CRITICAL CARE

REVIEW

# Year in review 2012: *Critical Care* – respiratory infections

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**Abstract**

Over the last two decades, considerable progress has been made in the understanding of disease mechanisms and infection control strategies related to infections, particularly pneumonia, in critically ill patients. Patient-centered and preventative strategies assume paramount importance in this era of limited health-care resources, in which effective targeted therapy is required to achieve the best outcomes. Risk stratification using severity scores and inflammatory biomarkers is a promising strategy for identifying sick patients early during their hospital stay. The emergence of multidrug-resistant pathogens is becoming a major hurdle in intensive care units. Cooperation, education, and interaction between multiple disciplines in the intensive care unit are required to limit the spread of resistant pathogens and to improve care. In this review, we summarize findings from major publications over the last year in the field of respiratory infections in critically ill patients, putting an emphasis on a newer understanding of pathogenesis, use of biomarkers, and antibiotic stewardship and examining new treatment options and preventive strategies.

## Introduction

Studies of respiratory infections in critically ill patients have improved our understanding of disease mechanisms, diagnosis, treatment, and prevention. In this era of patient management in the setting of limited health-care resources and the need to contain costs, it is important to achieve these goals in a targeted and effective fashion. This can be accomplished by a thorough understanding of disease risk and pathogenesis, which in turn can lead to the use of the most effective management strategies in an effort to reduce disease complications and length of stay and prevent readmissions.

## Disease mechanisms and pathogenesis

One of the major mechanisms responsible for the development of ventilator-associated pneumonia (VAP) is biofilm formation in the endotracheal tubes (ETTs). Previous studies have shown a reduced incidence of VAP with the use of inhibitors of biofilm formation, such as silver coating of the ETT, although mortality benefit is controversial [1]. In a prospective observational study, Gil-Perotin and colleagues [2] analyzed the relationship between endotracheal aspirate (EA) cultures (collected twice weekly), the presence of biofilm at the time of extubation (defined by scanning electron microscopy), and the concordance of cultures from EA (just prior to extubation) and biofilm cultures. In intubated patients (n = 75) during the 7-month study period, bacterial growth was present in 87% by surveillance cultures, and biofilm formation was observed in 95% of all ETTs. Biofilm was present as early as after 24 hours of intubation and was not associated with the duration of intubation, the administration of selective digestive decontamination, systemic antibiotics, or immunosuppression. *Acinetobacter baumannii* (32%) and *Pseudomonas aeruginosa* (22%) were the predominant organisms on surveillance cultures and achieved a concordance of 69% with ETT cultures on extubation. Despite a high prevalence of airway colonization and biofilm formation, only 17 episodes of VAP occurred during the study period (19%). Although appropriate therapy was given in 93%, the etiologic pathogen persisted in 50% of patients in the biofilm culture, and persistence in biofilm was commonly associated with treatment failure. These findings demonstrate the high prevalence of biofilm formation in ETTs and the potential implication of bacterial survival in biofilm as a reason for treatment failure in VAP, validating the current focus on reducing or eliminating bacterial biofilm formation.

Bacterial growth and infectivity can be facilitated by stress catecholamine, and the lungs are an active site of catecholamine metabolism. Freestone and colleagues [3] investigated the effects of inotropic catecholamine on the

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growth and virulence of *P. aeruginosa* in an *in vitro* system of ciliated human respiratory epithelium, incubated with clinically attainable levels of norepinephrine and dopamine. Using two different *Pseudomonas* strains, the authors found up to a 50-fold increase in bacterial numbers over unsupplemented control cultures. These inotropes were potent stimulators of bacterial growth and biofilm formation and facilitated rapid recovery from antibiotic challenge, but vasopressin and phenylephrine did not have a similar effect. The possible mechanism for these findings may involve transferrin-iron, with the inotrope enabling the bacteria to access the iron within transferrin, coupled with the direct internalization of the catecholamine. These findings suggest another mechanism for shock to be complicated by lung infection with drug-resistant Gram-negative bacteria and a possible strategy for intervention.

Antimicrobial peptides (AMPs) form part of the body's innate defense system, which is produced by white blood cells. Through various mechanisms, including disruption of cell membranes, interfering with metabolism, and targeting cytoplasmic components, AMPs neutralize bacterial toxins and kill invading microorganisms. Jendberg and colleagues [4] examined AMP concentrations in patients with community-acquired pneumonia (CAP) and determined whether levels of AMPs predicted clinical outcome or correlated with the causative microbe. In 89 patients with CAP, the mean plasma concentrations of secretory leukocyte protease inhibitor (SLPI) and bactericidal/permeability-increasing protein were significantly higher than in 63 healthy control subjects (85 versus 45 ng/mL, $P$ <0.001 and 48 versus 10 ng/mL, $P$ <0.001). However, the levels were not different from patients with non-respiratory infections and did not correlate with disease severity or etiologic pathogen. Male patients with CAP had higher concentrations of SLPI compared with females, raising the possibility that this mediator may be one of the ways to explain sex-dependent differences in the immune response.

Patients with pneumonia express distinctive pro-inflammatory and defensive proteins and these protein signatures can be studied with mass spectral analysis to recognize the presence of VAP in patients with associated acute lung injury (ALI). Nguyen and colleagues [5] studied the protein characteristics of bronchoalveolar lavage (BAL) fluid obtained from 35 patients – 5 normal patients and 30 patients with ALI (14 with VAP and 16 without) – by using tandem mass spectrometry. Of the 1,288 unique proteins identified in all patients, 75 distinct proteins were unique to patients with ALI, but there were different patterns of expression in those with and those without VAP. Patients with VAP and ALI had persistent inflammation with upregulation of proteins related to activation of anti-bacterial and immunologic pathways, whereas reparative mechanisms had been initiated in the lungs of ALI patients without VAP. The investigators recognized three proteins – S100A8, lactotransferrin (LTF), and actinin 1 (ACTN1) – which could be combined to create a good discrimination between patients with and those without VAP (93% sensitivity and 94% specificity). In another study using mass spectrometry analysis, Xiao and colleagues [6] applied matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry to identify the etiologic agents from 70 patients with CAP by using throat-swab samples. The MALDI-TOF methodology identified 210 of the 212 colonies that had been identified on blood agar. However, it is still not clear whether this highly sensitive test can distinguish colonization from infection. Further studies are needed to measure the diagnostic utility of these new mass spectroscopy tools to determine whether, in the proper clinical context, they might become rapid and cost-effective methods for identifying the presence of pneumonia and the etiologic pathogens, thus helping to lead to a more focused and responsible antibiotic use.

## Role of biomarkers

The host inflammatory response to different infective microorganisms is variable. Menendez and colleagues [7] studied the correlation between cytokine and biomarker activation patterns and their relation to the causative microorganisms in patients with CAP. The authors prospectively enrolled 658 admitted patients with CAP and measured procalcitonin (PCT), C-reactive protein (CRP), and cytokines, such as tumor necrosis factor-alpha (TNF-α), and interleukins (IL-1β, IL-6, IL-8, and IL-10). An etiologic diagnosis could not be reached, despite culture and serological testing, in 57% of the cases, but in the remaining 43%, the predominant organisms were *Streptococcus pneumoniae* (17.2%), *Legionella pneumophila* (3.5%), *P. aeruginosa* (2.6%), *Haemophilus influenzae* (2%), *Mycoplasma pneumoniae* (1.9%), and viruses (1.8%). PCT and CRP levels were significantly elevated in patients who had a known causative organism compared with those with an unknown cause, and the highest levels of cytokines, CRP, and PCT were found in patients who were bacteremic. Patients who had received antibiotics prior to admission (34%) had lower PCT ($P$ <0.01), IL-6 ($P$ <0.03), and IL-10 ($P$ <0.01) levels and higher IL-8 levels ($P$ <0.05). Patients infected with atypical bacteria had low PCT and IL-6 levels, similar to patients with viruses (low PCT but higher 1L-10). Patients with *S. pneumoniae* had high PCT, whereas those with Legionella had high CRP and TNF-α. PCT of at least 0.36 had an excellent negative predictive value (NPV) (98%) for positive blood cultures. PCT of not more than 0.5 mg/dL had a high NPV for bacteria versus viruses or atypical bacteria (99%/97%, respectively).

