Community-acquired pneumonia: identification and evaluation of nonresponders

João Gonçalves-Pereira, Catarina Conceição and Pedro Póvoa

Ther Adv Infect Dis

[2013] 1(1) 5–17

DOI: 10.1177/

2049936112469017

© The Author(s), 2012.

Reprints and permissions:

[http://www.sagepub.co.uk/](http://www.sagepub.co.uk/journalsPermissions.nav)

[journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Community acquired pneumonia (CAP) is a relevant public health problem, constituting an important cause of morbidity and mortality. It accounts for a significant number of adult hospital admissions and a large number of those patients ultimately die, especially the population who needed mechanical ventilation or vasopressor support.

Thus, early identification of CAP patients and its rapid and appropriate treatment are important features with impact on hospital resource consumption and overall mortality. Although CAP diagnosis may sometimes be straightforward, the diagnostic criteria commonly used are highly sensitive but largely unspecific. Biomarkers and microbiological documentation may be useful but have important limitations.

Evaluation of clinical response is also critical especially to identify patients who fail to respond to initial treatment since these patients have a high risk of in-hospital death. However, the criteria of definition of non-response in CAP are largely empirical and frequently markedly diverse between different studies. In this review, we aim to identify criteria defining non-response in CAP and the pitfalls associated with this diagnosis. We also aim to overview the main causes of treatment failure especially in severe CAP and the possible strategies to identify and reassess non-responders trying to change the dismal prognosis associated with this condition.

Keywords: antibiotic failure, community-acquired pneumonia, intensive care, nonresponders, reassessment

Introduction

Community-acquired pneumonia (CAP) is a relevant public health problem, constituting an important cause of morbidity and mortality [Garibaldi, 1985; Pimentel and McPherson, 2003; Arnold *et al.* 2007]. In Portugal, between 1998 and 2000, CAP accounted for about 3% of the total adult hospital admissions [Froes, 2003] and 71.6% of those patients were over 65 years. The overall hospital mortality was 17.3%, increasing with age to 21.5% and 24.8% in those over 65 and 75 years respectively [Froes, 2003]. Overall the population who needed mechanical ventilation or vasopressor support usually had a high mortality rate, which reached almost 50% [Froes, 2003; Rello, 2008].

Thus, early identification of patients with CAP and its rapid and appropriate treatment are important features in the approach, and will potentially have an impact on hospital resource

consumption and mortality [Houck *et al.* 2004]. Although CAP diagnosis may sometimes be straightforward, the diagnostic criteria commonly used, namely physical examination and chest X-ray, are highly sensitive but largely unspecific. Furthermore, biomarkers *per se* are not specific for CAP [Póvoa, 2008], microbiological documentation may not be feasible in 30–50% of patients [Lim *et al.* 2009], particularly for viral infections, and its results are usually unavailable before at least 48 h of clinical presentation.

Evaluation of clinical response is also critical, especially to identify patients whose condition fails to respond to initial treatment since these patients have a high risk of in-hospital death. However, the criteria of definition of nonresponse in CAP are largely empirical and frequently markedly diverse between different studies. According to the Infectious Diseases Society of America (IDSA) guidelines [Mandell *et al.* 2007],

Correspondence to:

João Gonçalves-Pereira, MD

Unidade de Cuidados Intensivos Polivalente, Hospital de Sao Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Estrada do Forte do Alto do Duque, 1449-005 Lisboa, Portugal
joaogpster@gmail.com

Catarina Conceição, MD
Polyvalent Intensive Care Unit, Sao Francisco Xavier Hospital, CHLO, Lisbon, Portugal

Pedro Póvoa, MD, PhD
Polyvalent Intensive Care Unit, Sao Francisco Xavier Hospital, CHLO, Lisbon and CEDOC, Faculty of Medical Sciences, New University of Lisbon, Lisbon, Portugal

treatment failure in hospitalized patients with CAP should only be considered after at least 72 h of initial treatment, which is the standard time required to achieve clinical stability and to reduce bacterial load [Halm and Teirstein, 2002]. This may be problematic because the evaluation of response relies mostly on normalization of the same unspecific clinical and radiological criteria, previously used for CAP diagnosis. Moreover, patient recovery may take longer than bacterial killing itself and the use of cultures to prove bacteria eradication may be misleading and is not recommended [Lim *et al.* 2009]. Therefore, nonresponse may easily be mistakenly stated.

Biomarkers may also help to identify patients with CAP with a complicated course. Recent data have linked the pattern of C-reactive protein (CRP) kinetics with treatment failure, namely persistence of elevated concentration after 3–4 days of antibiotic therapy [Coelho *et al.* 2007].

Nonresponse to antibiotics may simply unveil a wrong diagnosis. However, in the presence of true CAP, different factors related to the host, the bacteria and the antibiotic therapy itself may lead to treatment failure. Among them, antibiotic prescription delay or inadequacy, and failure to provide early and adequate resuscitation of severely ill patients are probably the most important modifiable risk factors [Vincent and Marshall, 2008].

In this review, we aim to identify criteria defining nonresponse in CAP and the pitfalls associated with this diagnosis. We also aim to overview the main causes of treatment failure, especially in severe CAP, and the possible strategies to identify and reassess nonresponders trying to change the dismal prognosis associated with this condition.

Assessing nonresponders

Prevalence. Several criteria, mostly subjective, have been used to classify nonresponse in CAP (Table 1).

In the absence of a consensus definition, the published nonresponse rate is related to both the selected criteria and the definition. Consequently, in distinct in-hospital populations, the frequency of nonresponsiveness ranges between 5% and 30% [Mandell *et al.* 2007]. Nevertheless, independently of the used criteria,

the reported CAP mortality rate for nonresponders is always in the higher range, usually near 20%, and much higher than that of responders (Table 1).

Among outpatients, treatment failure is usually defined as the need for hospitalization or for a change in the antibiotic therapy whilst treatment failure among hospitalized patients is mainly related to clinical deterioration and classified as early (within 72 h) or late, although slightly different definitions are used (Table 1). Early treatment failure is usually defined as the need to change antibiotics or clinical deterioration, namely septic shock or the requirement for mechanical ventilation. Late treatment failure is characterized by persistent or recurrent fever associated with respiratory symptoms, the need for mechanical ventilation or septic shock requiring intensive care unit (ICU) admission [Corrêa *et al.* 2009].

