Advances in community-acquired pneumonia

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***Abstract*:** Community-acquired pneumonia is one of the commonest and deadliest of the infectious diseases, yet our understanding of it remains relatively poor. The recently published American Thoracic Society and Infectious Diseases Society of America Community-acquired pneumonia guidelines acknowledged that most of what we accept as standard of care is supported only by low quality evidence, highlighting persistent uncertainty and deficiencies in our knowledge. However, progress in diagnostics, translational research, and epidemiology has changed our concept of pneumonia, contributing to a gradual improvement in prevention, diagnosis, treatment, and outcomes for our patients. The emergence of considerable evidence about adverse long-term health outcomes in pneumonia survivors has also challenged our concept of pneumonia as an acute disease and what treatment end points are important. This review focuses on advances in the research and care of community-acquired pneumonia in the past two decades. We summarize the evidence around our understanding of pathogenesis and diagnosis, discuss key contentious management issues including the role of procalcitonin and the use or non-use of corticosteroids, and explore the relationships between pneumonia and long-term outcomes including cardiovascular and cognitive health.

Keywords: bacterial, diagnosis, pneumonia, treatment

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Advances in diagnosis: what is pneumonia?

Although it is the leading infectious cause of death in the United States and most western countries,[1] pneumonia continues to escape a simple clinical definition. The clinical presentation and findings – symptoms of cough, fever, dyspnea, rales (or crackles) on exam, and infiltrate on chest imaging – are non-specific, with several alternative diagnoses. Because we only observe its manifestations, one might say that we never actually see pneumonia, but only have access to indirect views through perspectives offered by our diagnostic tools.

One changing perspective is imaging, with the widespread adoption of chest computed tomography (CT) and advancement of ultrasound technologies. Chest CT provides a more accurate view of lung parenchyma than X-rays, which have demonstrated both low sensitivity and positive predictive value when compared to chest CT.[2,3] The use of CT has dramatically increased in the past two decades,[4] which raises the question as to whether previous studies that employed chest radiographs as a gold standard carry the same meaning forward, or whether patients diagnosed by CT may be sufficiently different to indicate different treatment. One surveillance study of hospitalized patients with a pneumonia diagnosis compared 66 hospitalizations with CT-confirmed, radiograph-negative pneumonia to 2185 radiograph-positive cases, and found similar rates of pathogen detection, Intensive Care Unit (ICU) admission, and length of stay,[5] suggesting that we may be able to apply similar diagnosis and treatment approaches to newer populations. However, larger studies could examine these populations more thoroughly.

Ultrasound is also an emerging technology that has expanded in its availability of point-of-care tools with increasingly high quality. Several studies have suggested that lung ultrasound demonstrating airspace consolidation or focal distribution of B lines may have closer alignment

