Pneumonia as a Systemic Illness

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ABSTRACT

Purpose of the Review

This manuscript reviews the recent literature describing the occurrence, risk factors, recognition and treatment of sepsis, respiratory failure and multiple organ dysfunction in patients with community-acquired pneumonia (CAP).

Recent findings

CAP may present with varying degrees of disease severity ranging from an almost asymptomatic infection to a fulminant systemic disease with both respiratory failure and multiple organ dysfunction. Severe sepsis occurs early in the course of the infection in more than 30% of cases. It may involve several organ systems and is associated with the severity and mortality of CAP. A number of factors exist, which may promote the transition of CAP from a local to a systemic disease, particularly immunosuppression and poorly controlled inflammatory responses, which promote extrapulmonary dissemination of the causative pathogens. Although CAP may be associated with complications involving most organ systems, much recent research has focused attention on cardiac complications, particularly those associated with pneumococcal infections. Biomarkers as a strategy for discriminating between invasive and non-invasive CAP have been comprehensively studied. A number of treatment strategies using antibiotics and various adjunctive therapies have been studied in severe CAP.

Summary

Recent research highlights the fact that CAP is frequently a systemic illness.

Keywords

Bacteremia, biomarkers, community-acquired pneumonia, multiple organ dysfunction, sepsis

INTRODUCTION

It is well recognized worldwide that community-acquired pneumonia (CAP) remains an extremely common cause of infection, which is frequently associated with significant morbidity and mortality, particularly among cases needing intensive care unit (ICU) admission, such that it has been recommended that CAP should be treated as a medical emergency [1*, 2**]. However, CAP may present with markedly varying degrees of disease severity ranging from an almost asymptomatic infection to a relatively mild, localized condition to a fulminant systemic disease with both respiratory failure and multiple organ dysfunction [3]. Nevertheless, it has been reported for many years that CAP may be associated with severe sepsis, which occurs relatively frequently, involving more than 30% of cases (37.6% of cases in one study [4**]), that it occurs early in the course of the infection, that it may involve several organ systems and that it is associated with the severity and mortality of CAP [4▪▪, 5–7]. One recent study documented that the time to positive blood culture in patients with pneumococcal pneumonia is a good marker of disease severity and also predicts outcome [8*].

TRANSITION OF CAP FROM A LOCALIZED TO A SYSTEMIC INFECTION

The transition of CAP from an acute infection of the pulmonary parenchyma to severe sepsis, commonly defined as bacteremia-associated, new-onset, acute organ dysfunction, is a frequent complication of CAP, occurring in more than 30% of patients [7], which is consistent with the lungs being the most common primary site of infection in relation to development of sepsis and septic shock [9]. Administration of inappropriate antimicrobial chemotherapy to CAP patients infected with antibiotic-resistant pathogens is a recognized cause of bacteremia [10], as well as with a strong association with 30-day mortality in patients with CAP caused by the pneumococcus [11], and presumably other bacterial pathogens. In addition to this, a number of other factors exist, which may promote the transition of CAP from a local to a systemic disease, particularly immunosuppression and poorly controlled inflammatory responses, which promote extrapulmonary dissemination of the causative pathogens.

Immunosuppression

Foremost among conditions associated with impairment of pulmonary host defenses are immunosenescence, primary and acquired antibody deficiency syndromes, HIV infection, and smoking. In the case of immunosenescence, Marrie *et al.* in a prospective observational study covering the period 2000–2014, to which 2435 cases of invasive pneumococcal disease (IPD) were included, investigated the effect of age on the frequency and manifestations of this severe infection [12**]. The authors reported that although patients in the age group ≥65 years accounted for only 27.3% of the cases, the mortality rate of 48% in this age group was disproportionately high. Indeed, the case fatality rate was found to increase with increasing age, being 9.6% and 31.7% in patients aged 17–54 years and ≥75 years respectively [12**]. As stated by the authors "the rate of IPD is highest in the very elderly."