Accordingly, in a study assessing patients with CAP admitted to wards, early failure was identified in 83 (6%) patients and was associated with a fourfold increase in mortality (27% *versus* 4%) [Roson *et al.* 2004], despite the fact that resistant bacteria were isolated in only 31% of those patients. Similar findings were noted in another study including 453 patients with CAP, in which early nonresponse was identified in 8.4%, and 10.2% had late failure [Menendez *et al.* 2008]. Both groups had a high mortality rate, 24% and 43.7%, respectively.

A broader definition, including the need to enlarge antibiotic spectrum, was applied to another CAP cohort who presented a nonresponse rate of 15.9% and an in-hospital mortality of 17.3% (compared with 5.2% of responders) [Ott *et al.* 2012]. The nonresponse rate was lower when moxifloxacin [odds ratio (OR) 0.43] or a combination of a macrolide and a β -lactam (OR 0.68) was selected as first-line therapy [Ott *et al.* 2012].

Reasons for nonresponse were systematically evaluated in 62 patients with CAP [Genne *et al.* 2006]. A host-related cause (including suppurative complications) was the most frequent, accounting for 61% of cases, 18% had a drug-related cause and resistant bacteria was identified in only 16%. Overall, bacteria resistance to antibiotics seems to be seldom found in patients with

Table 1. Nonresponse according to the prespecified definitions.

	N	Definition		Setting	Risk factors or causes of failure	Prevalence	Mortality
		Early failure	Late failure				
Menendez <i>et al.</i> [2008]	453	MV, shock, or death <72 h	Persistence of fever, radiographic progression, impairment of respiratory failure, MV or shock >72 h	In hospital	Elevated IL-6, PCT or CRP at day 3; PSI class = 5	Early failure 8%; late failure 10%	Early failure 24%; late failure 43.7%; no failure 0.5%
Roson <i>et al.</i> [2004]	1383	Clinical and/or radiologic deterioration at 48–72 h, changes in antibiotic and/or invasive procedures, including MV and chest drainage		Ward	Younger age; PSI score >90; legionella or Gram-negative infection; multilobar infiltrates; inadequate antibiotics	Early failure 6%	Early failure 27%; no failure 4%
Arancibia <i>et al.</i> [2000]	444	Persisting fever 38°C and/or clinical symptoms after <72 h	MV and/or septic shock >72 h	In hospital	Infection related (38 patients); noninfection related (9 patients); other (8 patients)	Early failure 6.8%; late failure 4.3%	Failure 42.9%; no failure NA
Genne <i>et al.</i> [2006]	228	Clinical deterioration and fever >3 days or need to change antibiotics, severe side effect or death >48 h		In hospital	Neoplasia; neurological disease; aspiration pneumonia	Failure 24%	Failure 25.9%; no failure NA
Cilloniz <i>et al.</i> [2012]	568	Hemodynamic instability, impairment of respiratory failure, radiographic progression, or new metastatic infectious foci		Outpatients evaluated in an emergency room	NA	Failure 2.3%	Failure 23.1%; no failure NA
Ott <i>et al.</i> [2012]	1236	Need to switch antibiotics >72 h or broadening spectrum		In hospital	CURB65 class >1; antibiotics other than moxifloxacin or β -lactam + macrolide	Failure 15.9%	Failure 17.3%; no failure 5.2%
Minogue <i>et al.</i> [1998]	944	Hospitalization within 30 days		Outpatients	Pneumonia related (40 patients); comorbidities (26 patients); refused initial admission (5 patients)	Failure 7.5%	Failure 4.2%; no failure 0.3%

CRP, C-reactive protein; CURB, confusion, urea, respiratory rate and blood pressure score; IL-6, interleukin 6; MV, mechanical ventilation; NA, not available; PCT, procalcitonin; PSI, pneumonia severity index.

CAP with nonresponse [Roson *et al.* 2004; Genne *et al.* 2006].

In another cohort of 444 hospitalized patients with CAP, an 11% nonresponse rate was found, with an even higher mortality rate, 42.7% [Arancibia *et al.* 2000]. In 39 of these patients, nonresponse was due to an infection, either CAP progression or another hospital-acquired infection. In both studies, a small number of patients had a confounding noninfectious diagnosis, three and nine patients, respectively [Arancibia *et al.* 2000; Genne *et al.* 2006].

In the outpatient setting nonresponse was much lower, ranging from 2.3% [Cilloniz *et al.* 2012] to 7.5% [Fantin *et al.* 2001] or 8% [Minogue *et al.* 1998]. In all these studies, mortality rate was below 5% and appeared to be mainly related to the patient's comorbidities and not to antibiotic selection or to pneumonia itself [Minogue *et al.* 1998; Fantin *et al.* 2001; Cilloniz *et al.* 2012].

The role of biomarkers. To account for the diagnostic and prognostic uncertainty in CAP, the use of biomarkers has been proposed as a complementary tool. Several studies found an association between the early concentration of some biomarkers in CAP and patient outcomes [Hogarth *et al.* 1997; Hausfater *et al.* 2007; Seligman *et al.* 2008].

Moreover, biomarkers, mostly procalcitonin (PCT) and CRP, have also been shown to be useful in the diagnosis and monitoring of response in patients with CAP [Póvoa, 2008] and may improve diagnostic accuracy [Bafadhel *et al.* 2011], including the etiology itself [Garcia Vazquez *et al.* 2003]. However, they should be used with caution and not as a substitute for clinical outcomes [Wunderink, 2010].

The value of biomarkers (PCT and CRP) in the identification of nonresponders was addressed in a cohort of 394 in-hospital patients [Menendez *et al.* 2009]. Clinical stability at 72 h was found in 220 patients and predicted an uneventful CAP course during the whole in-hospital stay [area under the receiver operator characteristic curve (AUC ROC) of 0.77]. Both CRP (4.2 mg/dl *versus* 7 mg/dl) and PCT (0.33 ng/ml *versus* 0.48 ng/ml) presented lower levels in this subgroup. Moreover, CRP concentration changes over time improved the ability of clinical evaluation to predict a good

outcome (AUC ROC 0.84) but the same was not true for PCT (AUC ROC 0.77) [Menendez *et al.* 2009].