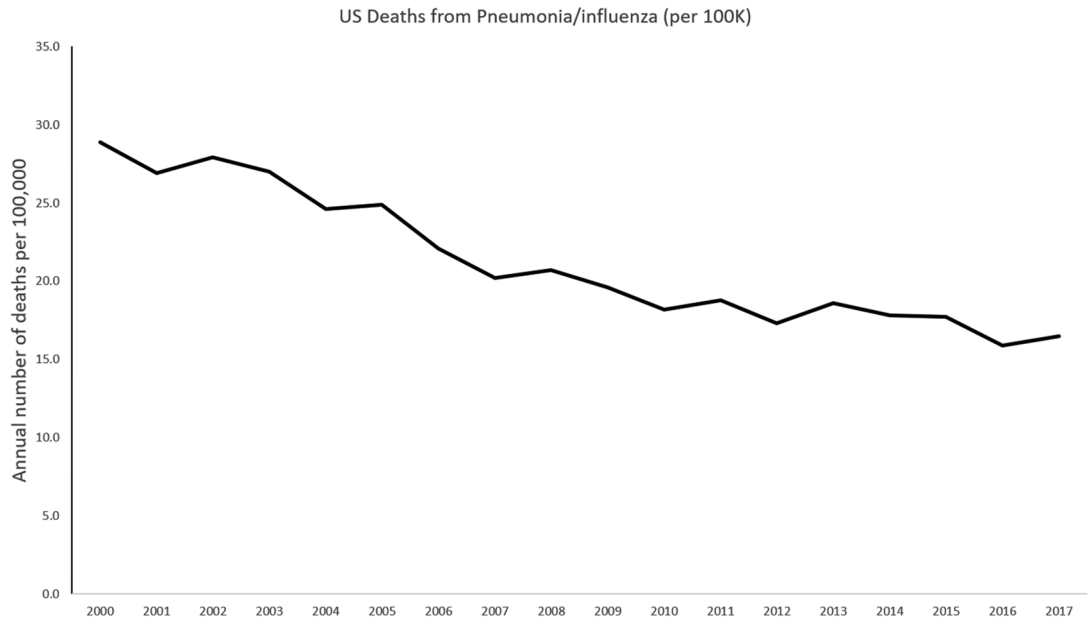

Figure 1. Timeline of annual number of US deaths from pneumonia by year, 2000–2017. Markers indicate milestones in treatment (blue) and research (red).

with the clinician diagnosis of pneumonia[6] or CT findings[7] than chest radiographs. However, the quality of chest ultrasound is dependent on both the skill of the technician and interpretation of images, both of which are less standardized in current practice than radiographic imaging. Further, no studies yet exist that examine whether lung ultrasound improves diagnosis or outcomes. The perceived relative advantage over chest radiographs, degree of adoption, and consistency with this technique will influence the role of this new technology in the future.

Advances in knowledge: what causes pneumonia?

Our perspective on the pathogenesis of pneumonia is also changing due to advances in microbial detection and clinical epidemiology (Figure 1). Previously thought to be a sterile space, the lung is now recognized as a complex ecosystem of microbes, with equally complex relationships to their host and each other, analogous to an 'adaptive island' with dynamic interactions that drive changes in species prevalence within a host.[8] Within this model, the theory of lung infection has changed from pathogen invasion of a sterile space to disruption of balance in existing microbes, with or without the introduction of a new pathogen. The characteristics of the host, and the interaction between the host and pathogen, are additional factors that influence the ultimate consequences of this disruption.[9]

The widespread availability of rapid molecular diagnostic testing has provided a new insight into etiologies of pneumonia that challenges paradigms set by earlier studies from microbiology cultures. One example is a large population-based prospective observational study of adults hospitalized with radiographically confirmed pneumonia,[10] which employed aggressive diagnostic testing including rapid molecular diagnostic testing and found a predominance of viruses, with rhinovirus and influenza overshadowing *Streptococcus pneumoniae* as the most commonly detected pathogens. Human metapneumovirus, respiratory syncytial virus, parainfluenza, coronaviruses, and adenoviruses were also identified, and multiple pathogens were detected in 13% of all cases in which a cause was identified. These findings were similar to other smaller studies,[11,12] with viruses being commonly identified with *S. pneumoniae*. Uncertainties remain as to the meaning of these findings: whether pathogens detected in the nasopharynx or sputa represent infection *versus* colonization *versus* co-infections with other undetected microbes remains unclear,

and the lack of a gold standard against which to measure the accuracy of new testing technologies continues to obscure our understanding. Further, only 38–63% of patients studied yielded a pathogen at all, which raises the question as to whether failure to detect pathogens in pneumonia reflects continued shortcomings of our diagnostic capabilities, novel pathogens yet to be discovered, or misclassification of non-infectious syndromes that mimic lung infection. Biomarkers, including C-reactive peptide, procalcitonin, and newer diagnostic technologies that combine microbial detection with inflammatory patterns[12] are a promising path to elucidate our understanding further and refine our paradigm of lung infection, but to date have yet to deliver meaningful clinical interventions.

The increasing detection of multiple potential pathogens in patients with Community-acquired pneumonia (CAP) is also a challenge to our classic model of lung infection. Whether these cases represent true co-infection, sequential infection or acute infection with one pathogen but chronic carriage of one or more other pathogens that are not responsible for the pneumonia remains to be seen, and only serial quantitative assays on lower respiratory tract specimens are likely to resolve this question.

