Concise Clinical Review

Management of Community-acquired Pneumonia in Adults

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Despite many advances in medical science, the mortality rate from community-acquired pneumonia (CAP) has changed little in the past four decades. Death and adverse outcomes from CAP result from a complex interplay between the pathogen and the host. Newer information about the effect of pneumonia on comorbidity and underlying diseases, especially long term, suggests this is an important additional axis that differs from the traditional triangular concept of pathogen, host defense, and antibiotic treatment. A number of clinical scoring systems have been developed to help physicians identify patients with CAP at risk of adverse outcomes. None of the criteria have been prospectively demonstrated to avoid late intensive care unit transfers or lower mortality, raising interest in the use of biomarkers such as procalcitonin. Quantitative bacterial genomic load represents a potentially important risk stratification. Optimal antibiotic management appears to include use of a macrolide, although the mechanism of benefit remains unclear. Attempts to improve CAP outcomes through setting measurable process of care standards are to be applauded, but making sure that these standards do not become the end in themselves, but rather that the entire process of care is improved, remains critical.

Keywords: pneumonia; antibiotics; intensive care unit; biomarkers; process of care

Community-acquired pneumonia (CAP) is the most common cause of severe sepsis and the leading cause of death from infection in United States, with an annual cost estimated to be $8.4 billion in 2001 (1). Despite many advances in medical science, the mortality rate from CAP has changed little in the past four decades, although widespread adoption of the 7-valent conjugate pneumococcal vaccine in children appears to have had a positive impact in adult disease including pneumonia (2). In this review, we discuss a number of significant advances in our understanding of the pathophysiology of severe CAP (Figure 1) and its optimal management. We also outline the current deficiencies in our understanding and the key priorities for future research.

DETERMINING PATIENTS AT RISK OF ADVERSE ACUTE OUTCOMES

Clinical Scoring Tools

A number of scoring systems have been developed to help physicians identify patients with CAP at risk of adverse outcomes. Examples of such scoring systems include the Pneumonia Severity Index (3), CURB-65 (4), CRB-65 (4), American Thoracic Society major and minor criteria (5), CURXO (6), SMART-COP (7), and CAP-PIRO (8). A significant volume of CAP research has been devoted to comparing the various systems to try and identify which is the most reliable (9). Overall the results of comparisons of the different systems depend on the use to which each is being put (e.g., determining inpatient vs. outpatient treatment, need for intensive care, predicting mortality, etc.), the particular hospital or health care system to which it is applied (reflecting differences in criteria for end points such as intensive care unit admission), and the severity of disease of the cohort studied. In general, all of the previously mentioned systems perform relatively well when applied to large cohorts of patients but all have limitations, particularly in younger patients, and cannot replace thorough clinical assessment.

A key factor often ignored by researchers is the significant difference between health systems in how issues such as the criteria for intensive care admission, the acceptance and uptake of "do not resuscitate" or "palliative" management, and the willingness to treat CAP in the outpatient setting affect the performance and reproducibility of these scoring tools. The use of intensive care unit (ICU) admission as an end point in particular is highly variable. Specifying need for therapeutic interventions unique to the ICU, such as mechanical ventilation, vasopressor support, or renal replacement therapy, is important to allow application of findings across multiple different health care settings.

Some patients present to hospital already severely ill, requiring mechanical ventilation or vasopressor support at the outset. Scoring tools are not needed to help physicians determine that this group of patients has severe disease and need for ICU care. Of more concern are patients initially triaged as having nonsevere pneumonia but who subsequently deteriorate and require ICU admission. Up to 50% of ICU admissions for CAP have been initially admitted to a non-ICU setting. Their high mortality rate may exceed that of patients who have equivalent illness at presentation but who are admitted directly to the ICU (10). Although poor outcome from "late transfer" ICU patients is an argument for initial intensive care admission, to date the optimal criteria to accurately identify these patients are still unclear, nor has any specific intervention been identified that would prevent the clinical deterioration. The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guideline minor criteria (5) have demonstrated good predictive value in retrospective studies. The CURXO and SMART-COP criteria are similar to the IDSA/ATS minor criteria. None of the criteria have been prospectively demonstrated to avoid late transfers or lower mortality.

