Personalizing the Management of Pneumonia

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INTRODUCTION

Lower respiratory tract infections (LRTIs) are the leading cause of death in developing countries and account for more than 4 million deaths per year worldwide.\(^1\) They result in the loss of 103,000 disability-adjusted life years annually, making pneumonia the single greatest contributor to human disease burden.\(^2,3\) It is astonishing, therefore, that diagnosis of pneumonia in most cases (even at academic centers) still relies on decades-old and highly unreliable clinical criteria such as the chest radiograph,\(^4\) which has a sensitivity less than 50% and positive predictive value less than 30%.\(^5\) The difficulty only increases in patients with underlying cardiopulmonary disease or immunosuppression; two of the populations at highest risk of death from LRTI. Microbiological culture, another pillar of pneumonia diagnosis, is similarly faulty, as it reveals a pathogen in less than half of cases.\(^6,7\)

In the absence of dependable diagnostic guideposts, clinicians faced with any suspicion of pneumonia have traditionally resorted to treating with empiric broad-spectrum antibiotics ‘just to be safe’. However, this time-worn adage is finally being questioned, as data have accumulated to show the danger of indiscriminate antimicrobial use both to society and to individual patients. On a population level, antibiotic administration for suspected respiratory infection is now appreciated as a major driver of antibiotic resistance,\(^2,8,9\) which in turn has been identified by the World Health Organization (WHO) as one of the biggest global threats to human health.\(^10\) Meanwhile, the harm of inappropriate antibiotics to patients is also becoming recognized.\(^11\) In addition to the risk of allergy and drug toxicity,
antibiotics produce profound and lasting alterations in the microbiome of the gut and lung (dysbiosis),12 which manifest overtly through secondary infections such as Clostridium difficile infection (CDI) but also more subtly through alterations in host response to infection and contributions to diabetes mellitus, atherosclerosis, inflammatory bowel disease, and asthma.13,14 It is likely that these direct hazards to the patient will serve as a greater deterrent to antibiotic overuse than less tangible risks such as breeding resistance.

If the current methods for diagnosing and managing pneumonia are inadequate, what are the alternatives? In general, there are 2 strategies. The first relies on guidelines, such as those put forth by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) for community-acquired pneumonia (CAP) and for hospital-acquired pneumonia (HAP) and ventilator-acquired pneumonia (VAP).15,16 These guidelines synthesize the best available data into an evidence-based approach for the management of pneumonia, with goals of simplicity and the ability to generalize. These goals are in part born of necessity, because guidelines must be accessible to nonspecialists, but it is also an inescapable consequence of the large, unstratified patient populations in studies that inform the guidelines. Recommendations are similarly monolithic and therefore have limited relevance for uncommon infections and unique hosts, such as those with compromised immune or cardiopulmonary function. Diagnosis and management become significant challenges in these patients, especially during critical illness. In such cases especially, an alternative strategy is needed, one that combines greater diagnostic granularity with individually tailored therapy: so-called personalized medicine.

The first step toward personalized medicine is refinement of diagnostic categories. For pneumonia, this requires subclassification of the syndrome, which is currently defined broadly by (1) evidence of systemic infection (leukocytosis, fever, or chills), (2) respiratory symptoms (dyspnea, cough, sputum), and (3) new radiographic infiltrates.17 This highly inclusive entity could, for instance, be divided into viral pneumonia, bacterial pneumonia, and noninfectious respiratory disease using additional diagnostic techniques (eg, biomarkers)- a preliminary degree of endotyping referred to as stratified medicine.18 Such subgroups remain large enough to enable well-powered clinical trials and, thus, endotyping at this level may leverage conventional evidence-based medicine to guide management.

However, the full realization of personalized medicine requires a complete delineation of disease mechanisms, advanced diagnostics for interrogating these mechanisms in patients, and targeted therapies for modulating them. The closest approximation to this vision is in oncology, where tumors are sequenced to identify driver mutations for selective targeting (eg, with tyrosine kinase inhibitors), and the host immune response is assessed to determine candidacy for checkpoint inhibitors. Thus, the field is beginning to adopt a “tissue-agnostic” approach, wherein therapy is guided not by histologically defined tissue of origin but by the molecular biology and immunology of the tumor and host; a dramatic departure from traditional oncologic management.

Respiratory infection has much to learn from this paradigm. For pneumonia, personalization would require a comprehensive molecular description of the pathogen, the host, and the immunologic phenomena that stem from their interaction. This description will allow management decisions to be determined by not only data from empiric trials but also basic microbiological and immunologic principles. Examples include delivery of highly selective antimicrobials based on pathogen taxonomy and susceptibility, and rational manipulation of dysregulated host responses to promote pathogen clearance and limit immunopathology.

A useful framework for understanding the complex interplay of host and pathogen, based on the concepts of resistance and tolerance, has been defined by Ayres and Schneider19,20 (graphically represented in Fig. 1). Resistance refers to the host’s ability to clear microbes, whereas tolerance is a term borrowed from ecological immunology that describes the host’s ability to endure a microbial insult. Resistance comprises the host’s defenses against an invading pathogen, including intrinsic epithelial mechanisms, innate immunity, adaptive responses, and others as described later. Tolerance is influenced by a more varied set of factors, including the pathologic consequences of immune effectors (eg, reactive oxygen species [ROS] released from infiltrating neutrophils) as well as mechanisms unrelated to resistance (eg, myocardial infarction in patients with influenza infection).21 To eliminate confusion with the traditional concept of immunologic tolerance, this article refers instead to resilience, following the example of Mizgerd and colleagues.22 Using this this framework, 4 phases in the personalized diagnosis and management of pneumonia can be described (summarized in Fig. 1).
**PHASE I: CHARACTERIZATION OF HOST AND PATHOGEN**

**Characterization of Host**

**Physiologic reserve**

One of the clinician’s first priorities when encountering a patient with pneumonia (or any patient) is to estimate the patient’s baseline level of health, which in turn helps determine the likelihood of their ability to survive the disease. This physiologic reserve (depicted as the Y intercept in Fig. 1A), is a composite of several parameters, including age and premorbid organ function. For instance, decreased FEV₁ (forced expiratory volume in 1 second) diminishes the patient’s ability to withstand an additional insult to lung mechanics. Likewise, impaired cardiac...
performance or coronary artery patency predisposes to heart failure and myocardial infarction, respectively. Such compromise of physiologic reserve should prompt more aggressive care, but this often manifests as broader-spectrum and less-judicious administration of antibiotics, a mistake partly based on the faulty assumption of antibiotic safety. The authors propose that aggressive care should instead translate into more comprehensive diagnostic characterization of host and microbe, which in turn enables a more highly individualized therapeutic plan that maximizes efficacy and minimizes side effects.

The initial clinical assessment also includes an appraisal of disease severity, as this guides clinical triage and immediate management. However, since this is a manifestation of the host response to pathogen, it is dealt with in relation to phase II.

**Resistance**

As defined earlier, resistance refers to the host’s ability to clear a pathogen load. This term comprises not only the innate and adaptive immune mechanisms enumerated in Box 1 but numerous other parameters, including adequacy of cough, ciliary clearance, mucus quality (influenced by periciliary pH and mucins), release of antimicrobial peptides and opsonins, ROS production, and the barrier function that prevents invasive infection.25 Opportunities to therapeutically modulate these mechanisms are touched on in relation to phase III and reviewed elsewhere.25 Graphically, inadequate resistance leads to a more rapid decline down the curve depicted in Fig. 1B.

