Published in final edited form as:

Clin Infect Dis. 2016 April 01; 62(7): 826–828. doi:10.1093/cid/civ1219.

Editorial Commentary: The Modern Quest for the "Holy Grail" of Pneumonia Etiology

Seema Jain[1], **Andrew T. Pavia**[2]

[1]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

[2]Division of Pediatric Infectious Diseases, University of Utah, Salt Lake City

Keywords

pneumonia; etiology; sputum; diagnostics

Defining the etiology of pneumonia is a messy business. Blood cultures are considered the "gold standard" for bacterial pneumonia but have low sensitivity, yielding a causative organism in only 5%–14% of adults with pneumonia, and even fewer in children [1, 2]. Urine antigen assays for *Streptococcus pneumoniae* and *Legionella pneumophila* have good specificity and improved sensitivity compared with culture but sensitivity is still only 70%–80%, and these assays cannot distinguish between colonization and infection in children [1-3]. Molecular assays for viruses and atypical bacteria represent important diagnostic advances. However, molecular detection of viruses that cause pneumonia from upper respiratory tract specimens may be due to milder infection confined to the upper airway or may represent remnants of past infections [4]. Potentially pathogenic bacteria can be part of the normal microbiome, and thus organisms detected in the nasopharynx may not represent the true etiology of infection in the lower respiratory tract. Furthermore, specimens from the site of infection in the lower respiratory tract are usually not available. When deep specimens are obtained, they are often contaminated with bacteria from the upper respiratory tract [3, 5]. Thus, sputum specimens are more likely to yield potential pathogens but have low specificity, making it hard to correlate detection with causation [3, 5]. Moreover, even the clinical diagnosis of pneumonia is fraught with difficulty. Radiographs are not always obtained. When radiographs are taken, variability between clinicians' readings is common in the determination of pneumonia [6]. For decades, the high proportion of pneumonia due to *S. pneumoniae* and *Haemophilus influenzae*, coupled with a false sense of security about the risks of antibiotic overuse, has led to recommendations for empiric antibiotic therapy for virtually all patients with presumed pneumonia [1]. However, the changing epidemiology due to the impact of pneumococcal and *H. influenzae* type B vaccines in the United States

Correspondence: S. Jain, Centers for Disease Control and Prevention, 1600 Clifton Rd, NE, MS A32, Atlanta, GA 30333 (bwc8@cdc.gov).

Potential conflict of interest. Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

and globally, combined with the growing threat of antimicrobial resistance, make it critical to understand pneumonia etiology in individual patients and populations [7, 8].

Recent prospective studies of the etiology of pneumonia using extensive diagnostic tests have failed to detect a pathogen in >50% of adults with pneumonia and approximately 20% of children [9-13]. New diagnostic methods are clearly needed. In this issue of *Clinical Infectious Diseases*, Gadsby and colleagues explore the use of quantitative multipathogen molecular testing of respiratory samples in adults hospitalized with community-acquired pneumonia [14]. They collected mucopurulent sputum samples (96%) and endotracheal aspirates (4%) from 323 adults with radiologically confirmed pneumonia admitted to 2 tertiary care hospitals in the United Kingdom. They performed both culture and multiplex real-time polymerase chain reaction (PCR) for 26 respiratory bacteria and viruses. The authors calculated bacterial loads for 8 of the bacteria. Using PCR, they identified a potential pathogen (bacterial or viral) in 87% of patients compared with 39% using culture alone. *Haemophilus influenzae* (40%) and *S. pneumoniae* (36%) were the most commonly detected pathogens, and more than 1 bacteria was detected in 32%. Bacteria were detected in 81% of specimens; however, when a reasonable cutoff of $\geq 10^5$ colony-forming units/mL was applied, this decreased to 72%. Importantly, PCR detected bacteria more frequently than culture in patients who had received antibiotics (77.6% vs 32.1%). The authors determined that the PCR results could have assisted in de-escalation in the number and spectrum of initial antibiotic therapy in 77% of patients.

These data are provocative and timely. Multipathogen PCR is available in many clinical settings in the developed world and may be easier to deploy than traditional microbiology close to the point of care and in middle-and lower-income countries [15]. However, there are a number of important caveats. While sputa have been useful for pathogen detection, including for viruses [16,17], contamination with saliva and oropharyngeal bacteria is common [3, 5]. The increased sensitivity of molecular methods only compounds this problem. Quality of sputum specimens is notoriously variable [3, 5], and Gadsby et al did not use microscopy to assess sputum quality as it is not routine local practice per the authors. The use of quantitative cutoffs holds promise. However, without using the same methods in a well-matched control group, it is difficult to know if detection indicates it is the cause of pneumonia. We clearly need additional confirmatory data.

Etiologic studies that use novel diagnostic methods, including molecular methods, are challenging in the absence of a true gold standard. Even with comprehensive testing, there is no ideal study design. However, validity could be improved by using strict case definitions, adjudicating radiographic review, and applying the same diagnostics to nasopharyngeal or sputum specimens in a control group [18]. Complex statistical methods, such as latent class analysis or other modeling techniques, while often burdened with assumptions, may assist in achieving more refined answers at the population level [19]. However, given the lack of specimens from the actual site of infection, the “holy grail” in pneumonia diagnostics remains elusive.

