FiO_2, PEEP). They were able to demonstrate that VAC events were associated with both increased length of stay in ICU and increased days of mechanical ventilation. In addition to these negative outcomes, Klompas et al. (2011) were able to demonstrate an increase in mortality associated with VAC diagnosis compared with traditional VAP criteria. Therefore, a prospective study with a larger sample size is required to evaluate the utility of VAC and IVAC surveillance before its implementation in Australian ICUs. The introduction of a common clinical information system platform in South East Queensland will help to facilitate more efficient multi-site data collection and collaboration for this purpose.

Summary and Conclusion

At the bedside there is no doubt that there is sporadically a need to treat respiratory tract infections in patients on a ventilator with antibiotics. Exactly when this is required and how this is defined is being questioned, as there is not a uniform, unequivocal diagnostic set of criteria for the diagnosis of VAP. This makes comparisons, incidences and outcomes difficult to compare and to track. Especially as regards a quality indicator, objective, commonly captured data for all patients on ventilators is a more logical way forward. VAC has been put forward to address this concern. All patients on a ventilator will have FiO_2, PEEP and PaO_2 regularly recorded, and with clinical information systems now permitting realtime tracking and recording of incremental changes in these parameters we believe VAC will replace VAP as a quality assurance tool. The incorporation of antimicrobial use into the IVAC tier will also permit more reliable comparisons of stewardship models, and by differentiating between probable and possible VAPs, the final tier of the VAE key will also allow for local variations in diagnostic specimen sampling. ■

Figure 1. Diagnostic Key for Ventilator-Associated Events



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INHALED ANTIBIOTICS IN THE ICU

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New delivery methods have been developed for aerosolised antibiotics in mechanically ventilated ICU patients. This therapy can reduce the need for systemic antibiotics in the therapy of gram-negative pneumonia.

Introduction

Inhaled antibiotics have been available for use in patients with a wide range of respiratory infections, but their role in mechanically ventilated patients has not been routine, and has been primarily as adjunctive salvage therapy for difficult infections. With the emergence of multidrug-resistant (MDR) pathogens as a cause of lower respiratory tract infection in the ICU, the need for new therapeutic approaches is acute. Inhaled antibiotics address this need in a variety of ways. They can be effective against emerging MDR pathogens, including Pseudomonas aeruginosa, Acinetobacter spp, and the Enterobacteriaceae, primarily because they achieve high local concentrations at the site of infection. In addition, they do so without increasing the risk of systemic drug toxicity. Although the concept of inhaled antibiotics is not new, the technology of drug delivery has improved in recent years, while the availability of systemic antibiotics that are effective against MDR pathogens has declined, and there are few new drugs being developed for infection with gram-negative pathogens.

> *"Based on recent findings it may be time to re-evaluate the use of aerosolised antibiotics in the ICU for therapy of lower respiratory tract infection"*

Historical Perspective

Topical antimicrobial therapy for ICU patients was popularised in the 1970s with a series of investigational interventions to prevent ventilator-associated pneumonia (VAP) (Klick et al. 1975). Although the intervention was successful in preventing many pneumonias, the patients who did develop pneumonia, in spite of this effort, were infected with highly resistant organisms, and the resulting infections had a high mortality, so that the net effect was no change in ICU death rate. The observation about the emergence of resistance was so concerning that interest in using topical antibiotics for pneumonia in the ICU declined rapidly. Since then, usage has been primarily sporadic and anecdotal, being applied in situations of infection with MDR pathogens, but never as routine adjunctive therapy of VAP (Hamer 2000).

For example, one recent report described a retrospective, matched case-control study of 43 patients in Greece with MDR VAP, treated with either IV colistin alone or combined aerosol and IV colistin. The population included 77% of patients having A. Baumanii as the pathogen. Although there was a trend to more clinical cure with adjunctive aerosol therapy, there was no difference in mortality, clinical success or bacterial eradication (Kofteridis et al. 2010). Other investigators have applied aerosol therapy as a last ditch salvage effort for patients with MDR pathogens, who were either failing systemic therapy, or who had infection with pathogens that were not susceptible to any available therapy. In these reports, some patients did recover, suggesting a role for aerosol therapy in this dire circumstance (Hamer 2000). In addition, some investigators have shown the efficacy of inhaled therapy for patients with ventilator-associated tracheobronchitis (Palmer et al 2008).

In all of these early studies the aerosol was delivered by either routine nebulisation, a jet nebuliser, an ultrasonic nebuliser, or no specific delivery system was specified. In general, all of these approaches were inefficient, sometimes with little drug getting into the patient, and even less being delivered to the distal lung, at the alveolar site of infection. Recently, nebulisation techniques have improved, with a better understanding of how to optimise delivery to ventilated patients, and these developments have opened up new possibilities for aerosol therapy of VAP.