In another very recent prospective, multicentre cohort study, which included 4070 patients hospitalized with CAP, 1529 (37.6%) of whom presented with severe sepsis, Montull *et al.* investigated both host- and pathogen-related characteristics associated with severe sepsis [4**]. The authors reported that older age (>65 years), chronic obstructive pulmonary disease (COPD) and renal disease, as well as alcohol abuse, were independently associated with severe sepsis [4**]. With respect to the causative pathogens, the pneumococcus and a mixed microbial etiology were found to be associated with severe sepsis, while, on the other hand, prior antibiotic therapy, and also somewhat surprisingly, diabetes mellitus, were found to be protective [4**]. Those patients with severe sepsis detected at the time of hospital admission had higher PSI and CURB-65 scores; however, more than half of these patients had a CURB-65 score of ≤2, which according to the authors is indicative of the limitations of applying scales for severity assessment [4**].

With respect to other causes of pulmonary immunosuppression which predispose for development of severe CAP, HIV infection is a well-recognized risk for bacteremia, but apparently not for increased mortality or time to clinical stability [13]. The adverse effects of smoking were described an earlier seminal publication by Nuorti *et al,* who found that the smoking habit was "the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, non-elderly adults" [14]. In the

case of antibody deficiency syndromes, it has recently been reported that decreased concentrations of the immunoglobulin (Ig) subclass, IgG_2, are associated with a poorer prognosis and a higher risk of mortality in patients hospitalized for CAP [15]. In this context, it is noteworthy that IgG_2 antibodies have a key protective role in opsonophagocytosis, via neutralization of the anti-phagocytic, polysaccharide capsule of the pneumococcus.

Inflammatory responses in CAP

Studies comparing inflammatory responses in severe and non-severe CAP have suggested that the former patients do not mount a robust local inflammatory response, but rather have a much more exuberant systemic inflammatory response suggesting that what drives CAP severity is the ability or not of the patient to mount an optimal local inflammatory response [16]. Other investigations documenting patterns of both local and systemic cytokines of importance in the pathogenesis of severe CAP have concluded that interleukin (IL)-1, IL-6, IL-8, IL-10, tumour necrosis factor alpha (TNFα) and interferon gamma (IFNɣ) play important roles, with systemic levels of these various cytokines being related to disease severity [17, 18]. In this context, higher IL-6 and TNFα levels on admission were associated with greater risk of death, need for mechanical ventilation and acute kidney injury [18].

SEPSIS AND ORGAN DYSFUNCTION

As mentioned above, Montull and colleagues reported that elderly patients, alcohol abusers, and patients with renal disease and COPD were more likely to develop community-onset severe sepsis, whereas prior antibiotic use was a protective factor and that the presence of bacteremia, infection with *Streptococcus pneumoniae* and infections of mixed etiology were the most common microbial causes [4**]. Similarly, Menendez and colleagues [2**] reported the occurrence of $\geq$2 organ dysfunctions in 11.3% of CAP patient at diagnosis, being associated with a greater 30-day mortality than cases without organ dysfunction (12.4% versus 3.4%) and that infections with the pneumococcus, or Gram-negative organisms and polymicrobial infections were the most common etiologies and that hepatic, renal and neurological disorders and COPD were main risk factors. Amaro and colleagues [19*] demonstrated that recent use of antibiotics prior to hospital admission in patients with CAP seemed to reduce

the incidence of septic shock and the need for mechanical ventilation. It has been suggested that assessment for organ dysfunction early on hospital admission of patients with CAP and/or even phenotyping CAP patients according to the presence or absence of acute respiratory failure and/or severe sepsis could facilitate appropriate clinical management, assisting in site-of-care decisions, assessment of infection severity and early initiation of optimal management [2**, 3].

Recent studies of the new screening tool for sepsis, namely the quick Sepsis-related Organ Failure Assessment (qSOFA), which has prognostic performance similar to the SOFA when used in patients outside the ICU, indicated that it was similar to (higher sensitivity and lower specificity) [20], or better than, the CRB-65 severity score (using confusion, respiratory rate, blood pressure, age $\geq$ 65 years) [21*] in patients with CAP. Furthermore, Ranzani and colleagues documented that the qSOFA and CRB outperformed the systemic inflammatory response syndrome (SIRS) criteria and appeared to be useful tools for CAP assessment in the emergency department [22*].