In an effort for early and accurate risk stratification of patients with CAP, Nowak and colleagues [8] enrolled 341 patients presenting to the emergency department with pneumonia. The authors compared the levels of three biomarkers – N-terminal pro-B-type natriuretic peptide (NT-proBNP), midregional pro-atrial natriuretic peptide (MR-proANP), and B-type natriuretic peptide (BNP) – with the pneumonia severity index (PSI) and CURB-65 score for predicting short- and long-term mortality; 63% of patients belonged to PSI class 4 and 5 combined, but the CURB-65 scores in the same cohort showed that only 17% patients were high-risk (groups 3 to 5). The levels of NT-proBNP ($r$ = 0.53, $P$ <0.001), MR-proANP ($r$ = 0.57, $P$ <0.001), and BNP ($r$ = 0.47, $P$ <0.001) gradually increased with increasing severity of CAP, which was classified according to the PSI score. The 30-day mortality rate in the cohort was 11%, but in those who died, the levels of all three biomarkers were high. Multivariable regression analysis noted NT-proBNP (cutoff admission level was 1,935 pg/mL) and PSI (calculated cutoff for admission was 101 points) to be independent predictors of death. Furthermore, the levels of biomarkers correlated with plasma creatinine and epidermal growth factor receptor but did not correlate with CRP level, leukocyte count, or oxygen saturation. The predictive potential of the NPs was independent of antibiotic treatment, appropriateness, and duration of therapy. Thus, a combined assessment using categorical PSI score and NT-proBNP levels seemed beneficial over a single-marker approach for short- and long-term risk stratification. However, the authors pointed out that elevated NP levels should be used with caution in patients with renal failure or heart failure. The findings are consistent with a recent meta-analysis of 12 studies, showing that BNP and NT-proBNP are powerful predictors of mortality in patients with sepsis [9].

PCT-based treatment algorithms have been shown to reduce antibiotic use in acute respiratory infections [10-12]. In a meta-analysis, Schuetz and colleagues [13] compared data from 14 trials, in which 4,221 adults with acute respiratory infections (ARIs) were enrolled and in which the initiation and duration of antibiotic treatment were based on PCT guidance. All of the studies were either European or Asian and consisted of patients with initial suspicion of ARIs. Adherence to PCT-based algorithms was variable (47% to 91%), and in none of the trials were caregivers or patients blinded to group allocation. The PCT group and control group had similar characteristics, and CAP was the most common diagnosis (48%), followed by chronic obstructive pulmonary disease (COPD). PCT levels were higher in patients admitted to the intensive care unit (ICU), but there was no difference in mortality in the various treatment settings (primary care, emergency room, and ICUs) in both the PCT group and control patients (5.7% versus 6.3%, adjusted odds ratio (OR) 0.94); however, patients in the PCT-guided group had less antibiotic exposure (adjusted difference in days, –3.47) in all clinical settings and across all ARI diagnoses. Treatment failure was similar in the two groups (PCT: 19.1% versus 21.9% in controls, adjusted OR 0.82). Even though the adherence to the PCT-guided protocol was variable (especially in the ICU), the lower antibiotic exposure, with similar mortality and treatment failure, is striking. Nonetheless, further studies are needed, especially in the critical care setting, to conclusively prove that PCT-based treatment is safe.

## Pneumonia risk factors, definitions, and risk stratification

### Community-acquired pneumonia risk factors and definitions

Thrombocytosis is considered to be an inflammatory marker of infection, but the relationship between platelet count outcomes in CAP is complex. In a prospective study, Prina and colleagues [14] assessed the outcomes of 2,423 hospitalized patients with CAP in relation to the platelet count on admission. Thrombocytosis was defined as a platelet count of at least $4 \times 10^5/mm^3$ and thrombocytopenia as less than $10^5/mm^3$. Fifty-three patients (2%) had thrombocytopenia, and 204 (8%) had thrombocytosis. Patients with thrombocytosis had more frequently received previous antibiotics, had a lower CURB-65 score at admission, and had higher respiratory complications, such as empyema and pleural effusion, than those without. On the other hand, those with thrombocytopenia had more frequent chronic heart and liver disease, were sicker, and had higher rates of severe sepsis, septic shock, and invasive mechanical ventilation and ICU admission than the rest of the population. Patients with thrombocytosis had a higher 30-day mortality (OR 2.720, $P$ = 0.001), but those with thrombocytopenia also had an increased rate of dying. Thus, there was a biphasic relationship between platelet count and mortality, with increased mortality, once the count was outside the range of 100,000 to $400,000/mm^3$. The authors did not measure serial platelet counts and hence it is not clear whether platelet counts improved with treatment. As noted in a previous study [15], the mortality was increased in patients with thrombocytosis but was not linked to higher thrombotic or cardiovascular events.

A biphasic relationship was also observed when relating CAP mortality to arterial partial pressure of carbon dioxide ($PCO_2$) on admission in a retrospective study of 453 CAP patients from two tertiary-care centers. Hypocapnia (<35 mm Hg) was present in 194, hypercapnia (>45 mm Hg) in 70, and normal values in 189 [16]. Patients with hypocapnia were younger; had multilobar infiltrates, metabolic alkalosis, or chronic liver disease;

and were less likely to have COPD, whereas patients with hypercapnia were more likely to have congestive heart failure, prior stroke, or COPD. After adjustments for disease severity, both patients with hypocapnia and those with hypercapnia had a greater 30-day mortality (ORs were 2.84 and 3.38, respectively) and a higher need for ICU admission (ORs were 2.88 and 5.35, respectively) compared with patients with a normal arterial partial pressure of carbon dioxide ($PaCO_2$). The differences persisted even after patients with COPD were excluded. The study did not differentiate patients with chronic carbon dioxide ($CO_2$) retention and consisted predominantly of male veterans. Further prospective studies are needed to validate these findings.