New Understanding to Improve Aerosol Delivery to the Lung

Attention to delivery of aerosolised antibiotics to the infected lung has prompted investigators to define

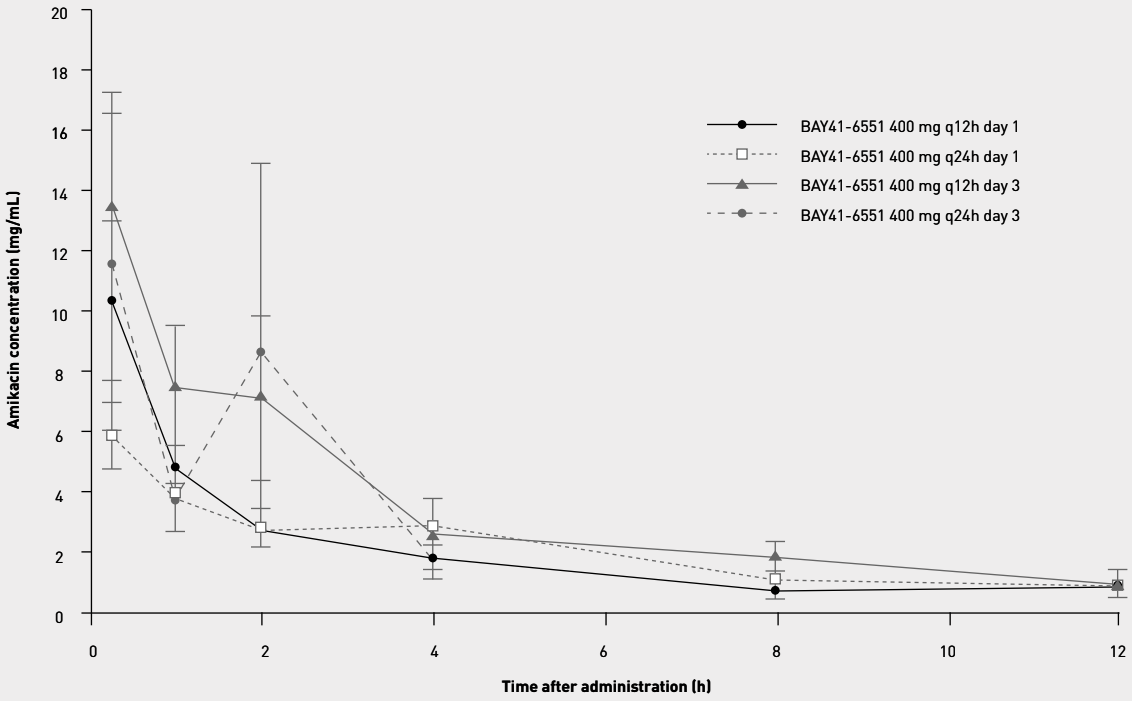
the optimal criteria for drug selection and drug delivery. The drug that is used must have high intrinsic activity against the most resistant pathogens causing respiratory infection. At the same time a limited systemic absorption from the respiratory site could minimise systemic toxicity. With both of these considerations in mind, recent studies have focused on inhaled use of aminoglycosides and colistin.

In considering how to deliver antibiotic to the lung, there are several issues that are relevant for mechanically ventilated patients with pneumonia. First, a delivery device should be able to generate small particles (< 5 microns) that are capable of reaching the alveoli, and not just depositing in the upper airway. In addition, whatever device is selected should be positioned in the ventilator circuit to maximise retention by the patient while minimising environmental contamination, which occurs if delivery is coordinated with the inspiratory cycle. In addition, it is important to consider whether an inhaled antibiotic can penetrate the pneumonic lung, or whether the presence of consolidation will prevent the deposition of antibiotic at the most affected site.

Deposition of inhaled agents in pneumonic lung is possible, but is not as effective as in non-consolidated tissue. Goldstein and colleagues studied piglets with bronchopneumonia from E. coli intrabronchial instillation, who were treated with amikacin given by an ultrasonic nebuliser (Goldstein et al. 2002). In the study 38% of the nebulised dose was retained in the lung, with higher concentrations in the lung areas that were less severely affected by the pneumonia. However, when lung concentrations were compared for aerosolised versus intravenous therapy, more drug was delivered, even to the severely bronchopneumonic area, with aerosol therapy than with intravenous therapy. However, there was more systemic drug absorption from the pneumonic area than from the non-pneumonic areas. Thus, the findings of this study suggested a utility for aerosol therapy, even for pneumonic lung, provided that serum levels were monitored to avoid too much systemic absorption.

