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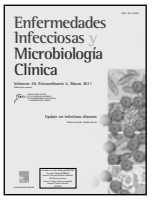

Severe, non-bacteremic infections in ICU patients

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A B S T R A C T

The present article is an update of the literature on various types of infections in ICU patients: ventilator-associated pneumonia, community-acquired pneumonia, the impact of the increasing vancomycin MIC in *Staphylococcus aureus* in the treatment of infections caused by this microorganism and the usefulness of biomarkers in identifying or ruling out septic complications in ICU patients. A multidisciplinary group of Spanish physicians with an interest in infections in critically-ill patients selected the most important recently published papers produced in the field. One of the members of the group discussed the content of each of the selected papers, with a critical appraisal by other members of the panel.

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Infecciones graves no bacteriémicas en pacientes de cuidados intensivos

Palabras clave:
Unidad de cuidados intensivos
Neumonía asociada a ventilación mecánica
Neumonía comunitaria grave
Staphylococcus aureus
Vancomicina
Concentración mínima inhibitoria
Marcadores biológicos

R E S U M E N

El artículo presente recoge una actualización bibliográfica de varios tipos de infecciones en pacientes de cuidados intensivos: la neumonía asociada a ventilación mecánica, la neumonía adquirida en la comunidad, la repercusión del incremento de la CMI a vancomicina en el tratamiento de las infecciones causadas por *Staphylococcus aureus* y la utilidad de los biomarcadores en el diagnóstico de las complicaciones infecciosas en estos pacientes. Un grupo multidisciplinario de clínicos españoles con experiencia en las infecciones en enfermos críticos seleccionó las publicaciones más importantes en este campo aparecidas recientemente. El contenido de cada uno de los artículos seleccionados fue expuesto y discutido por uno de los miembros del grupo, después de lo cual los miembros restantes efectuaron una revisión crítica.

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Introduction

This review highlights the changing spectrum of bacterial infections other than bloodstream infections in ICU patients. Many studies on community- and nosocomially-acquired infections affecting critically ill patients have been published in the last years. We selected a few relevant topics for discussion including the diagnosis of ventilator-associated pneumonia (VAP), community-acquired pneumonia (CAP), the impact of the resistance of *Staphylococcus aureus* to vancomycin and markers of inflammation in sepsis.

Ventilator-associated pneumonia

State of the art

VAP develops in approximately 20% of critically ill patients receiving mechanical ventilation (MV). Patients in whom VAP develops have a higher mortality rate, stay longer in the intensive care unit (ICU), and require more resources than those without the disease[1].

The diagnosis of VAP is still a matter of controversy. In 2005 the ATS/IDSA guidelines[2] proposed two types of strategies based on the studies available at that time: the clinical and the quantitative culturing strategy. On one hand, three Spanish randomized studies suggested that invasive techniques compared to quantitative (or qualitative cultures in one study) cultures of endotracheal aspirates

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did not influence the outcome of VAP[3-5]. On the other hand, a large French study[6] showed a decreased 14 day mortality in patients managed with bronchoscopic invasive methods (with quantitative cultures) compared to qualitative cultures of endotracheal aspirates. Both the Spanish studies and the French study had some criticisms and the question remains unsolved. In the first study on VAP revised here (see below the Canadian Critical Care Groups study) patients with suspected VAP were randomized to undergo either bronchoalveolar lavage (BAL) with quantitative cultures or endotracheal aspiration with non-quantitative cultures.

Early microbiological diagnosis and the administration of appropriate initial antibiotic therapy have proven to be associated with decreased rates of mortality in patients with VAP[7-9]. Results of conventional microbiological reports based on full bacterial identification and standard antimicrobial susceptibility tests rarely reach physicians who are attending to patients with VAP within 48–72 h of lower respiratory tract (LRT) sampling. In a second study Bouza and colleagues[10] analyze the clinical and economic impact of performing a rapid E-test with six key antimicrobial agents by applying the test strips directly to LRT samples. In a third study Garnacho-Montero et al evaluate the outcome of patients with *Pseudomonas aeruginosa* VAP treated with monotherapy compared with combination antibiotic therapy[11].

The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med. 2006;355:2619-30.[12]

Ideally, culture results should guide the treatment of patients with VAP. This is a randomized multicenter study in which patients who had received MV in the ICU for at least 4 days were eligible if they had suspected pneumonia, and then were randomized to undergo either BAL with quantitative cultures or endotracheal aspiration with non-quantitative cultures. Importantly, patients known to be colonized or infected by *Pseudomonas* species or methicillin-resistant *Staphylococcus aureus* (MRSA) were not included in the study. Each patient was also randomized to empirical therapy with meropenem alone or with meropenem plus ciprofloxacin; subsequently, antibiotic therapy was modified, based on culture results. Overall, the investigators enrolled 740 patients in 28 ICUs in USA and Canada: 374 in the endotracheal aspiration arm and 365 in the BAL arm. Clinical characteristics of patients were very similar in terms of severity, primary ICU diagnosis, comorbidities, length of stay and use of antibiotics in the previous 3 days before randomization. Overall, the percentage of microorganisms found in BAL samples was higher compared to endotracheal aspiration samples. However, the types of microorganisms were very similar. The overall 28 day mortality was 18.7%. The adjusted relative risk of death by day 28 in the BAL group was 1.01. There were no significant differences in mortality when considering different subgroups such as: APACHE greater than 24 vs. 24 or less, >7 or < 7 days of MV, antibiotics within 3 days before randomization, and, isolation of high risk vs. non-high-risk organisms. The treatment effect of the two diagnostic tests was the same regardless of the antibiotic therapy used, and the treatment effect of the two antibiotic therapies was the same regardless of the diagnostic test used. Other secondary end-points such as the discontinuation of MV, the discharge from the ICU, or the time to hospital discharge were similar in the two arms. Finally, the rates of targeted therapy were similar in the two groups, regardless of whether all patients were analyzed or only patients with negative or positive cultures were analyzed.

Comments. These researchers expected to see increased use of targeted therapy and improved outcomes with BAL, compared with endotracheal aspiration. But that's not what happened: outcomes were similar in the two groups. The findings suggest that either diagnostic approach is acceptable to choose an adequate initial antimicrobial treatment (the most important factor for a good prognosis) and to de-escalate antibiotics, which is a crucial strategy to limit the number of antibiotics prescribed and avoid the developing of resistance. However, these conclusions might not apply to certain patients, because of the enrollment exclusions noted above: at least 40% of screened patients who were excluded had risk factors for colonization or infection with potentially antimicrobial-resistant bacteria. In an accompanying editorial, Dr. Kollef states that these exclusions represent the majority of patients undergoing real-time evaluation for suspected VAP[13]. In our opinion this is very variable and depends on the type of ICU and the population admitted.