The available data suggest that CRP is the marker with the best performance to monitor treatment response in CAP [Póvoa, 2008]. Coelho and colleagues studied the patterns of CRP kinetics in 191 critically ill patients with CAP to assess therapeutic response [Coelho *et al.* 2012]. Using daily determinations of serum CRP concentration, the authors calculated the ratio between the CRP serum concentration after 5 days of therapy and its initial concentration. An association between a high CRP ratio (>0.5) and increased mortality, with a sensitivity of 0.81 and a specificity of 0.58 [Coelho *et al.* 2007], was found. Patients with a nonresponse pattern, defined as a CRP ratio >0.8 by day 7, had a high mortality rate of 36.4%, while in patients with a fast response pattern (CRP ratio ≤0.4 by day 5) only 4.8% died [Coelho *et al.* 2012]. The main finding of this study was the association between CRP ratio kinetics and clinical course, providing a useful and simple tool to identify patients who do not respond to their initial therapy. These findings were also noted to be independent of the presence of neutropenia [Póvoa *et al.* 2011] and of corticosteroid therapy [Salluh *et al.* 2011].

The PCT concentration and its relationship with clinical resolution has also been used to identify patients who may safely stop their antibiotic therapy [Christ-Crain *et al.* 2004; Bouadma *et al.* 2010]. However, these results have been disputed mostly due to the reported high exclusion rates, the high rate of protocol overruling and the long duration of antibiotic therapy usually employed in the control arms [Póvoa and Salluh 2012a]. Moreover, contrary to CRP, PCT is removed by hemodialysis [Dahaba *et al.* 2003].

Diagnosis

Exclusion of a confounding diagnosis. Treatment failure should be approached in an early, practical and systematized manner and its potential causes should be investigated before changes in the therapeutic regimen are made (Figure 1). A full diagnostic workup, including a detailed clinical history, physical examination, and reevaluation of laboratory and radiological exams should be routinely performed.

Figure 1. Proposed algorithm for the evaluation of nonresponse CAP at day 3–4. Persistence of signs of infection, elevated biomarkers or clinical deterioration in CAP should prompt consideration of nonresponse. Microbiologic evaluation should be performed to identify the cause of infection and help to select appropriate antibiotic therapy and dosage (accounting for the pharmacokinetic changes). Any suppurative complication should be properly addressed to ensure prompt source control. Appropriate testing to exclude alternative diagnoses should be performed according to clinical findings. CAP, community-acquired pneumonia; CHF, congestive heart failure; CRP, C-reactive protein; PCT, procalcitonin; PE, pulmonary embolism.

Failure to respond to antibiotics may merely unveil an alternative diagnosis. Indeed, several conditions may mimic the clinical presentation of CAP (Table 2), including congestive heart failure, lung cancer, pneumonitis, atelectasis, pleural effusion, fibrosis [File, 2001], increasing the diagnostic uncertainty. Accordingly, several studies assessing patients with CAP whose condition failed to respond to antibiotic therapy found a small group of patients, approximately 1–2%, who ultimately proved to have a noninfectious condition [Arancibia *et al.* 2000; Genne *et al.* 2006]. Cough, dyspnea and chest pain are

unspecific and may be found in several confounding clinical syndromes, not necessarily of infectious origin.

An initial suspicion of CAP may be challenged by the clinical course. Moreover a persistently low CRP [Póvoa *et al.* 2005] or PCT [Balc *et al.* 2003] may help to exclude the diagnosis of CAP. Additional tests should be performed according to the clinical setting, including chest ultrasound or computed tomography scan, to rule out pulmonary emboli, pleural effusions, lung abscess, lung cancer and airway obstruction.

Table 2. Clinical conditions that may mimic community acquired pneumonia.

Infectious diseases	Endocarditis, meningitis, arthritis, pericarditis, cholecystitis
Noninfectious	Congestive heart failure, myocardial infarction, pulmonary embolism, pulmonary infarction, lung cancer, pulmonary contusion, atelectasis, postenotic bronchial obstruction, foreign body, pulmonary effusions, pancreatitis.
Inflammatory diseases	Cryptogenic organizing pneumonia, hypersensitivity pneumonitis, eosinophilic pneumonia, sarcoidosis, Wegener's granulomatosis, acute interstitial pneumonitis, collagenosis, alveolar hemorrhage
Drug reaction	Drug fever
Acute respiratory distress syndrome	

The radiological pattern may also suggest an alternative noninfectious disease, such as cryptogenic organizing pneumonia.

Microbiological testing. In patients with CAP not responding to antibiotic therapy, a collection of samples for microbiological examination (if not already performed), including urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*, should be performed, particularly in patients with severe CAP or in those whose condition is deteriorating. Furthermore, microbiological culture data and antibiotic sensitivity pattern, not available at admission, may unveil the cause of treatment failure. In addition, a further history of any risk factors for infection for unusual pathogens, including viruses and fungus, may lead to the selection of appropriate testing.

The interpretation of respiratory sample cultures collected after prescription of antibiotic treatment is problematic because early colonization with resistant organisms is not uncommon [Visser *et al.* 2008]. Nevertheless, negative cultures for multidrug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* or *Pseudomonas aeruginosa*, provide strong evidence against their presence [Mandell *et al.* 2007].

The role of molecular testing in the diagnosis of nonresponding CAP is not yet defined, although it can reduce time and improve the rate of microbiological identification [Mancini *et al.* 2010]. However, this method still has limitations in providing information on resistance.

The use of invasive techniques, mainly bronchoscopy, may be useful to identify unusual resistant pathogens. In a study by Ortqvist and colleagues, bronchoscopy unveiled a microbiological etiology of nonresponsiveness in four out of the 18

patients with nonresponding CAP [Ortqvist *et al.* 1990]. However, the use of invasive *versus* noninvasive diagnostic strategies in a nonresponsive CAP population has never been properly evaluated.

The use of invasive microbiological sampling may be particularly advisable in the presence of risk factors for resistance, particularly recent hospitalization, nursing home residency [Shorr *et al.* 2008] and recent antibiotic therapy [El Solh *et al.* 2004]. Kikuchi and colleagues documented silent aspiration during sleep in 10 out of 14 older patients with CAP whose condition failed to respond to initial antibiotic therapy compared with 10% of the age-matched control subjects ($p < 0.02$). In that study, an invasive diagnostic strategy was able to identify a large number of resistant microorganisms (methicillin-resistant *S. aureus* in 33%, *P. aeruginosa* in 14% and other Gram-negative bacteria in 23%) [Kikuchi *et al.* 1994].