Aliberti and colleagues [17] assessed the risk factors for infection with multiple-drug resistance (MDR) pathogens in patients admitted with CAP or health care-associated pneumonia (HCAP) in a prospective observational study. The study enrolled a total of 935 patients, of whom 51% (n = 473) had at least one risk factor for acquiring MDR bacteria on admission according to the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) 2005 HCAP guidelines (hospitalization for at least 2 days in the preceding 90 days, residency in a nursing home or extended-care facility, home infusion therapy including antibiotics, home wound care, chronic dialysis within 30 days, family member with an MDR pathogen, antimicrobial therapy in the preceding 90 days, and immunosuppression). Patients with at least one risk factor for MDR pathogens had more severe pneumonia on admission and a higher prevalence of severe sepsis compared with those without (45% versus 29%, $P$ <0.001; 31% versus 21%, $P$ = 0.001). *S. pneumoniae* was the most common pathogen isolated in both study groups, but there was a higher prevalence of MDR pathogens in patients with risk factors compared with those without (6.1% versus 0.9%, $P$ <0.001). Of all the risk factors, hospitalization in the preceding 90 days (OR 4.87, 95% confidence interval (CI) 1.90 to 12.4, $P$ = 0.001) and residency in a nursing home (OR 3.55, 95% CI 1.12 to 11.24, $P$ = 0.031) were independent predictors of infection with a resistant pathogen and mortality, emphasizing the finding that not all of the studied risk factors contributed equally to the risk of infection by MDR pathogens. The authors developed a clinical prediction score for determining the risk of MDR, using four variables (comorbid conditions, nursing home resident, hospitalization in preceding 90 days, and chronic renal failure: 0.5, 3, 4, and 5 points, respectively). A score of greater than 0.5 had a sensitivity of 0.75 and a specificity of 0.71 for determining the risk of MDR pathogens. But more importantly, among patients with a score of not more than 0.5 on entry, the prevalence of resistant bacteria was 8%, compared with 38% in those with a score of at least 3 ($P$ <0.001). The findings suggest a way to stratify patients with HCAP, so that not all would have required empiric broad-spectrum therapy.

In a similar study, Shorr and colleagues [18] evaluated the ability of a clinical scoring system to predict the risk of infection with a resistant pathogen in a cohort of 977 patients admitted with CAP or HCAP. The risk score included four variables and assigned points to each as follows: recent hospitalization, 4; coming from a nursing home, 3; chronic hemodialysis, 2; and critically ill, 1. The most common organisms isolated were methicillin-resistant *Staphylococcus aureus* (MRSA) (22.7%), *P. aeruginosa* (19.1%), *S. pneumoniae* (19.1%), *Klebsiella pneumoniae* (5.6%), and *Acinetobacter* spp. (4.8%). Resistant pathogens were isolated from 46.7% of patients and these patients were severely ill and required ICU admission and mechanical ventilation more often than patients with no resistant pathogens isolated. Patients with MDR pathogens had a higher median score compared with those without (4 versus 1, $P$ <0.001). In contrast, 35% of screened patients who met the HCAP definition would have been over-treated for MDR pathogens if only this definition had been used as an indication for broad-spectrum therapy, compared with 24.3% with a risk score of greater than 0. A score of zero had a high NPV (84.5%) to rule out MDR pathogens and could potentially be used in the emergency room to avoid the unnecessary use of broad-spectrum antibiotics in patients with HCAP.

Pneumococcal pneumonia is the most important and common cause of severe pneumonia, and Mongardon and colleagues [19] determined the risk factors for mortality in patients who had this infection and who met the criteria for CAP as defined by the ATS 2001 guidelines. Using a retrospective analysis of data from two prospective studies, the authors identified 222 patients, of whom 45% had bacteremia, 84% (n = 186) required mechanical ventilation, and 77% (n = 170) had septic shock, leading to an ICU mortality of 26.6% (n = 59 patients). Independent risk factors for mortality were age (OR 1.05), male sex (OR 2.83), and renal replacement therapy (OR 3.78). Interestingly, medical comorbidities, macrolide administration, concomitant bacteremia, and penicillin non-susceptibility (present in nearly 40%) did not influence outcome. However, closer analysis of the data shows that non-survivors were sicker, having higher Simplified Acute Physiology Score II (SAPS II) values and a higher percentage of acute respiratory distress syndrome (ARDS) and septic shock. In addition, it is unclear whether the authors were reserving ICU admission for only the most severely ill, late in the course of illness, since 84% of the entire population needed mechanical ventilation, a relatively high number, suggesting that the ICU had not been used expectantly, and early in the disease process and therefore leading to higher mortality.

MRSA is an important cause of pneumonia in the community and often is a severe illness, needing ICU management. Moran and colleagues [20] defined the incidence and risk factors for this infection in a prospective study of 627 patients from 12 emergency departments across the US during two influenza seasons (2006-07). MRSA was isolated from 2.4% of all patients and 5% of patients admitted to the ICU, mortality rate was 14%, and all isolates were of the USA 300 strain. Those who had MRSA isolated were sicker on admission and were more likely to have multiple infiltrates or cavities on chest imaging, be intubated, or require vasopressors, compared with other patients. Other features associated with community-acquired MRSA were nursing home admission in the previous year, close contact in the previous month with someone with a skin infection, and severe illness (coma, intubation, and need for vasopressors). The authors concluded that empiric therapy for MRSA should be considered in patients with severe CAP until MRSA is ruled out. This conclusion is at odds with the findings in another study that found a similar incidence (3.2%) of MRSA in 621 ICU patients with CAP [21]. In that study, 57 patients received empiric MRSA therapy, and there were no differences in mortality, length of stay, or time to clinical stability [21]. The specific therapy of MRSA may be important, particularly if the organism present produces exotoxins such as the Panton-Valentine leukocidin (PVL). In a study of 133 patients with PVL-positive CAP, most of which was MSSA, the presence of MRSA did not increase mortality, but the use of therapies with anti-toxin effects (clindamycin, rifampin, and linezolid) was associated with a reduced mortality (6.1% versus 52.3%, $P$ <0.001), although only about one third of patients received this therapy [22].

Delayed admission to the ICU is a risk factor for mortality in CAP, and investigators have attempted to use the REA-ICU index (risk of early admission to the ICU) as a tool on admission to identify patients who had no obvious indications for ICU care but who subsequently required ICU management. The tool had been devised on the basis of a data set of nearly 5,000 patients, categorizing individuals into four risk groups, with an increasing likelihood of needing ICU care. The current study attempted to validate the tool with a retrospective analysis of 850 CAP patients who were enrolled in the Pro-Hosp study (a multicenter, prospective, randomized trial) and who had no obvious need for ICU care on admission (54 patients were admitted to the ICU in the first 3 days) [23]. In the validation study, 27.1% of patients in the highest-risk group (which represented only 3.4% of all patients) needed ICU care. The REA-ICU index performed better than PSI but was similar to other tools (like SMART-COP, CURXO-80, the 2007 IDSA/ATS minor severity criteria, and CURB-65) at defining the need for early ICU admission. It is possible that the predictive value of these tools could be further improved if stratification were combined with data from early measurement of serum biomarkers.

#### Nosocomial pneumonia risk factors and definitions

Hypothermia is a common finding in critically ill patients and may add to the risk of infection because it impairs humoral and cellular immunity, inhibiting the release of pro-inflammatory cytokines. A group of French investigators evaluated the risk of developing pneumonia and bloodstream infections in relation to the presence of hypothermia of all causes in 6,237 medical ICU patients [24]. Hypothermia was classified as mild (35.0°C to 35.9°C), moderate (32°C to 34.9°C), or severe (<32°C), and the cumulative incidence of at least one documented episode of hypothermia was 30% (1,849 out of 6,237). Seven hundred twenty-four patients (12%) developed nosocomial pneumonia, and 320 patients (5%) acquired bloodstream infections. The risks of developing pneumonia were 24.4% with severe hypothermia and 11.7% with no hypothermia, but the rate of lung infection was not increased by mild or moderate hypothermia. In multivariate analysis, severe hypothermia increased the risk of ICU infection in patients who did not present with severe sepsis or septic shock, and the hazard ratio was 2.76 (95% CI 1.44 to 5.28, $P$ = 0.0009). A lack of effect noted in those with infection on admission may have been related to the early use of antibiotics in this population. This study, though interesting, was retrospective and offers no good information about the impact of antibiotic use or the etiology of hypothermia. However, consistent with these findings is the observation in previous studies that therapeutic hypothermia after cardiac arrest is a risk factor for early-onset nosocomial pneumonia [25].