ORGAN DYSFUNCTION – CARDIAC COMPLICATIONS IN CAP

Although It is well recognized in patients with CAP that complications involving most of the organ systems beyond the lungs and pleura and including the brain, hematological, renal and endocrine systems, may occur, much recent research has focused attention on cardiac complications, particularly those in association with pneumococcal infections [23]. Some recent studies have indicated that assessment of the presence or absence of certain indicators of cardiac dysfunction using echocardiography (such as a decrease in tricuspid annular plane systolic excursion (TAPSE) and cardiac biomarkers (such as a raised N-terminal proB-type natriuretic peptide level)) may be useful since they are appear to be associated with an increased rate of complicated hospitalization and adverse events in patients with CAP [24, 25*]. Reyes and colleagues successfully developed a non-human primate model of severe pneumococcal pneumonia [26**]. In that model these researchers were able to confirm the findings of previous studies in murine models of pneumococcal pneumonia that the pneumococcus was able to invade the heart in severe pneumonia, and induce cardiomyocyte death by direct cytotoxic effects

(necroptosis and apoptosis) with subsequent cardiac scarring [27**]. Very interestingly, Shenoy and colleagues [28**] documented that contrary to current dogma, pneumococci resident in biofilm, rather than being passively immunoquiescent, are involved in immune cell killing, rapidly killing cardiac macrophages in a pneumolysin-dependent manner, promoting myocardial damage and dysfunction. Importantly, it is well recognized that cardiovascular complications occurring in patients with CAP are associated with both short-term and long-term mortality [29, 30].

BIOMARKERS WHICH MAY ENABLE DISTINCTION BETWEEN INVASIVE AND NON-INVASIVE CAP

Distinguishing between invasive and non-invasive CAP is of considerable importance due to the clinical management of patients, particularly in relation to re-assessment of antimicrobial therapy and possible implementation of adjunctive therapeutic strategies such as macrolide antibiotics and possibly corticosteroids. To achieve this objective, much recent research has focused on the inclusion of biomarkers as a strategy to reinforce the utility of clinical scoring systems in discriminating between invasive and non-invasive CAP. Biomarkers which have attracted recent attention in this context, include circulating mid-regional pro-adrenomedullin (MR-proADM), platelet counts, lactate, presepsin, and combinations of these with other biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT).

An earlier study undertaken in a small group (n=49) of CAP patients with sepsis or septic shock admitted to an intensive care unit (ICU) investigated the prognostic utility of measurement of circulating MR-proADM relative to that of CRP or PCT [31]. The authors reported that median levels of MR-proADM were significantly higher in non-survivors vs. survivors (5.0 and 1.7 nanomoles/liter respectively, $P<0.01$), as well as being superior to either CRP or PCT, and comparable with the PSI [31]. In a subsequent prospective observational study, undertaken by España *et al.*, a total of 491 patients with CAP was recruited, 256 and 235 of whom were admitted to hospital or treated as outpatients, respectively [32]. The authors, who evaluated the potential of three clinical scoring systems (PSI, CURB-65, SCAP) and three

biomarkers (CRP, PCT, MR-proADM) to discriminate between the two groups of patients, reported that the SCAP score and MR-proADM had the best AUCs of 0.83 and 0.84 respectively, while combining these increased the AUC to 0.88 [32].