Swift recognition of an immunocompromised state is critical, because it informs triage and empiric antibiotic therapy against unique pathogens to which a host may be susceptible. This

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**Box 1**

**Innate immune responses in pneumonia**

Innate immunity in the lung (reviewed in detail elsewhere23) mediates both host defense and immunopathology; as such, a description of its basic mechanisms is essential to understand the targets of host-directed diagnostics and therapeutics, fundamental components of personalized pneumonia management. In brief, alveolar macrophages and respiratory epithelial cells collaborate to clear low levels of pathogens. When these defenses are overwhelmed, danger-associated molecular patterns (DAMPs) released from damaged parenchyma and pathogen-associated molecular patterns (PAMPs) activate innate immune signaling pathways via PRRs, which are expressed by both epithelial and immune cells. This process leads to the release of chemokines and cytokines, which induce the extravasation of neutrophils and exudative fluid into the interstitium and airspaces.

Innate immune signaling: Viral nucleic acids activate PRRs in dendritic cells, macrophages, and alveolar epithelial cells, including the cytosolic RIG-I-like receptors and AIM-like receptors, as well as endosomal TLRs (eg, 3, 7, 8, and 9). Recognition of viral PAMPs by plasmacytoid dendritic cells (DCs) leads to production of type I IFNs, which promote antiviral defenses, whereas macrophages and conventional DCs generate cytokines such as tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-12, and IL-23, which stimulate type I and III innate lymphoid cells (ILCs) and initiate T helper (Th) 1 and Th17 adaptive responses. Type I ILCs (similar to Th1 cells) are characterized by robust production of IFNγ, whereas type III ILCs (similar to Th17 cells) generate IL-17 and IL-22.

In contrast, PAMPs derived from extracellular bacteria (eg, lipopolysaccharide) and fungi (eg, β-glucan) activate cell-surface PRRs, including TLRs (1, 2, 4, and 6) and C-type lectin receptors (eg, dectin-1, dectin-2, and mincle), leading to production of an overlapping set of cytokines (including TNFα, IL-1β, IL-6, IL-12, and IL-23) but less type I IFN. Similar signals derive from the NOD-like receptors, which mediate cytosolic recognition of bacterial PAMPs.

Sequelaes of pulmonary inflammation: Ideally, recruitment of neutrophils and other immune effectors leads to pathogen clearance with little collateral damage. However, overexuberant neutrophilic responses can be deleterious because they may induce parenchymal destruction per se (eg, via ROS and protease release), alveolar edema, and progression to acute respiratory distress syndrome.24 Therefore, the acute inflammatory phase must be tightly controlled in terms of both severity and duration. Several mechanisms mediate the resolution of lung inflammation, including a switch from proinflammatory to antiinflammatory innate signaling (thereby limiting further leukocyte recruitment) and clearance of apoptotic neutrophils via efferocytosis (see the text concerning phase IV).

It is worth noting that the pathogen may benefit from immune-mediated tissue destruction because it provides critical nutrients for further proliferation; this may help explain the presence of pathologic immune responses in certain infections, which would otherwise serve as an advantage to neither the host nor the pathogen.
point is most dramatically shown by the 1-hour door-to-needle time recommended for administration of antipseudomonal antibiotics in patients with neutropenic fever, who may rapidly decompensate and die within hours from gram-negative rod bacterial infection if not treated promptly (discussed later). However, subtler examples include hypogammaglobulinemic patients, who may require adjunctive therapies such as intravenous immunoglobulin, and those with altered immune responsiveness caused by pathogen recognition receptor (PRR) polymorphisms. This section describes some of the mechanisms that lead to impaired host resistance, both genetic and acquired. Characterizing these defects in individual patients would facilitate personalized therapy for acute pneumonia in several ways: through predicting severity of disease course, indicating pneumonia susceptibilities that will guide empiric antimicrobial coverage, and identifying deficient host immune pathways that may be therapeutically enhanced.

**Genetic determinants of reduced resistance**

The study of rare patients with primary immunodeficiencies helps to elucidate the pathogenesis of human infections, as shown by the case of a young child with interferon (IFN) regulatory factor 7 (IRF7) deficiency and severe influenza. This finding confirmed the putative role of the IRF7 pathway in the generation of protective type I IFN during influenza infection suggested by prior animal studies. However, to explain the interindividual variability of pneumonia severity observed in the general population, it is more valuable to identify common and benign genetic variants that influence disease susceptibility. Polymorphisms linked to influenza and legionella infections that take particularly variable clinical courses are highlighted here.

The best-studied genetic determinant of influenza susceptibility is IFN-induced transmembrane protein 3 (IFITM3), which associates with the endosome to block cytosolic delivery of the genome of RNA viruses, a necessary step in their replication. IFITM3 also plays a role in IRF3 activation and persistence of memory T cells within the lung. Through these mechanisms, IFITM3 polymorphisms impair tissue resistance, leading to higher viral burdens and worse clinical outcomes. For instance, the C allele produces severe disease when homozygous and is fairly prevalent, especially in Asian people, where it is observed in more than 50% of the Han Chinese and Japanese populations. Several smaller studies have identified additional disease-associated single nucleotide polymorphisms (SNPs; reviewed elsewhere), but their clinical significance is not yet clear; it is likely that influenza susceptibility is a complex trait influenced by several of these loci.

Legionella susceptibility has been linked to STING (Stimulator of IFN Genes, encoded by TMEM173/STING), an adaptor protein downstream of cGAS and IFI16, innate immune sensors of cytosolic DNA. Activation of this pathway elicits a type I IFN response important for host defense against viruses and certain bacteria, including Legionella. Human TMEM173/STING shows considerable interindividual variability; for instance, 20% of the population in the 1000 Human Genome Project database express the HAQ allele, which contains 3 nonsynonymous substitutions. Recently, Ruiz-Moreno and colleagues showed that carriage of this variant is associated with heightened susceptibility to legionella pneumonia in humans. Mutations in toll-like receptors (TLRs) have also been shown to affect Legionella susceptibility, as TLR5 truncation (affecting a surprising ~10% of individuals) and TLR2 mutation lead to increased risk, whereas certain TLR4 polymorphisms are protective.

Genetic risk modifiers for CAP (irrespective of etiology) have also been described. For instance, a genome-wide association study (GWAS) identified several common variants in the FER gene (a cytosolic tyrosine kinase that contributes to neutrophil recruitment and endothelial permeability) that afford marked protection from death from pneumonia. A deleterious polymorphism in interleukin (IL)-6 and a protective SNP within IL-10 have been recognized as well. Regarding noninfluenza viral pathogens, susceptibility to severe rhinovirus infection in children has been linked to a variant of cadherin-related family member 3 (CDHR3; the receptor for rhinovirus-C), and several genetic risk factors have been identified for pediatric respiratory syncytial virus (RSV) infection; because the focus is on adult disease here, readers are referred to recent reviews on these topics. In addition, although not all are specifically related to pneumonia, a plethora of additional polymorphisms in PRRs have been shown to predispose to viral, mycobacterial, and fungal infections (reviewed in Refs. and ).

The potential clinical utility of identifying susceptibility loci in patients with pneumonia is significant. In the acute setting, as noted earlier, such data could improve prognostication, guide the individualization of empiric antibiotics, and identify therapies that can augment defective resistance mechanisms. Furthermore, identification of high-risk patients could inform preventive strategies, including more aggressive vaccination, counseling on
exposure avoidance, and prompter administration of antimicrobial prophylaxis after exposure (eg, oseltamivir for influenza). These measures are considered later in relation to phase III.

**Acquired defects in resistance**

Certain forms of acquired immunocompromise, such as hypogammaglobulinemia, neutropenia, hematologic malignancy, steroid use, and acquired immunodeficiency syndrome (AIDS), are readily recognized on history and basic laboratory studies and cue clinicians to consider pertinent clinical syndromes, such as *Pneumocystis jiroveci* pneumonia (PJP) in AIDS. This level of personalized therapy is well established in clinical practice and needs no further elaboration here. However, more common conditions, such as diabetes, chronic kidney disease (CKD), cirrhosis, alcoholism, smoking, and advanced age (immunosenescence), also increase risk of pneumonia but in less definable ways. Predisposition to LRTI is also influenced by transient risk factors, such as air pollution, intermittent viral infections, sepsis (discussed later relation to phase IV), and antibiotic use. In addition, omission of vaccination and/or waning immunity caused by remote vaccination represent, in effect, missed opportunities to improve resistance.