ARDS has been considered an illness that is commonly complicated by VAP, but much of the data to support this relationship was collected prior to the treatment of ARDS with a low tidal volume ventilatory strategy. Cyclical stretching forces theoretically can promote bacterial growth in human alveolar cells and predispose patients to pneumonia, and thus the use of lung protective ventilation theoretically could reduce the incidence of VAP. Forel and colleagues [26] studied the incidence and outcomes of VAP in 339 patients who were enrolled in a multicenter, randomized, placebo-controlled, double-blind trial of cisatracurium besylate and who were ventilated with LPV for severe ARDS. VAP was diagnosed in 28.9% of included patients, the daily risk for bacterial VAP increased until day 9 and then decreased, and the median time of onset was day 10 of ARDS (Figure 1). Patients who had tracheostomy, enteral nutrition, or subglottic secretion-drainage device had fewer episodes

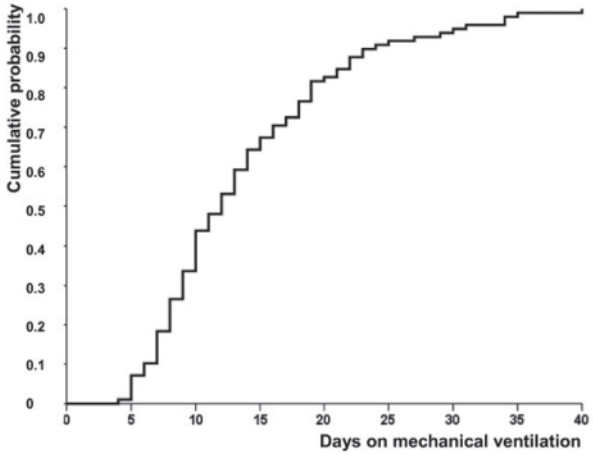


**Figure 1. Kaplan-Meier estimates of the cumulative probability of developing ventilator-associated pneumonia according to the number of days on mechanical ventilation in a group of 98 patients with severe acute respiratory distress syndrome.** Reprinted with permission from BioMed Central [26].

of VAP. ICU mortality rate was higher in patients with VAP compared with non-VAP patients (41.8% versus 30.7%, $P$ = 0.05), but VAP was not an independent predictor of mortality in multivariate analysis. These findings are not different from those in previously reported studies, when patients with ARDS were not receiving low tidal volume ventilation, thus confirming that ARDS is a risk for VAP, independently of the mode of ventilation.

In the ICU, there is a declining frequency of VAP, and some institutions claim that with the use of simple prevention methods and ventilator bundles, they have been able to achieve 'zero VAP'. One possible explanation for these findings is that there has not really been a reduction in VAP but rather 'gamesmanship' in defining VAP and that under-reporting has resulted from VAP definitions that are subjective and easily manipulated. In an effort to make the definitions of ICU-acquired pneumonia in ventilated patients more objective, the Centers for Disease Control and Prevention (CDC) and a number of investigators have proposed looking for ventilator-associated complications (VACs) rather than VAP. To make the process objective, the definition of VAC has generally relied on changes in oxygenation and not required a chest radiograph, although many patients with VAC probably do not have pneumonia. With this approach, VAC occurs when there is a rise in fraction of inspired oxygen ($FiO_2$) needs by at least 0.2, or a positive end-expiratory pressure (PEEP) increase by at least 3 cm of water, for at least 2 days after 2 days of stability or improvement. If there is fever and a new antibiotic is started for at least 4 days, then an infectious VAC (IVAC) is defined. The IVAC population is then divided into possible or probable VAP, depending on clinical data (but not a chest radiograph) and culture results [27].

To justify this new approach, Klompas and colleagues [28] have examined 8,735 episodes of mechanical ventilation and found that respiratory deterioration correlated best with mortality and that adding other signs did not enhance predictive value. Importantly, they have suggested that VAC can be evaluated electronically and objectively, minimizing the time for doing surveillance and reducing the subjectivity of the diagnosis. In Australia, Hayashi and colleagues [29], using an electronic medical record, applied the definition of VAC and identified 153 of 543 patients who met this definition. Of those with VAC, 47 had positive respiratory cultures and 40 received antibiotics, documenting that VAC was much more common than VAP. Interestingly, the presence of VAC correlated with increased ICU length of stay, days on mechanical ventilation, and antibiotic use but not with mortality [29]. Although this new approach is interesting, it remains to be seen whether the rate of VAC can be influenced by preventive measures and by improvements in quality of care, both of which are necessary if the monitoring of VAC rates is to be clinically meaningful.

## Severe community-acquired pneumonia and mortality

Pneumonia patients admitted to the hospital have a mortality up to 18%, and even higher if they need admission to the ICU. Regulatory agencies in the US are recommending the reporting of 30-day mortality of patients admitted with pneumonia, as a quality measure. In a retrospective analysis of a database comprising 21,223 Medicare patients who were 65 years old or older and who were admitted to the hospital between 2000 and 2001, Metersky and colleagues [30] determined the factors predicting in-hospital versus post-discharge mortality. The reported mortality was 12.1% within 30 days of admission; 1,343 (52.4%) of the deaths occurred during the hospital stay, and 1,218 (47.6%) after discharge but within 30 days of admission. Patients who were hypoxemic on admission needed mechanical ventilation; had bacteremia, hypotension (blood pressure of less than 90 systolic), respiratory rate of greater than 30 per minute, pH of less than 7.35, and renal failure; and had higher in-patient mortality (versus post-discharge mortality) on multivariate analysis. The timing of death (early versus late) was unrelated to baseline patient demographic factors or comorbidities, but in-patient mortality was related to the severity of illness. The present study is retrospective and from a relatively old database and lacks treatment variables. However, it is a large national database, and the finding that in-patient mortality was unrelated to patient comorbidities extends credibility to

using 30-day mortality as a benchmark for Center for Medicare performance measure in patients admitted with pneumonia.

Pneumonia can be complicated by cardiac events, including myocardial infarction and cardiac arrest. Carr and colleagues [31] sought to define the clinical associations and predictability of cardiac arrest in patients with CAP. The authors examined a database of 55,276 patients who had a cardiac arrest, of which 4,453 patients had had a diagnosis of pneumonia before in-hospital cardiac arrest. Only 62% of these events occurred in patients admitted to the ICU, and in this population, 52% were on vasopressors and 56% on mechanical ventilation. Cardiac arrest occurred earlier in the ICU than on the ward (at a median of 18.9 versus 28.4 hours), and of those with cardiac arrest on a medical ward, 52% were undergoing cardiac monitoring. Myocardial infarction and ischemia were present in 13.4% of patients with pneumonia, and the most common cause of cardiac arrest was an arrhythmia, generally not a shockable rhythm (asystole or pulseless electrical activity). In general, the findings are alarming because they suggest that patients with CAP in the hospital, or even the ICU, commonly have cardiac ischemia and that the event may be abrupt and without warning. Since time-sensitive interventions are important in preventing adverse cardiovascular events, it is important to identify pneumonia patients who might have myocardial ischemia or sepsis-related cardiomyopathy, but more studies are needed to define how to recognize these individuals at an early time point.