Advances in treatment: antimicrobials for pneumonia

Empiric therapy

Comparing the 2019 CAP guidelines published by American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA)[1] to the first published by these societies in 1993,[13] relatively little has changed in medical treatment for pneumonia over 25 years. Antibiotic therapy remains empiric because diagnostic techniques have still not progressed to a point where the pathogen can accurately be identified in a clinically useful period of time. Respiratory fluoroquinolones were introduced as an alternative to combination beta-lactam and macrolide therapy in the guidelines in 2001[14] based on randomized, controlled trials showing efficacy, and fear of increasing pneumococcal antibiotic resistance, although this remains a contentious recommendation particularly in the arena of antimicrobial stewardship. In some countries respiratory fluoroquinolones remain limited to patients with significant beta-lactam allergy due to concern about the over-use of these broader-spectrum antibiotics, but they are widely used in the United States and many European countries.

The largest change in the 2019 CAP guidelines[1] is the move away from the concept of healthcare-associated pneumonia (HCAP) in an attempt to limit the overuse of broad-spectrum antipseudomonal and anti-methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotics. Introduced in the 2005 hospital-acquired pneumonia guidelines,[15] HCAP was an attempt to recognize that in some centers there was a much larger number of patients presenting with pneumonia and organisms not covered by standard empiric therapy, typically *Pseudomonas aeruginosa* and MRSA. Fortunately, subsequent research showed that not only was this phenomena probably limited to relatively few centers,[16] the introduction of HCAP resulted in a massive increase in broad-spectrum antibiotic use[17] that almost certainly harmed more patients than it benefited.[17,18] The new guidelines recommend that *P. aeruginosa* and MRSA are only covered if risk factors are present AND local data have confirmed that these pathogens are problematic. Acknowledging that many centers may not have local data currently, the guidelines further recommend that sputum and blood cultures be taken whenever broad-spectrum antibiotic coverage is used to generate this information. The adoption of the rapid polymerase chain reaction nasal swab test for MRSA was also incorporated into the most recent guidelines, which recommend discontinuing or withholding anti-MRSA therapy based on a negative test due to its high negative predictive value.

Two new antibiotics, ceftaroline and lefamulin, have been approved by the United States Food and Drug Administration in the past few years. As both ceftaroline and lefamulin have very broad antimicrobial coverage including MRSA, under basic antimicrobial stewardship principles their current role is in patients with confirmed MRSA pneumonia.

Reflected in the recent ATS-IDSA CAP guidelines,[1] accumulated evidence over the past two decades is that the addition of a macrolide to a beta-lactam is associated with better patient outcomes, particularly in patients with severe disease.[19] Most of the macrolide data are however observational and retrospective. Two randomized controlled trials have attempted to address the

issue. Postma *et al.*[20] did not find a benefit of macrolides but that study is highly problematic with 25% of patients not having radiologically confirmed pneumonia, 40% of patients with supposed monotherapy being given macrolides and a huge discrepancy between macrolide use in the combination group (mostly erythromycin) and the macrolides used in the 'monotherapy' group who also got a macrolide (no erythromycin). Essentially Postma *et al.*[20] does not help inform the management of CAP. Garin and colleagues[21] took a different approach attempting to show that monotherapy was not inferior to the combination therapy of a beta-lactam and macrolide in a standard prospective, randomized, controlled trial of patients with CAP. As monotherapy did not reach statistical significance for non-inferiority, combination therapy remains the standard of care.

Biomarkers

Clinical judgment is needed in managing CAP patients, including the selection of appropriate antibiotics and assignment of the appropriate location of care. Thus biomarkers that might objectively determine appropriate choices, either by distinguishing bacterial *versus* viral infection or determining illness severity, would have significant appeal. The medical literature contains an enormous number of studies comparing biomarkers in CAP, either against each other or against traditional scoring systems like the pneumonia severity index of the CURB-65. The majority of biomarkers studied are acute phase reactants, which rise during a patient's inflammatory response. The best studied biomarker to date is procalcitonin, a peptide precursor of the hormone calcitonin that appears to rise disproportionately during responses to bacterial infection. Multiple studies have assessed its sensitivity and specificity for the presence of bacterial infection in a variety of lower respiratory tract infections.