In addition to narrowing of initially prescribed broad-spectrum antimicrobial regimens on the basis of microbiologic data, the shortening of the duration of antibiotic treatment is an important component of de-escalation. Patterns of excess administration of antibiotics, especially beyond 7 or 8 days in patients receiving MV, have been linked with subsequent infection with potentially resistant bacteria. These findings suggest that clinicians caring for patients with suspected VAP should use antimicrobial treatment strategies that minimize the prolonged and potentially unnecessary administration of antibiotics, in order to curtail resistance.

In summary, given the rapid emergence of antimicrobial resistance and the limited number of new antimicrobial agents, clinicians treating patients with suspected VAP not only must prescribe appropriate initial antimicrobial regimens to optimize outcomes but also must minimize the development of resistance by rigorously using a de-escalation strategy. When applied properly, BAL and endotracheal aspiration are tools that can facilitate de-escalation.

Bouza E, Torres MV, Radice C, Cercenado E, Diego R, Sánchez-Carrillo C, et al. Direct E-test (AB Biodisk) of respiratory samples improves antimicrobial use in ventilator-associated pneumonia. Clin Infect Dis. 2007;44:382-7.[10]

In this study the authors examine antimicrobial use and outcome of patients with VAP in a large teaching institution. To address this issue they performed a prospective randomized study over a 2-year period.

Patients who had a LRT infection that was acquired during MV and for whom respiratory tract samples were sent for culture were randomized to 1 of 2 groups. Samples were cultured for the control group, and results were reported using standard procedures. Samples were also cultured for the test subject group using standard procedures, but in addition, a rapid antibiogram was immediately performed by placing E-test antibiotic strips (AB Biodisk) directly on respiratory tract samples. Patients in the E-test group received a preliminary laboratory report when it became available. The two patient groups were compared according to the following variables: type and severity of underlying conditions, total days of antimicrobial use, number of defined daily doses of antibiotics, cost of acquisition of the antimicrobial agent per episode, days of fever, days receiving MV, days in the ICU, incidence of *Clostridium difficile*–associated diarrhea, and mortality.

During the study period (December 2003 - December 2005), 4829 patients were admitted to the adult ICU and 2779 LRT samples from 1220 patients were submitted to the Microbiology Laboratory. Microorganisms were observed by Gram staining in 387 samples sent to the laboratory that were obtained from patients who had suspected LRT infection. The resulting data from Gram staining were transmitted to ICU staff via telephone within a median of 111 min ± 73 min (range, 8 min–6 h). Of the 387 episodes of suspected LRT infection, 250 patients fulfilled the diagnostic criteria of VAP (167 were enrolled in the E-test group and 83 in the control group).

All microorganisms and their antimicrobial susceptibilities were ultimately identified using standard methods, and definitive reports were issued a mean of 4.2 days after samples were obtained. The preliminary E-test information regarding antimicrobial susceptibility

was included in the patient's chart within a mean of 1.4 ± 0.75 days (range, 1-4 days). Susceptibility results obtained using direct sampling were available within 24 h of receipt of the sample in 75.4% of cases of VAP. Antimicrobial susceptibility, as determined by E-test, was compared with the results of standard testing methods in 201 microorganisms and 704 antibiotics. In 679 antibiotics (96.44%), there was a good correlation between both methods. Fourteen major errors (1.98%; defined as isolates that were determined to be susceptible by E-test and resistant by the standard method) occurred, and 11 major errors (1.56%; defined as isolates that were determined to be resistant by E-test and susceptible by the standard method) occurred. Preliminary information provided by the rapid E-test led to an inadequate therapeutic decision in only 5 patients.

Patients from the E-test group had fewer days of fever per episode (4.61 vs. 7.84 days), required fewer days of antibiotic administration to resolve the VAP episode (15.72 vs. 18.92 days), consumed fewer antibiotics (i.e., received fewer DDDs; 31.43 vs. 42.72 doses) and experienced less *C. difficile*–associated diarrhea episodes (1.8% vs. 9.6%). Furthermore, the early availability of microbiological information led to an improvement in the adequacy of antibiotic therapy: a higher percentage of days of adequate therapy (95% vs. 76%) and a higher percentage of adequate DDD's prescribed (91% vs. 68%). All these differences were statistically significant. The cost of the antimicrobial agents prescribed per episode in the E-test group and control group were, respectively, € 666 and €984. Patients in the E-test group required less days of MV since the diagnosis of VAP (8 days vs. 12 days; *P* <.05). Trends towards a shorter total ICU stay (23 days vs. 27 days), fewer overall days receiving MV (17 days vs. 19 days), and a shorter stay in the ICU after diagnosis of VAP (13 days vs. 17 days) were observed, but did not reach statistical significance. No statistically significant differences in the rate of mortality of the episode (32% vs. 29%; P=0.7), the rate of mortality in the ICU (46% vs. 40%; *P* =.3), and the rate of mortality at discharge from the hospital (55% vs. 52%; *P* =.7) was found.

Comments. According to the findings by Bouza et al, preliminary information regarding antimicrobial susceptibility can be provided by the microbiology laboratory for patients with VAP. An early report based on the results obtained by directly applying six E-test strips to plated LRT secretion samples is associated with better antibiotic use, less antimicrobial misuse, and a decrease in antimicrobial-related adverse events.

Garnacho-Montero J, Sa-Borges M, Solé-Violán J, Barcenilla F, Escoresca-Ortega A, Ochoa M, et al. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. Crit Care Med. 2007;35:1888-95.[11]

The objective of this study was to evaluate whether one antibiotic achieves equal outcomes compared with combination antibiotic therapy in patients with *Pseudomonas aeruginosa* VAP.