## Surveillance strategies and antibiotic stewardship

Several strategies have been adopted over the past few years to prevent the development of VAP, but the role of surveillance itself is uncertain. Although earlier studies showed that VAP rates were reduced when surveillance was being done, it remains unclear whether this reduction was an artifact of observation (Hawthorne effect) or a true improvement in care. Benet and colleagues [32] took advantage of an interesting opportunity to observe the impact of disruption in the surveillance system for health care-acquired infection in one hospital. In a quasi-experimental study design from a single center in France, data from a medical-surgical ICU with surveillance disruption due to staff restructuring in 2007 (group A) was selected as the intervention group and compared with a medical ICU with continuous surveillance (group B), which served as the control group [32]. Prior to the disruption, period 1 (2004-6), and afterwards, period 2 (2008-10), both units had continuous surveillance in place. The VAP rate (number of VAPs per 100 intubated patients) increased in the intervention unit from period 1 to 2 (7.8% to 17.1%, $P$ <0.001), whereas the VAP rate did not change significantly in the control ICU during the same period (7.2% to 11.2%, $P$ = 0.17). In unit A, between periods 1 and 2, the all-cause mortality (13.5% versus 18.8%, $P$ = 0.028) and length of stay (12.2 versus 15.3 days, $P$ = 0.038) increased, but this did not occur in unit B. The authors theorized that the worse outcomes in unit A were due to lack of data feedback and counseling during the year of surveillance disruption. However, the authors did not provide data on VAP prevention measures and compliance in either group.

Antimicrobial stewardship can lead to a more judicious use of antibiotics in ICU patients, as demonstrated in a pre- and post-intervention study by Katsios and colleagues [33]. For ICU patients, the investigators initiated an antimicrobial stewardship program (ASP), which consisted of education, consultation, audit, and feedback, implemented by daily meetings between the ICU team and the ASP team, which consisted of a pharmacist and an infectious disease physician. The investigators compared 139 patients in the 2-month period before the team was started with 130 patients in the 2 months after the team began to work. The ASP team was successful in reducing the use of antibiotics for patients with positive cultures from non-sterile sites (46% from 71%, $P$ = 0.0002), representing possible colonization, and increasing the use of antibiotics for positive cultures from sterile sites (83% from 64%, $P$ = 0.01) (Figure 2). In addition, after the team intervened, there was greater use of defined antibiotic stop dates. The findings are encouraging and show the opportunity to use stewardship programs with a wide benefit for many ICU patients.

Most programs of antimicrobial stewardship have focused on nosocomial infections, and few programs have attempted to reduce the use of antibiotics in patients with CAP. A group of US investigators conducted a stewardship program for CAP patients on the basis of disease management education and prospective feedback about duration of therapy and specific antibiotic choices, comparing pre- and post-intervention periods (from 1 January 2008 through 31 March 2008 versus from 1 February 2010 through 10 May 2010) [34]. Sixty-two patients were in the baseline period and 65 were in the intervention period, pneumococcus and viral pathogens were the most common etiologic agents, and less than 10% of the patients were admitted to the ICU. The median lengths of stay were similar in the two groups (4 versus 5 days), but the duration of antibiotic therapy decreased from a median of 10 to 7 days ($P$ <0.001) with the intervention. In addition, 90% of patients in 2008, compared with 55% in 2010, received excessive duplicate antibiotic therapy within 24 hours. The study is limited by the small number of patients included but does document the feasibility of stewardship interventions in CAP, although the efficacy of this approach in ICU patients needs to be further studied.

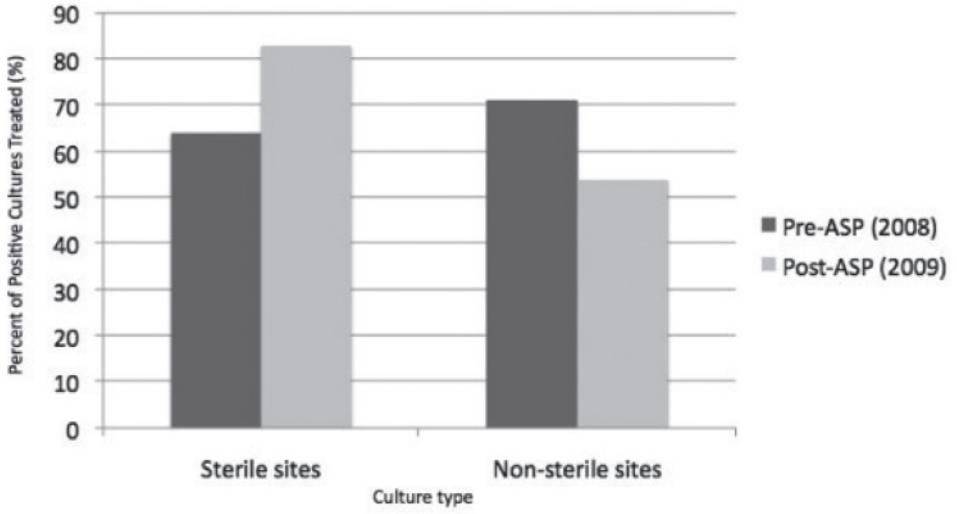


**Figure 2. Frequency of antibiotic therapy in relation to positive results obtained from different types of body sites, evaluated before and after antibiotic stewardship program (ASP) implementation.** The ASP consisted of a series of education, consultation, and reinforcement methods and was able to successfully reduce the use of antibiotics for patients with positive cultures from non-sterile sites and increase the use of antibiotics for positive cultures from sterile sites. Reprinted with permission from BioMed Central [33].

## New insights into treatment strategies

### Community-acquired pneumonia

The ATS/IDSA 2007 guidelines for the treatment of severe CAP recommend combination therapy (and not monotherapy) using either beta-lactam and fluoroquinolone (FQ) or beta-lactam and macrolide. In the setting of suspected or documented Legionella infection, quinolones may be more effective than macrolides, but in other situations, it is uncertain whether either regimen has an advantage over the other. Wilson and colleagues [35] retrospectively evaluated 1,989 patients who were admitted to the ICU of a Veterans Affairs hospital over a 5-year period and who were more than 65 years of age, and compared patients who received a beta-lactam plus FQ (44%) with those receiving a beta-lactam plus macrolide (56%). The 30-day mortality rates were similar in the two groups (27% for beta-lactam plus FQ and 24% for beta-lactam plus macrolide, $P = 0.11$); however, the use of beta-lactam plus FQ was associated with an increased mean length of stay of more than 7 days. Although the data were collected in a primarily older, male veteran population and may not be generalizable, the findings are provocative but unexplained. The authors speculated that the macrolide combination regimen may have had a benefit because of the anti-inflammatory effects of the macrolide or that, alternatively, the quinolone regimen may have been detrimental by predisposing patients to nosocomial infection with MDR pathogens.

