Commentary

Ventilator-associated pneumonia: monotherapy is optimal if chosen wisely

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See related research by Damas *et al*. in this issue [http://ccforum.com/content/10/2/R52]

Abstract

Traditionally, ventilator-associated pneumonia (VAP) has been treated either with double drug therapy or with monotherapy. Double drug therapy has been used to increase spectrum, for possible synergy, and to decrease the emergence of resistance. VAP therapy should be directed primarily against *Pseudomonas aeruginosa*, which also provides aerobic Gram-negative coverage, the usual pathogens in VAP. The potent anti-*P. aeruginosa* antibiotics available today have sufficient activity that double drug coverage is unnecessary. Double drug therapy does not decrease resistance if a 'high resistance potential' antibiotic is used in the combination. The study by Damas and colleagues in this issue of *Critical Care* supports monotherapy for VAP. Optimal therapy for VAP involves selecting a potent anti-*P. aeruginosa* antibiotic with a 'low resistance potential' that minimizes drug-drug interactions, minimizes resistance, and is cost effective. Monotherapy of VAP should be the standard of care.

Empiric antimicrobial therapy of ventilator-associated pneumonia (VAP) should possess a high degree of activity against aerobic Gram-negative bacilli (GNB). Although *Pseudomonas aeruginosa* is not the most common VAP pathogen, it is clearly the most virulent Gram-negative pathogen. Antibiotics with a high degree of *P. aeruginosa* activity are also effective against other aerobic GNB causing VAP, that is, *Escherichia coli*, *Klebsiella pneumoniae* and *Serratia marcescens*. It is as important to know what pathogens should be covered as it is to know which are not. In VAP, respiratory secretions are commonly colonized by nosocomial GNB that rarely cause VAP, for example, *Enterobacter* species, *Burkholderia (Pseudomonas) cepacia*, and *Sternotropmonas (Xanthomonas) maltophilia*. In 'early' VAP, *Streptococcus pneumoniae* is a potential pathogen, but in 'late' VAP, Gram-positive pathogens are uncommon. Anaerobes are not important VAP pathogens [1].

The difficulties in determining the etiological agent in VAP are well known. Many patients with fever, leukocytosis, and pulmonary infiltrates on chest X-ray do not have VAP. Culture of organisms from respiratory secretions in ventilated patients does not imply a causal relationship to fever, leukocytosis, and pulmonary infiltrates, and is not synonymous or diagnostic of VAP [1-3]. In the critical care unit, ventilated patients are commonly given antibiotics with good Gram-negative activity but limited Gram-positive activity. For this reason, colonization of respiratory secretions with *Staphylococcus aureus*, either methicillin-susceptible (MSSA) or methicillin-resistant (MRSA), is frequent, and the basis of National Nosocomial Infections Surveillance (NNIS) VAP data. Although respiratory secretion colonization with MSSA/MRSA is exceedingly common, proven *S. aureus* VAP is uncommon [1-3]. MSSA/MRSA pneumonia is a recognizable clinical syndrome characterized by high fever, cyanosis, and rapid cavitation on chest X-ray ≤72 hours. *S. aureus* necrotizing pneumonia is similar pathologically to *P. aeruginosa* necrotizing pneumonia. Recovery of MSSA/MRSA from respiratory secretions in ventilated patients with fever/leukocytosis, and infiltrates is not diagnostic of *S. aureus* VAP [1-4].

Besides potent anti-*P. aeruginosa* activity, the antibiotic selected should have a 'low resistance potential', that is, resistance not volume/duration related. 'Low resistance potential' antipseudomonal antibiotics, such as cefepime and meropenem, should be used preferentially over 'high resistance potential' antibiotics, such as ceftazidime and imipenem [5-7].

Monotherapy remains the rule for nearly all infections. Combination therapy has been used to increase spectrum,

GNB = Gram-negative bacilli; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

provide synergy, or prevent resistance. Given the wide spectrum of available antibiotics, it is rarely necessary to use double drug therapy for increased spectrum [1,4].

Double drug coverage was used when potent GNB antibiotics were limited and combinations were used for potential synergy. Antibiotic combinations may be indifferent or antagonistic and synergy is uncommon. Synergy should be demonstrated by testing. Possible synergy is not a reason for combination therapy, which may result in increased side effects/interactions. Currently, antibiotics for VAP have potent *P. aeruginosa* activity, and synergy is unnecessary [5,8].

Presently, prevention of resistance is the most frequently given justification for double drug coverage. Prevention of resistance by combining agents dates from decades past when carbenicillin was combined with gentamicin to prevent the emergence of *P. aeruginosa* carbenicillin resistance. This exception has been extrapolated/extended into a general concept, which it is not. Combination therapy *per se* does not prevent resistance, and is the exception rather than the rule. If ceftazidime, a 'high resistance potential' *P. aeruginosa* antibiotic, is combined with a 'low resistance potential' antibiotic, for example, amikacin, the high resistance potential of ceftazidime is not diminished/eliminated. The same is true for nearly all other antibiotic combinations using high/low resistance potential antibiotics. If 'low resistance potential' antibiotic monotherapy is selected for VAP, combination therapy provides no additional benefit and needlessly increases antibiotic costs [5-7]. Double drug therapy has no benefit over monotherapy for VAP. Extensive experience supports carefully selected empiric monotherapy for VAP as optimal [9-14].

De-escalation therapy is a variant of combination therapy, based on the notion that narrowing spectrum after initial empiric broad spectrum therapy, after culture information is reported, decreases resistance. Experience does not support this concept. Broad spectrum β-lactam therapy, for example, ceftriaxone, has been used extensively for decades for pneumococcal pneumonia without resultant ceftriaxone-induced *S. pneumoniae* resistance. Changing to narrower therapy, for example, penicillin after *S. pneumoniae* is identified, makes little sense and clearly has no effect on resistance [4]. Given the clinical difficulties of definitively determining the putative pathogen in VAP without lung tissue, narrow spectrum/specific therapy is often based on colonized respiratory secretion cultures, which are often misleading [3]. Potent anti-*P. aeruginosa* 'low resistance potential' monotherapy eliminates the rationale for de-escalation therapy. As the study by Damas and colleagues [15] demonstrates, double drug therapy for VAP offers no advantages over monotherapy. The authors have provided more data supporting monotherapy as optimal therapy for VAP. Pharmaco-economic imperatives argue strongly against combination therapy for VAP. In an era of limited healthcare resources, double drug therapy initially or for the duration of VAP therapy is unnecessary and wasteful. Several antibiotics are available for optimal empiric monotherapy of VAP, including meropenem, cefepime, piperacillin/tazobactam, levofloxacin, and so on. If clinicians choose wisely, selecting a potent anti-*P. aeruginosa* agent with a 'low resistance potential', empiric monotherapy for VAP is highly effective with minimal potential for resistance/drug interactions, and is cost effective.

Competing interests

The author declares that they have no competing interests.

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