Is it possible for clinicians to comprehensively catalog all of the resistance deficits present in a given patient, quantify their individual effects, integrate their collective impact, and use this information to meaningfully guide clinical management? At present, the answer is clearly no, but this a priori approach is not the only means of assessing a patient’s immunocompetence. An alternative, or complementary, strategy is to interrogate patient immune responsiveness directly, using in vivo or ex vivo assays. A well-known example of the former is the tuberculin hypersensitivity test, which reports on T-cell reactivity.52 Quantifying surface former is the tuberculin hypersensitivity test, which ex vivo assays. A well-known example of the immune responsiveness directly, using in vivo or complementary, strategy is to interrogate patient immuno-competence. An alternative, or approach is not the only means of assessing a patient present, the answer is clearly no, but this a priori information to meaningfully guide clinical management? At present, the answer is clearly no, but this a priori approach is not the only means of assessing a patient’s immunocompetence. An alternative, or complementary, strategy is to interrogate patient immune responsiveness directly, using in vivo or ex vivo assays. A well-known example of the former is the tuberculin hypersensitivity test, which reports on T-cell reactivity. Quantifying surface markers of T-cell exhaustion, a phenomenon observed in sepsis that predisposes to secondary infection (discussed further in relation to phase IV), has also been explored as a method for assessing adequacy of T-cell immunity in the clinical setting.53 Another conceivable approach is transcriptomic analysis of local immune responses at the respiratory epithelium. This approach may be particularly useful in the context of active infection, as defective resistance mechanisms could be identified in situ and targeted for therapy. Functional assays such as these effectively integrate genetic and acquired defects in resistance and may provide clinicians with more concrete data than patient history alone to guide empiric antibiotics, immunomodulation, and preventive strategies.

### Characterization of Pathogens

First introduced in the nineteenth century, plate-based microbiological culture remains the gold standard for identifying bacterial and fungal pathogens in the lung and for determining their antimicrobial sensitivity. However, it has 2 major drawbacks: long turnaround times (>36–48 hours) and poor sensitivity. The former requires at least 2 days of empiric antibiotics, with all of the attendant risks enumerated later in relation to phase III, and even then antimicrobial coverage may miss the offending pathogen (eg, in the case of an unexpected multi-drug resistant [MDR] organism). The prolonged incubation times required for fungal cultures (often >2 weeks) create further risks for inadequate antibiotic therapy, as empiric antifungal agents are rarely used outside of neutropenia.

The inadequate sensitivity of culture was shown by a landmark study in patients with CAP, which showed that conventional culture failed to provide a diagnosis in more than 60% of patients despite addition of an extensive list of infectious biomarkers. Similarly dismal numbers exist for patients with VAP, in whom more than 50% lack an identifiable pathogen. Reasons for this poor sensitivity include failure of culture to detect fastidious organisms and inadequate sampling methods (eg, underuse of invasive techniques). Clearly, improved microbiologic diagnostics are needed.

### Invasive sampling

Despite decades of debate, the question of when to obtain invasive cultures has not yet been answered. With regard to VAP, the European and American guidelines are at odds; the former favor quantitative distal sampling, whereas the latter recommend semiquantitative endotracheal aspiration. Two of the more commonly cited randomized control trials (RCTs) addressing this question are Fagon and colleagues’ demonstration that bronchoscopy increased antibiotic-free days, and the Canadian Critical Care Trial Group’s study showing no benefit. This discrepancy may be attributable in part to a lack of patient endotyping, and criteria for identifying appropriate patients for bronchoscopy should be pursued. However, methodological advances since the time of these trials should also be considered. For instance, combining invasive sampling with nucleic acid–based or mass spectrometry–based diagnostics (described later) might allow more effective assessment of pathogen identification, burden, and antibiotic sensitivity, and therefore increase the efficacy of bronchoscopy. More recent studies have shown the utility of this approach (reviewed in Ref.59).
Nonbronchoscopic sampling (via blind catheterization of the lower airways) is an alternative that addresses many drawbacks of the bronchoscopic approach. These drawbacks include expense, risk to the patient, and the need for highly trained operators, which often produces delays that compromise the yield of cultures due to antibiotic exposure before bronchoscopy. Although not guided specifically toward diseased portions of the lung, nonbronchoscopic methods still correlate well with their bronchoscopy in a range of patient populations and microbiological tests. Again, the utility of such methods is bound to increase when combined with rapid molecular diagnostics.

Bronchoscopy to diagnose pneumonia in the nonintubated immunocompromised population is another source of controversy; although it remains standard of care, evidence for this practice remains sparse. A good example comes from patients with hematological malignancies who present with pulmonary symptoms and/or infiltrates. A multicenter RCT showed that a noninvasive work-up in such patients (including imaging, traditional culture, and biomarkers) was noninferior to bronchoscopy with respect to rates of pathogen identification. The reliance on bronchoscopy in this population is called further into question by the impact of invasive procedures on patients’ quality of life, particularly at the end stages of disease; a host-specific aspect of personalized medicine that is often neglected. However, if combined with molecular microbiological testing, the yield of bronchoscopy in the immunocompromised may improve substantially.

A theoretic argument against invasive sampling comes from the cystic fibrosis literature, in which it has been shown that pathogens from different parts of the lung may express completely different resistance patterns, such that sampling error alone may lead to inappropriate antibiotic selection. Similar differences in microanatomic bacterial communities have been described for patients with advanced chronic obstructive pulmonary disease (COPD). Although the results relate less to acute pneumonia, prolonged residence in an intensive care unit (ICU), and the consequent acquisition of multiple MDR strains, could conceivably produce similar spatial heterogeneity.

Matrix-assisted laser desorption ionization time of flight mass spectrometry

In contrast with the conventional approach to microbial recognition using colony appearance on culture plates, matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) identifies pathogens via proteomic profiling. The technique is both (requiring only minutes) and inexpensive on a per-sample basis. Furthermore, it identifies not only pathogens but also certain resistance mechanisms by detecting products of β-lactam hydrolysis, fluoroquinolone acetylation, and proteins that mediate resistance (eg, penicillin binding protein 2a [PBP2a], encoded by MecA, which mediates methicillin resistance in Staphylococcus aureus). Additional techniques are being developed to allow direct assessment of antibiotic sensitivity via measurement of stable isotope-labeled amino acid incorporation into proteins; a surrogate of microbial growth with much faster kinetics than traditional growth curves.

Biomarkers

Pathogen-associated biomarkers are the most widely used complement to traditional culture techniques. Although they remain limited in the number of pathogens they can detect and cannot offer insight into antimicrobial resistance, they are widely available, rapid (because they require no microbial culture), inexpensive, and in some cases highly specific for their targets. The list includes Legionella and pneumococcal urinary antigens, Mycoplasma and Chlamydia antibodies, Histoplasma urine antigen, galactomannan (associated with aspergillosis), and β-glucan (a nonspecific fungal marker). An example of recent progress comes from Wunderink and colleagues, who showed a doubling in detection rate of pneumococcal CAP with the use of a second urinary antigen compared with a conventional assay alone (9.7% vs 5.4%). Although encouraging, it nevertheless reveals that the standard urinary pneumococcal antigen assay (one of the best and widely biomarkers) still misses at least 40% of diagnoses, highlighting the need for further work in this area.