At a threshold of 1.0 ng/mL, procalcitonin has a reasonably high predictive value for typical bacterial infection.[22,23] However, the use of a low procalcitonin to withhold antibiotic therapy on the presumption of a viral infection has significant limitations and is not recommended.[1] In the setting of Legionella and Mycoplasma, two common CAP pathogens, procalcitonin is often not elevated,[24,25] although reports suggest in severe Legionella it may be.[26,27] Several studies have also raised concern that procalcitonin has a poor sensitivity in the presence of mixed bacterial and viral infection.[24,25,28,29] A single interventional trial in the setting of CAP in adults attempted to withhold antibiotics on the basis of a low procalcitonin level.[30] In that study, 22 of 43 patients with procalcitonin concentrations below 0.25 ng/mL had antibiotics withheld, although five subsequently had antibiotics started because of a higher reading at 6 hours. No adverse effects of withholding antibiotics were observed. Given that the study was very small, has not been replicated, and clinicians ignored the procalcitonin-guided advice to withhold antibiotics in nearly 50%, this approach cannot be recommended.

Procalcitonin has also been explored as a tool to reduce the duration of antibiotic therapy. Several randomized studies that used serial procalcitonin measurement to determine the duration of antibiotic treatment in patients with CAP have shown a reduced length of therapy, but in all cases the standard therapy arm had durations well beyond 7 days,[30–33] much longer than recommended in current guidelines. Therefore, physicians should only use procalcitonin if their standard duration of antibiotic therapy exceeds that recommended in the guidelines.

Corticosteroids

A subgroup of patients with pneumonia progress to septic shock or acute respiratory distress syndrome despite appropriate antimicrobial therapy, outcomes which are considered to be driven by the patient's immune response. The desire to mitigate this response has led to the consideration of immune-modulating agents such as corticosteroids. A series of meta-analyses based on small trials with significant flaws has led to a significant increase in interest in corticosteroids in CAP,[34,35] with evidence of large scale overuse of these potentially toxic agents.[36] A more detailed discussion of the primary papers used by the meta-analyses has been published.[37] Of significance, Torres *et al.*[38] used an entry criteria of a C-reactive protein greater than 150 mg/dL, but found no difference in mortality or length of hospital stay in 120 patients. A composite endpoint of treatment success, driven mostly by improved radiology, was reported as improved by steroids ($p = 0.02$), but in the absence of any difference in mortality or organ failure it is difficult to know what this result

means. In contrast, Lloyd *et al.*,[39] in a randomized, placebo controlled study published after both the meta-analyses and the new CAP guidelines, found no benefit of steroids in 816 patients with CAP, but did find a higher rate of gastrointestinal bleeding in the steroid group. As further studies have questioned the safety of even short doses of corticosteroids,[40] and there is significant concern over the potential for increased mortality in influenza,[41] the CAP guidelines recommend against steroids in patients with CAP. While it remains possible that there may be a subgroup of patients who may benefit, this group has yet to be defined.

Cardioprotection

There is now a large volume of data demonstrating that CAP is associated with both a high rate of acute cardiac complications including myocardial infarction and arrhythmia,[42–44] as well as there being a substantially increased risk in survivors of myocardial infarction, stroke and heart failure for some years after the acute event.[45] At present there are no confirmed therapies to prevent either the acute or long-term adverse cardiovascular impacts of pneumonia. A small randomized controlled trial of 100 mg of aspirin in patients with CAP did not reduce the cardiovascular event rate;[42] however, an even smaller study of 300 mg of aspirin did significantly reduce the incidence of myocardial infarction.[46] One study observed that ticagrelor was associated with fewer cardiovascular events in the setting of pneumonia than clopidogrel,[47] but this has not been tested in a randomized, placebo controlled trial. Retrospective studies have suggested that statin therapy may be associated with better outcomes in CAP,[48–50] but this has not been a universal finding.[51] A small pilot randomized study of simvastatin suggested some benefit of therapy,[52] although larger studies are needed. A variety of other potential cardioprotective drugs have been studied without any consistent trends. Moving forward, cardioprotection in the setting of CAP remains a major area requiring research.