While neither of the aforementioned studies was designed with the primary objective of discriminating between systemic and non-systemic disease, they do, however, underscore the potential of MR-proADM to achieve this objective [31, 32]. This contention is supported by the findings of a more recent prospective observational study by Angeletti *et al.* undertaken with the objective of analysing the predictive potential of PCT and MR-proADM, individually and in combination, to distinguish between localized and systemic infections, as well as the prognosis thereof, in 382 patients with a diagnosis of bacterial infection (n=168 septic, 148 severe sepsis/septic shock, 66 with localized infections) [33*]. Scores were assigned to PCT and MR-proADM according to the magnitudes of the circulating concentrations of these biomarkers, while the combined scores were calculated by simply adding the individual values. The combined score AUCs for patients with severe sepsis/septic shock, sepsis and localized infections were 0.99, 0.96 and 0.88 respectively with corresponding likelihood ratios of 88.38, 80.1 and 7.1 [33*]. The authors conclude that the “combined PCT/MR-proADM score could represent a valid tool in the clinical practice to timely identify patients with bacterial infections and guide the diagnosis of sepsis and severe sepsis, conditions requiring a prompt treatment” [33*]. Clearly, however, a similar study focused specifically on CAP is required to ascertain the validity of this strategy in the setting of this condition.

Other recently described biomarkers with the potential to discriminate between localized and systemic infection in patients with CAP include: i) a bacteremia prediction model based on the combination of a platelet count of <130,000 cells/µL, albumin <3.3 mg/dL and CRP >17 mg/dL [34*]; ii) measurement of serum presepsin (a subtype of soluble CD14), which has been reported to be an accurate biomarker of sepsis [35]; iii) measurement of blood lactate [36]; and iv) applying a biomarker profile comprising CRP, PCT and B-type natriuretic peptide (BNP),because circulating levels of all three biomarkers are higher in patients with bacteremic CAP [37].

In addition to the aforementioned, other biomarkers which have the potential to distinguish between localized and systemic CAP, but which remain untested in this setting include: i) decreased IgG_2 as mentioned above [15]; ii) elevated circulating levels of intercellular adhesion molecule-1 (ICAM-1) [38]; iii) specifically in the case of pneumococcal CAP, the combination of a high bacterial DNA load in association with elevated levels of PCT and soluble urokinase plasminogen activator receptor (suPAR) [39]; and iv) a rising mean platelet volume in patients hospitalised with CAP [40].

These various biomarkers of severe disease are summarised in Table 1.

Table 1: Apparent and potential circulating biomarkers, which may distinguish between systemic and localized disease

Apparent	**Reference**
Increased mid-regional pro-adrenomedullin individually and in combination with either procalcitonin or the SCAP clinical scoring system	31, 32, 33*
Bacteremia prediction model consisting of: - Platelet count <130,000 cells/µl - Albumin <3.3 mg/dL - C-reactive protein >17 mg/dL	34*
Increased presepsin	35
Increased lactate	36
Biomarker profile consisting of increased: - C-reactive protein - Procalcitonin - B-type natriuretic peptide -	37
Potential	
Decreased immunoglobulin G_2	15
Increased intercellular adhesion molecule-1	38
Pneumococcal CAP biomarker profile consisting of increased: - Bacterial DNA load - Procalcitonin - Soluble urokinase plasminogen activator reaction -	39
Increased mean platelet volume	40

MANAGEMENT OF SEVERE CAP – ANTIBIOTICS AND BEYOND

One interesting recent review asked the question as to whether the use of lytic antibiotics, such as the beta-lactams, as opposed to non-lytic antibiotics such as macrolides and macrolide-like agents, in patients with severe invasive pneumococcal disease is optimal. This is because bactericidal antibiotics have been documented to increase the release of the highly proinflammatory toxin, pneumolysin, which is well recognized to participate in host tissue damage, such as the cardiac injury that occurs in pneumococcal CAP and is associated with a poorer outcome [41]. A number of years ago Restrepo and colleagues documented that the addition of a macrolide to the antibiotic regimen in patients with severe CAP and sepsis was associated with a lower mortality [42]. However, a more recent systematic review and meta-analysis comparing the combination of a fluoroquinolone or macrolide together with a beta-lactam antibiotic, in hospitalized patients with CAP, concluded that with low quality of data and absence of data from randomized controlled trials, no recommendations could be made with regard to either regimen [43]. It was interesting to note in the latter study that there was a difference in mortality (higher in the fluoroquinolone/beta-lactam group both overall and in the American, but not European, studies). Nevertheless, Pereira and colleagues [44*] in a *post hoc* analysis of a prospective multicenter observational study documented that combination antibiotic therapy with a macrolide in patients with severe CAP was independently associated with a reduction in hospital stay and 6-month mortality. However, it does not appear that the use of severity scores is helpful in predicting the likely response to macrolide therapy [45].