Biomarkers

The use of biological markers of infection to help guide physicians in making clinical decisions (such as the need for

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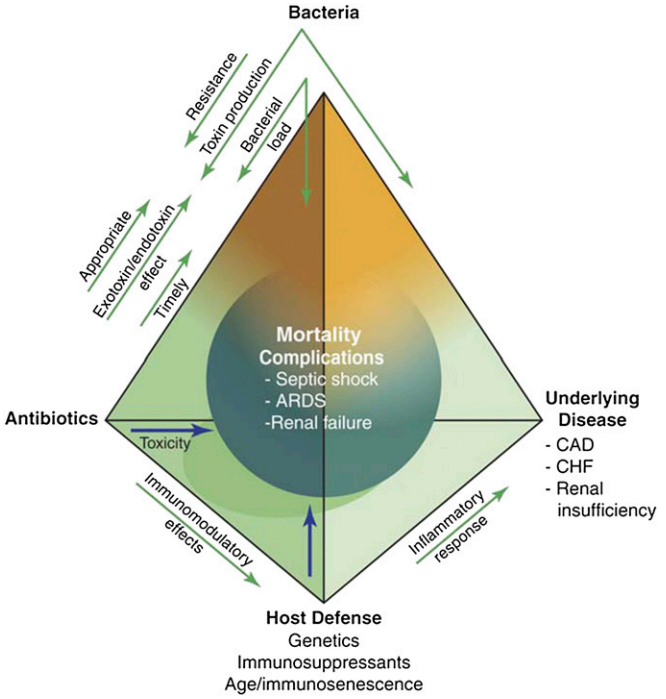

Figure 1. Major determinants of outcome in community-acquired pneumonia. ARDS = acute respiratory distress syndrome; CAD = coronary artery disease; CHF = congestive heart failure.

hospital admission, switching from intravenous to oral antibiotics, etc.) is not a new concept (3, 5, 11), abnormalities of peripheral white cell count (both neutropenia and marked leukocytosis) long being recognized as adverse prognostic indicators (11). Similarly, abnormalities in platelet counts, long recognized as adverse prognostic factors in sepsis, also may predict a worse outcome in severe pneumonia (12).

More recently serum levels of a number of inflammatory response proteins have been suggested to have sufficient sensitivity and specificity to be used routinely in the setting of CAP (Table 1). Possible applications for biomarkers include guiding antibiotic therapy (both initial treatment and duration of therapy) and more accurately stratifying patients into high- or low-risk groups. The deficiencies of the existing clinical scoring systems, discussed previously, directly correlate with the interest in biomarkers to stratify patients on the basis of risk. Precedence for biomarker use to triage patients comes from the successful use of lactate levels to detect occult hypoperfusion in sepsis and thus respond more aggressively (13).

Procalcitonin (PCT) is a calcitonin precursor that is elevated in infection as well as in trauma, burns, and neuroendocrine tumors. Although proposed as a relatively specific marker of bacterial infection (as distinct from viral), the clinical discriminating value of PCT remains unclear. Only 15% of patients with CAP were recommended as not needing antibiotics on the basis of PCT levels (14). This rate may be close to the incidence of true viral pneumonia. A subsequent study of 1,661 patients with CAP, which also used the most sensitive (Kryptor; B·R·A·H·M·S, Hennigsdorf, Germany) PCT assay, found inadequate sensitivity and specificity to reliably differentiate between bacterial or viral CAP (15). Acute and convalescent serology did indicate that some high-PCT CAP cases were caused by viral pathogens (14). Anecdotal experience with primary novel 2009 H1N1 influenza pneumonia confirms this observation. Although an increased number of patients from whom antibiotic therapy was withheld at the outset was demonstrated in the study by Christ-Crain and colleagues (16), more than 50% of physicians chose to override the PCT-guided recommendation to not commence antibiotics. Although bacterial infections are generally associated with higher PCT levels in children, the ability to discriminate between bacterial and viral etiology in individual cases is highly questionable (17–19). Although a high or low PCT value suggests bacterial or viral etiology, respectively, the accuracy appears too low to safely withhold antibiotic therapy in the setting of pneumonia. The discriminating value does appear adequate for use as an inclusion criterion for future pharmaceutical trials of antibiotics for CAP to ensure that patients with an adequate severity of infection and a high probability of bacterial pathogen are selected for randomization (20).