Implementation of best practice through bundled interventions

As the vast majority of pneumonia instances is likely to be cared for by non-pulmonary specialists,[53,54] healthcare systems have the opportunity and obligation to support generalist providers with up-to-date information and tools to ensure optimal and equitable care for patients presenting to all settings. Treatment bundles, a small, straightforward set of evidence-based practices that can be executed consistently,[55] take a systems and behavioral economics approach to clinical performance and quality improvement.[56,57] The most common elements included in bundled interventions for CAP include: timely, first-line antibiotics with appropriate de-escalation and duration; recognition and resuscitation of sepsis; use of validated severity assessment tools to guide site-of-care and other treatment decisions; consistent diagnostic work-up for microbial etiology and other diagnoses; and early mobilization. Bundled interventions have been suggested to improve outcomes dramatically for sepsis,[58,59] respiratory failure requiring mechanical ventilation,[60] and CAP,[61–63] and the widespread availability of electronic health record systems capable of decision support has further facilitated the adoption of bundled interventions in the form of informatics tools.[64] However, with the exception of one randomized controlled trial,[63] the conclusions that can be drawn from most studies examining bundled interventions for CAP are unclear due to their observational pre–post designs. In addition, it is sometimes unclear which components are effective.[39] For care to be the most effective, clinicians must find a balance between bundled care, diagnostic uncertainty, and individualization of care to their patients' needs.

Trends in incidence and short-term outcomes

Observational studies examining trends in outcomes have suggested steady overall declines in short-term mortality attributed to pneumonia over the past 20 years,[65,66] although some studies suggest the trend is not consistent for all settings.[67] Several mechanisms have been proposed, including changes in care processes,[68,69] changes in practice models such as staffing and performance measures, or mitigation of disease burden due to the adoption of childhood pneumococcal vaccines[70] and more comprehensive influenza vaccination programs. An additional contributing factor could be in the shift of the diagnostic labels surrounding pulmonary infection, as population studies often rely on diagnostic coding to identify cases, and increased attention to performance measures results in a shift from labelling of pneumonia as a

primary or principal diagnosis to sepsis and respiratory failure for patients.[71] Due to the lack of clinical data for the majority of the studies examining population-level trends, it is unclear how much of the reduced mortality we have seen in pneumonia is driven by changes in populations, illness presentation, or management.

Long-term outcomes from CAP

Another advancement in pneumonia is our understanding of its consequences on long-term health. While it is often conceptualized as an acute, completely reversible disease, numerous recent studies have documented that CAP survivors continue to have significantly greater mortality than expected over the following 2 to 5 years,[72–74] with some studies suggesting even longer-term adverse impacts[75,76] and reduced quality of life.[77] A significant proportion of this excess mortality may be due to cardiovascular disease, either myocardial infarction or stroke, and heart failure.[78,79] The mechanism(s) driving this excess of cardiovascular and cardiac disease has not been definitively determined, but accelerated atherosclerosis and direct cardiac damage during acute pneumonia are both strong hypotheses.[45] Prospective observational studies have also demonstrated a greater burden of long-term cognitive impairment, functional impairment, and depressive symptoms after pneumonia or sepsis.[80–82] The mechanism of this burden is also unclear and probably has many factors, but one hypothesis includes a similar pathway of endovascular inflammation. It is critically important that moving forward, pneumonia studies focus more on these longer-term outcomes which have significantly more impact on overall mortality, morbidity and healthcare utilization.

What outcome are we most interested in?