This was a retrospective, multicenter, observational, cohort study performed in five ICUs in Spanish university hospitals. The patients included were adult patients with monomicrobial episodes of VAP with significant quantitative respiratory cultures for *P. aeruginosa*. Data recorded were age, gender, severity of illness at admission to the ICU (APACHE II score), underlying diseases, concomitant bacteremia, adequacy of empirical antimicrobial therapy, use of monotherapy or combined therapy as well as the combination chosen empirically and in the definitive therapy. A total of 183 episodes of monomicrobial *P. aeruginosa* VAP were analyzed. Mean age was 56.3 ± 17.6 years. Mean APACHE II score at ICU admission was 19.1 ± 9.8. Patients were hospitalized in the ICU for a median of 10 days. Median time from intubation to VAP diagnosis was 8 days. Accompanying bacteremia was detected in 17 cases (9.3%), and sixty-nine patients died in the ICU (mortality 37.7%). Monotherapy alone was used empirically in 67 episodes, being significantly associated with inappropriate therapy (56.7% vs. 90.5%, *P* <.001). Hospital mortality was significantly higher in the 40 patients with inappropriate therapy compared with those at least on antibiotic with activity *in vitro* (72.5% vs. 23.1%, *P* <.05). Excess mortality associated with monotherapy was estimated to be 13.6% (95% confidence interval [CI], 2.6-29.9). The use of monotherapy or combination therapy in the definitive regimen did not influence mortality, length of stay, development of resistance to the definitive treatment, or appearance of recurrences. Inappropriate empirical therapy was associated with increased mortality (adjusted hazard ratio: 1.85; 95%CI, 1.07-3.10; *P* =.02) in a Cox proportional hazard regression analysis, after adjustment for disease severity, but not effective monotherapy (adjusted hazard ratio: 0.90; 95%CI, 0.50-1.63; *P* =.73) compared with effective combination therapy (adjusted hazard ratio 1). The other two variables also independently associated with mortality were age (adjusted hazard ratio: 1.02; 95%CI, 1.01-1.04; *P* =.005) and chronic cardiac insufficiency (adjusted hazard ratio: 1.90; 95%CI, 1.04 –3.47; *P* =.035).

Comments. This study showed that initial use of combination therapy significantly reduces the likelihood of inappropriate therapy, which is associated with a higher risk of death. However, administration of only one effective antimicrobial or combination therapy provides similar outcomes, suggesting that switching to monotherapy once the susceptibility is documented is feasible and safe.

Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: The NASCENT randomized trial. JAMA. 2008;300:805.[14]

The use of antimicrobial-impregnated vascular catheters has been associated with a significant reduction in the incidence of central vascular catheter–associated bloodstream infections. Might a similar technology help to reduce the incidence of VAP? In preliminary studies, use of an endotracheal tube that was coated internally and externally with silver ions dispersed in a polymer was associated with delayed bacterial colonization on the tube's inner surface and with decreased colonization of the airway. Now, with funding from the manufacturer, investigators have conducted a multicenter, single-blind, randomized, controlled trial comparing the silver-coated endotracheal tube with an uncoated but otherwise identical tube in adults expected to require mechanical ventilation for ≥24 hours. The two patient groups were comparable except for a higher incidence of chronic obstructive pulmonary disease (COPD) in the control group. Among the 1509 participants who were intubated for ≥24 hours, the incidence of microbiologically defined VAP was 4.8% in coated-tube recipients and 7.5% in control patients (*P* =.03); when VAP did develop, time to onset was delayed in the patients with coated tubes. No significant between-group differences were seen in duration of intubation, duration of ICU or hospital stay, or mortality rates.

Comments. Although use of the silver-coated tubes decreased VAP incidence, it did not reduce the duration of intubation, the duration of ICU or hospital stay, or mortality rates. In addition, as noted by an editorialist, the single-blind study design and the higher COPD incidence in the control group could bias the results in favor of the silver-coated tube. More data are needed before use of these tubes is adopted as a routine preventive measure for VAP.

Rello J, Afessa B, Anzueto A, Arroliga AC, Olson ME, Restrepo MI, et al. Activity of a silver-coated endotracheal tube in preclinical models of ventilator-associated pneumonia and a study after extubation. Crit Care Med. 2010;38:1135-40.[15]

The objective of this study was to elucidate the mechanism of action of the silver-coated endotracheal tube in models of the

early pathogenesis of VAP. This was an open-labeled, prospective, controlled, sequentially conducted, preclinical study, and in vitro assessment of tubes from patients. It was carried out in three different settings: the microbiology laboratory of a device manufacturer, the animal research facility of a university, and a tertiary medical center. Endotracheal tubes were similar except for the silver coating. In the 21-day in vitro elution model, tube samples were incubated in saline solution at 37.8 degrees C. In the in vitro adherence model, coated and uncoated tubes were exposed to 21 respiratory isolates of radiolabeled microorganisms for 2-4 hrs. In the animal model, 12 healthy white rabbits were intubated for 16 hrs with noncuffed silver-coated or uncoated tubes and challenged with buccal administration of *P. aeruginosa*. In the in vitro assessment, tubes from 16 patients underwent quantitative culture assessment and qualitative confocal laser scanning microscopy. After in vitro incubation, the mean residual silver concentration was 2.6 microg/cm, confirming that the coating was not entirely depleted. In vitro adherence to the silver-coated endotracheal tube was less than that of the uncoated tube for 12 of 21 isolates and equivalent for seven. For example, adherence to the silver-coated endotracheal tube was reduced >90% for all five isolates of *P. aeruginosa* (P <.05). In rabbits, *P. aeruginosa* colonization on the silver-coated endotracheal tube was reduced 99.9% compared with that on the uncoated tube (P <.0001); colonization in the tracheal and lung tissue was reduced ≥99% (P <.05). In the in vitro assessment, pathogens were detected on none of nine silver-coated tubes from patients and three of seven control tubes (P >.05).

Comments. The collective findings of this series of studies demonstrated that the silver-coated endotracheal tube was active in models designed to mimic the early pathogenesis of VAP.

Community-acquired pneumonia

State of the art

Community-acquired pneumonia (CAP) remains one of the leading causes of hospital admission and represents a burden to the health care system. In recent decades, mortality among hospitalized patients with CAP has been reduced, but the rate remains elevated among patients admitted to the ICU.

In the vast majority of patients with CAP who present to the hospital, the type of antibiotic regimen does not seem to have a relevant impact on outcome. Most treatment regimens, including those that involve beta-lactams, cephalosporins, or fluoroquinolones, provide similar results in terms of clinical success rates and survival, and no single regimen appears to be superior to another[16].

For severe CAP that requires ICU admission or for bacteremic pneumococcal CAP, the debate regarding ideal therapy remains open. Combination therapy has been advocated for the treatment of severe CAP by most scientific societies. These recommendations have been based mostly on large, retrospective studies, but the results were consistent in terms of outcome, especially for patients with bacteremic pneumococcal pneumonia. In these studies, however, the antimicrobial associations were variable, and the studies did not always reach similar conclusions regarding the optimal combination. The small sample size and baseline severity of illness for patients who received dual-drug therapy may explain this observation. Although published studies indicate that the addition of an advanced macrolide to a beta-lactam–based treatment regimen is associated with reduced mortality, it remains to be clarified whether the benefit is associated with the spectrum of pathogens covered or with the class of antibiotics used. It has been suggested that combination therapy mainly benefits the most severely ill patients. In the study revised here the authors analyze if a combination antibiotic therapy improves survival in patients with CAP and septic shock.