Christ-Crain and colleagues (16) randomized 302 patients with CAP to usual care or a PCT-assisted therapy arm in which physicians were given a recommendation about whether to treat or withhold antibiotics based on an algorithm derived from a previous study (14). PCT was remeasured 4, 6, and 8 days after admission in the intervention group with the same recommendations given to physicians with respect to continuing or ceasing antibiotic therapy. Length of antibiotic therapy was substantially decreased in the PCT group (median, 5 vs. 12 d), suggesting that a fall in PCT level may be a useful indicator of adequate therapy. However, in patients with severe or bacteremic CAP, PCT can remain elevated above the 0.25-ng/ml threshold used by Christ-Crain and colleagues to recommend ceasing therapy for more than 1 week, suggesting that the value of PCT may be limited to those with mild to moderate disease (21).

The marked reduction in total duration of antibiotic use observed by Christ-Crain and colleagues for the PCT-guided therapy group was striking (16). However, the appropriate length of treatment for patients with CAP has never been well established, with marked variation between and within different countries and health care settings, independent of factors such as disease severity (22). A randomized, placebo-controlled trial in mild to moderate pneumonia showed that more than 5 days of antibiotic therapy is not associated with better outcomes than 5 days of antibiotic therapy (23, 24). Indeed. some data suggest that 3 days of antibiotic therapy may be sufficient (25, 26) and even a single dose may cure up to 70% of mild to moderate cases of CAP (27). An early switch from intravenous to oral antibiotic therapy clearly does not compromise outcome but does decrease length of hospital stay and economic cost (23, 28–30). Therefore, the findings of Christ-Crain and colleagues (16) need to be replicated in a health care system already oriented to 5 days of antibiotic treatment. Substantial potential remains for PCT to improve economic outcomes from pneumonia by providing the additional reassurance required for physicians to accept that antibiotic therapy can be safely discontinued or switched from intravenous to oral administration earlier.

It has also been proposed that biomarkers may either simplify or add greater predictive power to the clinical predictive tools already discussed. PCT levels clearly correlate with increasing severity of CAP (based on the PSI or CURB-65) (15, 31–33). In a study of 1,651 patients from 28 centers in the United States, Huang and colleagues demonstrated that PCT less than 0.1 ng/ml (using the Kryptor assay; B·R·A·H·M·S) was associated with a good prognosis regardless of the PSI score, and that PCT greater than 0.5 ng/ml did increase the likelihood of mortality in patients with PSI grade V (31). In this study (31), PCT did not appear to be a good predictor of the development of severe sepsis either acutely or after 24 hours, suggesting that PCT may be predicting non–sepsis-related deaths. In contrast to Huang and colleagues (31), in a study of 453 patients with CAP

TABLE 1. BIOMARKERS SUGGESTED AS BEING USEFUL IN THE SETTING OF COMMUNITY-ACQUIRED PNEUMONIA

Name	Main Findings	Reference(s)
Procalcitonin	Reduced duration of antibiotic therapy	16
	Inadequate sensitivity and specificity to reliably differentiate bacterial and viral infection	15
	Questionable ability to differentiate between bacterial and viral pathogens in children with pneumonia.	17–19
	Correlates well with PSI and CURB-65 measures of severity	31–33
	Does not improve predictive ability of PSI, CURB-65, and CRB-65 scores	33
C-reactive protein	Improves predictive ability of the PSI, CURB-65, and CRB-65	33
	Higher with bacterial infection and in inpatients	104
Proadrenomedullin	Associated with severity of CAP	105
B-natriuretic peptide	Associated with severity of CAP	37, 38
Troponin-I	Correlates with degree of hypoxia	36

