

AMERICAN THORACIC SOCIETY DOCUMENTS

Understanding the Host in the Management of Pneumonia An Official American Thoracic Society Workshop Report

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Abstract

Pneumonia causes a significant burden of disease worldwide. Although all populations are at risk of pneumonia, those at extremes of age and those with immunosuppressive disorders, underlying respiratory disease, and critical illness are particularly vulnerable. Although clinical practice guidelines addressing the management and treatment of pneumonia exist, few of the supporting studies focus on the crucial contributions of the host in pneumonia pathogenesis and recovery. Such essential considerations include the host risk factors that lead to susceptibility to lung infections; biomarkers reflecting the host response and the means to pursue host-directed pneumonia therapy; systemic effects of pneumonia on the host; and long-term health outcomes after pneumonia. To address these gaps, the Pneumonia Working Group of the Assembly

on Pulmonary Infection and Tuberculosis led a workshop held at the American Thoracic Society meeting in May 2018 with overarching objectives to foster attention, stimulate research, and promote funding for short-term and long-term investigations into the host contributions to pneumonia. The workshop involved participants from various disciplines with expertise in lung infection, pneumonia, sepsis, immunocompromised patients, translational biology, data science, genomics, systems biology, and clinical trials. This workshop report summarizes the presentations and discussions and important recommendations for future clinical pneumonia studies. These recommendations include establishing consensus disease and outcome definitions, improved phenotyping, development of clinical study networks, standardized data and biospecimen collection and protocols, and development of innovative trial designs.

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Pneumonia continues to contribute significantly to the burden of disease globally and affects all people despite the widespread use of antibiotic and vaccine strategies (1, 2). Progress in the understanding of etiology and treatment of pneumonia, combined with the development of new antimicrobials and vaccines, has led to improved survival in the past half century. Despite advances in therapy, death and disability continue to occur frequently with pneumonia. Patients with pneumonia are susceptible to dying of overwhelming sepsis and septic shock. A disproportionate number of deaths from cardiovascular and other conditions occur after hospitalization for pneumonia. Viral etiologies in adult pneumonia are increasingly recognized; the host response to and recovery from both known and emerging pathogens, such as pandemic influenza and coronavirus, are less well understood. A dysregulated host response (insufficient in some, overly exuberant in others) is increasingly recognized and frequently dictates clinical outcome. Host immunity changes due to aging and comorbidities predispose to pneumonia, which not only causes morbidity and mortality in the acute term but further accelerates the preexisting processes of unhealthy aging and the course of chronic heart, lung, and other diseases in survivors. Better understanding of host factors underlying pneumonia susceptibility and outcome will lead to new approaches and more personalized strategies for preventing or treating pneumonia to diminish the direct and indirect burden of this disease.

Most microbes triggering pneumonia are ubiquitous and commensal organisms more than pathogens. These organisms proliferate as true pathogens in the lung to cause pneumonia only under certain circumstances that depend on the host's immune function, which ranges from a state of immunosuppression to one of immune overexuberance. Pathogen virulence and initial inoculum are also important. Failures of host defense pathways and other host factors lead to pneumonias that result in poor outcomes caused by acute morbidities and chronic sequelae. Pneumonia hospitalization has a high risk of death relative to other admitting diagnoses, and clinicians' ability to forecast mortality is limited (3–5). Among survivors, morbidity is significant. Episodes of acute pneumonia accelerate pulmonary function decline in chronic obstructive pulmonary disease (COPD), increase heart attacks and stroke, and cause or exacerbate

cognitive decline, depression, physical limitation, and shortened lifespan (6). A first episode of pneumonia has long-term consequences equivalent to a stroke, but the ability to differentiate the survivors of pneumonia at greatest risk of subsequent decline is limited, and the responsible biological mechanisms are poorly understood. Improved understanding of host factors altered by pneumonia to influence longer-term and extrapulmonary outcomes and patients' quality of life might provide new potential approaches to fighting these diseases.

Much needed updates of clinical guidelines for management of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and community-acquired pneumonia (CAP) have been recently completed (7–9). However, these guideline documents, by design, do not comprehensively address host-dependent factors because they are derived from existing clinical evidence that has historically not focused on the host, the host response, and consequences on the host. Important steps are needed to improve our approach to pneumonia management in a more personalized and precise manner wherein the host is considered.