Rodríguez A, Mendia A, Sirvent JM, Barcenilla F, De la Torre-Prados MV, Solé-Violán J, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med. 2007;35:1493-8.[17]

To address this issue, Rodríguez et al performed a secondary analysis of a prospective observational study[17]. The study was conducted between December 1, 2000 and February 28, 2002 in 33 ICUs in Spain. The primary endpoint of the study was 28-day survival. Patients with and without shock were compared. Shock was defined as the need for vasopressors for >4 hours after fluid replacement at the time of ICU admission. Combination therapy was defined as administration of the same two antibiotics within the first 2 days of ICU admission. Overall, 529 patients (≥18 yrs) were included in the study, of whom 270 (51%) developed shock. A total of 148 patients (27.9%) died in the ICU. The risk of death was higher in patients with shock than in those without (48.1% vs. 6.9%; P <.01). Bacteremia was present in 22.6% of patients with shock vs. 10.8% of patients without (P <.01). *Streptococcus pneumoniae* (46.2%) was identified as the leading pathogen in patients with shock, followed by *Staphylococcus aureus* (10.1%), *Legionella pneumophila* (8.8%), and *Pseudomonas aeruginosa* (8.2%). Two hundred and eighteen (80.7%) patients with shock and 196 (75.7%) patients without shock received combination therapy. The two most frequent combination therapies prescribed for patients with shock were β-lactam/macrolides (n=131; 48.5%) and β-lactam/fluoroquinolones (n=54; 20%). The adjusted 28-day in-ICU mortality was similar (P =.99) for combination antibiotic therapy and monotherapy in the absence of shock. However, in patients with shock, combination antibiotic therapy was associated with higher adjusted 28-day in-ICU survival (hazard ratio: 1.69; 95%CI, 1.09-2.60; P =.01) in a Cox hazard regression model. This difference remained statistically significant when 26 patients who died within first 48 hours were excluded. Even when monotherapy was appropriate, it achieved a lower 28-day in-ICU survival than an adequate antibiotic combination (hazard ratio: 1.64; 95%CI, 1.01-2.64; P =.04).

Comments. The findings of Rodríguez et al support the hypothesis that combination therapy achieves significant lower adjusted mortality rates than monotherapy. What is not clear is the mechanism by which combination therapy apparently achieves this beneficial effect. Postulated mechanisms have included immunomodulatory effects of macrolides added to β-lactams, antimicrobial synergy between β-lactams and other antibiotic classes, increased probability of covering unidentified pathogens, or the presence of *in vivo* resistance to certain antibiotics in monotherapy despite apparent *in vitro* susceptibility, so called antibiotic tolerance[18]. The results of Rodríguez et al concur with other observational studies suggesting that combination therapy improves survival in critically ill patients with pneumococcal pneumonia[19].

Martín-Loeches I, Lisboa T, Rodríguez A, Putensen C, Annane D, Garnacho-Montero J, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med. 2010; 36:612-20.[20]

Continuing with this topic, a recent study has been conducted to explore whether the benefit derives from combination therapy or from the use of macrolides rather than fluoroquinolones[20]. Researchers studied 218 intubated patients with severe CAP (mean age, 60) who were participating in a prospective observational cohort investigation. The original study, conducted in 27 ICUs in nine European countries, involved 2436 immunocompetent patients who needed invasive mechanical ventilation for >48 hours. Participants

had a mean SAPS II score of 48 at ICU admission; 76% of them had severe sepsis or septic shock, and 38% died in the ICU. Microbiological documentation, obtained for 47% of the patients, showed pneumococci to be the most prevalent pathogen (32%), followed by *Staphylococcus aureus* (23%) and *Haemophilus influenzae* (11%); etiology was similar between survivors and nonsurvivors and between patients with and without severe sepsis or septic shock. Twenty percent of the patients received monotherapy, and 80% received combination therapy. Empirical antibiotic therapy, documented as inadequate in 5% of patients, was IDSA/ATS guideline–compliant for only 46% (54 patients who received quinolones and 46 who received macrolides). Among these 100 patients, ICU and 30-day mortality rates were significantly lower for macrolide recipients than for quinolone recipients. The same was true after adjustment for etiology and for disease severity.

Comments. This study, like several previous ones, showed a higher survival rate with macrolides than with fluoroquinolones among patients with severe CAP. This benefit might stem from the immunomodulatory effects of macrolides rather than from their antimicrobial activity. An editorialist notes that, although the issue has not been addressed in a prospective controlled trial, macrolides should be obligatory in cases of severe CAP, given their positive effects, good tolerability, and moderate cost.

Heyland DK, Dodek P, Muscedere J, Day A, Cook D. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med. 2008;36:737-44.[21]

Treatment regimens for VAP often include the use of combination therapy for suspected Gram-negative organisms. The reasoning for this strategy is to attempt to improve the adequacy of initial antimicrobial therapy, since appropriate empirical regimens can reduce mortality by as much as 50%. While broadly accepted, lack of clinical trial data to prove the merits of this strategy has led to much debate.

Heyland et al conducted a multicenter, randomized trial of 740 immunocompetent, critically ill patients with suspected VAP. They hypothesized that combination therapy would improve clinical outcomes compared with monotherapy by improving the appropriateness of the initial empirical regimen. Patients were randomized to receive monotherapy with meropenem 1 g i.v. every 8 hours or combination therapy with meropenem 1 g and ciprofloxacin 400 mg i.v. every 12 hours. The investigators found that initial combination therapy was adequate (in vitro susceptibility against the organism in the enrollment specimen) significantly more often than was initial monotherapy (93.1% versus 85.1%, respectively; P =.01). This effect was more pronounced for patients (n=56) who had at least one Pseudomonas species, Acinetobacter species, or other multidrug-resistant gram-negative organism present in the enrollment culture (84.2% versus 18.8%, respectively; P <.001). No differences were found in overall mortality, ICU or total hospital length of stay, clinical response, or micro-biological outcome. However, these endpoints did reveal a trend toward better outcomes with combination therapy in the subgroup of patients with Pseudomonas species, Acinetobacter species, or other multidrug-resistant gram-negative organisms.