Definition of abbreviations: CAP = community-acquired pneumonia; CURB-65 = a six-point score, one point for each of confusion, urea >7 mmol/L, respiratory rate ⩾30/minute, and blood pressure (low systolic, <90 mm Hg; or diastolic, ⩽60 mm Hg), age ⩾65 years; PSI = pneumonia severity index.

from Spain, Menendez and colleagues found that PCT did not increase the accuracy of the PSI for predicting mortality (33), although small improvements were found when C-reactive protein was added to the PSI, CURB-65, or CRB-65 score. At this time, a clear role for PCT as an adjunct to existing clinical scoring systems remains unproven. Although some small increase in predictive ability is quite possible, the data so far suggest that this is likely to be only a small incremental benefit rather than a major shift in clinical utility.

As shown in Table 1, a number of other biomarkers have been suggested to be useful in the setting of CAP. C-reactive protein (CRP) appears to be even more generic for inflammation, rather than only infection, than PCT and is likely to have all the issues discussed previously for PCT. Given publications highlighting the high prevalence of acute cardiac complications in patients with CAP (34, 35), the suggested association of markers of cardiac stress, such as troponin-I (36) and B-type natriuretic peptide (37, 38) with CAP outcomes is interesting.

At present the role of biomarkers remains unclear in the setting of CAP. None so far described has sufficient accuracy to distinguish bacterial from viral infection reliably, nor have any markedly improved the prognostic accuracy of existing clinical decision tools such as the PSI or CURB-65. The most promising application may be support for the clinical decision to shorten the duration of antibiotic therapy. As yet, insufficient studies comparing different biomarkers exist to be able to recommend any specific test.

Quantitative Bacterial Load in Blood

The use of viral load in the management of viral diseases such as hepatitis C and human immunodeficiency virus is well accepted. Although previous molecular diagnostic tests for the most part did not achieve sufficient sensitivity or specificity to be routinely useful in CAP, a more recently developed assay to detect pneumococcal DNA in whole blood (39) was found to be twice as sensitive as blood cultures (40), with a specificity approaching 100% (41). More importantly, bacterial load (measured as copy number/ml) was a strong predictor of the risk of shock and the risk of death (40). The observation that bacterial load influences outcomes challenges the current paradigm of sepsis and multiorgan system failure as an overexuberant host response rather than being related to bacterial factors. A smaller study using an older, less sensitive pneumococcal assay has also found a correlation between bacterial load in blood and clinical outcome (42). Similar findings for meningococcemia lend additional support to this approach (43).

The PCR-based pneumococcal assay can deliver results to clinicians within 3 hours, is relatively inexpensive (under U.S. $20), and determination of penicillin susceptibility by PCR is also theoretically possible (44), either sequentially or concurrently. If validated by further studies, whole blood pneumococcal bacterial load promises to be a significant new clinical diagnostic and prognostic tool in patients with CAP.

Use of whole blood genomic load and other molecular techniques holds great promise to increase the etiologic diagnosis and potentially decrease use of inappropriately broad antibiotic therapy. The clinical correlates of genomic bacterial load contradict many of the tenets of "spiraling empiricism" (45), including the fallacies that sicker patients require broader spectrum antibiotics, sicker patients require more antibiotics, and that failure to respond is failure to cover.

OPTIMAL ANTIBIOTIC THERAPY IN SEVERE COMMUNITY-ACQUIRED PNEUMONIA

The increased mortality in patients with severe CAP who do not receive empiric antibiotics that cover the infecting pathogen(s) is well documented (46–49). Therefore, although traditional microbiological tests such as sputum and blood cultures have limited value in most cases of CAP (50, 51), pathogen identification is more likely and pathogen-directed therapy is associated with a trend to better outcome in patients with severe disease (52).