Falcone and colleagues [46], in an observational study, with correction of all the relevant effect estimates and p values using propensity score analysis, noted that in patients with pneumonia (CAP or healthcare-associated pneumonia) and septic shock, receipt of aspirin and a macrolide was associated with a better survival. However, a further *post hoc* exploratory analysis of a randomized controlled trial was undertaken in patients with severe CAP and a high inflammatory response (C-reactive protein > 150mg/l) [47]. After taking into account potential confounders, no difference in treatment failure or in-hospital mortality was noted in those receiving the

combination of a glucocorticoid and a beta-lactam/macrolide compared with any other combination (i.e. beta-lactam/fluoroquinolone plus glucocorticoid or either antibiotic combination without the glucocorticoid) [47].

CONCLUSIONS

Severe sepsis occurs relatively frequently in patients with CAP. It occurs early in the course of the infection, may involve several organ systems and is associated with the severity and mortality of CAP. A number of factors are recognized which promote the transition of CAP from a local to a systemic disease. Much recent research has focused attention on cardiac complications. Biomarkers as a strategy for discriminating between invasive and non-invasive CAP and a number of treatment strategies using antibiotics and various adjunctive therapies have been studied in severe CAP.

Key points

- CAP may present with markedly varying degrees of disease severity ranging from an almost asymptomatic infection to a relatively mild localized condition to a fulminant systemic disease with both respiratory failure and multiple organ dysfunction
- A number of factors exist, which may promote the transition of CAP from a local to a systemic disease, particularly immunosuppression and poorly controlled inflammatory responses, which promote extrapulmonary dissemination of the causative pathogens.
- Although It is well recognized in patients with CAP that complications involving most of the organ systems beyond the lungs and pleura and including the brain, hematological, renal and endocrine systems, may occur, much recent research has focused attention on cardiac complications, particularly those in association with pneumococcal infections
- Distinguishing between invasive and non-invasive CAP is of considerable importance due to the clinical management of patients, particularly in relation to re-assessment of antimicrobial therapy and possible implementation of

adjunctive therapeutic strategies such as macrolide antibiotics and possibly corticosteroids.

- Much recent research has focused on the inclusion of biomarkers as a strategy to reinforce the utility of clinical scoring systems in discriminating between invasive and non-invasive CAP

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REFERENCES AND RECOMMENDED READING

1. *Phua J, Dean NC, Guo Qi, *et al*. Severe community-acquired pneumonia: timely management measures in the first 24 hours. Crit Care 2016; 20:237.
   This study reviewed the literature to explore how early and aggressive management of severe CAP, implemented within 24 hours of diagnosis, impacted on mortality.
2. **Menéndez R, Montull B, Reyes S, *et al*. Pneumonia presenting with organ dysfunctions: Causative microorganisms, host factors and outcome. J Infect 2016; 73:419–426.
   This interesting study characterized the host risk factors for organ dysfunction in patients with CAP presenting to the emergency room and also documented the causative organisms and the impact of organ dysfunction on 30-day mortality.
3. Aliberti S, Brambilla AM, Chalmers JD, *et al*. Phenotyping community-acquired pneumonia according to the presence of acute respiratory failure and severe sepsis. Respir Res 2014; 15:27.
4. **Montull B, Menéndez R, Torres A, *et al.* Predictors of severe sepsis among patients hospitalized for community-acquired pneumonia. PLoS One 2016; 11:e0145929.
   These authors determined the host risk factors for severe sepsis in patients hospitalized with severe CAP and also documented the most common microorganisms involved.
5. Beutz MA, Abraham E. Community-acquired pneumonia and sepsis. Clin Chest Med 2005; 26:19–28.