Thoracocentesis should also be performed for evaluation and drainage of parapneumonic effusions, especially to rule out empyema. Transbronchial and open lung biopsies can also be useful in the appropriate setting.

Due to the high mortality rate of this population, and while test results are pending, temporary empirical broadening of the antibiotic regimen and transfer to a higher level of care is probably appropriate [Mandell *et al.* 2007].

Treatment failure in community-acquired pneumonia

In the presence of true CAP, several factors may contribute to treatment failure, which may be related to the bacteria, the antibiotic or the host, and their interactions.

Bacteria factors. Resistance to antibiotics seldom represents a cause of antibiotic failure in CAP, except in patients at high risk of multidrug-resistant microorganisms [El-Solh *et al.* 2002; Shorr *et al.* 2008]. In fact, in a cohort of 444 patients, bacteria resistant to antibiotics were found in only six of the 23 patients with persistent CAP [Arancibia *et al.* 2000].

Bodi and colleagues evaluated the impact of adherence to 2000 IDSA guidelines for CAP on the outcome of a cohort of 529 ICU patients with severe CAP [Bodi *et al.* 2005]. The proportion of patients who were not treated according to the guidelines (42.2%) had a significantly higher ICU mortality rate (33.2% *versus* 24.2%, OR 1.7). In the same cohort the isolation of *P. aeruginosa* was the main risk factor for initial antibiotic inadequacy (15 out of 20 cases). *P. aeruginosa* pneumonia was associated with concomitant chronic obstructive pulmonary disease (OR 17.9), malignancy (OR 11.0), previous antibiotic exposure (OR 6.2) and radiographical findings demonstrating rapid spread of disease (OR 3.9).

Polymicrobial and viral CAP may also contribute to nonresponse. In a study of 196 patients with microbiologically documented CAP admitted to an ICU, polymicrobial pneumonia was found in 39 (19.8%), of whom 15 presented both viral and bacterial etiology [Cilloniz *et al.* 2011]. This was associated with more severe disease and proved to be a risk factor for antibiotic inadequacy and response failure, which in turn independently predicted hospital mortality (39% *versus* 10%, $p < 0.001$). Similar findings were seen in another cohort of patients with CAP admitted to the wards. The 35 patients presenting with both bacteria and viral pneumonia had a more severe CAP than those with monomicrobial bacterial infection (OR 4.98) [Johansson *et al.* 2011], resulting in a significantly longer hospital stay. Also community-acquired methicillin-resistant *S. aureus*, although an infrequent cause of CAP, has been associated with severe necrotizing pneumonia and a high mortality rate [Micek *et al.* 2005; Webster *et al.* 2007; Nazareth *et al.* 2011]. In addition, different *S. pneumoniae* serotypes may express diverse virulence factors, including pneumolysin, causing a severe sepsis syndrome with slow resolution, which may mimic nonresponse [Dockrell *et al.* 2012].

Bacterial inoculum may also influence CAP outcomes. This was documented in a cohort of

93 patients with CAP caused by *S. pneumoniae* (36.5% of whom had positive blood cultures), using real-time polymerase chain reaction (rt-PCR) performed in whole blood samples [Rello *et al.* 2009]. A positive rt-PCR assay was associated with higher mortality (OR 7.08), shock (OR 6.29) and the need for mechanical ventilation (OR 7.96). Within this subgroup, 29% of the patients with the highest bacterial load, more than 10^3 copies/ml, had a statistically significant higher risk for septic shock (OR 8.00), need for mechanical ventilation (OR 10.50) and hospital mortality (OR 5.43).

Similar results were reported in a prospective observational study of patients with severe community-acquired sepsis, 60.6% of whom had CAP. The 162 patients with positive blood cultures at admission (39.6% with CAP) had higher ICU mortality (42.4% *versus* 27.2%, $p = 0.016$) [Gonçalves-Pereira *et al.* 2012].

The worst outcome associated with large bacteria inoculum may contribute to the higher mortality observed with the late initiation of antibiotic therapy [Houck *et al.* 2004], which allows time for increased bacterial proliferation.

Antibiotic factors. Nonadherence with the prescribed antibiotic therapy, especially in an outpatient setting, is a cause of nonresponse and should always be excluded before assuming treatment failure.

Moreover, antibiotic efficacy is not easily assessed. The median time to achieve clinical stability is around 3 days for all patients, but some, usually those with severe CAP, may take over 6 days to stabilize [Halm *et al.* 1998]. Radiological improvement takes even longer and initial increase in infiltrates is not uncommon [American Thoracic Society, 1996]. Conversely, after clinical stability has been reached, subsequent deterioration and transfer to the ICU is uncommon.

Therefore diagnostic testing should be tempered before at least 72 h of antibiotics. Therapeutic changes within this period should only be considered for patients with marked deterioration or whenever new culture or epidemiologic data suggest alternative microbiological etiologies.

Even in patients receiving appropriate therapy, active against the causative microorganism,

clinical resolution may not be achieved because of inadequate antibiotic concentrations. In fact, in severely infected patients, an increase in the volume of distribution [Gonçalves-Pereira and Póvoa, 2011] of some antibiotics (especially β -lactams) is always to be expected, in particular in the presence of organ failure [Ulldemolins *et al.* 2011], due both to host response to sepsis and to therapeutic procedures. Furthermore, creatinine clearance, which generally correlates with clearance of several antibiotics [Lipman *et al.* 2003], may also be increased, but commonly used formulas to compute it are useless [Baptista *et al.* 2011]. Consequently, PK parameters measured in the healthy population may not correctly predict antibiotic concentrations in critically ill patients with sepsis, particularly at the early stages of severe pneumonia [Hansen *et al.* 2001; Roberts and Lipman, 2006] and higher dosages may be needed [Pea and Viale, 2009]. Moreover, in critically ill patients with sepsis it has been suggested that larger antibiotic concentrations and time of exposure are necessary to achieve infection control [McKinnon *et al.* 2008].