Rouby and colleagues have conducted a number of animal and human studies of aerosol therapy of pneumonia, and have suggested ways to optimise drug delivery to the lung in mechanically ventilated patients (Rouby et al. 2012). They have generally advocated for the use of a new type of vibrating mesh plate nebuliser, rather than a jet nebuliser, although they have also suggested some value with the use of an ultrasonic nebuliser. Vibrating mesh plates are able to generate a uniform particle size, keeping all

Figure 1. Tracheal aspirate amikacin concentrations (mean + standard error) over time on day 1 and day 3 (all treated patients). Values are for all treated patients with tracheal aspirate amikacin concentrations at the relevant time point. q12h every 12h, q24h every 24 h



With kind permission from Springer Science+Business Media: Intensive Care Medicine, BAY41-6551 achieves bactericidal tracheal aspirate amikacin concentrations in mechanically ventilated patients with Gram-negative pneumonia, Vol. 38, 2012, 263-71, Michael S. Niederman, Jean Chastre, Kevin Corkery, James B. Fink, Charles-Edouard Luyt, Miguel Sánchez García, figure 2.

the particles less than 5 microns. In the studies by Rouby et al., the nebuliser is placed in the inspiratory limb, before the Y connector , and it can be synchronised with inspiration, so that at least 60% of the reservoir dose is deposited in the lung. In selecting the nebulised dose, they recommend using the systemic dose of the antibiotic, plus the amount of drug that is estimated to deposit in the tubing and expiratory filter. They also recommend using a tidal volume of 7-9 cc/kg, in a controlled ventilatory mode, with the patient sedated, using constant inspiratory flow, at a 1:1 inspiratory to expiratory ratio. They suggest using an inspiratory pause of at least 20% of the duty cycle, and to do the nebulisation with the heat moisture exchange filter removed.

We have recently completed a trial of nebulised amikacin for patients with gram-negative ventilator associated pneumonia (VAP), using a vibrating mesh plate nebuliser, and our delivery method was not exactly the same as specified by Rouby et al. In our study, the nebuliser was placed distal to the Y connector, before the origin of the endotracheal tube, and delivery was only in the inspiratory cycle (Niederman et al. 2012). Delivery was coordinated by a pressure control module that sensed the pressure in the inspiratory limb of the ventilator tubing, and delivery could be optimised by stopping nebulisation in the last 25% of the inspiratory cycle, to 'wash in' the inhaled agent to the deep lung. Using this method, any mode of ventilation was allowed, and patients did not need sedation to facilitate drug delivery. In the study, 71% of the patients were on assist-control ventilation, with the rest being on pressure support. The goal of the delivery system was to achieve a tracheal aspirate concentration of amikacin of > 6400 micrograms/ ml (> 25 times an MIC of 256 micrograms / ml). Using a dose of 400 mg amikacin every 12 hours, this high concentration was achieved in 50% of the patients. Tracheal concentrations were higher after twice daily administration than after once daily administration. Tracheal concentrations were higher at day 3 than on day 1, but at both times serum concentrations remained < 10 micrograms/ml, and generally much lower than this level, with a mean of 3.16 micrograms/ml (see Figure 1).

Recent Findings With Inhaled Antibiotics

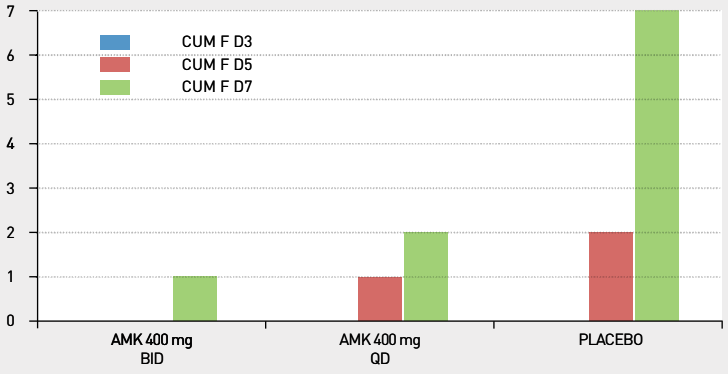
With the advent of new aerosol delivery methods, it is necessary to re-evaluate the efficacy and trial design of inhaled antibiotics for patients with gram negative pneumonia, treated with mechanical ventilation. When an inefficient nebuliser is used, along with too low a dose, efficacy is unlikely. For example, in one study of 100 patients with gram-negative pneumonia, a jet or ultrasonic nebuliser of 75 mg of colistin was added to systemic therapy, every 12 hours, with no benefit on clinical outcome (Rattanaumpawan 2010). Future trials may need to consider endpoints other than cure or mortality. These trials should probably focus on a patients with an enhanced risk of infection with MDR gram-negatives, use aerosol as an adjunct to systemic therapy, and look at endpoints such as early failure, without adjunctive aerosol therapy, and the ability of aerosol therapy to lead to clinical success with the use of less systemic therapy, than without adjunctive aerosol. Some of these ideas have been tested in recent trials.