No current diagnostic test is adequately sensitive to detect all bacterial pneumonia or to exclude bacterial-viral coinfection when a virus is detected. Biomarkers such as

procalcitonin or C-reactive protein may help in ruling out bacterial infection when the levels are very low, and clinical trials have shown that they can be safely incorporated into treatment algorithms [20,21]. In many cases, however, the clinician is left to aggregate the results from imperfect microbiological assays and equivocal biomarker results with clinical acumen to make the best diagnosis and treatment plan for the patient. Thus, faced with uncertainty and motivated by the desire to avoid harming patients who may have bacterial infection, the default has been to treat virtually all pneumonia patients with antibiotics. Overuse in a variety of settings has resulted in an epidemic of antibiotic resistance, and we increasingly recognize the importance of *Clostridium difficile* infections and other complications of antibiotic use [8, 22]. If perfectly accurate diagnosis of pneumonia etiology is out of reach, we can still improve care by defining strategies that allow antibiotics to be started less often, de-escalated, or stopped sooner. With the high sensitivity of bacterial detection using bacterial load reported by Gadsby et al and with the potential for contamination from sputum specimens, these data may be more informative when combined with data from other microbiological tests and biomarkers. Integration of these data into in an algorithm with a high negative predictive value may allow for more targeted antibacterial and antiviral therapy for those patients most likely to benefit. Since the positive predictive value of such algorithms may not be adequate, a margin of safety can be built in by treating those at relatively moderate risk of bacterial infection.

Worldwide, 900 000 children aged <5 years die from pneumonia every year [23]. Pneumonia is a leading infectious cause of hospitalization and death among US adults, resulting in more than $10 billion annual expenses [24]. While immunization remains a primary tool to prevent pneumonia in children and adults and improved antibiotics and antivirals are needed, more precise diagnostics are critical to providing targeted and effective therapy while minimizing collateral damage [25].

Disclaimer.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

References

1. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44:S27–72. [PubMed: 17278083]
2. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis 2011; 53:617–30. [PubMed: 21890766]
3. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. Clin Infect Dis 2011; 52(suppl 4):S296–304. [PubMed: 21460288]
4. Self WH, Williams DJ, Zhu Y, et al. Respiratory viral detection in children and adults: comparing asymptomatic controls and patients with communityacquired pneumonia. J Infect Dis 2015; DOI: 10.1093/infdis/jiv323.
5. Bartlett RC. Medical microbiology: quality, cost and clinical relevance. New York: John Wiley & Sons, 1974:24–31.

6. Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. Bull World Health Organ 2005; 83:353–9. [PubMed: 15976876]
7. Griffin MR, Zhu Y, Moore MR, Whitney CW, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med 2013; 369:155–63. [PubMed: 23841730]
8. CDC. Antibiotic resistance threats in the United States, 2013. Atlanta, GA: US Department of Health and Human Services, CDC; 2013. Available at: https://www.cdc.gov/drugresistance/threat-report-2013. Accessed 11 December 2015.
9. Jain S, Self WH, Wunderink R, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015; 373:415–27. [PubMed: 26172429]
10. Jennings LC, Anderson TP, Beynon KA, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. Thorax 2008; 63:42–8. [PubMed: 17573440]
11. Johnstone J, Majumdar SR, Fox JD, et al. Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. Chest 2008; 134:1141–8. [PubMed: 18689592]
12. Charles PGP, Whitby M, Fuller AJ, et al. The etiology of community-acquired pneumonia in Australia: why penicillin plus doxycycline or a macrolide is the most appropriate therapy. Clin Infect Dis 2008; 46:1513–21. [PubMed: 18419484]
13. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015; 372:835–45. [PubMed: 25714161]
14. Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. Clin Infect Dis 2016; 62:817–23. [PubMed: 26747825]
15. Caliendo AM. Multiplex PCR and emerging technologies for the detection of respiratory pathogens. Clin Infect Dis 2011; 52(suppl):S326–30. [PubMed: 21460291]
16. Lahti E, Peltola V, Waris M, et al. Induced sputum in the diagnosis of childhood community-acquired pneumonia. Thorax 2009; 64:252–7. [PubMed: 19052043]
17. Johansson N, Kalin M, Tiveljung-Lindell A, et al. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis 2010; 50:202–9. [PubMed: 20014950]
18. Levine OS, O'Brien KL, Deloria-Knoll M, et al. The Pneumonia Etiology Research for Child Health Project: a 21st century childhood pneumonia etiology study. Clin Infect Dis 2012; 54:S93–101. [PubMed: 22403238]
19. Butler JC, Bosshardt SC, Phelan M, et al. Classical and latent class analysis evaluation of sputum polymerase chain reaction and urine antigen testing for diagnosis of pneumococcal pneumonia in adults. J Infect Dis 2003; 187:146–23.
20. Branche AR, Walsh EE, Vargas R, et al. Serum procalcitonin measurement and viral testing to guide antibiotic use for respiratory infections in hospitalized adults: a randomized controlled trial. Clin Infect Dis 2015; 212:1692–700.
21. Gilbert DN. Where do we go from here? Clin Infect Dis 2015; 212:1687–9.
22. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015; 372:825–34. [PubMed: 25714160]
23. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015; 385:430–40. [PubMed: 25280870]
24. Pfunter A, Wier LM, Steiner C. Costs for hospital stays in the United States, 2011 (Statistical Brief No. 168). Rockville, MD: Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project, 2013.
25. Caliendo AM, Gilbert DN, Ginocchio CG, et al. Better tests, better care: improved diagnostics for infectious diseases. Clin Infect Dis 2013; 59:S139–70.