Conventional dosage may be misleading in patients with severe infection. In fact, in one study, ceftazidime was found to be in the therapeutic range in less than half of the patients (36.9% had low concentration and 27.2% had toxic levels) [Aubert *et al.* 2010]. The same was noted in a larger population, mostly receiving β -lactam antibiotics by continuous infusion, in whom around half of the patients had a steady-state concentration below the intended target of four times the minimum inhibitory concentration [Roberts *et al.* 2010]. Furthermore, even patients with renal failure receiving modern renal replacement therapy may experience lower than expected antibiotic concentrations [Fish *et al.* 2005]. Also the epithelial lining fluid concentration of several antibiotics, mainly β -lactams, in infected patients [Boselli *et al.* 2003, 2004a, 2004b, 2005a, 2005b, 2006, 2008] was lower than expected.

Systematic therapeutic drug monitoring has been proposed to address the PK of critically ill patients with sepsis to avoid both underdosage and accumulation of the antibiotics [Sime *et al.* 2012]. However, target concentration guidance criteria are poorly defined and a clear-cut relationship between antibiotic serum or lung concentrations and outcomes has not been well demonstrated.

Another controversial issue is the usage of combination antibiotic therapy. In a large multicenter CAP study the prevalence of atypical microorganisms has been found to range from 20% to 28% worldwide. In this study the use of antibiotics with atypical coverage was associated with better outcomes, including lower mortality (7% versus 11.1%) [Arnold *et al.* 2007].

In patients with CAP admitted to an ICU, combination antibiotic therapy was associated with increased survival, but only in patients with septic shock (hazard ratio 1.69, $p=0.01$) [Rodriguez *et al.* 2007]. Again the benefit of combination therapy in CAP may be attributed to the concomitant use of macrolides [Giamarellos-Bourboulis *et al.* 2008; Martin-Loeches *et al.* 2009], although this remains controversial [Eliakim-Raz *et al.* 2012]. Recent data have also unveiled a survival benefit of patients receiving dual therapy with a macrolide and a β -lactam, but again only in patients with severe CAP [Rodrigo *et al.* 2012].

Overall we think that atypical microorganisms should be strongly considered in patients experiencing nonresponse who are not receiving antibiotics with atypical coverage [Mandell *et al.* 2007]. At that timepoint, the addition of a macrolide to the therapy may be useful, especially if the patient is in shock, although data supporting this approach are sparse.

Host factors. Many host-related factors have been identified as possible causes of inadequate clinical response in severe CAP. Old age, comorbid conditions, alcohol consumption and smoking have all been associated with slow CAP resolution [Menendez *et al.* 2004] and may be misinterpreted as nonresponse. Initial severe clinical presentation, multilobar pneumonia, empyema and bacteremia, but not chronic obstructive pulmonary disease, were also risk factors for slow CAP resolution [Menendez *et al.* 2004; Roson *et al.* 2004], even in immunocompetent patients. Splenectomy [Tajiri *et al.* 2007], malignancy [Genne *et al.* 2006], neurological disease [Genne *et al.* 2006; Cilloniz *et al.* 2012] and immunosuppression [Japanese Respiratory Society, 2009] have all been suggested to increase CAP severity and treatment failure rate.

In addition, suppurative complications, such as empyema or abscess [File, 2001, Genne *et al.* 2006], may lead to treatment failure, probably

related to low antibiotic concentration in the infection site as well as to their slow resolution. Therefore, thoracic drainage or a surgical approach may be needed to achieve clinical cure.

Genetic polymorphisms may also be implicated in different patterns of host susceptibility and response to infection. These polymorphisms concern several steps of immune response to infection, such as antigen recognition, proinflammatory and anti-inflammatory responses and effector mechanisms. Both basally elevated interleukin 6 (IL-6) and tumor necrosis factor (TNF) were associated with a high risk of developing CAP, at least in older patients [Yende *et al.* 2005]. In addition, mutation of the toll-like receptor 4 gene is associated with a greater propensity for severe infections. The same is true for some TNF polymorphisms, associated with higher mortality [Menendez and Torres, 2007]. Conversely, patients with the GG genotype of IL-6, which is associated with lower production of this cytokine, have better outcomes in sepsis [Menendez and Torres, 2007]. In fact, an exaggerated inflammatory response seems to contribute to slow or even nonresponse and a poor outcome [Ioanas *et al.* 2004].

Although antibiotic therapy is of utmost importance, particularly in severe CAP, adequate antibiotic therapy alone, even when optimally used, is probably not sufficient to reduce mortality [Lode, 2009]. Therefore, interest in nonantibiotic, adjunctive therapy has continued to grow [Cohen, 2009].

The single most studied pharmacological intervention is the use of corticosteroids. Several effects in the immune system have been described that could theoretically account for an improved host response in CAP [Prigent *et al.* 2004]. However, a recent review on the topic [Póvoa and Salluh, 2012b] found that, despite the fact that corticosteroids were largely used to treat patients with CAP, there was no proven benefit of these drugs. Moreover, in most of the studies evaluated, adverse events such as superinfections and hyperglycemia were more frequent in patients receiving corticosteroids [Póvoa and Salluh, 2012b].

Even the use of nonsteroid anti-inflammatory drugs in CAP may be associated with a more invasive disease and more pleuropulmonary complications, such as empyema and lung

cavitation even in young, healthy patients [Voiriot *et al.* 2011].

Yet no single drug has been proved to be beneficial in patients with CAP and use of a single drug in patients with nonresponse cannot be recommended at present.

Conclusion

Nonresponse in CAP is associated with increased morbidity and mortality. Bacteria inoculum and virulence, resistance to antibiotics as well as host immune dysfunction, PK changes and suppurative complications may all be responsible for treatment failure.

Early identification of nonresponse and timely use of diagnostic and therapeutic procedures can help to improve the outcomes of these patients.

A clear definition of nonresponse in CAP and a systematic clinical approach to treating patients whose condition fails to respond to initial antibiotic therapy are needed.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

JG-P has received honoraria and served as an advisor for Pfizer, Astra-Zeneca, Gilead, Abbott, Wyeth-Lederle, Janssen-Cilag, Merck Sharp & Dohme, and received an unrestricted research grant from Astra-Zeneca. PP has received honoraria and served as an advisor for Astra Zeneca, Ely-Lilly, Gilead, Janssen-Cilag, Merck Sharp & Dohme, Novartis and Pfizer and received unrestricted research grants from Brahms and Virogates. CC has no competing interests to declare.