6. Laterre PF, Garber G, Levy H, *et al*. Severe community-acquired pneumonia as a cause of severe sepsis: data from the PROWESS study. Crit Care Med 2005; 33:952 – 961.
7. Dremsizov T, Clermont G, Kellum JA, *et al*. Severe sepsis in community-acquired pneumonia. When does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest 2006; 129:968–978.
8. *Cillóniz C, Ceccato A, de la Calle C, *et al*. Time to blood culture positivity as a predictor of clinical outcomes and severity in adults with bacteremic pneumococcal pneumonia. PLoS One 2017; 12:e0182436.
   In a prospective observational study the authors documented that the time to positivity of blood cultures in patients with bacteremic pneumococcal pneumonia was a good marker of severity of pneumonia, as well as predictor of outcome.
9. Klastrup V, Hvass AM, Mackenhauer J, *et al.* Site of infection and mortality in patients with severe sepsis or septic shock. A cohort study of patients admitted to a Danish general intensive care unit. Infect Dis 2016; 48:726–731.
10. Torres A, Cillóniz C, Ferrer M, *et al.* Bacteraemia and antibiotic-resistant pathogens in community acquired pneumonia: risk and prognosis. Eur Respir J 2015; 45:1353–1363.
11. van Mens SP, van Deursen AMM, de Greeff SC, *et al.* Bacteraemic and non-bacteraemic/urinary antigen-positive pneumococcal community-acquired pneumonia compared. Eur J Clin Microbiol Infect Dis 2015; 34:115–122.
12. **Marrie TJ, Tyrrell GJ, Majumdar SR, Eurich DT. Effect of Age on the manifestations and outcomes of invasive pneumococcal disease in adults. Am J Med 2017; doi: 10.1016/j.amjmed.2017.06.039 [Epub ahead of print].
   This is a large prospective observational study, which clearly demonstrates that the highest rates of development of, as well as mortality from, invasive pneumococcal disease are highest in the very elderly.
13. Almeida A, Boattini M. Community-acquired pneumonia in HIV-positive patients: an update on etiologies, epidemiology and management. Curr Infect Dis Rep 2017; 19:2.
14. Nuorti JP, Butler JC, Farley MM, *et al.* Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 2000; 342:681–689.

15. de la Torre MC, Palomera E, Serra-Prat M, *et al.* IgG2 as an independent risk factor for mortality in patients with community-acquired pneumonia. J Crit Care 2016; 35:115–119.
16. Fernandez-Botran R, Uriarte SM, Arnold FW, *et al*. Contrasting inflammatory responses in severe and non-severe community-acquired pneumonia. Inflammation 2014; 37:1158–1166.
17. Paats MS, Bergen IM, Hanselaar WE, *et al*. Local and systemic cytokine profiles in nonsevere and severe community-acquired pneumonia. Eur Respir J 2013; 41:1378–1385.
18. Bacci MR, Leme RCP, Zing NPC, *et al*. IL-6 and TNF-α serum levels are associated with early death in community-acquired pneumonia patients. Braz J Med Biol Res 2015; 48:427–432.
19. *Amaro R, Sellarés J, Polverino E, *et al*. Antibiotic therapy prior to hospital admission is associated with reduced septic shock and need for mechanical ventilation in patients with community-acquired pneumonia. J Infect 2017; 74:442–449.
    In this study cohort, recent use of antibiotics prior to hospital admission for CAP seemed to be associated with a lower incidence of septic shock on admission and lesser need for ICU admission during hospitalization.
20. Kolditz M, Scherag A, Rohde G, *et al*; CAPNETZ Study Group. Comparison of the qSOFA and CRB-65 for risk prediction in patients with community-acquired pneumonia. Intensive Care Med 2016; 42:2108–2110.
21. *Chen YX, Wang JY, Guo SB. Use of CRB-65 and quick sepsis-related organ failure assessment to predict site of care and mortality in pneumonia patients in the emergency department: a retrospective study. Crit Care 2016; 20:167.
    The authors documented that the qSOFA was better than the CRB-65 score in patients with pneumonia at predicting high-risk of mortality and need for ICU admission.
22. *Ranzani OT, Prina E, Menéndez R, *et al*. New sepsis definition (sepsis-3) and community-acquired pneumonia mortality: A validation and clinical decision-making study. Am J Respir Crit Care Med 2017; doi: 10.1164/rccm.201611-22620C [Epub ahead of print].
    These authors documented that the qSOFA and CRB score performed better than the SIRS criteria in the assessment of CAP patients presenting to an

emergency department, although the PSI appeared to be the best decision making tool.