Quantitative polymerase chain reaction

Simple, rapid assays using quantitative polymerase chain reaction (qPCR) may be used to identify pathogens and resistance mechanisms using primers designed according to sequenced genomes. Polymerase chain reaction (PCR) is extremely effective for diagnosis of viral infection and is in common use for detecting respiratory viruses in the upper respiratory tract; a surrogate for LRTI. Several caveats of this technique exist, including the potential dissociation between upper respiratory tract infection and LRTI and the poor sensitivity for Herpesviridae (eg, herpes simplex virus [HSV] and cytomegalovirus [CMV]). The latter is an important weakness given the potential pathogenic role of these viruses even in immunocompetent hosts (discussed later in relation to phase III).
PCR has valuable application in the diagnosis of bacterial infections as well, for instance in identifying the MecA gene in *S. aureus*. qPCR can be used to assess relative microbial burdens and pathogen dominance; an important indicator of potential pathogenicity, as discussed later. This assessment may be achieved by normalizing the amount of pathogen to the total bacterial community, which is assessed using general bacterial primers.

The rapidity of PCR is one of its greatest strengths, and could help to remove the need for empiric antibiotics in pneumonia. The present guidelines recommend antibiotic therapy within 4 hours based on data showing increased mortality with delays in therapy (although even these data have been questioned\(^77\); thus, the prompt performance of a PCR-based diagnostic, which takes ~2 hours, may allow immediate delivery of targeted antimicrobial therapy.

**Metataxonomics and metagenomics**

An important limitation of qPCR is its inapplicability to microbes and resistance genes not yet fully sequenced. High-throughput techniques, including 16s (metataxonomics) and whole-genome sequencing (WGS; shotgun metagenomics), which offer the ability to define the respiratory microbiome in a comprehensive and unbiased manner, overcome this hurdle. They also allow the identification of fastidious organisms such as mycobacteria that grow poorly using conventional culture.\(^78,79\)

16s sequencing relies on the use of primers against highly conserved sequences in the ribosomal RNA of bacteria to amplify the variable region of the gene, which in turn is used to identify individual taxa. Semiquantitative relative abundance may also be assessed. The technique is rapid and inexpensive compared with WGS but provides no insight into nonribosomal genes, including those that mediate resistance and virulence. WGS, which completely characterizes the genomes of recovered microbes, holds the promise of predicting antimicrobial susceptibility, but it is not yet approved for this application.\(^80\) The reason is that the effects of subtle genetic variants (eg, SNPs in antibiotic target genes) on resistance have not yet been characterized. To address this issue, research groups are pursuing large GWAS analyses on thousands of clinical isolates to create a comprehensive catalog of resistance loci; this will serve as both a reference for patient WGS and a basis for developing models that predict resistance in novel variants.\(^81–83\)

An additional challenge to overcome, which affects both high-throughput sequencing techniques, is distinguishing colonizer from true pathogen. This challenge is a general caveat for any microbiological diagnostic, even with the far less-sensitive plate-based culture; an isolated microbe may represent anything from beneficial commensals to harmful microbiota, to colonizing pathogen, to disease-causing pathogen. One fairly straightforward method of defining a pathogen is to demonstrate its ecological dominance in the recovered bacterial population. For instance, Wunderink and colleagues\(^84\) proposed the following criteria for discriminating pathogen from colonizer on bronchoalveolar lavage (BAL) or tracheal aspirate; total bacterial density of greater than \(10^4\) colony-forming units (CFU)/mL, high total bacterial DNA burden, low community diversity, and a high abundance of the pathogen.\(^85,86\)

However, complexities arise from interspecies interactions, which are known to critically affect the virulence of a given pathogen. For example, a dominant pathogen may be detectable but not the source of disease because it is held in check by 1 or more cocolonizers (protective microbiota).\(^87\) An alternative is to assess for expression of genes, including virulence factors, which are expressed only after a microbe makes the phenotypic switch from colonizer to pathogen.\(^88,89\) Triggers for this switch include interaction with commensals, viral infections, cigarette smoking, and air pollution.\(^2\) As an example, Molyneaux and colleagues\(^90\) showed a significant increase in overall bacterial burden as well as an outgrowth of *Haemophilus influenzae* specifically in patients with COPD after rhinovirus infection.

Additional complications of metaomics include turnaround time, risks of contamination, inability to discriminate live from dead microbes, the extremely low abundance of microbial DNA compared with host, and cost. For now, this approach may only be applicable to the ICU patients, whose condition is tenuous enough and care is costly enough to justify the additional expense. Patients with chronic respiratory infections represent another potential target.

**PHASE II: CHARACTERIZE THE HOST RESPONSE TO PATHOGEN**

As described in Box 1, the central host response to lung infection is neutrophilic infiltration. This response explains not only the histopathologic hallmark (neutrophilic alveolitis) but also the classic clinical symptoms (dyspnea, cough, purulent sputum), signs (fever and hypoxemia), laboratory abnormalities (leukocytosis and bandemia), and radiographic findings (infiltrates). However,
the poor specificity of each of these clinical features leads to the frequent overdiagnosis of pneumonia and unnecessary administration of antibiotics. Identification of respiratory microbes by means of the diagnostics described in relation to phase I is helpful but only indicates the presence of potential pathogen; it does not prove that it is causing a clinically meaningful infection. In addition, microbiologic cultures, still the gold standard diagnostic, take days to mature. Thus, it is essential to develop more sophisticated methods for interrogating host responses that will (1) enable accurate and rapid identification of patients with pneumonia; and (2) discriminate between bacterial, viral, and other pathogen classes to guide empiric antibiotics. The first is a sine qua non of pneumonia management, whereas the second is the first step toward personalization (ie, endotyping).

The Use of Host Response to Diagnose Pneumonia

Protein biomarkers

Biomarkers (often present in serum, quantitative, rapidly processed, and potentially amenable to point-of-care testing) represent a highly attractive diagnostic modality. In the context of pneumonia diagnosis, biomarkers are used as reporters of the inflammatory neutrophilic response in the lung parenchyma. Balk and colleagues provide a more complete description in this issue, but the 2 most commonly used biomarkers, procalcitonin (PCT) and C-reactive protein (CRP), are briefly discussed here.

The biology of PCT is still incompletely understood, but it is known to be produced by immune and parenchymal cells in most tissues in response to stimulation with pathogen-associated molecular patterns (PAMPs), danger-associated molecular patterns (DAMPs), and inflammatory cytokines (see Box 1). PCT appears in serum at about 4 hours and peaks at 6 hours, making it an effective early indicator of pneumonia. One of the principal limitations of biomarkers in current use is their poor specificity; CRP and PCT levels are increased during inflammation from virtually any source, acute and chronic alike, including neoplastic, rheumatologic, necrotic (eg, pancreatitis or trauma), and infectious (with little discrimination between pathogen classes). Thus, they are indicators of systemic inflammation, not of pneumonia, and as such largely remain a complement to the similarly nonspecific markers of neutrophilic alveolitis in common use, such as fever, cough, sputum, leukocytosis, and radiographic infiltrates.

Neutrophilia in lower airway secretions

Sputum neutrophilia is the quintessential surrogate for the alveolar purulence that characterizes bacterial pneumonia. In immunocompromised and intubated patients, tracheal aspirates or direct alveolar assessment via invasive sampling has proved particularly useful. For instance, in a population consisting mostly of patients with hematologic malignancy and solid organ transplants, BAL neutrophilia was shown to have better area under the curve (AUC) for diagnosing pneumonia than either PCT or CRP, using quantitative culture as a gold standard. More recently, Choi and colleagues showed that BAL neutrophil count greater than 510/µL was a highly effective predictor of bacterial pneumonia, with an odds ratio of 13.5. BAL neutrophil count also effectively
discriminated bacterial from viral pneumonia, with an AUC of 0.855; its performance further improved when combined with CRP.

**Transcriptomics**

In contrast with the focused interrogation of clinically available biomarkers, transcriptomics provides a global view of differential gene expression in response to infection. Clustering analysis is used to identify distinct RNA expression patterns that correlate with presence or absence of infection, different classes of pathogens, disease severity, and prognosis. Given the inclusion of tens or even hundreds of genes in such immune response signatures, their potential sensitivity and specificity is far more robust than biomarker-based diagnostic strategies.