Given the lack of clinical studies and trials focused on the host in pneumonia, the Pneumonia Working Group of the Assembly on Pulmonary Infection and Tuberculosis organized a workshop at the American Thoracic Society (ATS) International Conference in San Diego, California, in May 2018. This report summarizes the Workshop Group conclusions and recommendations in the following three main areas: host risk factors for susceptibility to lung infections, host biomarkers and their use in host-directed pneumonia therapy, and the host systemic effects and long-term health outcomes of pneumonia. This workshop brought together national and international participants from multiple disciplines with expertise in lung infection, pneumonia, sepsis, immunocompromised patients, translational biology, data science, genomics, systems biology, and clinical trials. The participants also included clinical researchers, clinical trialists, and clinicians. The structure of the workshop was intended to stimulate and inform critical clinical research to enhance understanding of the susceptibility, diagnosis, management, and sequelae of pneumonia from the perspective of the host.

Workshop Agenda and Format

The workshop participants were selected on the basis of their respective areas of clinical and research expertise and interests by the co-chairs (C.S.D.C. and R.G.W.) and vetted for conflicts of interest according to ATS policies. C.S.D.C. and R.G.W. were co-chairs of the ATS Pulmonary Infection and Tuberculosis Assembly Pneumonia Working Group. Although recognizing that pneumonia involves the intricate interaction of microorganisms and the host, the workshop largely addressed understanding pneumonia from the host perspective. Thus, the workshop focused on 1) host risk factors and susceptibility to lung infections, 2) host diagnostics and host directed therapy, and 3) systemic and long-term host consequences of pneumonia, each of which were discussed in three distinct general sessions. Each general session concluded with panel discussions. Invited speakers presented in each of the above identified area of focus, followed by interactive question-and-answer discussions at the end of each session, with subsequent sessions to tackle ideas and approaches to the various area of focus in pneumonia and the host. Biomedical literature searches were conducted by the speakers and co-chairs. The co-chairs collected summaries from speakers, and a writing group prepared the document for review by the workshop participants. For each of these topics, the speakers and participants highlighted current knowledge, addressed important knowledge gaps, and developed consensus recommendations on how best to address these knowledge gaps. This committee collated the information into a single document with recommendations. Differences were resolved by discussion and consensus.

Overall Perspective on the Current State of Pneumonia

Lower respiratory tract infection is the most common infectious cause of death in the world, with almost 3.5-million deaths yearly (10). In the United States, the annual age-adjusted incidence for CAP is 649 patients per 100,000 adults, which corresponds to 1.5-million unique CAP hospitalizations every year (4). Almost 9% of patients hospitalized for CAP will be rehospitalized because of a new episode of CAP in the same year. The large, prospective, population-based EPIC (Etiology of Pneumonia in the Community) study of CAP in the United States reported that the

annual incidence of CAP requiring hospitalization is 24.8 cases per 10,000 adults (11). The overall CAP incidence in the Europe is 1.07 per 1,000 person-years. The incidence is higher in men (1.22 per 1,000 person-years) than in women (0.93 per 1,000 person-years) and much higher in patients with age >65 years (14.0 per 1,000 person-years), COPD (22.4 per 1,000 person-years), or human immunodeficiency virus (HIV) (12.0 per 1,000 person-years) (12). CAP is increased in patients with comorbid conditions such as COPD, congestive heart failure, stroke, and diabetes. Various lifestyle factors are associated with increased CAP risk, including smoking, alcohol and drug use, being underweight, and obesity (12, 13). Other important risk factors include poor dental hygiene, dysphagia, ambient air pollution, and contact with sick children. Several classes of medications have been associated with increased risk of pneumonia (for example, inhaled corticosteroids, proton pump inhibitors, and antipsychotic drugs). Finally, previous pneumonia is a major risk factor for subsequent pneumonia. These epidemiologic findings point to the need for continued action globally to accelerate the reduction of morbidity and mortality associated with this disease. In addition, increasing incidence of antibiotic resistance stresses the importance of enhancing our knowledge of key host defense mechanisms that have the potential to influence the outcome of pneumonia (14).