Comments. The authors concluded that there were no differences in outcome measurements between empirical mono-therapy and combination therapy in an environment with a low rate of high-risk, gram-negative organisms. However, the study was not adequately powered for a setting with a high rate of high-risk, gram-negative organisms. This study reinforces other recent literature that supports the initial use of combination therapy for pseudomonal VAP, with the use of deescalation to monotherapy once the final organism and susceptibility patterns are known.

Renaud B, Santin A, Coma E, Camus N, Van Pelt D, Hayon J, et al. Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. Crit Care Med. 2009;37:2867-74.[22]

Up to 45% of patients with CAP who are admitted to ICUs are initially admitted to non-ICU settings. In a secondary analysis of data from four multicenter studies that involved 453 noninstitutionalized adult patients with CAP, researchers compared outcomes in a cohort of 111 patients who were directly admitted to an ICU and 111 patients who were transferred to an ICU within 3 days of presentation. The researchers used propensity score analysis to simulate randomization. After adjustment for baseline characteristics, multivariate regression analysis showed a significantly shorter hospital stay in the direct-admission group than in the delayed-admission group (median, 7 vs. 13 days) and a significantly lower 28-day death rate (11.7% vs. 23.4%). Results were similar in a subsequent analysis that excluded patients with obvious cardiovascular or respiratory compromise in the emergency department.

Comments. Identifying patients with CAP who would benefit from ICU admission even though they do not have obvious signs of a life-threatening condition on initial ED presentation is challenging. This study suggests that a subgroup of adult patients with CAP would have shorter hospital stays and lower mortality rates if they were admitted directly to the ICU, but it does not explain how to identify them.

In two recent studies[23,24], researchers retrospectively reviewed charts of patients with discharge diagnoses of community-acquired pneumonia (CAP) to assess concordance of initial antibiotic regimens with the 2007 guideline from the Infectious Diseases Society of America and the American Thoracic Society and to determine if concordant-therapy improves outcomes.

McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. Arch Intern Med. 2009;169:1525-31.[23]

McCabe and colleagues reviewed charts of 54,619 non–ICU patients aged 18 and older (mean, 71) at 113 hospitals in the U.S. Sixty-five percent of patients received guideline-concordant therapy, and these patients had a significantly lower risk for in-hospital death than those who received nonconcordant therapy (odds ratio [OR]: 0.70), along with shorter length of stay (mean reduction, 0.66 days) and duration of parental antibiotic therapy (mean reduction, 0.57 days). The benefit persisted across all levels of illness as measured by the Pneumonia Severity Index. Patients whose initial therapy included second- or third-generation cephalosporins, macrolides, and fluoroquinolones had significantly lower risk for death than those who received broader-spectrum agents (e.g., vancomycin, carbapenems), presumably because of activity against atypical agents, particularly *Legionella*.

Arnold FW, LaJoie AS, Brock GN, Peyrani P, Rello J, Menéndez R, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. Arch Intern Med. 2009;169:1515-24.[24]

Arnold and colleagues reviewed charts of 1649 patients aged 65 and older at 43 centers in 12 countries. The authors defined nonconcordant therapy to include both undertreatment and overtreatment. Fifty-nine percent of patients received concordant initial antibiotic therapy, and these patients achieved clinical stability significantly sooner than those who received nonconcordant therapy (71% vs. 57% of patients transitioned to oral therapy by 7 days) and had significantly shorter hospital stays (median, 8 vs. 10 days) and lower in-hospital all-cause mortality (8.4% vs. 18.3%) and CAP-related mortality (4.2% vs. 9.9%).

Comments. These clear outcome benefits associated with recommended antibiotics for CAP should remove any remaining skepticism.

Articles that, according to the authors, deserve special consideration are the following:

Venditti et al[25] reported in a study from Italy the comparison of epidemiology and outcome of CAP with health care-associated pneumonia (HCAP) in hospitalized adults in internal medicine wards of 55 hospitals in Italy. Patients with HCAP had higher mean Sequential Organ Failure Assessment scores, were more frequently malnourished and had higher fatality rates and longer mean hospital stay. Three factors were associated independently with excess inpatient mortality: depressed level of consciousness (odds ratio [OR]: 3.2), leukopenia (OR: 6.2), and receipt of an empirical antibiotic that is not guideline recommended (OR: 6.4).

Regarding prognosis of patients with severe CAP, Lisboa et al[26] compared the predictive outcome of bacteremia and progression of lung infiltrates in chest X rays in 457 patients with CAP admitted to the ICU. Rapid radiographic spread had a greater risk for shock and an increased risk of ICU death, while patients with bacteremia and no radiographic spread had none.

The issue of the impact of the presence of pneumococcal bacteremia in the evolution of hospitalized patients with CAP was evaluated in the CAPO cohort[27]. Overall 125 subjects with pneumococcal bacteremic CAP were compared with 1,847 subjects with nonbacteremic CAP. The multivariable regression analysis revealed a lack of association of pneumococcal bacteremic CAP and time to clinical stability, length of hospital stay, all-cause mortality and CAP-related mortality.

Impact of the resistance of *Staphylococcus aureus* to vancomycin

State of the art

Staphylococcus aureus resistance to vancomycin is one of the greatest concerns in infectious diseases. Over the past 50 years this common pathogen has demonstrated a remarkable ability to overcome many classes of antibiotics; however, vancomycin has largely remained unscathed. Unfortunately, MRSA rates now approach or exceed 50% in many countries, and the emergence of this pathogen also in outpatient infections has resulted in a marked increase in the use of vancomycin. Not surprisingly, worrisome events have followed this increase in vancomycin use. Increasing reports of vancomycin clinical failures in *S. aureus* infections with minimum inhibitory concentrations (MICs) considered susceptible, vancomycin-intermediate *S. aureus* (VISA), hetero-VISA, and vancomycin-resistant *S. aureus* (VRSA) have emerged over the past several years[28,29].

In the article by Soriano et al revised here the authors showed that a vancomycin MIC higher than 1.5 μg/mL is associated with an elevated mortality in patients with bacteremia caused by MRSA. This and other studies call into question how best to manage MRSA infections that have clinically failed vancomycin or have MICs that would raise concerns regarding the efficacy of vancomycin.

