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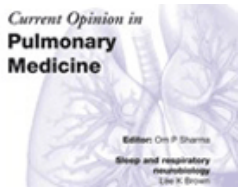
Ventilator-associated Pneumonia Caused by ESKAPE Organisms



Cause, Clinical Features, and Management

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Abstract and Introduction

Abstract

Purpose of review: Despite important geographical variations, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* species (ESKAPE) pathogens constitute more than 80% of ventilator-associated pneumonia (VAP) episodes. Their clinical importance relies on their virulence and ability in developing mechanisms to decrease susceptibility to antimicrobials, increasing inappropriate therapy and affecting negatively on ICU patients' outcome. This review updates information on VAP due to ESKAPE pathogens.
Recent findings: Although methicillin-resistant *Staphylococcus aureus* VAP may be clinically similar to that caused by susceptible strains, it is associated with poorer outcomes despite adequate treatment. Local colonization determines treatment options. The contribution of tracheobronchitis is an important issue. Minimum inhibitory concentration should be considered for nonfermentative Gram-negative bacteria VAP to prescribe extended infusion b-lactam treatment due to an increase of resistant strains. Strategies promoting antimicrobial diversity may protect against emergence and spread of resistance by ESKAPE pathogens.
Summary
VAP due to ESKAPE pathogens represents a global challenge that can be prevented using stewardship programmes promoting diversity.

Introduction

In 2008, Rice[1] grouped the 'top six bugs' for their wide distribution and their ability to escape the effects of antibacterial drugs under the acronym 'ESKAPE' (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* species). However, other authors[2,3] have proposed moving forward the term 'ESKAPE' to a more inclusive acronym termed 'ESCAPE' in order to represent *Clostridium difficile* (as the new C) and Enterobacteriaceae (as the new final E) (includes *Klebsiella pneumoniae*, *Enterobacter* species as well as *Escherichia coli* and *Proteus mirabilis*), encompassing more fully all the current problem pathogens that challenge the well tolerated and efficacious treatment of infectious diseases.

The present review addresses epidemiology, clinical characteristics, treatment options and preventive measures of ESKAPE ventilator-associated pneumonia (VAP).

Ventilator-associated Pneumonia Due to ESKAPE Pathogens

According to the 2004–2008 SENTRY Antimicrobial Surveillance Program,[4•] with the exception of *E. faecium*, ESKAPE pathogens were among the top six causative agents of VAP, representing overall 80% of episodes. Similar results can be seen in several large multinational studies,[5,6] as well as other national[7] and local clinical trials[8••] (Table 1).

Table 1. Frequency of different ESKAPE pathogens in ventilator-associated pneumonia in different geographical locations

	SENTRY[4•]		ENVIN[7]	Sandiumenge et al.[8••]
	All regions (%) n = 7496[a]	United States (%) *n* = 2585[a]	Spain (%) *n* = 788	Tarragona (%) *n* = 157
Staphyloccocus aureus	19.5	31.9	17.1	29.6
Pseudomonas aeruginosa	26.6	21.4	17.3	19.7
Enterobacter spp.	7.0	8.8	6.9	1.3
Klebsiella spp.	10.2	6.6	7.8	6.4
Serratia spp.	4.1	6.5	4.0	0.0

Acinetobacter spp.	14.3	5.3	9.2	8.9

[a]Number of total hospital-acquired pneumonia and VAP cases.

The clinical importance of ESKAPE pathogens relies on their virulence and ability to develop mechanisms to decrease susceptibility to antimicrobials, increasing inappropriate therapy (Table 2). The SENTRY Antimicrobial Surveillance Program[4•] reported a yearly 1% generalized decrease in drug susceptibility in hospital-acquired pneumonia (HAP) and VAP isolates of the top six pathogens. Geographic differences were also noted in the type of antimicrobial resistance as shown in Table 3. Our group[8••] prospectively studied 129 VAP episodes, reporting that 65.6% of all VAP isolates were ESKAPE organisms, almost 20% being resistant.