Barriers to Better Clinical Studies and Trials in Pneumonia

The committee identified a number of barriers that hampered clinical studies and trials in pneumonia. The workshop members discussed the importance of addressing the definition of pneumonia, the heterogeneity of the study population, and more sensitive clinical outcome measures that would be important for future clinical studies and trials. A standard definition for the diagnosis of pneumonia that is precise and accurate, as well as risk factors, is lacking. Information about immunological profiles in pneumonia is scarce. Immunocompetency profiling of patients at risk and immune response measurements during infection are needed. Interpretation of study results in populations at the extremes of ages, as well as the immunocompromised, requires better understanding given limited well-controlled studies focused on these groups. Better biological markers and diagnostic tools are

clearly needed to identify etiology of pneumonia. The lack of well-designed longitudinal clinical studies is a major deficiency. There have been only limited national and international collaborative studies because of lack of funding for clinical studies in pneumonia. In addition, a lack of targeted incentive programs to stimulate the development and advancement of novel antimicrobial therapies has further hampered timely clinical development efforts in pneumonia (15). Multisite and collaborative studies in pneumonia are limited, especially from resource-limited regions around the globe. Coordination and resource support for studies between sites and investigators are needed. Expertise in clinical trial design and implementation is limited at some sites.

Pneumonia Definition

Despite pneumonia being first described centuries ago, the lack of a clear and universally accepted definition of pneumonia remains. The inadequacy of the current definition and classifications has recently been discussed (16). In usual clinical care, the accuracy of emergency department pneumonia diagnosis versus expert panel review at hospital discharge is only 62.0–75.9% (17, 18). Suggestions for improvement include defining the lung infection by pathogens or by incorporating clinical, radiographic, diagnostic, and/or biomarker measures. Computed tomography (CT) chest imaging or lung ultrasonography have been used to aid in accurate determination of parenchymal infiltrates (19, 20). Using chest CT rather than portable chest radiographs improves sensitivity and specificity for acute onset of parenchymal infection (21). Some studies have used an inflammatory biomarker (elevated white blood cells and immature polymorphonuclear leukocytes, CRP [C-reactive protein], and procalcitonin) to increase the likelihood of bacterial infection with reactive host inflammation (22). Requiring microbiologic confirmation of pathogens, unfortunately, only identifies a minority of patients (11). Novel molecular diagnostics offer enhanced opportunities to identify respiratory pathogens. Culture-independent assays, such as metagenomic sequencing, and strategies that interrogate the host response provide opportunities to rethink what defines true pneumonia (23, 24). Because the lung is no longer viewed as being a sterile organ, some propose a reconceptualized view of pneumonia, in which the development of

pneumonia is believed to result from disruption of the complex homeostasis of a microbial ecosystem interacting with the multiple complex growth conditions (25). Though speculative, focusing on disruption of host microbiome homeostasis in the definition of pneumonia may be particularly relevant to patients experiencing extreme manipulations of their immune function, such as those engrafting after hematopoietic stem cell transplantation or those receiving immune checkpoint inhibitors for cancer therapy.

Clinical Outcome Measures in Pneumonia

Clinical outcome measures used in pneumonia research often reflect processes of care, although adjustment for severity of illness at diagnosis is important. Thirty-day all-cause mortality has been used capture short-term pneumonia-related mortality, although almost 50% of deaths are attributable to comorbid illness, advanced age, and preexisting end-of-life limitations (26–28). A recent study suggests that in-hospital deaths did not appear to be preventable despite in-hospital pneumonia care efforts (28). Ninety-day, 1-year, and 5-year mortality capture late cardiovascular and cerebrovascular deaths but can be influenced by deaths unrelated to the pneumonia episode (29). Treatment failures clearly increase mortality, but treatment failures that do not result in death shortly after diagnosis are often measured by unplanned emergency department visits and secondary hospital admissions within 7 days after initial treatment (22, 30). Time to clinical stability is preferable to length of hospital stay and direct cost of care for hospitalized patients because it more objectively reflects response to treatment and is less affected by comorbid illnesses and social factors (31). Time to symptom resolution and return to baseline function may also be important. Thirty-day readmission rates after pneumonia episodes are widely measured for public reporting, but most readmissions are unrelated to quality of care (32). Patient-oriented outcomes such as functional impairment, cognitive dysfunction, loss of independence, and quality of life are also important to capture. Better selection of patients for inclusion and exclusion also improves assessment of clinical outcome in studies of pneumonia. In studies aiming to reduced mortality, those with advanced age and severe life-limiting comorbid illnesses are typically excluded. The ability to differentiate

poor outcome from pneumonia versus destabilization of comorbidity is poorly developed. Identification of clinically meaningful “intermediate outcomes,” such as biological markers, to rapidly inform clinicians regarding the efficacy of their treatment is also a great need.