Early transcriptomic studies established that much of the immune response in pneumonia is consistent across pathogen classes, but specificity can be found in the activation of distinct signaling pathways downstream of particular PRRs (e.g., TLR4 activation by extracellular gram-negative bacteria vs TLR3 activation by RNA viruses). An example of is the transcriptomic analysis performed by Ramilo and colleagues, who examined blood from 36 pediatric patients acutely infected with influenza A and 16 with *Streptococcus pneumoniae* (mostly pneumonia) and identified a 35-gene panel that discriminated viral from bacterial infection with 95% accuracy in an independent cohort. Similarly, Zaas and colleagues were able to establish a 30-gene viral signature based on blood transcriptomes from human volunteers subjected to viral challenge with rhinovirus, RSV, and influenza A. This finding was validated in an independently acquired data set, showing 100% accuracy for identifying viral infection and 93% for bacterial infection. Tang and colleagues subsequently assayed whole blood from ICU patients in respiratory failure caused by influenza, bacterial pneumonia, and presumed sterile systemic inflammatory response syndrome (SIRS). Again, they showed an ability to robustly identify viral infection throughout the 5 days of follow-up, largely based on upregulation of ISGs and inhibition of innate inflammatory cytokines, which indicates a profound state of immunosuppression in influenza. However, they were unable to establish a bacterial signature that could distinguish between bacterial infection and sterile SIRS. Of note, there was surprisingly little concordance between viral signatures in the 3 studies, perhaps because of differences in training cohorts or in bioinformatic techniques. However, the few common genes were all IFN-inducible.

Although these studies laid important groundwork for the application of transcriptomics in pneumonia endotyping, their utility was limited by 2 issues. First, gene panels were too extensive (>25 transcripts) to permit analysis in standard clinical laboratories. Second, they had not addressed the fundamental problem of how to identify patients who need antibiotics.

The first issue was addressed in a follow-up study by Zaas and colleagues, who were able to translate their viral signature into a real-time PCR-based assay using commercially available probes. Landry and Foxman studied nasopharyngeal swabs from patients and showed that a set of only 3 transcripts in these samples (CXCL10, IFIT2, and OASL) could predict viral infection with 97% accuracy. More recently, Tang and colleagues reported a single serum biomarker capable of discriminating influenza from bacterial infection with an AUC of 91% in a large, newly enrolled cohort: IFI27, an ISG that is upregulated in plasmacytoid dendritic cells (DCs) in response to TLR7 activation. These studies represent some of the best examples to date of the translation of transcriptomic analysis into the development of robust but technically feasible clinical assays.

Substantial progress toward solving the second problem was made by Tsalik and colleagues, who assessed host expression profiles in patients with confirmed viral infection, bacterial infection, coinfection, and sick but noninfected controls. The use of this last control was a unique and important feature of the study because it helped to directly address the question of how to identify patients with sterile respiratory illness. Although the 4 signatures each required large numbers of probes (up to 71), they had superb test characteristics with AUCs between 90% and 99% in external validation analyses. A similar aim guided Ramilo and colleagues in their study of an analogous set of patients with viral and bacterial monoinfections, coinfection, and controls. Using advanced bioinformatics techniques, they identified a parsimonious 10 gene classifier with a sensitivity of 95% for bacterial infection (compared with 38% sensitivity of PCT); another step toward establishing a rule-out test to guide withholding of antibiotics. Note that 7 of these 10 genes overlap with the biosignature identified independently by Zaas’s group using unique analytical methods, suggesting the field may be converging on a common classifier. Further studies will be necessary to confirm the utility of this probe set in larger cohorts and in the immunocompromised, a population that is particularly prone to overtreatment with antimicrobials.
A final study worth mentioning compared the immune response in patients with sepsis caused by peritonitis versus pneumonia. There was little to distinguish between these two cohorts, suggesting that transcriptomic analysis is unable to delineate the anatomic source of infection, at least when applied to peripheral leukocytes in late-stage sepsis (see Fig. 1A).112

Use of Host Response to Define Severity at Presentation and Guide Prognostication

As mentioned earlier, the severity of clinical presentation in pneumonia primarily depends on the host response to the pathogen and the associated bystander immunopathology (Fig. 2). The existing measures of severity, including CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥65 years) and pneumonia severity index (PSI), are clinical scoring scales used to assess the end-organ consequences of this inflammatory response (eg, renal dysfunction) and are principally used for triage. PSI additionally accounts for comorbidities and therefore incorporates the concept of physiologic reserve described in relation to phase I. In contrast, biomarkers report directly and quantitatively on the inflammatory tone of the host in response to infection. They have been used to gain insight into additional clinical parameters, including acute stability and prognosis, as well as response to infection, as discussed in relation to phase III. The use of biomarkers in this context is discussed briefly here and in detail by Balk and colleagues elsewhere in this issue (also see Torres and colleagues113 recent review).

As might be predicted, systemic levels of inflammatory cytokines (including IL-6, IL-10, and IFNγ) are significantly higher in patients with severe CAP than in patients with nonsevere CAP and in healthy individuals.98,114 Furthermore, IL-6 correlates with clinical scoring scales115,116 and predicts 30-day mortality in hospitalized patients with CAP.98,114 Addition of CRP to a composite clinical index including both PSI and CURB-65 improves 30-day mortality prediction, achieving an AUC of 0.88.114 PCT on its own shows similar prognostic accuracy to CURB-65 and scales with severity.117 Van Vught and colleagues118 provided an important caveat to these findings, showing that systemic cytokines do not correlate with PSI in the elderly.

Given that the progression to sepsis (discussed further in relation to phase IV) portends a worse outcome in patients with pneumonia, it is of prognostic value to detect this transition. Protracted, smoldering inflammation marks the later phase of sepsis; evidence of this in patients recovering from acute pneumonia, as marked by increased levels of IL-6 and IL-10, was shown to correlate with increased mortality at 1 year.119 In contrast,

![Figure 2](image)

**Fig. 2.** Host response to pathogen. (A) Patterns of inflammation in severe pneumonia. Failure of resistance mechanisms allows progression of infection (in the absence of antibiotics). However, when the severity of infection reaches a threshold, it may lead to an irreversible decline caused by uncontrollable inflammatory syndromes such as sepsis or ARDS. The specificity of host immune signatures decreases at these end stages of infection because the inflammatory response degenerates to a common pattern regardless of microbe class and initial site of infection. (B) Immune responses to influenza. Influenza represents a useful example of host response during infection, given its highly variable course. In most patients, influenza is cleared effectively, with or without antiviral medication. In some, however, secondary bacterial infection complicates the illness. Still others are predisposed to excessive immune responses (poor resilience) and therefore follow the more precipitous clinical course depicted by the dotted line on the left. Such patients would benefit from vaccination, which leads to rapid clearance after exposure (top left arrow).
local immune responses at the respiratory epithelium, as revealed by sputum cytokine profiles, are blunted in severe CAP despite exaggerated inflammation in the periphery.\textsuperscript{120} This discordance between lung and systemic immune compartments highlights the importance of site selection when assessing host responses. In influenza infection, Oshansky and colleagues\textsuperscript{121} showed the potential for using mucosal-specific host responses to predict clinical outcomes, showing that a nasal cytokine profile characterized by increased monocyte chemoattractant protein-3 (MCP-3) and IFN-\( \gamma \) could predict progression to severe disease independently of age, viral load, and neutralizing antibody titers.