References

- American Thoracic Society. (1996) Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med* 153: 1711–1725.
- Arancibia, F., Ewig, S., Martinez, J., Ruiz, M., Bauer, T., Marcos, M. *et al.* (2000) Antimicrobial treatment failures in patients with community-acquired

- pneumonia: causes and prognostic implications. *Am J Respir Crit Care Med* 162: 154–160.
- Arnold, F., Summersgill, J., Lajoie, A., Peyrani, P., Marrie, T., Rossi, P. *et al.* (2007) A worldwide perspective of atypical pathogens in community-acquired pneumonia. *Am J Respir Crit Care Med* 175: 1086–1093.
- Aubert, G., Carricajo, A., Coudrot, M., Guyomarc'h, S., Auboyer, C. and Zeni, F. (2010) Prospective determination of serum ceftazidime concentrations in intensive care units. *Ther Drug Monit* 32: 517–519.
- Bafadhel, M., Clark, T., Reid, C., Medina, M., Batham, S., Barer, M. *et al.* (2011) Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. *Chest* 139: 1410–1418.
- Balc, I., Sungurtekin, H., Gurses, E., Sungurtekin, U. and Kaptanoglu, B. (2003) Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit. *Crit Care* 7: 85–90.
- Baptista, J., Udy, A., Sousa, E., Pimentel, J., Wang, L., Roberts, J. *et al.* (2011) A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. *Crit Care* 15: R139.
- Bodi, M., Rodriguez, A., Sole-Violan, J., Gilavert, M., Garnacho, J., Blanquer, J. *et al.* (2005) Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. *Clin Infect Dis* 41: 1709–1716.
- Boselli, E., Breilh, D., Cannesson, M., Xuereb, F., Rimmel, T., Chassard, D. *et al.* (2004a) Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 G/0.5 G administered to critically ill patients with severe nosocomial pneumonia. *Intensive Care Med* 30: 976–979.
- Boselli, E., Breilh, D., Duflo, F., Saux, M., Debon, R., Chassard, D. *et al.* (2003) Steady-state plasma and intrapulmonary concentrations of cefepime administered in continuous infusion in critically ill patients with severe nosocomial pneumonia. *Crit Care Med* 31: 2102–2106.
- Boselli, E., Breilh, D., Rimmel, T., Djabarouti, S., Saux, M., Chassard, D. *et al.* (2005a) Pharmacokinetics and intrapulmonary diffusion of levofloxacin in critically ill patients with severe community-acquired pneumonia. *Crit Care Med* 33: 104–109.
- Boselli, E., Breilh, D., Rimmel, T., Djabarouti, S., Toutain, J., Chassard, D. *et al.* (2005b) Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med* 33: 1529–1533.
- Boselli, E., Breilh, D., Rimmel, T., Guillaume, C., Xuereb, F., Saux, M. *et al.* (2008) Alveolar concentrations of piperacillin/tazobactam administered in continuous infusion to patients with ventilator-associated pneumonia. *Crit Care Med* 36: 1500–1506.
- Boselli, E., Breilh, D., Rimmel, T., Poupelin, J., Saux, M., Chassard, D. *et al.* (2004b) Plasma and lung concentrations of ceftazidime administered in continuous infusion to critically ill patients with severe nosocomial pneumonia. *Intensive Care Med* 30: 989–991.
- Boselli, E., Breilh, D., Saux, M., Gordien, J. and Allaouchiche, B. (2006) Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator-associated pneumonia. *Intensive Care Med* 32: 2059–2062.
- Bouadma, L., Luyt, C., Tubach, F., Cracco, C., Alvarez, A., Schwebel, C. *et al.* (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet* 375: 463–474.
- Christ-Crain, M., Jaccard-Stolz, D., Bingisser, R., Gencay, M., Huber, P., Tamm, M. *et al.* (2004) Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 363: 600–607.
- Cilloniz, C., Ewig, S., Ferrer, M., Polverino, E., Gabarrus, A., Puig De La Bellacasa, J. *et al.* (2011) Community-acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis. *Crit Care* 15: R209.
- Cilloniz, C., Ewig, S., Polverino, E., Marcos, M., Prina, E., Sellares, J. *et al.* (2012) Community-acquired pneumonia in outpatients: etiology and outcomes. *Eur Respir J* 40: 931–938.
- Coelho, L., Póvoa, P., Almeida, E., Fernandes, A., Mealha, R., Moreira, P. *et al.* (2007) Usefulness of C-reactive protein in monitoring the severe community-acquired pneumonia clinical course. *Crit Care* 11: R92.
- Coelho, L., Salluh, J., Soares, M., Bozza, F., Verdeal, J., Castro-Faria-Neto, H. *et al.* (2012) Patterns of C-reactive protein ratio response in severe community-acquired pneumonia: a cohort study. *Crit Care* 16: R53.
- Cohen, J. (2009) Non-antibiotic strategies for sepsis. *Clin Microbiol Infect* 15: 302–307.
- Corrêa, R., Lundgren, F., Pereira-Silva, J., Frare e Silva, R., Cardoso, A., Lemos, A. *et al.* (2009) Brazilian guidelines for community-acquired pneumonia in immunocompetent adults – 2009. *J Bras Pneumol* 35: 574–601.
- Dahaba, A., Rehak, P. and List, W. (2003) Procalcitonin and C-reactive protein plasma concentrations in nonseptic uremic patients undergoing hemodialysis. *Intensive Care Med* 29: 579–583.
- Dockrell, D., Whyte, M. and Mitchell, T. (2012) Pneumococcal pneumonia: mechanisms of infection and resolution. *Chest* 142: 482–491.