One recent study has shown the value of inhaled high dose colistin in treating pneumonia caused by MDR pathogens. In this study 43 patients with ventilator-associated pneumonia (VAP) caused by Acinetobacter baumanii or Pseudomonas aeruginosa were treated with high dose inhaled colistin (5 million units every 8 hours with a vibrating mesh plate nebuliser) either with or without (n=28) systemic antibiotics. The clinical cure rate was 67%, virtually identical to the success in treating 122 patients with VAP caused by sensitive strains of the same pathogens, that had been treated exclusively with intravenous antibiotics (Lu et al 2012). In areas of confluent pneumonia, the use of aerosolised colistin led to an increase in thoracic gas volume.

In another study by the same group of investigators, a randomised comparative trial was conducted in 20 patients with sensitive or intermediate strains of P. aeruginosa who were treated with inhaled amikacin plus inhaled ceftazidime, and a group of 20 patients with similar organisms who were treated with only intravenous ceftazidime plus intravenous amikacin or ciprofloxacin (Lu et al. 2011). After 8 days both groups had similar rates of treatment success, but acquired antibiotic resistance only occurred in those getting intravenous therapy. There were 4 patients with intermediately sensitive organisms who had bacterial eradication from the use of only aerosol therapy. Drug delivery by aerosolisation was efficient, with over 60% of the nebulised dose being retained in the lung. This study suggested that aerosol therapy alone, and not just as adjunctive therapy, was effective to treat VAP, although the use of this approach is not likely to be widespread.

In another recent study Niederman et al. examined whether the use of adjunctive aerosolised amikacin could have a clinical benefit other than clinical or microbiologic cure rates (Niederman et al. 2012). In a randomised trial of 69 mechanically ventilated patients with gram-negative pneumonia (with more than half having either P. aeruginosa or Acinetobacter spp), amikacin was given with a vibrating mesh plate nebuliser at either 400 mg twice daily, 400 mg once daily, or a placebo was given via aerosol. All patients received systemic antibiotics, and at the end of a week, in this blinded trial, the patients receiving the highest dose of amikacin were receiving less systemic therapy than the patients receiving either placebo or lower dose amikacin. In addition, systemic therapy was escalated (more or broader spectrum agents used) in 14% of the high dose inhaled amikacin patients, 38% of the lower dose inhaled amikacin patients and in 58% of those receiving inhaled placebo. Clinical failure was defined by serial measurement of the Clinical Pulmonary Infection Score, with failure defined as a rise >2 points at day 3, a failure to fall

Figure 2. Cumulative number of clinical failures at day 3, day 5 and day 7 for each of 3 treatment groups. Clinical failure was defined by serial measurement of the Clinical Pulmonary Infection Score.



CUM= cumulative, F= failures, D= Day, AMK= amikacin, BID= every 12 hours, QD= every 24 hours.

by >1 point at day 5 or >2 points at day 7. By this definition, there were fewer failures with the amikacin twice daily dosing than with other regimens (see Figure 2). Thus, the use of adjunctive aerosol therapy had the benefit of leading to less systemic antibiotic exposure, by leading to a more rapid clinical response than in those patients receiving only systemic antibiotics, and leading to less clinical failure, suggesting a possible role for aerosol therapy to reduce systemic antibiotic exposure in the ICU therapy of pneumonia.

Is It Time for Routine Use of Inhaled Antibiotics as Adjunctive Therapy for VAP?

Based on recent findings, it may be time to re-evaluate the use of aerosolised antibiotics in the ICU for therapy of lower respiratory tract infection. While they may be useful as adjunctive therapy of pneumonia caused by MDR pathogens, they may also have a role as routine adjunctive therapy, to reduce the duration of systemic antibiotic therapy of pneumonia. Chastre et al. have demonstrated that 8 days of antibiotic therapy may be as effective as 15 days in VAP, but when non-fermenting gram-negatives are present, 8 days of therapy may lead to more microbiologic failures (Chastre et al 2003). The use of routine adjunctive aerosol therapy may address this issue by providing more 'up-front' therapy, thereby permitting short duration of systemic therapy, even for non-fermenting gram-negatives.

More data are needed to determine if nebulised antibiotics should be used routinely in the therapy of gram-negative pneumonia in ventilated patients. If the data are positive,we may be able to extend this approach to non-ventilated patients, since the same aerosol technology is becoming available for this population as well. Other targets of aerosol therapy in the ICU are patients with ventilator-associated tracheobronchitis, which may be a predecessor of VAP, and which may be effectively treated with topical tracheobronchial antibiotics, without the use of systemic therapy. In the conduct of future studies, it is also important to evaluate the efficacy of current inhaled agents on gram-positive pathogens, where they may have efficacy, or it may be necessary to combine the current agents with another agent active against MDR gram-positives such as methicillin-resistant S. aureus, since many patients have mixed gram-negative and gram-positive infections. ■

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