Host Risk Factors for Lung Infections

Host factors contribute to pneumonia susceptibility in incompletely understood ways. Although pneumonia is an important cause of death in all populations, some individuals are clearly at elevated risk for lower respiratory tract infections (33). Understanding elevated pneumonia risk will require first elucidating the mechanisms protecting against severe respiratory infection, particularly in populations with lower risk. Healthy immune defense mechanisms against pneumonia are a knowledge gap. Populations that face exceptional risk for pneumonia include those with profound immune impairment associated with hematologic malignancies, ongoing cytotoxic therapies, immunosuppression related to autoimmune diseases or allogeneic transplantation, and advanced HIV disease (34–36). However, beyond these well-established groups, entire new categories of patients at increased risk for pneumonia have recently arisen as a consequence of novel treatments for cancer and end-stage organ dysfunctions (37, 38), growing indications for transplantation, and biologic agents for immune-mediated inflammatory diseases (39, 40). Clinical management of pneumonia in immunocompromised patients is inherently challenging, as these infections are caused by a wider array of both common and unusual organisms (35, 36, 41, 42) and disproportionately require critical care (43–45). Moreover, the nature of host immunocompromise directly impacts both the spectrum of pathogens to which an individual is susceptible and the likelihood of survival of an established infection. Although some individuals are made vulnerable by a single, profound defect (e.g., severe and prolonged neutropenia), it is likely that most patients at increased risk for pneumonia become so as an aggregate of multiple less severe defects. But despite the increasing number and complexity of cases, no formal society guidelines to aid the management of these vulnerable patients exist. Indeed, the ATS/Infectious Diseases Society of America (IDSA) guidelines for managing patients with CAP and nosocomial (HAP/

VAP) pneumonia explicitly exclude their application to immunocompromised patients (7, 46). A recent consensus statement highlighted such a need for establishing treatment strategy for these patients (47).

In contrast to the above listed groups, many patients are hospitalized with pneumonia in the absence of a prior diagnosis of a traditionally defined immunocompromizing condition or active immunosuppressive therapy (48). Yet, host contributions to susceptibility are apparent, as annual pneumonia risk associates positively with chronic comorbidities, such as COPD, cystic fibrosis, cardiovascular disease, congestive heart failure, and lung cancer (12, 49–51). Classical risk factors for chronic heart and lung diseases, including cigarette smoking, obesity, diabetes, alcohol abuse, and exposure to pollution, are independent risk factors for pneumonia (12, 52, 53), supporting the hypothesis that common biological pathways underlie pneumonia susceptibility and chronic diseases. Indeed, it is argued that pneumonia itself is a manifestation of chronic disease. Our lack of understanding of the host factors that place patients at an elevated risk for pneumonia is exemplified by aging. Annual risk for pneumonia is significantly elevated in patients >65 years of age (12), and these individuals have aggregated greater exposures to risks than younger patients; however, two-thirds of patients hospitalized for pneumonia in the United States without a known immunocompromizing condition are <65 years of age. Although pneumonia is

typically thought of as an isolated event driven by stochastic pathogen exposure, improved understanding of the host contributions to pneumonia susceptibility is needed.

Presently, no consensus exists regarding which patients should be considered immunocompromised nor what degree of host defense impairment places individuals at an elevated risk for pneumonia. These determinations are critical to understanding which patients are most likely to develop pneumonia when they encounter common respiratory pathogens, which patients are at risk for pneumonia caused by unusual or opportunistic pathogens, and which patients are likely to require particularly intensive management. A summary of recommendations for future investigation of host susceptibility to and risk factors for pneumonia is shown in Table 1.