**Assessment of Resilience**

As mentioned in the context of host resistance, there is remarkable interindividual variability in the severity of pneumonia caused by a given pathogen, ranging from mild infection treated in the outpatient setting to fulminant sepsis requiring ICU admission. Physiologic reserve, pathogen burden, and resistance contribute substantially to this variability, but host resilience, defined as the host’s ability to tolerate a pathogen load, also plays a critical role. Simply put, 2 patients with similar baseline health and pathogen load may develop widely discordant disease severities, a phenomenon largely attributable to the host’s predisposition toward immunopathology. A unique example is shown in Fig. 1B, which shows the increased resilience to PJP observed in patients with AIDS; although driven by a pathologic process (ie, severe immunocompromise), the patient is able to tolerate an extraordinary pathogen burden with minimal pulmonary inflammation.

The data presented by Oshansky and colleagues\textsuperscript{121} exemplify the more common pattern observed in practice: decreased host resilience leading to more severe disease. Despite similar physiologic reserve (indicated by age in these otherwise healthy children), host resistance (indicated by neutralizing antibodies), and pathogen burden (indicated by viral load), a subset of patients progressed to severe influenza, suggesting an underlying immunologic susceptibility. Although the investigators focused on the prognostic value of the signature, it is notable the biomarkers (eg, IFN-\( \gamma \)-2) are known components of the cytokine storm that mediates immunologic disorder, organ dysfunction, and death in extreme cases.\textsuperscript{122,123} Therefore, these markers could potentially function as theranostics in influenza, both guiding initiation of immunosuppression and indicating response to therapy.

Substantial efforts have been made to identify the genetic underpinnings of susceptibility to influenza infection and other forms of pneumonia (see Fig. 2). The topic has been reviewed elsewhere,\textsuperscript{124,126} and more extensively in the context of sepsis,\textsuperscript{125} but, in these analyses, susceptibility loci are not clearly stratified by mechanism (ie, whether they affect resistance or resilience). One genetic variant that seems to specifically compromise resilience affects CD55, which protects the respiratory epithelium from complement deposition, a process implicated in the immunopathogenesis of severe influenza.\textsuperscript{126} A second study used an integrated genomic approach to identify susceptibility loci in patients with CAP that progressed to sepsis.\textsuperscript{127} First, unsupervised transcriptomic analysis divided the study cohort into 2 endotypes using a 7-gene classifier; one expressing sepsis response signature 1 (SRS1, marked by an immunosuppressed phenotype and increased 14-day mortality), and the other expressing SRS2. Next, genetic analysis identified a set of approximately 4000 quantitative trait loci that predisposed to the higher-risk phenotype, SRS1.

At present, the clinical utility of disease-associated SNPs is limited, but several potential applications can be envisioned as the list expands and host genomics come into more routine clinical practice. For instance, identification of variants that compromise resilience may prompt more aggressive immunosuppression. Also, from a research perspective, disease-associated SNPs give mechanistic insight into human infection and represent future therapeutic targets.

In closing, we propose that personalized analysis of host immune responses should ideally (1) confirm true infection; (2) identify bacterial processes that require antibiotics; (3) estimate severity to guide triage and prognostication; (4) assess host resistance, as discussed in relation to phase I; and (5) characterize host resilience. The last 2 should be performed with sufficient granularity to identify specific pathways for modulation as described in relation to phase III. In addition, as indicated by studies, including that by Oshansky and colleagues,\textsuperscript{121} test performance may improve with integration of local respiratory epithelial and systemic immune responses.

**PHASE III: PERSONALIZED TREATMENT AND ASSESSMENT OF THERAPEUTIC RESPONSE**

Armed with a clinical dataset that confirms the presence of pneumonia, identifies the offending pathogen and its susceptibilities, and describes the host’s immune competence and immunopathologic diatheses, clinicians are prepared to devise
a treatment plan. This plan will have the following aims: (1) to reduce pathogen burden, both through direct attack on the microbe (eg, with antibiotics) and through support of host-intrinsic resistance mechanisms; and (2) to optimize host resilience, largely through suppression of hyperactive and maladaptive immune pathways.

A key principle that informs the following discussion is that clearance of bacteria in patients treated for pneumonia is a collaboration between host resistance and antimicrobials (Fig. 3A). Some patients with pneumonia may have sufficiently robust immunity to eradicate the infection without therapy (Fig. 3B). On the other end of the spectrum are neutropenic patients dependent on antibiotics until count recovery (Fig. 3C). The remainder of patients are somewhere in between these extremes, and clinicians are responsible for personalizing an antibiotic regimen that balances the patient’s reliance on antibiotics against the substantial hazards of these drugs. Antibiotic choice, dose, and duration are considered, as are so-called antibiotic-sparing interventions, including nonantimicrobial pharmaceutics (eg, recombinant antimicrobial peptides).

**Antibiotic Therapy for Bacterial and Fungal Pneumonia**

**Hazards of antibiotics**

As mentioned at the outset, there is a widespread misconception that antibiotics are benign medications, but the risks of antibiotic use are myriad, with none more ominous than the growing specter of resistance (see Fig. 1C)\(^{128}\).

The clinical use of antimicrobials, an estimated 50% of which is unnecessary,\(^{129}\) leads to the spread of resistance in a fairly well-described sequence. First, antibiosis creates a selection pressure that leads to enrichment of microflora and pathogens with preexisting resistance, as well as generation of de novo resistance.\(^{130}\) Subsequent transfer of resistance determinants between organisms in vivo and human-to-human transmission of resistant organisms (eg, by the fecal-oral route in the community and via clinicians’ hands in hospital) leads to dissemination within a population.\(^{131}\) If this process continues unchecked, the WHO warns,\(^{132}\) a postantibiotic era will soon begin, with an estimated loss of 10 million lives to antimicrobial resistance per year by 2050.\(^{133}\) Even rapid deescalation of antibiotics (in cases in which a pathogen is isolated) carries a substantial risk of selecting resistant bacteria because their macrobiotic effects are rapid and persist for months after exposure.\(^{12,134}\)

Additional hazards of antibiotics include their adverse drug-drug interactions and class-specific toxicities, such as the nephrotoxicity observed with vancomycin, aminoglycosides, amphotericin, and polymyxins; a particular concern in the ICU.\(^{135,136}\) Furthermore, new mechanisms of toxicity continue to emerge, such as the ability to induce mitochondrial dysfunction and

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**Fig. 3.** Mechanisms of reducing pathogen burden. (A) Pathogen clearance via antibiotics and host resistance. In healthy hosts, brief antibiosis reduces pathogen burden to a level that allows eradication by immune mechanisms. (B) Pathogen clearance via host resistance alone. If the inoculum is small enough, healthy hosts can clear pathogens without specific therapy. (C) Pathogen clearance in the setting of impaired resistance. When immunocompromise affects resistance mechanisms against particular pathogens, antimicrobial therapy is essential, as is exemplified by neutropenic patients infected with pyogenic bacteria. Impaired resistance also leads to rapid progression of infection. This finding contrasts with the immunocompromise observed in patients with AIDS with opportunistic infections, which affects resilience (see Fig. 1B).
ROS damage,\(^{137}\) indicating the field’s incomplete knowledge on the subject. Antibiotics may also induce potentially catastrophic hypersensitivity reactions, such as anaphylaxis, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms (DRESS) in susceptible hosts.

In addition, antimicrobial agents destabilize the microbiome, producing a state known as dysbiosis. As mentioned earlier, this may affect the development and course of various disease, including diabetes, atherosclerosis, and asthma.\(^{13,14}\) However, more immediate for patients is the risk of CDI, which accounts for roughly 29,000 deaths per year in the United States.\(^{138}\) All antibiotics, even low-risk classes, predispose to CDI, and their effects are cumulative with respect to number of agents, dose, and duration.