The past decade has seen an increasing body of evidence that outcomes are considerably better in patients with severe CAP when a combination of antibiotics is used rather than a single agent (Table 2). The odds ratio for death among patients receiving monotherapy after adjusting for severity of illness across these studies ranges from one and a half to six times greater than that for patients receiving combination therapy. Not surprisingly, the mortality benefit is seen largely in those with the most severe disease (53–57).

What has become increasingly clear from these analyses is that the benefit of combination therapy in severe CAP is seen only when a macrolide antibiotic is part of the regimen (56–59). Despite the large number of publications, obligatory use of a macrolide in severe CAP has so far not been included in guidelines because of the observational, and usually retrospective, nature of all the studies that showed a clear benefit. Unfortunately, prospective, randomized, double-blind pharmaceutical industry trials that could have provided key data either failed to enroll patients with severe CAP or did not include a macrolide in at least one arm of therapy.

At least three plausible explanations exist for the observed benefit of macrolides. Studies confirm that atypical bacterial pathogens frequently coinfect patients with CAP, possibly in as much as one-third of cases of pneumococcal pneumonia (60–63). Atypical pathogens are often unrecognized unless specifically tested for by serology or molecular detection. Supportive evidence for this hypothesis includes the differential benefit of

TABLE 2. STUDIES SHOWING A BENEFIT OF COMBINATION THERAPY IN COMMUNITY-ACQUIRED PNEUMONIA

Authors (Ref. No.)	Year	No. of Patients	Patient Cohort
Mufson and Stanek (106)	1999	373	BPP
Dudas *et al.* (107)	2000	2,963	CAP
Waterer *et al.* (53)	2001	225	BPP
Houck *et al.* (64)	2001	10,069	CAP
Brown *et al.* (108)	2003	44,814	CAP
Martinez *et al.* (109)	2003	409	BPP
Baddour *et al.* (54)	2004	844	BPP
Weiss *et al.* (110)	2004	95	BPP
Garcia Vazquez *et al.* (111)	2005	1,391	CAP
Metersky *et al.* (66)	2007	2,009	BPP
Lodise *et al.* (112)	2007	261	CAP PSI grade V
Rodriguez *et al.* (56)	2007	270	CAP with shock
Tessmer *et al.* (55)	2009	1,854	CAP
Restrepo *et al.* (57)	2009	237	Severe CAP
Martin-Loeches *et al.* (65)	2009	218	CAP requiring intubation

Definition of abbreviations: BPP = bacteremic pneumococcal pneumonia; CAP = community-acquired pneumonia; PSI = Pneumonia Severity Index.

combination therapy observed over different years (consistent with known fluctuations in annual *Mycoplasma* prevalence) (64), and a number of studies have shown that fluoroquinolones do not provide the same benefit. Although much fewer in numbers, data exist that tetracyclines also do not provide the same protective benefit as macrolides (58, 59, 65). Macrolides have some activity against respiratory syncytial virus in children, and thus even viral coinfection may be affected by macrolides. A single-pathogen animal model also showed a clear advantage of macrolides, even with macrolide-resistant pathogens (66). Therefore, although it is possible that coverage of atypical pathogens contributes, this seems the least likely explanation for the large mortality benefit seen with macrolide therapy in combination with another antibiotic in severe CAP.

The antiinflammatory properties of macrolides are well documented (67), as are their efficacy in diseases such as panbronchiolitis, obliterative bronchiolitis, and cystic fibrosis (68). The mechanism by which macrolides alter immune response is still not well elucidated, but it may involve modification of the heat shock protein-70 and p38 signaling pathways (69). Macrolides may also improve the chemotactic and phagocytic functions of macrophages, possibly aiding in the removal of apoptotic material from the airway and thereby reducing inflammation (70). Given the well-documented role of the inflammatory response in driving organ injury in patients with sepsis, the immunomodulating properties of macrolides likely play a major role in their beneficial effects.