23. Restrepo MI, Reyes LF, Anzueto A. Complication of community-acquired pneumonia (including cardiac complications). Semin Respir Crit Care Med 2016; 37:897–904.
24. Yildirim B, Biteker FS, Basaran Ö, *et al*. Is there a potential role for echocardiography in adult patients with CAP? Am J Emerg Med 2015; 33:1672–1676.
25. *Biteker FS, Basaran Ö, Doğan V, *et al*. Prognostic value of transthoracic echocardiography and biomarkers of cardiac dysfunction in community-acquired pneumonia. Clin Microbiol Infect 2016; 22:1006.e1-1006.e6.
    This study investigated the prognostic role of echocardiography and NT-proBNP in patients with CAP and its most important finding was that evidence of a decreased right ventricular systolic function was associated with an increased rate of adverse events during hospitalization (complicated hospitalization).
26. **Reyes LF, Restrepo MI, Hinojosa CA, *et al*. A non-human primate model of severe pneumococcal pneumonia. PLoS One 2016; 11:e0166092.
    This is a study describing the development of a novel primate model of severe pneumococcal pneumonia that mimics the clinical presentation, inflammatory response and infection kinetics seen in humans. It has multiple potential uses including the testing of novel therapies or vaccines, and the measurement of inflammatory biomarkers for diagnosis of CAP and the prediction of its outcome.
27. **Reyes LF, Restrepo MI, Hinojosa CA, *et al*. Severe pneumococcal pneumonia causes acute cardiac toxicity and subsequent cardiac remodeling. Am J Respir Crit Care Med 2017; 196:609–620.
    Using the primate model described in the previous reference, the authors documented that the pneumococcus invades the myocardium during infection, that it induces cardiac injury by necroptosis and apoptosis, followed by cardiac scarring after antibiotic treatment
28. **Shenoy AT, Brissac T, Gilley RP, *et al*. *Streptococcus pneumoniae* in the heart subvert the host response through biofilm-mediated resident macrophage killing. PLoS One 2017; 13:e1006582.
    This interesting study documented that pneumococci that invade the heart develop a mature biofilm and actively suppress the host response through

pneumolysin-mediated immune cell killing contradicting the notion that pneumococci in biofilm are immunoquiescent.

29. Cangemi R, Calvieri C, Falcone M, *et al*. Relation of cardiac complications in the early phase of community-acquired pneumonia to long-term mortality and cardiovascular events. Am J Cardiol 2015; 116:647–651.
30. *Violi F, Cangemi R, Falcone, *et al*. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. Clin Infect Dis 2017; 64:1486–1493.

    This study documented that cardiovascular events, mainly cardiac, occur in up to 30% of patients hospitalized with CAP, and that these events are associated with a 5-fold increase in 30-day CAP mortality.
31. Suberviola B, Castellanos-Ortega A, Llorca J, *et al.* Prognostic value of proadrenomedullin in severe sepsis and septic shock patients with community-acquired pneumonia. Swiss Med Wkly 2012; 142:w13542.
32. España PP, Capelastegui A, Mar C, *et al.* Performance of pro-adrenomedullin for identifying adverse outcomes in community-acquired pneumonia. J Infect 2015; 70:457–466.
33. *Angeletti S, Ciccozzi M, Fogolari M, *et al.* Procalcitonin and MR-proAdrenomedullin combined score in the diagnosis and prognosis of systemic and localized bacterial infections. J Infect 2016; 72:395–398.