Based on abundant mouse data, it is likely that gut dysbiosis predisposes to pneumonia as well\(^{139–144}\); consistent with this is clinical evidence that oral probiotics protect ICU patients from VAP, as described in relation to phase IV. Furthermore, antibiotic use may lead to secondary pneumonia courtesy of pathobionts: normally benign flora that may overgrow and cause infection in the setting of dysbiosis, analogously to \(C\) difficile\(^{145}\). In addition, it has been shown in humans that carriage of certain taxa within the nasal microbiome correlates with improved adaptive immunity to respiratory pathogens, namely responses to influenza A vaccination.\(^{146}\) Antimicrobials may compromise this component of the microbiota as well.

Considering this litany of potential hazards, it is not surprising that the unnecessary use of antibiotics has been shown to increase mortality in certain patient populations, including those with sepsis in the ICU.\(^{147}\)

**Antibiotic selection**

Selection of a particular antibiotic is guided largely by susceptibilities, but, except in cases of MDRs, a fair breadth of choice usually remains. Personalizing this decision should first take into account potential adverse reactions, perhaps in the future using pharmacogenomic techniques to predict toxicity,\(^{148}\) although this approach may find more use in the context of chronic lung infections, which require more prolonged courses of therapy.\(^{149}\) Second, clinicians must decide between bacteriostatic versus bactericidal agents, although, as argued by Spellberg and colleagues,\(^{150}\) the distinction is arbitrary and in general populations there seems to be no advantage to bactericidal drugs despite the folklore belief. Nevertheless, there are specific circumstances in which each may be desirable. Drawing on the example of endocarditis and meningitis, for which bactericidal drugs are recommended based on the relative paucity of immune effectors at these sites of infection, heavily immunosuppressed patients may benefit more from bactericidal drugs. In contrast, bacteriostatic drugs that inhibit protein synthesis may improve immune resilience; for instance in postviral pneumonia.\(^{151,152}\) In addition, an argument has been made for the use of bacteriostatic drugs in pneumococcal pneumonia because lytic agents increase the generation of pneumolysin, a proinflammatory toxin with numerous harmful effects, including myocardial toxicity.\(^{153}\)

**Antibiotic dosing**

In recent years, some of the basic assumptions on which current dosing protocols are based have been called into question.\(^{154–156}\) For instance, the practice of administering antibiotics at their maximum tolerable dose is based on the prevailing notion that low doses create selection pressure for the emergence of resistance, whereas high doses of antibiotics kill microbes before resistance can develop.\(^{157}\) Among others, Read and colleagues\(^{155}\) have challenged this belief, arguing that, when MDRs are present at the start of infection, they are likely held in check by other microbiota not affected by resistance mechanisms that compromise microbial fitness; in the presence of antibiotics, these protective microbiota are killed, allowing the resistant organisms to flourish unabated, a phenomenon called competitive release. In contrast, when MDRs are absent at the outset, they recommend a high-dose regimen for preventing development of resistance according to the conventional argument.

The implications of this model for patients with pneumonia are potentially practice-changing. Patients with severe infection or immunocompromise would still be given the conventional high-dose protocol, but, for those with robust physiologic reserve and fairly mild disease, outpatient therapy with the lowest clinically effective dose may be the optimal regimen. However, close follow-up to monitor for underdosing and treatment failure (a particular concern in drug hypermetabolizers) would be essential. Given this risk, and that subtherapeutic antibiotic resistance may promote resistance,\(^{158}\) navigating this lower bound of the therapeutic window would require great vigilance if adopted into clinical practice.

**Duration of therapy**

Determining the optimal duration of therapy is a crucial feature of personalizing pneumonia management. Antibiotic courses have shortened to as little as 5 days, and effort has been made to
identify biomarkers that may guide even earlier cessation. For instance, protocols such as stopping therapy when PCT decreases to 20% of its peak have been shown to reduce antibiotic days.\textsuperscript{159} Taking abbreviated courses to the extreme, it has been shown that even a single day of antibiotics can have significant clinical effect, as a dose of ceftriaxone given before a course of linezolid substantially improved cure rates.\textsuperscript{160} Besides minimizing antibiotic exposure, an additional theoretic benefit of short courses is suggested by models showing that brief therapeutic pulses may reduce the risk of inducing resistance without compromising pathogen killing.\textsuperscript{161}

Conceptually, the optimal duration is a function of pathogen burden, adequacy of host resistance, and efficiency of chemotherapeutic killing. Rather than attempting to predict this a priori, it may be preferable to use a theranostic strategy that follows an indicator of microbial persistence, either indirectly using host response (eg, PCT) or directly using a microbial marker (eg, serum galactomannan and $\beta$-glucan in aspergillosis).\textsuperscript{162} CAP guidelines do incorporate a fair degree of personalization, as the recommended length of therapy varies depending on host response indicators. Given the success of the current guideline-based approach, as shown in a large RCT by Uranga and colleagues,\textsuperscript{163} the bar would be high for any potential alternatives.

### Antimicrobial Therapy for Viral Pneumonia

The administration of neuraminidase inhibitors such as oseltamivir for influenza is well established in clinical practice, but management of other forms of viral pneumonia is less clear despite their substantial clinical burden. In one series of patients in the ICU with severe CAP, 36% had a viral cause without bacterial coinfection on BAL, and, within this group, rhinovirus, parainfluenza, and human metapneumovirus were all more frequently recovered than influenza.\textsuperscript{164} HSV may be an additional contributor to severe respiratory disease, even in immunocompetent hosts, as it has been shown that 21% of nonimmunocompromised patients on prolonged mechanical ventilation have evidence of HSV bronchopneumonitis by high viral titer on BAL-specific and HSV-specific nuclear inclusions in cells recovered on BAL or biopsy.\textsuperscript{165} Likewise, CMV may have pathogenic effects in previously immunocompetent critically ill patients.\textsuperscript{166}

In immunocompromised populations, these pathogens are routinely treated,\textsuperscript{167} but it may be advantageous to treat in select immunocompetent patents as well. For instance, ribavirin is highly effective therapy for upper and lower respiratory tract infection from RSV in hematological malignancy and carries few side effects, particularly in the oral formulation.\textsuperscript{168筹集} Among these features, as well as its additional activity against parainfluenza and human metapneumovirus, ribavirin may prove useful in immunocompetent patients with severe viral pneumonia, although data to this end are currently lacking.

### Nonantibiotic Pathogen-Directed Therapies for Pneumonia

An alternative, or complement, to chemotherapy-based regimens for pneumonia is a diverse collection of therapeutics that includes synthetic antimicrobial peptides,\textsuperscript{171} engineered bacteriophage lysins,\textsuperscript{172} neutralizing antibodies (eg, against influenza),\textsuperscript{173} and antibodies targeting pathogen-associated toxins (eg, pneumolysin).\textsuperscript{174} These therapeutics are reviewed by Czaplewski and colleagues\textsuperscript{175} but are also mentioned here for their utility in personalized therapy.

Lytic bacteriophages epitomize this class of ‘antibiotic alternatives’.\textsuperscript{176} Reemerging after their initial description in the preantibiotic era, these viruses have potent bactericidal effects on actively replicating cells and are highly specific for particular bacterial species, so their dysbiotic effects are minimal. In addition, they have low potential for generating antimicrobial resistance or host toxicity. Although still largely the purview of basic research, this approach may eventually translate to the clinic, perhaps as a last resort for respiratory pathogens with extended drug resistance.