One concern about the empiric use of FQs in CAP is that if they are used in areas that are endemic for tuberculosis (TB) in cases that are mistakenly diagnosed as CAP, they could mask or delay the diagnosis of TB because of their good *in vitro* and *in vivo* bactericidal activity against *Mycobacterium tuberculosis*. FQs can also be used as a second-line anti-TB therapy, and their empiric use in CAP may result in the emergence of drug-resistant TB. In a retrospective study from Taiwan, investigators examined 77 patients who had culture-confirmed pulmonary TB that was initially diagnosed as severe CAP and who were admitted to the ICU [36]. Patients were divided into two groups, depending on whether their initial treatment included an FQ. Forty-three patients (56%) were in the FQ group, and 34 (44%) were in the non-FQ group. The 100-day mortality rates were 40% and 68% for the FQ and non-FQ groups, respectively ($P = 0.02$, OR for death 0.36, $P < 0.01$). There was no delay in the initiation of anti-TB therapy in either group (FQ 24.1 ± 15.6 and non-FQ 24.7 ± 17.2 days, $P = 0.89$). Although the study was retrospective and relatively small, the findings did demonstrate that, contrary to classic teaching, the empiric use of FQs in severe CAP that later proves to be TB does not lead to a delay in proper treatment and may actually have a possible mortality benefit. The reasons for benefit are not clear, but in the study, molecular diagnostic methods for TB were not being used, and thus there was a long delay before the diagnosis of TB was established with conventional methods. In this setting, FQs may have reduced the infectious burden of TB since 65% of the FQ-treated patients had sputum conversion on quinolone monotherapy.

The benefit of anti-inflammatory therapy in CAP has been suggested by the findings of improved outcome

when using a combination therapy with macrolide, as mentioned above. However, the role of corticosteroids as routine adjunctive therapy in severe CAP remains controversial. Several earlier studies and one recent randomized trial have suggested that steroids have the benefit of leading to a more rapid resolution of fever and hypoxemia and less need for mechanical ventilation [37]. Polverino and colleagues [38], in a retrospective study, found that routine steroid therapy had no benefit in patients with CAP if it was not used for another established indication. In a population of 3,257 patients with CAP, 260 received corticosteroids, generally because of chronic respiratory illness or a severe clinical presentation, but there was no benefit in mortality and there was a longer length of stay (9 versus 6 days, $P$ <0.01). The lack of benefit also applied when those with a more severe illness (PSI classes IV and V) were examined. The mixed findings of steroid benefit may reflect the fact that there is a subset of CAP patients who can benefit, but steroids are being used in a non-selective fashion. Remelts and colleagues [39] analyzed data from a previous randomized controlled trial of steroid therapy in CAP and found that in the subset of patients with high cytokine levels and low cortisol (23 out of 275 patients), steroids substantially reduced mortality compared with placebo. However, in patients with high cytokine levels and high cortisol and in those with low cytokine levels, steroids had no benefit compared with placebo. Thus, in the future, we may be able to individualize our anti-inflammatory interventions by measuring the inflammatory and biochemical milieu of our patients to define those who can most benefit from specific therapies.

#### Nosocomial pneumonia

The 2005 ATS/IDSA guidelines recommended early empiric therapy with broad-spectrum antibiotics for nosocomial pneumonia patients at risk for MDR pathogen infection, with subsequent de-escalation of antibiotics, once clinical and microbiologic data become available. Using an open-label randomized design, investigators from Korea randomly assigned 109 medical ICU patients with HAP to empiric therapy with imipenem (0.5 g every 6 hours) plus vancomycin (15 mg/kg every 12 hours), followed by de-escalaton (54 patients) versus conventional therapy (non-carbapenem, non-vancomycin empiric antimicrobials) without de-escalation (55 patients) [40]. The de-escalation strategy was based on culture results on day 3 and the Clinical Pulmonary Infection Score. The conventional therapy group received antibiotics according to the ATS 2005 guidelines, except that none received carbapenems or vancomycin: piperacillin/tazobactam plus ciprofloxacin (63.6%), piperacillin/tazobactam plus aminoglycoside (20%), and ceftazidime plus either ciprofloxacin or aminoglycoside (9.1%). The initial antimicrobial was adequate more often in the de-escalation group compared with the conventional therapy group (75.9% versus 48%, $P$ = 0.035), particularly for MRSA, and broad-spectrum agents were discontinued more often in the former group (vancomycin was discontinued in 83.3% and imipenem/cilastatin in 84.8%). Interestingly, there was no measureable outcome benefit to the de-escalation protocol, there was no difference between the two groups in overall length of ICU stay or mortality, and patients in the de-escalation group had a higher incidence of emergence of MRSA in subsequent cultures, compared with the conventional group (27.6% versus 9.5%, $P$ = 0.059). It is difficult to understand the lack of benefit of the de-escalation approach, particularly since it did lead to more initially adequate therapy and less antibiotic usage, although relatively few patients had VAP (<10%) and more patients in the de-escalation group had MDR pathogens than in the control group.

Duration of treatment for VAP has been subject to intense debate, but although a duration of 8 days seems to be effective if MDR pathogens are not present, the optimal duration for MDR pathogen VAP is uncertain. Doripenem is a carbapenem antibiotic that has been previously shown, at a dose of 500 mg three times per day, to be non-inferior to piperacillin-tazobactam and imipenem for nosocomial pneumonia in a 7- to 14-day course. Doripenem has shown to have *in vitro* activity against *P. aeruginosa* that is better compared to other carbapenems. In an effort to optimize the duration of VAP therapy (including infection with MDR Gram-negative bacteria), a multicenter randomized double-blind study was done to compare a 7-day course of high-dose (1 g) doripenem given as a 4-hour infusion, to a 10-day course of 1 g dose imipenem each given every 8 hours. The investigators hypothesized that by using a highly active carbapenem given by prolonged infusion, it would be possible to optimize the killing of potentially resistant Gram-negative bacteria, facilitating short-duration therapy for these organisms [41]. The study was prematurely stopped because of documented inferiority of the 7-day regimen, particularly for VAP caused by *P. aeruginosa*. The microbiological intent to treat (MITT) population (167 patients: 79 doripenem and 88 imipenem-cilastatin) was the subset of patients who had received at least one study drug and had at least one Gram-negative pathogen identified in significant concentrations in BAL, sensitive to imipenem. The clinical cure rate at the end of therapy for the MITT population was numerically lower for doripenem than imipenem (45.6% versus 56.8%, 95% CI −26.3% to 3.8%), including those with *P. aeruginosa*. All-cause 28-day mortality was also higher in the doripenem arm compared with imipenem, though not significantly (21.5% versus 14.8%), but mortality was statistically higher for patients with *P. aeruginosa* who

were treated with doripenem. The authors attributed the failure of doripenem, despite the use of the prolonged infusion protocol, to not using a long enough duration of therapy for patients with non-fermenting Gram-negative pathogen infection.

The doripenem study attempted to optimize the pharmacokinetics of antibiotic administration, an area of interest in the ICU setting. In another study, Chytra and colleagues [42] investigated the clinical and bacteriological efficacy of a continuous infusion of meropenem compared with bolus administration in critically ill patients with severe infection, at a single center. Patients who had severe infection and who required meropenem were randomly assigned either to the infusion group (n = 120) (loading dose of 2 g of meropenem followed by a continuous infusion of 4 g of meropenem over 24 hours) or to the bolus group (n = 120) (2 g of meropenem over 30 minutes every 8 hours). Although the two groups had comparable clinical success (83% versus 75%, $P$ = 0.180), patients who received continuous infusion had a higher rate of microbiological cure compared with the bolus group (OR 2.977, 90.6% versus 78.4%, $P$ = 0.020). Patients who received the infusion regimen also had a shorter ICU stay, lower total dose of meropenem, and fewer days on meropenem. The bactericidal effect of carbapenems is time-dependent (the time the free drug concentrations remain above the minimum inhibitory concentration of pathogens), and thus the greater efficacy observed with continuous infusion can be explained by better bacteriologic clearance as a result of optimized pharmacokinetics.