Table 2. Resistance mechanisms of ESKAPE pathogens

Microorganism	Resistance mechanism	Antimicrobial target
Enterococcus faecium	Low-affinity Pbp Altered peptidoglycan precursor Mutant ribosomal RNA genes Unclear mechanisms	Ampicillin Vancomycin Linezolid Daptomycin
Staphylococcus aureus	Beta-lactamase Low-affinity Pbp Cosntitutive erm expression Unclear mechanisms	Penicillin Oxacillin Clindamycin Vancomycin
Klebsiella spp.	ESBLs (variety) KPC-type beta-lactamases Mutant topoisomerases Efflux pumps Qnr enzymes Modifying enzyme	Cephalosporins Carbapenems Quinolones
Acinetobacter baumannii	Carbapemenases Metallo-beta-lactamases Efflux pumps Mutational gyrases Inactivating enzymes Outer membrane impermeability	Penicillins, cephalosporins Carbapenems Aminoglycosides Quinolones
Pseudomonas aeruginosa	ESBLs (variety) AmpC Efflux pumps Mutational gyrases Inactivating enzymes Outer membrane impermeability	Penicillins, cepahalosporins Carbapenems Aminoglycosides Quinolones
Enterobacter spp.	CTX-metallo-beta-lactamases Efflux pumps Mutant topoisomerases Qnr enzymes Modifying enzymes	Cephalosporins Quinolones

ESBLs, extended spectrum betalactamases; KPC, Klebsiella pneumoniae carbapenase; Pbp, protein-binding proteins.

Table 3. Drug resistance in the ESKAPE pathogens causing hospital-acquired bacterial pneumonia and ventilator-associated pneumonia in different parts of the world

	Antimicrobials with more than 5% increase in resistance	Antimicrobials with more than 10% increase in resistance
North America		
Staphylococcus aureus	–	–
Klebsiella pneumoniae	Cefepime, ceftazidime, meroenem, doripenem	Levofloxacin

Escherichia coli	Piperacillin–tazobactam	
Acinetobacter baumannii	Levofloxacin, cefepime	Meropenem, doripenem
Pseudomonas aeruginosa	Meropenem	
Enterobacter spp.		
Europe		
S.aureus		
K. pneumoniae	Levofloxacin, cefepime, ceftazidime	
E. coli	Gentamicin, levofloxacin, cefepime, ceftazidime, piperacillin–tazobactam	
A. baumannii	Gentamicin, levofloxacin, ceftazidime, piperacillin–tazobactam, doripenem	
P. aeruginosa doripenemp	–	
Enterobacter spp.	Levofloxacin	
Latin America		
S. aureus	Oxacilin, gentamicin, cefepime, ceftazidime, piperacillin–tazobactam, meropenem, doripenem	
K. pneumoniae	Levofloxacin, ceftazidime	Gentamicin, cefepime, piperacillin–tazobactam
E. coli		
A. baumannii	Levofloxacin, ceftazidime	Piperacillin–tazobactam, meropenem, doripenem
P. aeruginosa		
Enterobacter spp.	Levofloxacin	Ceftazidime

From SENTRY Antimicrobial Surveillence Program 2004–2008. Modified from [4•].

The prognostic impact of specific microorganisms on patient outcome has been widely debated. Some authors state that VAP morbidity and mortality is related to the presence of resistant pathogens through the higher proportion of inadequate treatment reported for these pathogens. Although appropriateness of the initial treatment was not evaluated in the above-mentioned work,[8••] VAP caused by resistant ESKAPE pathogens doubled mortality compared with that in patients with VAP caused by other pathogens [relative risk 2.25; 95% confidence interval (CI) 1.67–9.48], and prolonged mechanical ventilation. In contrast, Damas *et al.* [9••] did not identify infection by any particular group of organisms to be a risk factor for ICU mortality in a large series of ICU-acquired pneumonias.

Enterococcus Faecium

E. faecium has been consistently identified as the third most frequent cause of nosocomial bloodstream infection in the USA. However, its role in VAP has been only described in testimonial case reports.[10]

Staphylococcus Aureus

S aureus has been for decades one of the main causative agents of nosocomial pneumonia worldwide. This pathogen has shown a trend to rapidly developing resistance to new antibiotic classes as they have been introduced into clinical use. Such was the case of the first oxacillin/methicillin- resistant strains of *Staphylococcus aureus* (MRSA) that emerged only a few years after these agents were commercialized in the 1960s. Since then MRSA has globally disseminated, and now approximately 60% of *S. aureus* isolates are resistant to methicillin in some areas of the USA. Current data from the ENVIN Study,[7] a Spanish yearly ICU infection surveillance study, reported that 25% of all ICU pneumonias due to *S. aureus* were caused by methicillin- resistant strains, suggesting a trend to decreasing incidence. However, this rate was higher (45.4 vs. 33.3%) in the Latin VAP study when compared with the EU-VAP study.[11••] Interestingly, this new study suggests that variables associated with empirical anti-MRSA therapy for pneumonia are different from classical risk factors. Although VAP due to MRSA may have similar chest radiograph patterns and clinical course than that casued by methicillinsusceptible *S. aureus*, it may produce alpha-toxin,[12] suggesting opportunities to