Host Diagnostics and Host-directed Therapy

Host responses to pneumonia are increasingly being investigated to identify biomarkers that can guide diagnosis and pneumonia management (24, 54). Conventional tools to measure host response include clinical illness severity assessments such as the Pneumonia Severity Index, CURB-65 (confusion, urea, respiratory rate, blood pressure, and 65 years of age), or National Early Warning Score; laboratory markers such as leukocytosis, immature neutrophil count, platelet count, CRP, and procalcitonin; and chest radiography (55, 56). Others have shown lymphopenia to be associated with increased

Table 1. Recommendations: Host susceptibility and risk factors

- Improve phenotyping of patients with pneumonia to establish thresholds for what constitutes immunocompromised host pneumonia, both for isolated and aggregate immune defects. Focus on nontraditional risk factors, such as metabolic disease, and study the complex comorbid patients in a more integrated manner.
- Investigate whether everyone hospitalized for pneumonia has some evidence of an immunocompromised condition.
- Define the immune and biological mechanisms protecting most healthy lungs from severe infection.
- Investigate the role of aging, chronic comorbidities, and medications in the development of pneumonia.
- Investigate therapeutic strategies that leverage/manipulate immune elements that persist unimpaired in patients who have defects in other elements of their immune responses.
- Investigate the effects of novel biological therapies on pneumonia susceptibilities, including drugs targeting inflammatory mediators and immune checkpoint inhibitors.
- Investigate optimized strategies to reduce pneumonia susceptibility by reversing immune defects or moderating/discontinuing immunosuppressive therapies in a targeted manner.
- Establish networks of investigators in immunocompromised host pneumonias to enhance data sharing, trial design, and trial enrollment.
- Develop clinical practice guidelines to address management of pneumonia in patients with immunocompromizing conditions.

mortality from pneumonia (57). Recent advances in molecular technologies allow investigators to further evaluate host responses in pneumonia, including evaluations of host transcriptomics, proteomics, and metabolomics in lung and blood specimens. It is important that these kinds of approaches are further developed to enable accurate and clinically helpful measures of the patient's host response to infections, possibly discerning patients with pneumonia from those with alternative diagnoses, discriminating between bacterial, viral, and other pathogen classes to guide empiric antibiotic use, and addressing the heterogeneity of pneumonia through better endotyping measures (24, 58, 59). The hope is that these newer molecular tools will allow clinicians to manage pneumonia more effectively according to the patient's immune response to the infection, whether it be hyperinflammation or immunosuppression. This will provide for improved patient stratification or subclassification with regard to their responses to infection.

Host-directed therapies can be categorized as those that enhance resistance (i.e., promote pathogen clearance) and those that improve resilience (i.e., prevent or limit immunopathology associated with the antipathogen host response) (60). When considering appropriate host-directed therapies, investigations to assess time course of changes in immune status is important. Changes of balance between immune hyperactivity and immune suppression include innate immune dysregulation and adaptive immune suppression (61). Revealing these changes would help determine when and what kind of host-directed therapies are needed. Immunotherapeutics to bolster host response have been explored with strategies involving the use of granulocyte-macrophage colony-stimulating factor, immune stimulants, immunoglobulin, or chimeric antigen receptor T therapy for pneumonia (62, 63). Inhaled innate immune ligands have been proposed to induce tissue resistance to protect against pulmonary infections (64). Supportive therapies to promote nonimmunologic aspects of host resistance may also be important. Some patients with pneumonia, including those mechanically ventilated or with chronic lung diseases or neuromuscular weakness, may have impaired secretion clearance that could benefit from measures to improve mucus rheology or accumulation, such as DNase or cystic fibrosis

transmembrane regulator modulators (65). Host biomarkers such as CRP have been used to track inflammatory phenotypes and to identify the subpopulation of pneumonia patients who might benefit from therapy such as corticosteroids (31, 66). Medications such as HMG-CoA reductase inhibitors and angiotensin receptor blockers might be repurposed to target host immune and endothelial dysfunctions seen in pneumonia (67). Modulation of inflammatory resolution and repair from pneumonia will also be important to address the longer-term consequences of pneumonia. Effective vaccines have been the stalwart of respiratory infections and will continue to be a vital component of the host-directed approach against pneumonia (68). A summary of the recommendations for future study of host diagnostics and host-directed therapy is shown in Table 2.