The outcome of infection with a pathogen is determined by the virulence of the organism, the bacterial load, and the immune response of the host. The benefit of macrolides may also be nonbactericidal/static effects on the microorganism itself. In a number of organisms, including those with innate macrolide resistance (71–73) and macrolide-resistant pneumococci expressing both the *mec* and *erm* genes (74, 75), macrolides have been shown to reduce the production of key virulence factors, including quorum sensing, toxin production, and biofilms. In an animal sepsis model of macrolide-resistant *Escherichia coli*, clarithromycin produced a survival benefit nearly equivalent to that of a microbiologically effective amikacin (76). Data indicating that patients with severe CAP frequently have large numbers of pneumococci in their blood (40) raise another potential explanation for the mortality benefit of macrolides. Use of β-lactams in these patients may result in significant cell wall lysis and release of immunologically reactive components, leading to an exaggerated proinflammatory response. In contrast, a macrolide may reduce the bacterial load without significant cell wall lysis, resulting in a more gradual reduction in bacterial load and lower inflammatory response.

Although the weight of observational data clearly supports macrolide use in severe CAP, some negative data exist (77–80), although much more limited in the key population group of severe disease, especially bacteremic pneumococcal pneumonia. However, until randomized, prospective, controlled trials directly comparing a β-lactam/macrolide combination with nonmacrolide monotherapy are completed, questions will remain concerning possible uncontrolled biases in patient population or selection. Despite the current limitations, we believe that current evidence supports obligatory macrolide therapy in all cases of CAP with physiological compromise, especially those with or deemed at risk for septic shock or mechanical ventilation. Whether the optimal regimen is a β-lactam/macrolide, a quinolone/macrolide, or some other agent/macrolide combination is also not clear. Whether an individual macrolide is best versus a class effect of all macrolides, and whether the basic structure can be further modified to produce a greater benefit than that already observed, will also need to be defined.

In contrast, empirical antibiotic therapy of patients who have no risk factors for severe CAP likely does not require a macrolide per se, although a cephalosporin/macrolide combination is still an excellent option. Monotherapy, particularly with agents that cover atypical pathogens, is also adequate in most patients (64, 65).

OPTIMAL PROCESS OF CARE OR CLINICAL PATHWAY IN PATIENTS WITH CAP

The management of CAP has been subject to intense scrutiny by health care payors. Not only are significant health care costs associated with it, but also as an illness CAP is much easier to define than generic lower respiratory tract infections. Unfortunately, a large proportion of patients receive therapies different from recommended guidelines and agreement of clinical practice with guidelines remains a great challenge (81). The availability of reasonable tools to allow comparison between institutions with differing patient demographics is also a key consideration.

Among key quality-of-care markers proposed and/or adopted have been the performance of blood cultures (82), the delivery of the first dose of antibiotics within a set period (82, 83), and adherence to antibiotic guidelines. Although all of these markers have some validity and are worthwhile in themselves, the logic that meeting these set performance criteria will improve clinical outcomes is seriously flawed. For example, delivery of antibiotics in the United States was recommended on the basis of two retrospective, observational studies in large Medicare databases showing increased mortality in patients over 65 years of age receiving antibiotics after 8 hours (82) or 4 hours (83). Introduction of time to first antibiotic dose within 4 hours (subsequently relaxed to 6 h [84]) as a quality criterion for public reporting has had significant negative effects, such as overdiagnosis of CAP (85), overuse of antibiotics (86), and antibiotic toxicity including *Clostridium difficile* colitis (87). Although the negative effects of the antibiotic timing performance measure have been questioned (88, 89), the lack of evidence of improved outcomes from achieving the measure has led to strong calls for it to be dropped (90).

Analysis of the causes of delay in delivering antibiotic therapy found that this complex phenomenon is linked to patient comorbidities that reduce clinical suspicion of pneumonia (91). Furthermore, the same substantial comorbidities leading to delay in initial antibiotic dose also impact mortality, leading to a correlation that is not true cause-and-effect. The accuracy of retrospective database studies to record key variables such as

confusion or subtle chronic organ failure is questionable, raising the likelihood of inadequately controlling for them in prior analyses (91). Perhaps more important still, given that at least half of CAP mortality is thought to be nonsepsis related (92), reduction in mortality is likely to be dependent on addressing key comorbid factors such as cardiac failure, cardiac ischemia, thrombosis prophylaxis, adequate hydration, nutrition, diabetes, and aspiration risk. Indicators such as slower antibiotic delivery times, failure to take blood cultures, or failure to comply with antibiotic guidelines in the emergency department are almost certainly likely to be associated with less attention to other key management issues such as adequate fluid management, appropriate recognition of associated cardiovascular compromise including myocardial ischemia, venous thrombosis prophylaxis, and glycemic control. Overworked or overwhelmed institutions are also much less likely to attend to other factors that may improve outcomes, such as early ambulation (93).