improve outcomes with immunotherapy. In a systematic review, Athanassa *et al.* [13] confirmed that both in-hospital and ICU mortality of patients with VAP due to *S. aureus* were higher in the presence of methicillin resistance. Moreover, the European Prevalence of Infection in Intensive Care (EPIC) II study investigators confirmed these findings in a subanalysis of MRSA episodes.[14••] Interestingly, MRSA pneumonia is associated with significantly higher ICU mortality in Latin America.[15] Overall, treatment failure rates as high as 40% have been reported and attributed to inadequate duration of therapy. MRSA VAP is a difficult-to-treat infection with longer times to clinical resolution and duration of mechanical ventilation when compared with other pathogens, even if appropriate therapy is delivered.[16] Therefore, duration of therapy should be based on individualized follow-up for resolution of signs and symptoms of infection. A meta-analysis compared clinical success in patients with or without culturepositive MRSA pneumonia.[17••]

The cost–benefit ratio of strategies aimed to maintain serum concentration of vancomycin at high levels is still under discussion.[18] In addition, the association of a combination of two agents may be considered in patients with poor resolution.[19] Randomized controlled trials with linezolid have been criticized due to possible underdosage of vancomycin when administered at recommended dosages. Data on its potential superiority of clinical response even when vancomycin dosage was modified according to blood levels, in a population with MRSA pneumonia with low risk of death (overall 17%), will represent an important new contribution.[20] Agents such as quinuspristin–dalfpristin, daptomycin or tigecycline[21] have been associated with disappointing results in pulmonary infections. The contribution of potential newer agents, such as todazolid, ceftaroline or telavancin[22•] still has to be determined.

Acinetobacter Baumannii

Nosocomial pneumonia caused by *A. baumannii* represented almost 20% of all episodes of ICU nosocomial pneumonia in Europe.[23] However, important variability has been reported among countries (Table 1). Risk factors for VAP due to this organism are different from those of *P. aeruginosa* and include previous neurosurgery, head trauma or large-volume aspiration as well as prolonged hospital stay and mechanical ventilation, prior episodes of sepsis, reintubation and prior antibiotic use.[24]

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Acinetobacter spp.	14.3	5.3	9.2	8.9

[a]Number of total hospital-acquired pneumonia and VAP cases.

A unique feature of *A. baumannii* is its rapid acquisition of multiple antibiotic-resistance mechanisms and the ability to coexist in the environment. Carbapenems have been considered the treatment of choice.[25] Unfortunately, resistance is rapidly increasing and previous exposure to imipenem has been associated with VAP due to imipenem-resistant *A. baumannii* (odds ratio 4.0; 95% CI 1.1–29.8).[24] For this reason, minimum inhibitory concentration (MIC) determination is highly recommended in order to optimize antibiotic treatment.[26•] Doripenem, although theoretically less active *in vitro*, has been reported to be superior to imipenem and meropenem in 87 *A. baumannii* clinical isolates.[27] The extended infusion or highdose carbapenems, and association with other antibiotics could improve their therapeutic effects against multidrug-resistant (MDR) *A. baumannii*.[28•] Sulbactam at high dosage has shown good clinical and bacteriological cure rates in the treatment of MDR *A. baumannii* VAP patients whether alone[29] or in combination with colistin.[30] Unfortunately, a steady increase in the resistance to sulbactam has been observed in the last decade[31] and its use is mainly recommended for catheterrelated bacteremia. Rifampicin maintains a high level of activity both *in vitro* and *in vivo* against *A. baumannii* even in carbapenem-resistant strains, but its use in monotherapy is not recommended due to the rapid emergence of strains resistant to this antimicrobial.[31] Colistin retains a high in-vitro activity against *A. baumannii* and does not promote cross-resistance. Clinical data reveals that colistin is similar to imipenem in the treatment of VAP caused by *A. baumannii* susceptible to imipenem[32] as well as effective when administered alone[33] or combined with rifampicin[34] for the

treatment of VAP caused by MDR strains. The use of aerosolized colistin for *A. baumannii* VAP should be as adjunctive therapy to intravenous antibiotics.[35•]

Pseudomonas Aeruginosa

P. aeruginosa VAP has been associated with high mortality and costs[36•,37] even among patients receiving appropriate antimicrobial therapy. El Solh *et al*.[38] confirmed previous studies in *P. aeruginosa* VAP patients stating that expression of genes encoding type III secretory proteins were associated with lower survival rates and that its eradication was not achieved after a 7-day course of antibiotics.