- Eliakim-Raz, N., Robenshtok, E., Shefet, D., Gafer-Gvili, A., Vidal, L., Paul, M. *et al.* (2012) Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev* (9): CD004418.
- El-Solh, A., Aquilina, A., Dhillon, R., Ramadan, F., Nowak, P. and Davies, J. (2002) Impact of invasive strategy on management of antimicrobial treatment failure in institutionalized older people with severe pneumonia. *Am J Respir Crit Care Med* 166: 1038–1043.
- El Solh, A., Pietrantoni, C., Bhat, A., Bhora, M. and Berbary, E. (2004) Indicators of potentially drug-resistant bacteria in severe nursing home-acquired pneumonia. *Clin Infect Dis* 39: 474–480.
- Fantin, B., Aubert, J., Unger, P., Lecoœur, H. and Carbon, C. (2001) Clinical evaluation of the management of community-acquired pneumonia by general practitioners in France. *Chest* 120: 185–192.
- File Jr, T. (2001) Optimal treatment strategies for community-acquired pneumonia: non-responders to conventional regimens. *Chemotherapy* 47(Suppl. 4): 11–18.
- Fish, D., Teitelbaum, I. and Abraham, E. (2005) Pharmacokinetics and pharmacodynamics of imipenem during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother* 49: 2421–2428.
- Froes, F. (2003) [Pneumonia in the adult population in continental Portugal – incidence and mortality in hospitalized patients from 1998 to 2000]. *Rev Port Pneumol* 9: 187–194.
- Garcia Vazquez, E., Martinez, J., Mensa, J., Sanchez, F., Marcos, M., De Roux, A. *et al.* (2003) C-reactive protein levels in community-acquired pneumonia. *Eur Respir J* 21: 702–705.
- Garibaldi, R. (1985) Epidemiology of community-acquired respiratory tract infections in adults. incidence, etiology, and impact. *Am J Med* 78: 32–37.
- Genne, D., Sommer, R., Kaiser, L., Saaidia, A., Pasche, A., Unger, P. *et al.* (2006) Analysis of factors that contribute to treatment failure in patients with community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 25: 159–166.
- Giamarellos-Bourboulis, E., Pechere, J., Routsis, C., Plachouras, D., Kollias, S., Raftogiannis, M. *et al.* (2008) Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. *Clin Infect Dis* 46: 1157–1164.
- Gonçalves-Pereira, J. and Póvoa, P. (2011) Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. *Crit Care* 15: R206.
- Gonçalves-Pereira, J., Póvoa, P., Lobo, C. and Carneiro, A. (2012) Bloodstream infections as a marker of community-acquired sepsis severity. results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study). *Clin Microbiol Infect* 23 January (E-pub ahead of print).
- Halm, E., Fine, M., Marrie, T., Coley, C., Kapoor, W., Obrosky, D. *et al.* (1998) Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 279: 1452–1457.
- Halm, E. and Teirstein, A. (2002) Clinical practice. management of community-acquired pneumonia. *N Engl J Med* 347: 2039–2045.
- Hansen, M., Christrup, L., Jarlov, J., Kampmann, J. and Bonde, J. (2001) Gentamicin dosing in critically ill patients. *Acta Anaesthesiol Scand* 45: 734–740.
- Hausfater, P., Juillien, G., Madonna-Py, B., Haroche, J., Bernard, M. and Riou, B. (2007) Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department. *Crit Care* 11: R60.
- Hogarth, M., Gallimore, R., Savage, P., Palmer, A., Starr, J., Bulpitt, C. *et al.* (1997) Acute phase proteins, c-reactive protein and serum amyloid A protein, as prognostic markers in the elderly inpatient. *Age Ageing* 26: 153–158.
- Houck, P., Bratzler, D., Nsa, W., Ma, A. and Bartlett, J. (2004) Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 164: 637–644.
- Ioanas, M., Ferrer, M., Cavalcanti, M., Ferrer, R., Ewig, S., Filella, X. *et al.* (2004) Causes and predictors of nonresponse to treatment of intensive care unit-acquired pneumonia. *Crit Care Med* 32: 938–945.
- Japanese Respiratory Society. (2009) Pneumonia in immunocompromised patients. *Respirology* 14(Suppl. 2): S44–S50.
- Johansson, N., Kalin, M. and Hedlund, J. (2011) Clinical impact of combined viral and bacterial infection in patients with community-acquired pneumonia. *Scand J Infect Dis* 43: 609–615.
- Kikuchi, R., Watabe, N., Konno, T., Mishina, N., Sekizawa, K. and Sasaki, H. (1994) High incidence of silent aspiration in elderly patients with community-acquired pneumonia. *Am J Respir Crit Care Med* 150: 251–253.
- Lim, W., Baudouin, S., George, R., Hill, A., Jamieson, C., Le Jeune, I. *et al.* (2009) BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 64(Suppl. 3): iii1–iii55.
- Lipman, J., Wallis, S. and Boots, R. (2003) Cefepime versus ceftazidime: the importance of creatinine clearance. *Anesth Analg* 97: 1149–1154.
- Lode, H. (2009) Bacterial community-acquired pneumonia: risk factors for mortality and supportive therapies. *Intensive Care Med* 35: 391–393.
- Mancini, N., Carletti, S., Ghidoli, N., Cichero, P., Burioni, R. and Clementi, M. (2010) The era of