Both epidemiological and experimental studies comparing treatments for CAP have historically used endpoints that are easy to measure, including short-term mortality, or resolution of clinical symptoms or microbiological clearance if they study milder disease (as is common for pharmaceutical trials). However, these outcomes may represent only the extreme measures for pneumonia and may be poor surrogates for other meaningful outcomes, without clear causal relationships to the interventions that we are studying. Death is arguably a meaningful outcome for many patients. However, mortality in pneumonia is often driven by unmodifiable factors including advanced age, comorbidity, and patient preferences toward aggressive care. Many patients with pneumonia have goals of care restrictions such as 'not for resuscitation' or 'not for intensive care'.[83] Equally, some studies suggest that a large proportion of deaths in the first 30 days after a diagnosis of pneumonia occur after discharge from hospital,[84,85] rendering much of inpatient mortality neither preventable nor meaningful for measurement,[86] and not reflective of the quality of care provided. However, return to independence, baseline physical and cognitive function, social engagement, patient experience, and quality of life are all meaningful, potentially modifiable outcomes to patients of all ages that thus far have been understudied.

A clinically far more valuable but more difficult concept is preventable mortality and the prevention of other key outcomes (Table 1).[87] Moving from our long-held standard of all-cause mortality to a different paradigm of identifying patients in whom a specific intervention might modify outcomes that are clinically meaningful to individual patients will be challenging, requiring more elegant approaches to both observational and experimental study design. However, it is necessary if we are to move forward and truly improve outcomes. A starting point will be abandoning pneumonia researchers' long-standing fascination with classifying patients based on a static forecast of 30-day death, which does very little to guide effective interventions, primarily because most mortality is in patients of advanced age and/or comorbidity when there is either no intent to avoid death or no prospect of doing so.[87] With respect to pharmaceutical trials in CAP, we can no longer be satisfied with clinical and/or microbiological improvement as the primary outcome. The significant evidence discussed in this review on the longer-term outcomes of CAP, and especially the cardiovascular impact need to be properly considered. Presently, we do not know if acute therapy of CAP makes any difference to longer-term outcomes but we clearly need to know. We must move beyond measuring only what is easy to measuring what is meaningful.

There remains much work to be done to translate the recent advances in our understanding of lung

Table 1. Proposed outcomes for community-acquired pneumonia.

	Mechanism	Quantitative measures	Limitations	Solutions
Longer-term outcomes beyond 30 days	Cardiovascular, cognitive impairment, debilitation from acute diseases, dysbiosis, confounding comborbidities	90-Day, 180-day, 365-day mortality Cardiovascular events	Direct attribution to pneumonia may be difficult	Large populations, longitudinal
Modifiable mortality	Care processes Dx, Site of care, abx, resp/hemodynamic support	OBS: Propensity matched/weighted risk differences Trials: cluster-RCTs with bundled interventions?	Causal inference/confounding, dynamic/time-varying exposures	Large populations, granular data, prospective pragmatic trials/SMART
Cardiovascular impairment	Endothelial inflammation, dysbiosis, stress axis	ACS events Heart failure new diagnoses	Confounding	
Neurologic impairment	Endothelial inflammation, dysbiosis, delirium/post-ICU syndrome, hypoxemia/hypoperfusion	CVA events New diagnoses dementia	Causal inference/confounding Ascertainment/ Recall bias	Concurrent matched control population
Functional impairment	Debilitation/immobility, endothelial inflammation, post-ICU syndrome	Return to work, loss of independence, job loss, homelessness, separation/divorce	Recall bias	Concurrent control population
Patient experience	Care processes, organization factors, patient factors	Survey Healthcare engagement	Influenced by patient factors	Longitudinal pre/post data
Misdiagnosis	Patient complexity, provider/organizational factors	Diagnostic discordance Re-admission ?Lung cancer dx		
Surrogate endpoints:				
CRP	Patient immune response			
Procalcitonin	Patient immune response, pathogen (bacterial *versus* viral)			
Clinical stability	Patient immune response, pathogen			

abx, antibiotics; ACS, acute coronary syndrome; CRP, c-reactive protein; CVA, cerebrovascular accident; dx, diagnosis; ICU, intensive care unit; RCT, randomised controlled trial; SMART, Sequential, multiple assignment, randomized trials.

infection, technological advances in diagnostic tools, and leveraging of clinical data into real improvements in management options and outcomes for patients with pneumonia. By challenging existing definitions, advancing technology, and adopting more elegant research designs that accommodate the complexity of our patients and the host–pathogen interaction, we hope for substantial changes in diagnosis and treatment options in pneumonia in the next two decades.

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