Soriano A, Marco F, Martínez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimal inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2008;46:193-200.[30]

The hypothesis of this study was that if there were any detrimental effect of higher vancomycin MIC values on the efficacy of this antibiotic in patients with MRSA bacteremia, then a progressive increase in the risk of mortality associated with the empirical use of vancomycin as the susceptibility of the involved strain diminishes was likely to occur. It was a retrospective analysis of a prospectively collected cohort in a tertiary hospital. From 1991 to 2005, 414 episodes of MRSA bacteremia were followed up. The vancomycin MIC of the first isolate was determined by E-test and clinical variables recorded were: age, comorbidities, prior administration of vancomycin, use of corticosteroids, prognosis of underlying disease, source of bacteremia, the need for MV, the presence of shock and mortality. A "treatment group" variable was created to evaluate the influence of vancomycin MIC in the efficacy of this antibiotic and defined as follows: *a)* empirical vancomycin and MIC=1 μg/mL (VMIC1, n=38); *b)* empirical vancomycin and MIC=1.5 μg/mL (VMIC1.5, n=90; *c)* empirical vancomycin and MIC=2 μg/mL (VMIC2, n=40), and *d)* inappropriate empirical therapy (NA, n=246). Univariate and multivariate analysis were performed to identify predictors of mortality.

The authors found an inverse relationship between vancomycin MIC and the risk of septic shock, suggesting a correlation between pathogenicity and the level of resistance. This finding is crucial to understand the final results of the study. Although the prevalence of shock was higher in VMIC1 group, it is of note that the mortality rate in 3 MIC groups was similar. Therefore, after adjusting in multivariate analysis for shock (and other factors), VMIC2 (OR: 6.39; 95%CI, 1.68-24.3) and NA (OR: 3.62; 95%CI, 1.20-10.9) treatment groups were independently associated with a higher mortality risk. Other variables associated with mortality were increasing age (OR: 1.02; 95%CI, 1.00-1.04), use of corticosteroids (OR: 1.85; 95%CI, 1.04-3.29), an ultimately or rapidly-fatal underlying diseases (OR: 10.2; 95%CI, 2.85-36.8 and OR: 1.81; 95%CI, 1.06-3.10, respectively), high-risk (OR: 3.60; 95%CI, 1.89-6.88) and intermediate-risk (OR: 2.18; 95%CI, 1.17-4.04) sources of bacteremia and shock (OR: 7.38; 95%CI, 4.11-13.3).

The authors discuss that these results could be explained in terms of pharmacokinetic and pharmacodynamic (PK/PD) parameters. AUC/MIC is the best predictor of vancomycin activity against *S. aureus*, therefore, a change in the MIC from 1 to 2 μg/mL reduces the AUC/MIC ratio to half. The main limitation of this study was the lack of information about the serum vancomycin concentrations.

Comments. In conclusion, this article shows that mortality of MRSA bacteremia was significantly higher when the empirical antibiotic was inappropriate and when vancomycin was empirically used for strains with a high vancomycin MIC (>1 μg/mL).

Emerging reports of decreasing susceptibility of *S. aureus* to vancomycin and increasing clinical failures in apparently susceptible MRSA infections raise serious concerns. In spite of the recent reduction in the vancomycin breakpoint for *S. aureus* to 2.0 mg/L by the CLSI, an increasing amount of clinical literature questions this figure. Furthermore, *S. aureus* continues to evolve in the face of increasing vancomycin pressure, and many of these changes may not be readily apparent by MIC.

Fortunately, although antibiotic development for Gram-negative infections has come to a standstill, the pharmaceutical industry has continued to develop newer compounds that possess activity against not only MRSA but also VISA isolates, as in the case of linezolid and daptomycin. However, the newer generation of lipoglycopeptides must overcome concerns regarding cross-resistance with vancomycin. Areas for future research should include the appropriate breakpoint for vancomycin against *S. aureus*, the role of new anti-infective agents in a variety of MRSA infections, and finally the role of combination therapy for severe MRSA infections.

Pillai SK, Wennersten C, Venkataraman L, Eliopoulos GM, Moellering RC, Karchmer AW. Development of reduced vancomycin susceptibility in methicillin-susceptible *Staphylococcus aureus*. Clin Infect Dis. 2009;49:1169-74.[31]

Researchers have recently reported VISA in an isolate of *S. aureus* with preserved methicillin susceptibility[31]. A patient who was receiving long-term oxacillin for spinal osteomyelitis developed

hepatotoxicity, which was presumed to be oxacillin-related: vancomycin was substituted. After receiving 8 weeks of vancomycin with documented therapeutic blood levels, the patient experienced breakthrough *S. aureus* bacteremia with a strain that was found to have significantly reduced vancomycin susceptibility, reduced daptomycin susceptibility, and preserved methicillin susceptibility. The patient ultimately completed treatment successfully with a combination of nafcillin, rifampin, and levofloxacin. Microbiologic investigation of the patient's isolates revealed stepwise reductions in vancomycin and daptomycin susceptibility characteristic of a heteroresistant *S. aureus* population in which antibiotic susceptibility worsens with continued exposure to the antibiotic. This case is noteworthy because clinicians routinely assume that, in cases of allergy to or toxicity from penicillins, vancomycin can be used to treat patients with methicillin-resistant *S. aureus* infections. Now we have evidence that organisms with potential to become resistant if exposed to vancomycin lurk even among methicillin-sensitive strains. Clinicians should be alert to this possibility if a patient fails to respond to treatment.

The spread of multidrug-resistant organisms within the ICU results in substantial morbidity and mortality. Climo et al[32] have demonstrated that daily bathing with a chlorhexidine-containing solution in ICU patients decreased the acquisition of MRSA by 32% and of VRE by 50%.

The increasing frequency of MRSA and the problems associated with vancomycin therapy highlight the need for alternative therapies. Chamberlain et al[33] report on the use of daptomycin in patients with severe surgical site infection (SSI) enrolled in the Cubicin Outcomes Registry and Experience (CORE-2007). Of 962 patients in the registry, 104 (11%) had a SSI. The overall success rate of daptomycin was 91%. The median final daptomycin dose was 5.5 mg/kg. The median duration of daptomycin therapy was 14 days. Prior vancomycin was used in 45% of patients; 24% failed. Among vancomycin failures, the daptomycin success rate was 91% (10/11). High success rates were achieved in patients with infection caused by MRSA .