Host Clinical Consequences of Pneumonia

Important systemic complications related to pneumonia include direct progression of the disease in the lungs to involve the pleural space or indirect effects on other organ systems such as the central nervous system, hematological, cardiac, renal, endocrine, and/or hepatic systems, and others (69–71). Workshop participants emphasized the concept that pneumonia is not a disease solely confined to the lung parenchyma but should be considered to be a systemic disease leading to organ dysfunction with impacts on short-term and long-term outcomes. In addition, pneumonia should be considered a dynamic process that could start with mild disease and progress to severe disease in a short

period of time (72). This progression involves a complex set of interactions between the affecting agent (e.g., bacteria, viruses, fungi, or parasites), the host (e.g., previous comorbid conditions, immunological status, aging process, etc.), and pharmacotherapies (e.g., immunizations, medications, and prior antibiotics). Recent epidemiological data suggest that after the development of a pneumonic process one of three patients will die within 1 year of clinical presentation (4). This concerning fact supports the hypothesis that an acute insult such as pneumonia might cause the emergence, progression, or further dysfunction of a chronic process. For instance, cardiovascular complications such as myocardial infarction, arrhythmias, and heart failure are reported during the acute phase of pneumonia and the pneumonia convalescent period (73–77). The impact of pneumonia on other organs is just beginning to be better understood. It has been suggested that postpneumonia sequelae could be part of a steady downward decline for some patients given that pneumonia is common among those who are already experiencing systemic deterioration (such as those with old age and comorbidities), similar to what has been described in post-intensive care unit syndrome (78).

Organ dysfunction and death are the most important outcomes related to the progression of the disease. With the initial pathogen-mediated injury, activation of inflammation, immunosuppression, and organ damage may occur, followed by a period of repair and resolution. Inflammation is higher and sustained for the first week in patients who die with sepsis and pneumonia. However, in a large proportion of patients,

Table 2. Recommendations: Host diagnostics and host-directed therapy

Improve our understanding of the timing and dynamic immunological responses to pneumonia.
Improve our measurements of local lung responses and systemic responses to pneumonia to identify applicable host-derived biomarkers to aid with diagnosis and treatment of pneumonia.
Incorporate pathogen information with host information to inform management of pneumonia.
Differentiate clinically relevant phenotypes of pneumonia pathophysiology based on host responses.
Investigate improved measurements of host factors in clinical practice.
Investigate the full spectrum of host responses from asymptomatic to symptomatic to severe disease to recovery after pneumonia.
Investigate not only ways to augment host response in clearing pathogen but also ways to limit consequent damage and augment tissue repair to homeostasis.

inflammatory markers remain elevated even after hospital discharge. Identification of biomarkers that could potentially determine sustained inflammation and predict cardiovascular complications, organ dysfunction, and death are topics of high interest. During this period of repair and resolution, regulation of inflammation and tissue regeneration will determine the final outcome. Other related factors, such as the development of widespread dysbiosis that follows disruption of the microbiomes of multiple organ systems, can also occur. Therefore, it is strongly suggested to assess pneumonia events as an active, complex, and dynamic process that might impact short-term and long-term outcomes. A summary of recommendations for investigation of host consequences of pneumonia is shown in Table 3.

Road to Next-Generation Clinical Studies and Trials in Pneumonia

Therapeutic trials for pneumonia, especially with antibiotics, have generally been driven by the pharmaceutical industry. As such, the funded and published studies do not necessarily align with clinical priorities. For example, patients with severe pneumonia (requiring vasopressors or mechanical ventilation) and immunocompromised conditions are often excluded from clinical trials; yet, optimal treatment options are unclear for these patient populations. Major differences exist between CAP and HAP/VAP. Generally, new antibiotics are not needed for CAP; the overwhelming majority of cases are caused by pathogens susceptible to currently available antibiotics. The greater need is for better diagnostics to avoid empirical undertreatment for the small number caused by more resistant pathogens. However, CAP mortality persists despite early provision of appropriate antibiotics (79). Thus, host-based therapies may be more critical to improve CAP outcome.

The converse is true for HAP/VAP; a need for new antibiotics, especially new classes of antibiotics, clearly exists, but some patients survive despite having pneumonia due to pan-resistant pathogens (80). Better understanding of these discrepant results may reduce the ambiguity in clinical trials of HAP/VAP. The majority of HAP/VAP etiologies are susceptible to currently available antibiotics