    These authors propose that a biomarker score based on combining measurement of circulating procalcitonin and mid-regional pro-adrenomedullin may aid in distinguishing sepsis/severe sepsis from localized bacterial infections.
34. *Kim B, Choi J, Kim K, *et al.* Bacteremia prediction model for community-acquired pneumonia: external validation in a multicentre retrospective cohort. Acad Emerg Med 2017; 24:1226–1234.

    These authors have developed and evaluated a bacteremia prediction model in a large number of patients with community-acquired pneumonia; the model is based on combining measurement of circulating platelet counts, albumin and C-reactive protein.
35. Klouche K, Cristol JP, Devin J, *et al.* Diagnostic and prognostic value of soluble CD14 subtype (Presepsin) for sepsis and community-acquired pneumonia in ICU patients. Ann Intensive Care 2016; 6:59.

36. Frenzen FS, Kutschan U, Meiswinkel N, *et al.* Admission lactate predicts poor prognosis independently of the CRB/CURB-65 scores in community-acquired pneumonia. Clin Microbiol Infect 2017; doi: 10.1016/j.cmi.2017.07.007. [Epub ahead of print].
37. Bordon JM, Fernandez-Botran R, Wiemken TL, *et al.* Bacteremic pneumococcal pneumonia: clinical outcomes and preliminary results of inflammatory response. Infection 2015; 43:729–738.
38. Chang PY, Tsao SM, Chang JH, *et al.* Plasma levels of soluble intercellular adhesion molecule-1 as a biomarker for disease severity of patients with community-acquired pneumonia. Clin Chim Acta 2016; 463:174–180.
39. Loonen AJ, Kesarsing C, Kusters R, *et al.* High pneumococcal DNA load, procalcitonin and suPAR levels correlate to severe disease development in patients with pneumococcal pneumonia. Eur J Clin Microbiol Infect Dis 2017; doi: 10.1007/s10096-017-2963-2 [Epub ahead of print].
40. Gorelik O, Tzur I, Barchel D, *et al.* A rise in mean platelet volume during hospitalization for community-acquired pneumonia predicts poor prognosis: a retrospective observational cohort study. BMC Pulm Med 2017; 17:137.
41. Brown LA, Mitchell AM, Mitchell TJ. *Streptococcus pneumoniae* and lytic antibiotic therapy: are we adding insult to injury during invasive pneumococcal disease and sepsis? J Med Microbiol 2017; doi: 10.1099/jmm.0.000545 [Epub ahead of print].
42. Restrepo MI, Mortensen EM, Waterer GW, *et al.* Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. Eur Respir J 2009; 33:153–159.
43. Vardakas KZ, Trigkidis KK, Falagas ME. Fluoroquinolones or macrolides in combination with ß-lactams in adult patients hospitalized with community acquired pneumonia: a systematic review and meta-analysis. Clin Microbiol Infect 2017; 23:234–241.
44. *Pereira JM, Gonçalves-Pereira J, Ribeiro O, *et al*. Impact of antibiotic therapy in severe community-acquired pneumonia: Data from the Infauci study. J Crit Care 2017; 43:183–189.

    This study suggested that combination antibiotic therapy with a macrolide appears to be to be associated with better short-term (hospital mortality) and long-term (6-month mortality) outcomes with CAP, but prolonged antibiotic

therapy overall (> 7 days) had no survival benefit and was associated with longer length of ICU and hospital stay.

45. Singanayagam A, Aliberti S, Callóniz C, *et al*. Evaluation of severity score-guided approaches to macrolide use in community-acquired pneumonia. Eur Respir J 2017; 50:1602306.
46. Falcone M, Russo A, Farcomeni A, *et al.* Septic shock from community-onset pneumonia: is there a role for aspirin plus macrolides combination? Intensive Care Med 2016; 42:301–302.
47. Ceccato A, Cilloniz C, Ranzani OT, *et al*. Treatment with macrolides and glucocorticosteroids in severe community-acquired pneumonia: A post-hoc exploratory analysis of a randomized controlled trial. PLoS One 2017; 12:e0178022.