Attempts to improve CAP outcomes through setting measurable process of care standards are to be applauded. Simple measures, such as quick assessment of oxygenation in the emergency department, had a great potential to influence outcomes (94). However, making sure that these standards do not become the end in themselves but that the entire process of care is improved remains critical. Real outcomes (e.g., inpatient and 30-d mortality), rather than surrogate or intermediate outcomes, should remain the primary standard against which care is measured.

LONG-TERM CONSEQUENCES OF COMMUNITY-ACQUIRED PNEUMONIA

Perhaps the greatest shift in our understanding of the impact of pneumonia on the host has been the documentation of the substantial continuing excess mortality for more than 2 years after surviving an episode of CAP. Brancati and colleagues first identified a high 2-year mortality rate in survivors of pneumonia in all age groups (95). However, their cohort included patients with HIV, malignancy, and other severe comorbid diseases, leading to some question regarding the true association. Using a large U.S. Medicare database, Kaplan and colleagues found that CAP hospital survivors had a 1-year mortality rate 2.5 times greater than that of age- and sex-matched control subjects, but no specific cause was identified (96). Vergis and colleagues demonstrated similar results in a smaller study of elderly patients from residential care facilities (97). Analysis of the 5-year survival from the cohort used to validate the PSI showed substantial excess mortality compared with age- and sex-matched population control subjects (98). As comorbid illnesses represents one of the key potential causes of excess longer term mortality in patients with CAP, the finding that 2-year mortality in patients with no comorbid diseases was markedly higher than population-based controls is significant (81).

Although the exact cause of mortality remains to be definitively shown, substantial evidence suggests a predominantly cardiovascular disease effect (94). As previously discussed, publications have highlighted a high risk of acute cardiovascular complications in CAP (34, 35). Conversely, epidemiologic data demonstrate a strong association between acute respiratory infections and subsequent myocardial infarction (99–101). Acute inflammation is known to destabilize atheromatous plaques as well as inducing a procoagulant state (102). The inflammatory response (measured by IL-6 and IL-10) at discharge is a strong predictor of 90-day mortality (103). The possibility that an episode of CAP accelerates underlying cardiovascular disease remains to be proven, but the circumstantial evidence is compelling.

Given the high mortality rates among survivors of CAP, and the probability that acceleration of cardiovascular disease is likely to impact on long-term health even in survivors, further studies are desperately needed. In particular, which subjects are at highest risk of delayed mortality and what the most appropriate interventions are to reduce the risk need to be defined. Obvious drug candidates for study are those recommended for secondary cardiovascular disease prevention, such as HMB-CoA reductase inhibitors and aspirin, although other antiinflammatory strategies may also be appropriate. In any event, the switch from treating CAP as an acute illness to one that has long-term health implications is a profound shift in our current treatment paradigms.

CONCLUSION

After decades of relatively slow change, the clinical ground in CAP is now shifting quickly. The potential for biomarkers and particularly molecular assessment of bacterial load offer exciting new avenues diagnostically, prognostically, and as therapeutic guides. The realization that CAP has long-term health implications is also a major shift in clinical thinking with significant therapeutic implications. Even traditional beliefs regarding antimicrobial therapy have changed, at least with respect to bacteremic pneumococcal pneumonia. A significant amount of research needs to be done to answer key unresolved issues highlighted in this discussion, but there is much to be optimistic about in terms of the potential to significantly improve the outcome of patients with CAP over the next 5 to 10 years.

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