Table 3. Recommendations: Host consequences

To improve outcomes in patients with pneumonia, focus is needed on all three phases of the disease.
Primary prevention, initiated before pneumonia occurs, should address reducing or eliminating causative risk factors, including comorbidities, chronic pharmacotherapies, and medications.
Secondary prevention should be implemented after pneumonia begins but before the systemic consequences occur by identifying poor prognosis factors and instituting aggressive treatment.
Tertiary prevention, beginning after a systemic or long-term consequence is established, should focus on interventions preventing organ dysfunction that will lead to the development of chronic diseases or death.
Investigate the period of pneumonia resolution and tissue repair. This vulnerable period of tissue repair after a pneumonia event is a key determinant of progressive organ dysfunction, the development of pulmonary fibrosis, and the potential link to chronic diseases.
Develop long-term pneumonia outcome studies that evaluate patients after discharge to assess persistent organ dysfunction after clinical recovery.
Explore the role of sustained inflammation after a pneumonia event in chronic diseases.
Develop noninvasive techniques and biomarkers that could help stratify patients to be included in interventional studies.
Evaluate the microbiome and the impact of dysbiosis in the recovery period. This may aid understanding of the effects of viral and bacterial pathogens on the gastrointestinal–lung axis and the development of collateral damage, such as infection due to <i>Clostridiodes difficile</i> .
Develop novel means to improve the host response to inflammation and prevent immunosuppression associated with pneumonia.

but with a much greater likelihood of resistance than that of CAP. However, antibiotic treatment success remains unacceptably low (usually in the 60% range) despite initial susceptibility to the antibiotic (81). Host-based therapies may therefore also be required to improve HAP/VAP outcomes but likely through different strategies than those for severe CAP. Similarly, studies are needed on the stewardship of antimicrobial agents as well as host immune modulators to minimize antimicrobial resistance and over-immune suppression (and thus the development of super infections), respectively.

Future clinical studies and trials in pneumonia will need better outcome measures. Antibiotic appropriateness cannot be the sole measure, clinical response alone is too subjective, and all-cause mortality is a very blunt discriminator. The critical endpoint issue is accurate discrimination between successful and unsuccessful treatment, independent of underlying disease. Endpoints must also be tailored to interventions under investigation and, as such, will likely be different for studies of host-based therapy as opposed to antibiotic-focused studies. The emerging data on cardiovascular events, functional impairment, and late deaths after CAP also require incorporation into outcome assessments.

An immediate need is for better phenotyping of both pathogen and host immune status. For CAP, pathogen etiology is critical—treating severe viral pneumonia with antibiotics is unlikely to have the same benefit as for a documented bacterial pneumonia. Increased recognition of viral etiology (11, 82) and the emerging availability of rapid diagnostic tests for viral and bacterial etiology offers hope that future studies can differentiate groups on the basis of the infecting organism rather than combine all etiologies into a syndrome. For HAP/VAP, rapid diagnostic tests are likely to improve efficiency of clinical trials by defining etiology early and avoiding the need for unhelpful empirical coverage (e.g., methicillin-resistant *Staphylococcus aureus* (MRSA) coverage for a clinical trial of gram-negative agents). A variety of rapid assays for MRSA are already available (83), and their routine use could avoid inappropriate inclusion of up to 60% of patients with other etiologies (84).

Improved host endotyping is similarly critical. Inclusion of immunocompromised patients in pneumonia clinical trials is essential to advance the understanding of the benefit of specific agents (80) as well as the impact of specific immune status. However, clinical characterization of host immune status remains rudimentary. Although certain types of immunocompromise are better

characterized (e.g., HIV disease with high or low CD4 counts or acute vs. chronic renal transplant), the increased use and the variety of immunomodulatory agents present new challenges. The ability to characterize underlying diseases that result in occult immune deficits is also poorly developed. In addition, the limited means of endotyping patients with pneumonia into distinct pathophysiological processes contributing to disease confounds clinical trials in pneumonia and prevents the precise application of therapies to the subpopulations of patients who are most responsive. Therefore, biomarkers that can better define the immune status are clearly needed. Some studies have defined the need but are compromised by a syndromic approach (acute respiratory distress syndrome [ARDS] or sepsis) that does not include etiology or pathophysiology (85–87).

Because the quality and reproducibility of research supporting treatment guidelines are critical, it is essential to establish consensus disease definitions and outcome definitions to allow comparability across studies. Rigor in methods is also required, including standardized data collection forms, investigator and site personnel training requirements, independent blinded outcomes adjudication strategies, and mechanisms to reduce missing data, as well as means to ensure sufficient enrollment capacity. Endeavors with high standards are expensive, particularly if studied in low-risk groups with low event rates. Conversely, the large sample sizes needed for rigorous studies may be difficult to achieve. Because concern for pneumonia and antimicrobial resistance go hand in hand, the most efficient funding may be to provide the infrastructure to study both antimicrobial and host-based interventions.