The contribution to tracheobronchitis is controversial and some authors suggest that commonly accepted clinical criteria used to diagnose VAP do not readily identify all patients with *P. aeruginosa* infection.[39•]

P. aeruginosa is notorious for its ability to acquire antibiotic resistance, especially in cases of previous colonization or infection by MDR *P. aeruginosa* or previous exposure to antibiotics during the ICU stay.[40] Resistance emergence may occur as early as 10 days after initiation of antipseudomonal antibiotics in ventilated patients,[41] increasing mortality and prolonging length of stay and a rise in costs.[42] Emergence of resistance in *P. aeruginosa* is rapidly increasing for most antimicrobials. Two systematic reviews[43•,44] confirm clinical experience reporting that many *P. aeruginosa* isolates are resistant to imipenem at the initiation of treatment and, importantly, are likely to develop treatmentemergent resistance to this agent. According to these findings and despite controversial results on the efficacy of combination therapy vs. monotherapy,[45] early initiation of combination therapy with an antipseudomonal b-lactam agent and aminoglycoside or quinolone should be recommended as soon as *P. aeruginosa* pneumonia is suspected. Emergence of MDR and pan-resistant strains is a real concern, particularly in lung transplant patients or respiratory chronic diseases. When treated with high doses of b-lactams in combination with aminoglycosides, 78% of patients with VAP survived to discharge and only one death was attributable to VAP in a small trial.[46••] Colistin may be used instead of aminoglycosides (10MU loading dose, followed by 4.5MU b.i.d) when MIC of tobramycin is higher than 8.[32]

Enterobacteriaceae

In 2010, these pathogens were responsible for over 40% of VAP reported in the ENVIN study,[7] *E. coli* and *Klebsiella* being the most prevalent ones. Approximately 20% of *K. pneumoniae* infections and 31% of *Enterobacter* spp infections in ICUs in the United States now involve strains not susceptible to third-generation cephalosporins due to extended spectrum betalactamases (ESBLs).[47] Similar features were reported in a recently published study in which 30% of *Klebsiella* spp VAPs were ESBL producing.[8••] Damas *et al*.[9••] reported a lower rate of ESBL-producing Enterobacteriaceae (36/198) in a 4-year prospective study of 453 patients with ICU-acquired pneumonia in France. Infections with ESBL-producing Enterobacteriaceae have significantly adverse impact on clinical outcomes.[48]

Carbapenems have been considered the most effective drugs against lung infections caused by ESBL-producing Enterobacteriaceae, including pneumonia. However, carbapenem-resistant Enterobacteriaceae have been described as constituting a threat in countries like Greece and Turkey, but only a few are associated with VAP.[49]

Prevention Strategies

Stewardship programs consisting of a package of measures directed to rationalizing antimicrobial use, such as antimicrobial restriction, antimicrobial cycling or de-escalation, have been proposed to curb resistance and preserve efficacy of the existing agents.[50] However, these strategies are not always easy to implement and their use remains controversial.[51•] Mathematical models using theoretical scenarios have predicted the superiority of heterogeneous antibiotic strategies over temporary peaks on antimicrobial pressure resulting from homogeneous antibiotic patterns for prevention of antimicrobial resistance.[52] However, in the clinical field there is no consensus on the best strategy to guarantee antimicrobial diversity, mainly due to difficulties in measuring the degree of heterogeneity attained with the implementation of a given antimicrobial strategy. Using a previously proposed index to quantify diversity of antimicrobial use,[53] our group evaluated the impact of three different strategies of antimicrobial empirical prescription for VAP on the emergence of ESKAPE pathogens.[8••] Although incidence of ESKAPE organisms was similar among periods, ESKAPEresistant strains increased significantly after implementation of strategies favouring homogeneous antimicrobial use, mostly due to an increase of carbapenem-resistant *A. baumannii* (Fig. 1). This finding was not only of academic interest, as it may be associated with changes in ICU mortality and duration of mechanical ventilation.