In the therapy of MRSA nosocomial pneumonia, previous studies have not resolved whether there is an advantage to choosing linezolid over vancomycin, although a previous *post hoc* subset analysis of prospective studies did show a higher cure rate and clinical efficacy for linezolid, especially for patients with documented MRSA pneumonia [43]. To address the criticism of the retrospective nature of these data, a prospective, randomized, double-blind, multicenter study comparing linezolid with vancomycin for documented MRSA nosocomial pneumonia was conducted [44]. Patients were randomly assigned to receive intravenous linezolid (600 mg every 12 hours) or vancomycin (15 mg/kg every 12 hours, with the dose optimized, based on trough levels and renal function) for 7 to 14 days. In total, 448 patients (linezolid 224 and vancomycin 224) were included in the modified intent-to-treat population, and 348 (linezolid 172 and vancomycin 176) were in the per-protocol population. The primary end point was clinical outcome at end of study in the per-protocol patients, and linezolid therapy led to a significantly higher response than vancomycin (57.6% versus 46.6%, $P$ = 0.042). However, the 60-day mortality rates were similar in the two groups, although nephrotoxicity occurred more frequently with vancomycin (18.2% versus 8.4%). The lack of mortality difference should be viewed in the context of previous data since the mortality of patients treated with vancomycin was lower than in prior studies, whereas the mortality rate of patients treated with linezolid was comparable to prior studies. The relative 'improvement' in mortality with vancomycin in this study may have been related to the fact that vancomycin dosing was optimized and that patients failing vancomycin could be treated with linezolid (unlike in earlier studies). In this latter circumstance, if the salvage therapy prevented mortality, although the patient would be a vancomycin clinical failure, the patient was also reported as vancomycin non-mortality.

In the therapy of severe sepsis, previous studies have shown that the use of appropriate combination therapy, compared with the use of appropriate monotherapy, led to a reduced mortality, particularly in patients with pneumonia [45]. Diaz-Martin and colleagues [46] evaluated this issue by conducting an analysis of a large database from a prospective Spanish sepsis trial. They included 1,372 patients with a community-acquired source of sepsis in 74.5% and a nosocomial source of sepsis in 25.5%. Pneumonia, the most common infection, was present in 36.6%. The investigators found that mortality was lower (34% versus 40%, $P$ = 0.042) when therapy was given with a combination therapy that included at least two antimicrobials with different mechanisms of action (given in 28.3%) compared with monotherapy and with combination therapy that did not include agents with two different mechanisms of action (given in 71.7%). When different class combination therapy was administered, the most commonly used agents were beta-lactams, quinolones, aminoglycosides, and carbapenems, in that order. Unfortunately, the study did not have microbiologic data to explain the mechanism for benefit of the combination therapy, but the authors speculated that it may have been due to a synergistic effect of using two agents with different mechanisms or could have been the result of including immunomodulatory agents such as macrolides and quinolones.

## Viral pneumonia

The role of viral infection in severe CAP was evaluated in a retrospective analysis of a prospective cohort of 198 adult ICU patients from a single center in Korea [47]. Patients had HCAP (n = 134) and CAP (n = 64), and 36% tested positive for a viral organism by either a nasopharyngeal swab (n = 159) or BAL (n = 104). The most commonly identified viruses were rhinovirus (23.6%), parainfluenza virus (20.8%), human metapneumovirus (18.1%), influenza virus (16.7%), and respiratory syncytial

virus (13.9%). Patients with HCAP and patients with CAP had similar rates of viral infections (34.3% versus 40.6%, $P$ = 0.43). There were no significant differences in mortality rates between patients with bacterial infections, viral infections, and bacterial-viral co-infections (25.5%, 26.5%, and 33.3%, respectively; $P$ = 0.82). Among patients with a viral pathogen isolated, rhinovirus was associated with the highest mortality (52.9%), followed by influenza virus (33.3%). The findings show a high frequency of viral infection in the ICU but may have overestimated the importance of viruses since some patients may have had false-negative findings for bacteria because of the use of antibiotics before admission. In addition, the study did not establish the etiologic role of viruses, just their presence by polymerase chain reaction, which may have represented colonization and not infection.

In a prospective study, Gianenella and colleagues [48] examined tracheal aspirates for the presence of influenza by using polymerase chain reaction-based methods in 105 intubated ICU patients during peak influenza season. Influenza was detected in 31 patients and was predominantly H1N1 (87%), but of all the positive influenza cases, 48.4% were clinically unsuspected and 42% were hospital-acquired. Suspicion of influenza was lower in older patients, in those admitted to the ICU for surgical conditions, in those who stayed for a longer time in the hospital and ICU, and in those who did not have a cough or diffuse pulmonary infiltrates. There were no significant differences in mortality and length of ICU stay among patients who had suspected or unsuspected influenza. Admission to surgical ICU (OR 37.1, $P$ = 0.01) and having a localized infiltrate on chest radiograph (OR 27.8, 95% CI 1.3 to 584.1, $P$ = 0.03) were noted to be independent risk factors for unsuspected influenza. Overall mortality at 30 days was 29% and did not differ in those with suspected or unsuspected influenza, even though antiviral treatment was started late in unsuspected cases. The findings led the authors to recommend routine influenza screening in intubated patients during influenza season.

## Fungal pneumonia

Bloodstream infection related to Candida species is commonly treated in the ICU, and associated morbidity and mortality are high. Ylipalosaari and colleagues [49] examined the risk factors and outcomes of patients with ICU-acquired candidemia (ICUAC) (acquired after 48-hour ICU stay) and those who required ICU care for candidemia acquired prior to ICU admission or within the first 48 hours (non-ICUAC group). Data from a single-center mixed ICU with positive blood cultures for Candida species were included in the retrospective analysis, which documented that when Candida bacteremia was treated in the ICU, it was more often non-ICUA infection than infection arising in the ICU (82 patients: 46.3% in ICUA and 53.6% non-ICUA). *C. albicans* was the most common cause of candidemia in both groups, followed by *C. glabrata*. Patients with ICUAC had more frequent central venous catheters, previous surgeries, and fluconazole prophylaxis (40% versus 13.3%, $P$ = 0.007), whereas those with non-ICUAC had a higher frequency of comorbidities and malignancy. The overall mortality, use of antibiotics, and length of hospital stay were similar in the two groups. Severity of illness was related to mortality in different ways for each group. In patients with an APACHE II (Acute Physiology and Chronic Health Evaluation II) score of greater than 25, the mortality was lower in the ICUAC group than the non-ICUAC group (65% versus 87.5%). The opposite applied for those with an APACHE II score of less than 25, with a higher mortality in the ICUAC group. Although the authors did not provide a clear explanation of the reported differences in mortality among patients with a higher APACHE II score, the findings could be related to early institution of prophylactic anti-fungal therapy in sicker patients in the ICUAC group compared with the non-ICUAC group.

Using data from a multicenter observational study including 524 critically ill patients with positive endotracheal cultures for *Aspergillus*, Blot and colleagues [50] tested a clinical algorithm to help distinguish invasive aspergillosis from colonization. The algorithm required a positive lower respiratory tract sample for *Aspergillus* spp., along with compatible signs and symptoms, radiographic abnormalities, and either the presence of host risk factors or a positive semiquantitative culture of BAL fluid. The authors validated the algorithm in 115 patients who had histologic data, of whom 79 had proven invasive aspergillosis, showing a sensitivity of 92% and a specificity of 61% for the algorithm. The positive predictive value of the algorithm varied widely with changes in host factors and the prevalence of *Aspergillus*, but the NPV remained high, regardless of the circumstances. This led the authors to conclude that the algorithm was valuable because of its high sensitivity, but when it suggested that infection was not present, this finding might permit safe withholding of empiric antifungal therapy.