One appealing strategy to enhance the yield of trials from pneumonia-focused investigators is the development of clinical trial networks/research collaboratives or Centers of Excellence in pneumonia, similar to those developed for ARDS or sepsis. Research in pneumonia is difficult, and retention of trained research coordinators/investigators with standardized protocols and data collection instruments will enhance study data quality and integrity. Coordinated site selection can enhance inclusion of underrepresented patient populations,

including those in parts of the world with limited resources. Incorporation of both observational and interventional trials in these multicenter networks could promote quality in numerous types of investigations. Biobanking of clinical samples could allow robust assessments of biomarkers of clinical success/failure that could be considered for incorporation into future trials. Validation of innovative endpoints can be performed in parallel to standard evaluations. Furthermore, collaborative approaches are required to advance understanding of complex diseases such as pneumonia. This requires the support of scientific communities that bring together scientists of different disciplines as well as patients representing diverse populations. Such a clinical trial network could allow for next-generation clinical trials such as those with adaptive and platform trial designs, in which sharing of control patients could allow more efficient study of several interventions, promoting rapid transition to a superior therapy and minimizing patient risk (88). All of these

improvements in pneumonia clinical trials are unlikely to be rapidly accomplished with the current piecemeal approach of industry-based interventional trials or with smaller single-site studies. Some strategies discussed for next-generation pneumonia trials are listed in Table 4.

Personalized Precision Medicine in Pneumonia

The future of pneumonia care is personalized and precision medicine. Personalizing the management of pneumonia requires more precise diagnostic and host measurement tools to advance the field. We will need superior diagnostics and endotyping of pneumonia. Identification of host genetic, clinical, and biological factors contributing to host susceptibility to pneumonia, disease severity, response to infection, and drug treatment will be important. Prioritization of such approaches can be on specific areas such as severe pneumonia or a well-identified group of patients that is pathogen based. Future work

Table 4. Strategies for next generation pneumonia trials

Better phenotyping	Pathogen: routine use of rapid diagnostic tests Host: well-defined immunocompromise categories, well-defined pathophysiology endotypes, and biomarkers for immune status Standardized approaches for diagnostics and immune measurements
Clinical trial networks/research collaboratives/centers of excellence	Standardization of protocols with ability to rapidly develop standard disease definition and clinical outcomes Methods for rapid independent reviewer adjudication of disease states and clinical events Standardized data collection instruments Shared electronic medical records Enhanced data quality and integrity Increased cost effectiveness of trials Standardization of clinical endpoints Inclusion of underrepresented populations Retention of trained research coordinators Support of multidisciplinary teams of investigators with diverse expertise Use of existing and encouraging new funding opportunities and trials Partnering with industry
Biobanking of clinical samples	Retrospective determination of biomarkers of prognostic significance
Adaptive trial design	Rapid transition to superior therapy Sharing of control patients for multiple interventions
Innovative outcomes	Development of innovative endpoints Validation of standard evaluations Follow patients after pneumonia

will likely include artificial intelligence and machine learning approaches to integrate all the data to develop risk and prognostic algorithms. It will take well-coordinated and robust clinical study and trial data in these areas to achieve this goal. In addition, as we learn more about the risks for chronic outcomes from pneumonia, approaches to intervene and manage these patients will require personalization. The personalized and targeted management now standard in other disease states is a model for what can be achieved in pneumonia.

Conclusions

Reducing the global burden of pneumonia requires better understanding of the ever-expanding lists of host susceptibility factors, the implications of individual host responses to pneumonia, and the lingering medical consequences that result from lung infections. To achieve progress in our future management of pneumonia, an integrated strategy must be developed that targets the etiological pathogen of pneumonia (rapid molecular diagnostics and new antimicrobials) and the host responses to pneumonia (short-term and long-term consequences). The panel views improved diagnostic definitions of pneumonia incorporating enhanced clinical and molecular data that define both host and pathogen contributions to pneumonia as central to progress. In addition to better disease and host phenotyping, the panel views the development of pneumonia-focused trial networks as essential to maximizing the clinical and scientific yield of trials, allowing for coordinated biobanking, novel adaptive designs, and innovative outcome measures. The importance of an improved approach to pneumonia and the need for an integrated pneumonia trial network is highlighted more than ever by the current coronavirus disease (COVID-19) pandemic. ■

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