Jang HC, Kim SH, Kim KH, Kim CJ, Lee S, Song KH, et al. Salvage treatment for persistent methicillin-resistant *Staphylococcus aureus* bacteremia: efficacy of linezolid with or without carbapenem. Clin Infect Dis. 2009;49:395-401.[34]

Persistent bacteremia caused by MRSA is a growing clinical problem. To date, no treatment strategy has been established for such infections. Some clinicians continue vancomycin and add either an aminoglycoside or a rifamycin; others switch to linezolid with or without a carbapenem. In a recent retrospective study performed at a single large medical center in South Korea, researchers examined the effectiveness of linezolid-based therapy. Thirty-five cases of persistent MRSA bacteremia (i.e., bacteremia persisting for ≥7 days despite ≥5 days of appropriate antibiotic therapy) occurred during the 27-month study period. In 32 patients, the vancomycin MIC was ≤1.0 µg/mL; in 31 patients, the vancomycin trough level was >10 µg/mL. In 19 cases, vancomycin was continued, either alone or in combination with an aminoglycoside or rifampicin; in 16 cases, linezolid was prescribed, alone or with a carbapenem. Conversion of blood cultures to negative within 72 hours was significantly more likely with linezolid-based therapy than with continued vancomycin. The *S. aureus*–related mortality rate was also lower with linezolid-based therapy (13% vs. 53%; *P* =.03). In no case was the addition of an aminoglycoside or rifampicin successful. Thrombocytopenia developed in 58% of the patients on linezolid.

Comment. In these cases of persistent MRSA bacteremia, linezolid-based regimens significantly outperformed continued vancomycin therapy, with or without the addition of an aminoglycoside or rifampicin, even in cases with no vancomycin resistance or evidence of undertreatment.

Markers of inflammation in sepsis

State of the art

Sepsis-related organ failure is the leading cause of death and accounts for an overall mortality of up to 60% in surgical ICUs. Among a broad spectrum of inflammatory abdominal conditions, peritonitis is one of the most important sources of abdominal sepsis, carrying considerable morbidity and mortality. Secondary peritonitis is an essential surgical condition that requires immediate repair of the underlying abdominal abnormality. After the initial procedure, persisting or new onset abdominal sepsis continues to be a major problem in the postoperative course.

It has been well recognized that timely re-intervention in proven septic abdominal foci significantly contributes to improved survival in these critically ill group of patients. However, repeated or even unnecessary surgical procedures are an additional risk factor for the patient and may further enhance morbidity.

Facing this clinical dilemma, there is major interest in the search for an optimum diagnostic tool for an early, noninvasive, and reliable diagnosis of abdominal infections and sepsis. Clinical scoring systems allow satisfactory prediction of an overall prognosis and are an established means of inter-institutional comparison of patient groups for study purposes. In contrast, biochemical variables for stratifying disease severity in secondary peritonitis are poorly studied, with inconclusive results due to non-comparable study populations and non-standardized assay techniques.

An accurate and readily available biochemical marker for identifying patients at risk for abdominal infections would definitely contribute to easier and safer diagnosis. Procalcitonin (PCT) is the inactive 116–amino acid precursor of the biologically active hormone calcitonin. It has been largely confirmed that PCT is the only one in a large array of biochemical markers that closely correlates with the inflammatory host response to microbial infections[35,36]. In peritonitis, two studies have shown that PCT is a reliable indicator of non survival[37,38]. However, neither study assessed the potential of this marker for predicting septic complications[39,40]. In the absence of representative studies, this is the first prospective, international multicenter trial in patients with secondary peritonitis.

Rau BM, Frigerio I, Büchler MW, Wegscheider K, Bassi C, Puolakkainen PA, et al. Evaluation of procalcitonin for predicting septic multiorgan failure and overall prognosis in secondary peritonitis: a prospective, international multicenter study. Arch Surg. 2007;142:134-42.[35]

The main goal of the present study was to compare the usefulness of PCT and C reactive-protein (CRP) in predicting septic multiple organ failure (s-MODS), septic single organ failure (S-SOF) and death, in patients with proven secondary peritonitis

In this prospective, multicenter cohort study, 82 patients were enrolled with the following inclusion criteria: *a)* peritonitis confirmed at the surgical procedure; *b)* no more than 96 hours elapsed from the onset of symptoms; and c) presence of systemic inflammatory response syndrome (SIRS). PCT and CRP were daily measured for up to 21 consecutive days. Also, APACHE II, MODS and SOFA scores were assessed during the study overall. The best cut off values of PCT and CRP were also calculated by receiver operative curve (ROC) analysis from the highest two consecutive values. Also, the predictive values of PCT and CRP were calculated. Additionally, the sensitivity, specificity, positive and negative predictive values and area under curve of ROC analysis were also assessed.

Fifty-eight out of 82 patients were microbiologically evaluable. The main focus of peritonitis was: colon perforation (27%), small-bowel perforation (26%) and complicated appendicitis (21%). The median APACHE II and SOFA scores values at 24 hours were 9 (0-27) and 2 (0-12), respectively. Intraabdominal infection was the most

Table 1
Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and optimum cutoff level based on early (days 1 and 2) postoperative procalcitonin (PCT) levels in 82 patients with peritonitis

	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Septic MODS					
PCT (ng/mL)	≥13.0	65	92	83	81
CRP (mg/L)	≥230	65	50	44	69
Persisting abdominal sepsis					
PCT (ng/mL)	≥15	64	80	33	93
CRP (mg/L)	≥300	82	36	36	93
Death					
PCT (ng/mL)	≥16	67	81	30	95
CRP (mg/L)	≥300	89	36	15	96

CRP: C-reactive protein; MODS: multiorgan dysfunction syndrome.

frequent postoperative complication (71%) and the overall mortality was 11%.

Early increase of PCT levels was higher in those patients eventually affected with s-MODS. Also, levels of CRP were significantly higher in such patients after the sixth postoperative day. Regarding mortality, PCT levels were significantly higher during the observation period overall in those patients that died in comparison with patients that survived.

Sensitivity, specificity, positive and negative predictive values, and optimum cutoff levels of PCT and CRP on early postoperative period (days 1 and 2) are displayed below (Table 1).

Comments. The usefulness of biological markers such as PCT and CRP relies on their ability in alerting the clinician early of secondary peritonitis during the postoperative period, when the patient may still benefit from an adequate treatment of persistent infection. Data from this study might indicate that some objectives were not planned in advance. For instance, there is no agreement between the number of patients in which both PCT and CRP were measured. Furthermore, it is hard to understand why the analysis of mortality was performed in a different biological marker curve. And finally, the information on patients censored because of death or because they were discharged from the hospital is not provide. The researchers conclude that PCT is clearly superior to CRP in predicting s-MODS. In such circumstances, the diagnostic accuracy of the biological marker should be enough to alert the clinician to start diagnostic procedures in order to demonstrate an intra-abdominal abscess or to redesign the initial antibiotic treatment. Then, it is easy to exclude false positive results by ruling out other infections such as postoperative pneumonia, urinary sepsis or catheter-related bacteremia.