## Prevention

Oral care with chlorhexidine solution has been found to reduce the risk of VAP [51]. However, the role of oral care with toothbrushing in reducing the incidence of VAP remains unclear. A meta-analysis of four randomized controlled trials including 828 patients was conducted to assess the impact of toothbrushing as part of oral care [52]. In two of the studies, chlorhexidine was used in both the intervention and control groups. Toothbrushing did not significantly reduce the incidence of VAP, ICU

mortality, duration of mechanical ventilation, ICU stay, antibiotic-free days, or mechanical ventilation-free days. Previous observational studies have shown beneficial effects of toothbrushing, and although the results from the current meta-analysis are not encouraging, there was significant heterogeneity of the study populations, the oral care protocols, and the study designs, so that more data are needed to exclude a value of toothbrushing.

Prolonged colonization with *P. aeruginosa* can lead to VAP with this organism, and interruption of the progression from colonization to infection could be beneficial. One mechanism that allows this progression is termed 'quorum sensing' (QS), a process by which organisms promote their own proliferation into biofilm by the release of QS-regulated virulence factors in the form of rhamnolipids (class of glycolipid). Macrolides, such as azithromycin, have been shown to interfere with QS and thus could prevent VAP by interfering with organism growth to high concentrations in biofilm. Considering these concepts, van Delden and colleagues [53] conducted a randomized double-blind multicenter trial in 92 patients with *P. aeruginosa* to determine whether therapy with 300 mg/day azithromycin, in comparison with placebo, could prevent VAP. Overall, there was no benefit to the use of azithromycin, but there was a slight decline in the frequency of VAP (4.7% versus 14.3%, $P = 0.16$). However, 23 patients in the azithromycin arm and 18 in the control group had organisms with either high or intermediate levels of rhamnolipid production, and in those patients (who presumably had QS-dependent colonization), the use of azithromycin led to a nearly significant reduction in VAP ($P = 0.07$). As a proof-of-concept study, the data are interesting and suggest that this novel approach to VAP prevention in patients with *P. aeruginosa* colonization may merit further study.

*A. baumannii* infections are on the rise in ICUs worldwide, and it is necessary to develop control and prevention strategies for the ICU. Infected and colonized patients (carriers) can cause horizontal transmission and spread to non-infected patients, and infection control methods could be beneficial. Arvaniti and colleagues [54] conducted a prospective observational study to define the role of colonization pressure (carriers' patient-days × 100/all patients' patient-days) and patient-related factors in the acquisition of MDR *A. baumannii* infection in ICU patients. The investigators collected screening samples on admission to the ICU, and the colonization pressure and absolute number of carriers were measured on a weekly basis. Of the 284 patients screened, 16 patients (5.6%) were positive on admission and 32 patients (15.7%) developed acquisition during the ICU stay. Acquisition of *A. baumannii* correlated with weekly colonization pressure ($P = 0.004$) and with the number of carriers per week ($P < 0.001$). More than one carrier per week increased the acquisition risk proportionately (2 or 3 carriers, OR 12, $P = 0.028$; 4 or more carriers, OR 25, $P = 0.004$). Medical patients with extended administration of antibiotics (OR 1.24) and longer duration of mechanical ventilation in the ICU (OR 1.08) were the most vulnerable to acquisition. Although similar results were obtained with previous studies on MRSA and vancomycin-resistant *Enterococcus*, the present study is the first to demonstrate a correlation between colonization pressure and subsequent *Acinetobacter* acquisition in the ICU. The study suggests that appropriate ICU infection control strategies should include assessment of colonization pressure and patient-related risk factors to avoid endemic MDR *Acinetobacter*-related nosocomial infections.

## Conclusions

Risk stratification of critically ill patients by using a combination of severity scores and biomarkers is promising but should be used with the understanding that the host inflammatory response to various pathogens is different. Certain biomarkers, such as PCT and NPs, may be falsely elevated in patients with renal and cardiac dysfunction and must be used cautiously in this setting. However, use of a PCT-based algorithm can lead to shorter duration of antibiotic therapy and de-escalation because of the high NPV for ruling out bacterial infection. However, more data are needed in ICU patients. In an effort to avoid the overuse of broad-spectrum empiric therapy for the heterogeneous group of patients with HCAP, several investigators have developed tools to predict which patients are at risk for infection with MDR pathogens and which are not.

VAC refers to a new definition introduced by the CDC to identify patients who have VAP and other conditions and is defined objectively be a persistent need for increased oxygen concentrations or PEEP. This definition can identify patients with a poor prognosis, but it is still unclear whether the frequency of VAC can be reduced by the use of VAP prevention methods and whether the rate of VAC is a measure of the quality of care. Surveillance strategies and antimicrobial stewardship can lead to effective and streamlined use of antibiotics and may even prevent infection with MDR pathogens. However, effective teamwork and reinforcement with educational modules and reminders are key components for these programs to be successful.

In choosing antibiotics for the treatment of critically ill patients, clinicians should not base the decision only on the appropriate spectrum but also on factors such as pharmokinetics, pharmacodynamics, route of delivery, and local resistance patterns. Use of anti-inflammatory medications such as corticosteroids is controversial in

pneumonia and may do more harm than good in some patients with severe pneumonia. Prevention of MDR pathogen pneumonia requires identifying individuals who are colonized by these organisms, and isolating them, to limit person-to-person spread in the ICU. VAP pathogenesis studies have shown the importance of ETT biofilm, and there may be new approaches, including pharmacologic interventions, that can limit biofilm formation.

**Abbreviations**

ALI, acute lung injury; AMP, antimicrobial peptide; ARDS, acute respiratory distress syndrome; ARI, acute respiratory infection; ASP, antimicrobial stewardship program; ATS, American Thoracic Society; BAL, bronchoalveolar lavage; BNP, B-type natriuretic peptide; CAP, community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CURB-65, confusion of new onset (defined as an abbreviated mental test of 8 or less), urea greater than 7 mmol/L (19 mg/dL), Respiratory rate of 30 breaths per minute or greater, blood pressure less than 90 mm Hg systolic or diastolic blood pressure 60 mm Hg or less, age 65 or older; EA, endotracheal aspirate; ETT, endotracheal tube; FQ, fluoroquinolone; HCAP, health care-associated pneumonia; ICU, intensive care unit; ICUAC, intensive care unit-acquired candidemia; IDSA, Infectious Diseases Society of America; IL, interleukin; IVAC, infectious ventilator-associated complication; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight; MDR, multiple-drug resistance; MR-proANP, midregional pro-atrial natriuretic peptide; MRSA, methicillin-resistant *Staphylococcus aureus*; NP, natriuretic peptide; NPV, negative predictive value; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PCT, procalcitonin; PEEP, positive end-expiratory pressure; PSI, pneumonia severity index; PVL, Panton-Valentine leukocidin; QS, quorum sensing; REA-ICU, risk of early admission to the intensive care unit; SLPI, secretory leukocyte protease inhibitor; TB, tuberculosis; TNF-α, tumor necrosis factor-alpha; VAC, ventilator-associated complication; VAP, ventilator-associated pneumonia.

**Competing interests**

The authors declare that they have no competing interests.

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