- molecular and other non-culture-based methods in diagnosis of sepsis. *Clin Microbiol Rev* 23: 235–251.
- Mandell, L., Wunderink, R., Anzueto, A., Bartlett, J., Campbell, G., Dean, N. *et al.* (2007) Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 44(Suppl. 2): S27–S72.
- Martin-Loeches, I., Lisboa, T., Rodriguez, A., Putensen, C., Annane, D., Garnacho-Montero, J. *et al.* (2009) Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Med* 36: 612–620.
- McKinnon, P., Paladino, J. and Schentag, J. (2008) Evaluation of Area under the inhibitory curve (AUC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int J Antimicrob Agents* 31: 345–351.
- Menendez, R., Cavalcanti, M., Reyes, S., Mensa, J., Martinez, R., Marcos, M. *et al.* (2008) Markers of treatment failure in hospitalised community acquired pneumonia. *Thorax* 63: 447–452.
- Menendez, R., Martinez, R., Reyes, S., Mensa, J., Polverino, E., Filella, X. *et al.* (2009) Stability in community-acquired pneumonia: one step forward with markers? *Thorax* 64: 987–992.
- Menendez, R. and Torres, A. (2007) Treatment failure in community-acquired pneumonia. *Chest* 132: 1348–1355.
- Menendez, R., Torres, A., Zalacain, R., Aspa, J., Martin Villascaras, J., Borderias, L. *et al.* (2004) Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax* 59: 960–965.
- Micek, S., Dunne, M. and Kollef, M. (2005) Pleuropulmonary complications of panton-valentine leukocidin-positive community-acquired methicillin-resistant *Staphylococcus aureus*: importance of treatment with antimicrobials inhibiting exotoxin production. *Chest* 128: 2732–2738.
- Minogue, M., Coley, C., Fine, M., Marrie, T., Kapoor, W. and Singer, D. (1998) Patients hospitalized after initial outpatient treatment for community-acquired pneumonia. *Ann Emerg Med* 31: 376–380.
- Nazareth, R., Goncalves-Pereira, J., Tavares, A., Miragaia, M., De Lencastre, H., Silvestre, J. *et al.* (2011) Community-associated methicillin-resistant *Staphylococcus aureus* infection in Portugal. *Rev Port Pneumol* 18: 34–38.
- Ortqvist, A., Kalin, M., Lejdebom, L. and Lundberg, B. (1990) Diagnostic fiberoptic bronchoscopy and protected brush culture in patients with community-acquired pneumonia. *Chest* 97: 576–582.
- Ott, S., Hauptmeier, B., Ernen, C., Lepper, P., Nuesch, E., Pletz, M. *et al.* (2012) Treatment failure in pneumonia: impact of antibiotic treatment and cost analysis. *Eur Respir J* 39: 611–618.
- Pea, F. and Viale, P. (2009) Bench-to-bedside review: appropriate antibiotic therapy in severe sepsis and septic shock – does the dose matter? *Crit Care* 13: 214.
- Pimentel, L. and McPherson, S. (2003) Community-acquired pneumonia in the emergency department: a practical approach to diagnosis and management. *Emerg Med Clin North Am* 21: 395–420.
- Póvoa, P. (2008) Serum markers in community-acquired pneumonia and ventilator-associated pneumonia. *Curr Opin Infect Dis* 21: 157–162.
- Póvoa, P., Coelho, L., Almeida, E., Fernandes, A., Mealha, R., Moreira, P. *et al.* (2005) C-reactive protein as a marker of infection in critically ill patients. *Clin Microbiol Infect* 11: 101–108.
- Póvoa, P. and Salluh, J. (2012a) Biomarker-guided antibiotic therapy in adult critically ill patients: a critical review. *Ann Intensive Care* 2: 32.
- Póvoa, P. and Salluh, J. (2012b) What is the role of steroids in pneumonia therapy? *Curr Opin Infect Dis* 25: 199–204.
- Póvoa, P., Souza-Dantas, V., Soares, M. and Salluh, J. (2011) C-reactive protein in critically ill cancer patients with sepsis: influence of neutropenia. *Crit Care* 15: R129.
- Prigent, H., Maxime, V. and Annane, D. (2004) Clinical review: corticotherapy in sepsis. *Crit Care* 8: 122–129.
- Rello, J. (2008) Demographics, guidelines, and clinical experience in severe community-acquired pneumonia. *Crit Care* 12(Suppl. 6): S2.
- Rello, J., Lisboa, T., Lujan, M., Gallego, M., Kee, C., Kay, I. *et al.* (2009) Severity of pneumococcal pneumonia associated with genomic bacterial load. *Chest* 136: 832–840.
- Roberts, J. and Lipman, J. (2006) Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. *Clin Pharmacokinet* 45: 755–773.
- Roberts, J., Uldemolins, M., Roberts, M., McWhinney, B., Ungerer, J., Paterson, D. *et al.* (2010) Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. *Int J Antimicrob Agents* 36: 332–339.
- Rodrigo, C., McKeever, T., Woodhead, M. and Lim, W. (2012) Single versus combination antibiotic therapy in adults hospitalised with community acquired pneumonia. *Thorax* 16 October (E-pub ahead of print). doi: 10.1136/thoraxjnl-2012-202296.
- Rodriguez, A., Mendia, A., Sirvent, J., Barcenilla, F., De La Torre-Prados, M., Sole-Violan, J. *et al.* (2007) Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med* 35: 1493–1498.

- Roson, B., Carratala, J., Fernandez-Sabe, N., Tubau, F., Manresa, F. and Gudiol, F. (2004) Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 164: 502–508.
- Salluh, J., Soares, M., Coelho, L., Bozza, F., Verdeal, J., Castro-Faria-Neto, H. *et al.* (2011) Impact of systemic corticosteroids on the clinical course and outcomes of patients with severe community-acquired pneumonia: a cohort study. *J Crit Care* 26: 193–200.
- Seligman, R., Papassotiriou, J., Morgenthaler, N., Meisner, M. and Teixeira, P. (2008) Copeptin, a novel prognostic biomarker in ventilator-associated pneumonia. *Crit Care* 12: R11.
- Shorr, A., Zilberberg, M., Micek, S. and Kollef, M. (2008) Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med* 168: 2205–2210.
- Sime, F., Roberts, M., Peake, S., Lipman, J. and Roberts, J. (2012) Does beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. *Annals of Intensive Care* 2: 35.
- Tajiri, T., Tate, G., Enosawa, T., Akita, H., Ohike, N., Masunaga, A. *et al.* (2007) Clinicopathological findings in fulminant-type pneumococcal infection: report of three autopsy cases. *Pathol Int* 57: 606–612.
- Ulldemolins, M., Roberts, J., Lipman, J. and Rello, J. (2011) Antibiotic dosing in multiple organ dysfunction syndrome. *Chest* 139: 1210–1220.
- Vincent, J. and Marshall, J. (2008) Surviving sepsis: a guide to the guidelines. *Crit Care* 12: 162.
- Visscher, S., Schurink, C., Melsen, W., Lucas, P. and Bonten, M. (2008) Effects of systemic antibiotic therapy on bacterial persistence in the respiratory tract of mechanically ventilated patients. *Intensive Care Med* 34: 692–699.
- Voiriot, G., Dury, S., Parrot, A., Mayaud, C. and Fartoukh, M. (2011) Nonsteroidal antiinflammatory drugs may affect the presentation and course of community-acquired pneumonia. *Chest* 139: 387–394.
- Webster, D., Chui, L., Tyrrell, G. and Marrie, T. (2007) Health care-associated *Staphylococcus aureus* pneumonia. *Can J Infect Dis Med Microbiol* 18: 181–188.
- Wunderink, R. (2010) Surrogate markers and microbiologic end points. *Clin Infect Dis* 51(Suppl. 1): S126–S130.
- Yende, S., Tuomanen, E., Wunderink, R., Kanaya, A., Newman, A., Harris, T. *et al.* (2005) Preinfection systemic inflammatory markers and risk of hospitalization due to pneumonia. *Am J Respir Crit Care Med* 172: 1440–1446.

Visit SAGE journals online
<http://tai.sagepub.com>

SAGE JOURNALS
 Online