Conflict of interest

The authors declare they have not any conflict of interest.

References

1. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med. 1999;159 4 Pt 1:1249-56.
2. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388-416.
3. Sánchez-Nieto JM, Torres A, García-Córdoba F, El-Ebiary M, Carrillo A, Ruiz J, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. Am J Respir Crit Care Med. 1998; 157:371-6.
4. Ruiz M, Torres A, Ewig S, Marcos MA, Alcón A, Lledó R, et al. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. Am J Respir Crit Care Med. 2000;162:119-25.
5. Solé Violán J, Fernández JA, Benítez AB, Cardenosa Cendrero JA, Rodríguez de Castro F. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. Crit Care Med. 2000;28:2737-41.
6. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med. 2000;132:621-30.
7. Chastre J. Conference summary: ventilator-associated pneumonia. Respir Care. 2005;50:975-83.
8. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. Chest. 1998;113:412-20.
9. Álvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Med. 1996;22:387-94.
10. Bouza E, Torres MV, Radice C, Cercenado E, De Diego R, Sánchez-Carrillo C, et al. Direct E-test (AB Biodisk) of respiratory samples improves antimicrobial use in ventilator-associated pneumonia. Clin Infect Dis. 2007;44:382-7.
11. Garnacho-Montero J, Sa-Borges M, Solé-Violán J, Barcenilla F, Escoresca-Ortega A, Ochoa M, et al. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. Crit Care Med. 2007;35:1888-95.
12. The Canadian Critical Care Trials Group. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med. 2006;355:2619-30.
13. Kollef MH. Diagnosis of ventilator-associated pneumonia. N Engl J Med. 2006;355: 2691-3.
14. Kollef MH, Afessa B, Anzueto A, Veremakis C, Kerr KM, Margolis BD, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. JAMA. 2008;300:805-13.
15. Rello J, Afessa B, Anzueto A, Arroliga AC, Olson ME, Restrepo MI, et al. Activity of a silver-coated endotracheal tube in preclinical models of ventilator-associated pneumonia and a study after extubation. Crit Care Med. 2010;38:1135-40.
16. Nazarian DJ, Eddy OL, Lukens TW, Weingart SD, Decker WW. Clinical policy: critical issues in the management of adult patients presenting to the emergency department with community-acquired pneumonia. Ann Emerg Med. 2009;54:704-31.
17. Rodríguez A, Mendia A, Sirvent JM, Barcenilla F, De la Torre-Prados MV, Solé-Violán J, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. Crit Care Med. 2007;35:1493-8.
18. Waterer GW. Monotherapy versus combination antimicrobial therapy for pneumococcal pneumonia. Curr Opin Infect Dis. 2005;18:157-63.
19. Baddour LM, Yu VL, Klugman KP, Feldman C, Ortqvist A, Rello J, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. Am J Respir Crit Care Med. 2004;170:440-4.
20. Martín-Loeches I, Lisboa T, Rodríguez A, Putensen C, Annane D, Garnacho-Montero J, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. Intensive Care Med. 2010;36:612-20.
21. Heyland DK, Dodek P, Muscedere J, Day A, Cook D. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med. 2008;36:737-44.
22. Renaud B, Santín A, Coma E, Camus N, Van Pelt D, Hayon J, et al. Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. Crit Care Med. 2009;37:2867-74.
23. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. Arch Intern Med. 2009;169:1525-31.
24. Arnold FW, LaJoie AS, Brock GN, Peyrani P, Rello J, Menéndez R, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. Arch Intern Med. 2009;169:1515-24.

25. Venditti M, Falcone M, Corrao S, Licata G, Serra P. Outcomes of patients hospitalized with community-acquired, health care-associated, and hospital-acquired pneumonia. Ann Intern Med. 2009;150:19-26.
26. Lisboa T, Blot S, Waterer GW, Canalis E, De Mendoza D, Rodríguez A, et al. Radiologic progression of pulmonary infiltrates predicts a worse prognosis in severe community-acquired pneumonia than bacteremia. Chest. 2009;135:165-72.
27. Bordon J, Peyrani P, Brock GN, Blasi F, Rello J, File T, et al. The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. Chest. 2008;133:618-24.
28. Howden BP, Ward PB, Charles PG, Korman TM, Fuller A, Du Cros P, et al. Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. Clin Infect Dis. 2004;38:521-8.
29. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med. 2006;166:2138-44.
30. Soriano A, Marco F, Martínez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2008;46:193-200.
31. Pillai SK, Wennersten C, Venkataraman L, Eliopoulos GM, Moellering RC, Karchmer AW. Development of reduced vancomycin susceptibility in methicillin-susceptible *Staphylococcus aureus.* Clin Infect Dis. 2009;49:1169-74.
32. Climo MW, Sepkowitz KA, Zuccotti G, Fraser VJ, Warren DK, Perl TM, et al. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. Crit Care Med. 2009;37:1858-65.
33. Chamberlain RS, Culshaw DL, Donovan BJ, Lamp KC. Daptomycin for the treatment of surgical site infections. Surgery. 2009;146:316-24.
34. Jang HC, Kim SH, Kim KH, Kim CJ, Lee S, Song KH, et al. Salvage treatment for persistent methicillin-resistant *Staphylococcus aureus* bacteremia: efficacy of linezolid with or without carbapenem. Clin Infect Dis. 2009;49:395-401.
35. Rau BM, Frigerio I, Buchler MW, Wegscheider K, Bassi C, Puolakkainen PA, et al. Evaluation of procalcitonin for predicting septic multiorgan failure and overall prognosis in secondary peritonitis: a prospective, international multicenter study. Arch Surg. 2007;142:134-42.
36. Schroder J, Staubach KH, Zabel P, Stuber F, Kremer B. Procalcitonin as a marker of severity in septic shock. Langenbecks Arch Surg. 1999;384:33-8.
37. Reith HB, Mittelkotter U, Wagner R, Thiede A. Procalcitonin (PCT) in patients with abdominal sepsis. Intensive Care Med. 2000;26 Suppl 2:S165-9.
38. Marshall JC, Vincent JL, Fink MP. Measures, markers and mediators: toward a staging system for clinical sepsis: a report of the fifth Noronto Sepsis Roundtable. Crit Care Med. 2003;31:1560-7.
39. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993; 341:515-8.
40. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004;39:206-17.