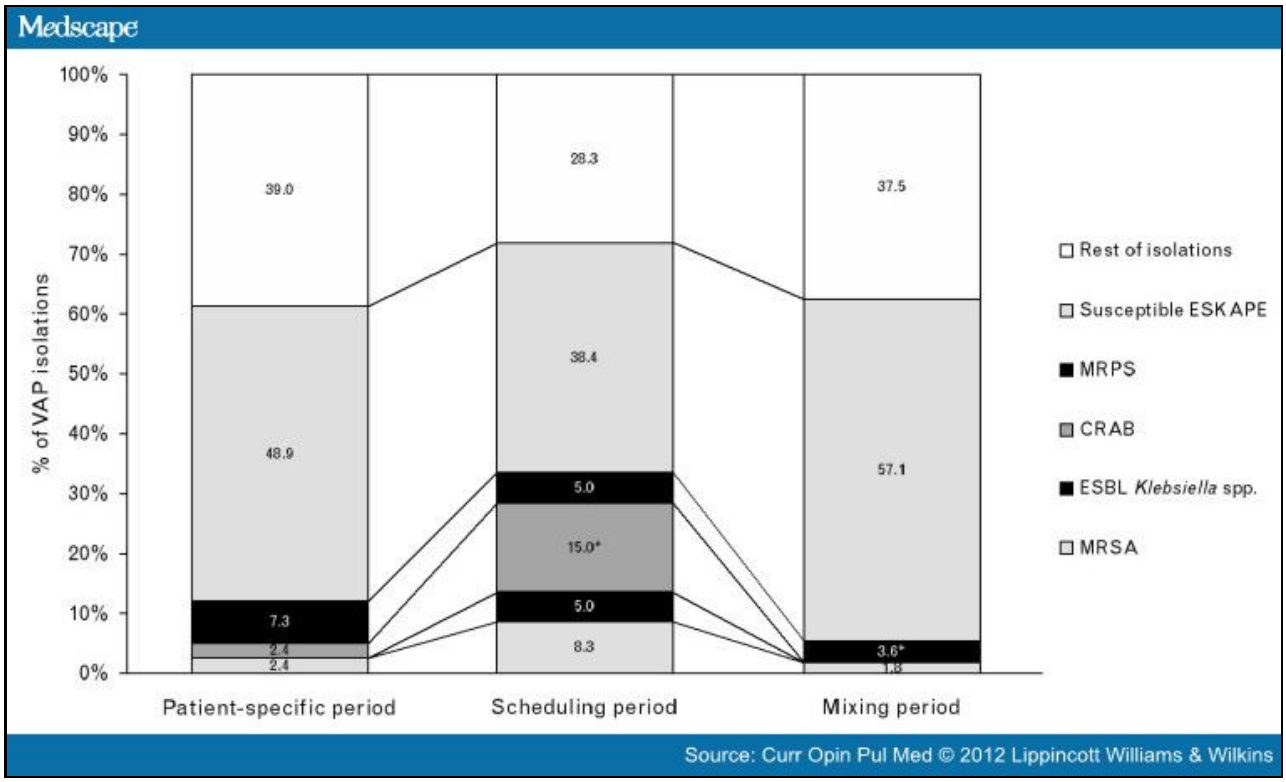

Figure 1. Percentage of ESKAPE pathogens isolated from VAP episodes. Modified with permission from figure 4 of Sandiumenge *et al.*[8••] **P*<0.05 for scheduling period (homgeneous antimicrobial pattern) with respect to patient-specific period (diverse antimicrobial pattern). ***P*<0.05 for scheduling period with respect to mixing period (diverse antimicrobial pattern). CRAB, carbapenem-resistant *Acinetobacter baumannii;* ESBL, extended spectrum betalactamase; MRPA, multiresistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant ***Staphylococcus aureus*.

Conclusion

VAP due to ESKAPE pathogens represents a global challenge due to its increasing incidence, outcome impact and difficult treatment. Strategies promoting antimicrobial diversity may protect against emergence and spread of resistance by ESKAPE pathogens.

Sidebar

Key Points

- Ventilator-associated pneumonia (VAP) due to *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter* species (ESKAPE) pathogens continues to increase in frequency and resistance profile in ICUs worldwide.
- ESKAPE pathogens impact negatively on the outcome of critically ill patients suffering from VAP, limiting the treatment options.
- Whereas new antimicrobials still have to prove their value, new prescription strategies seem to be a reasonable option in the therapy of ESKAPE VAP.
- Strategies promoting antimicrobial diversity may protect against emergence of resistance in ESKAPE VAP.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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