### Host-Directed Therapies for Improving Host Resistance

Most of the measures discussed earlier promote pathogen clearance predominantly through direct toxic effects on the microbe. However, some function by blunting virulence (eg, antibodies that target bacterial toxins or neutralize viruses), leaving host resistance mechanisms to clear the attenuated pathogen. A third strategy, not mutually exclusive with the others, is to bolster host resistance directly using immunotherapeutics.\textsuperscript{177} To this point, the clinical application of such therapy has largely been restricted to chronic infections with mycobacteria and aspergillus unresponsive to antimicrobials.\textsuperscript{178,179} The use of such strategies as chimeric antigen receptor-T therapy and supplemental cytokine therapy in this context provides an instructive model for acute pneumonia. A notable example from this literature is the administration of recombinant IL-2 to a patient with...
idiopathic CD4+ lymphopenia and antibiotic-refractory *Mycobacterium avium-intracellulare* lung disease, with resultant resolution of infection.\(^{180}\) Another concept worth exploring is the use of supportive therapies that promote nonimmunologic aspects of host resistance, such as secretion clearance, including routine chest physiotherapy, which has been shown to decrease the incidence of VAP.\(^{181}\) Along similar lines, cough augmentation may be useful in a select group of patients to prevent or manage VAP, although meta-analyses show that it does not seem to improve time to extubation in the general ICU population.\(^{182}\) An as-yet unexplored direction would be to counteract the known defects in mucociliary clearance in critically ill\(^{183}\) and intubated\(^{184}\) patients by improving mucus rheology. One approach to doing so is the use of cystic fibrosis (CF) transmembrane regulator (CFTR) modulators such as ivacaftor, which has been shown to potentiate the function of CFTR in patients without CF.\(^{185,186}\)

**Host-Directed Therapies for Improving Resilience**

As stated earlier, the principal determinant of severity in most cases of pneumonia is the immunopathology associated with the host response, not the virulence of the pathogen. A portion of this immunopathology is attributable to collateral damage from essential immunological defense mechanisms, while another is simply due to excessive inflammation. Ideally, immunosuppressive agents should selectively target the latter, but in practice, medications like glucocorticoids potently inhibit both. However, when simultaneously treating with antibiotics, resistance mechanisms play a less pivotal role in eradication of microbes, and therefore the impaired resistance induced by immunosuppressive therapy may be an acceptable sacrifice for the reduction of pathologic inflammation. Macrolides represent a unique example among antibiotics in that they simultaneously clear pathogen and dampen inflammation. The latter effect was strikingly revealed by a meta-analysis that showed a mortality benefit in CAP even in patients with macrolide-resistant bacteria.\(^{167}\) Similar dissociation of clinical efficacy from microbicidal activity was shown in CF.\(^{188}\)

Antimicrobial therapy also has the potential to exacerbate immunologic disorders. This exacerbation occurs via release of PAMPs from lysed pathogens; the so-called Jarisch-Herxheimer reaction (see Fig. 1C). Often observed in the early stages of treatment of cellulitis and spirochetal disease, this phenomenon is best known for its role in PJP therapy in patients with AIDS. In such patients, the insufficiency of host defenses permits the proliferation of fungi to high levels within the lungs. On initiation of antimicrobial therapy, fungal lysis leads to a massive bloom of cell wall components, including \(\beta\)-glucan, which elicits an intense inflammatory response through dectin-1 that may result in ARDS.\(^{189}\) It is therefore common practice to treat these patients simultaneously with steroids to avert the potential immunopathologic response. More targeted approaches have also been explored, such as cotreatment with \(\beta\)-glucan synthesis inhibitors (echinocandins), which has shown efficacy in mouse models.\(^{189}\) What role the Jarisch-Herxheimer reaction might play in other causes of pneumonia has not been explored in detail.

A more heated debate surrounds the use of immunosuppression in non-PJP pneumonia. Torres and colleagues\(^{190}\) were able to solve this problem using a fairly simple endotyping strategy as they limited administration of steroids to patients with a hyperinflammatory phenotype, as indicated by CRP level greater than 150 mg/dL. A contemporaneous study similarly showed a benefit to steroid use in severe pneumonia; unsurprisingly, the mean CRP in the study cohort was also greater than 150 mg/dL.\(^{191}\) These successes highlight the value of personalizing therapy, even if to a rudimentary degree. As the sophistication of host diagnostics increases, it should be possible to endotype in much finer detail, enabling more effective prediction of response to immunosuppression.

Another possible explanation for the failure of steroids in early trials relates to the immunologic nonspecificity of these agents. In this sense, steroids might be considered antipersonalized therapy because they indiscriminately inhibit immune pathways across the spectrum from protective to pathologic. Instead, patient stratification according to immune pathway dysregulation should be used to target immunotherapy and minimize side effects. One such targeted therapeutic strategy is the use of PRR antagonists,\(^{192}\) which could in principle halt the inflammatory paroxysm at its source. However, the TLR4 antagonist, eritoran, failed to improve outcomes in sepsis (even in a subgroup analysis of the 50% with pneumonia)\(^{193}\) despite its demonstrated protection against endotoxemia in healthy volunteers.\(^{194}\) It may be that PRR antagonism is most effective early in the disease process (as suggested by animal models as well\(^{195}\)), and that advanced disease requires a very different approach (including immunostimulation, for instance), as explored in relation to phase IV.
PHASE IV: SECONDARY THERAPIES TO ADDRESS THE CONSEQUENCES OF INFECTION AND TREATMENT

Addressing the Immunopathology of Pneumonia-Associated Sepsis

As alluded to in Box 1, lung infection may run an uncomplicated course with an appropriate immune response that results in pathogen clearance followed by prompt resolution of inflammation. However, severe infection in susceptible hosts (ie, those with poor resilience) may result in a complex syndrome of immune dysregulation known as sepsis. The pathophysiologic details are beyond the scope of this article and not yet fully established, but two of the key features are uncontrolled, persistent inflammation and a profound state of immunosuppression that affects both innate and adaptive immunity, called immunoparalysis. Therapeutic measures for modulating both aspects have been explored and are discussed here.

Resolution of proinflammatory response

The initiating phase of sepsis involves a hyperinflammatory reaction to microbial PAMPs and DAMPs produced by damaged tissue, followed by activation of complement, endothelial cells (which leads to tissue edema and leukocyte extravasation), neutrophils (which induce damage caused by ROS and proteases), and the coagulation cascade (causing microthrombosis and coagulopathy), all of which interact in potentially amplifying loops that may degenerate into a severe systemic state of inflammation. However, numerous immune mechanisms are in place to control the magnitude and promote the resolution of this potentially devastating process. Proresolving mechanisms include elimination of proinflammatory cytokines, neutrophil apoptosis and efferocytosis, and a switch in macrophage phenotype from inflammatory to reparative (or replacement via monocyte influx). Steroids were discussed earlier, the antiinflammatory properties of which may help to limit the magnitude of inflammatory response in sepsis, but therapeutics designed to stimulate resolution have also been proposed.

Much attention in inflammatory resolution has been focused on the use proresolving mediators, including lipids known as resolvins, lipoxins, and maresins, but most studies to date have been preclinical. However, some intriguing observational data indicate a protective role in CAP (smooth aspirin, which is known to generate potent lipoxins; prospective studies are now underway to evaluate for an ameliorative effect in sepsis. Similarly, statins lead to the production of lipoxins, and established use before presentation is associated with a reduced incidence of CAP (in a retrospective analysis of the JUPITER [Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin] trial), and possibly an improvement in mortality. However, conflicting studies and potential confounders such as the so-called healthy user effect must be addressed before drawing definitive conclusions.

Personalized modulation of inflammatory resolution is likely to require metabolomic analysis, first in research studies to establish the differences in lipid milieu between normally resolving pneumonia and protracted disease and then in patients to detect specific molecular deficiencies. Supplementing these patients with synthetic analogues to steer the immune response toward homeostasis may prove a valuable complement to immunosuppressive agents that are intended to dampen its severity.

Reversal of immunosuppression

Within the lung, local immune responses are blunted in the wake of viral and bacterial infection through several mechanisms, including generation of a reparative, antiinflammatory milieu dominated by transforming growth factor beta. However, as pneumonia progresses to sepsis, a profound state of immunosuppression seems to develop after about 3 days, placing patients at high risk of secondary infection, about half of which is respiratory. It is during this late stage of sepsis, termed compensatory antiinflammatory response syndrome (CARS), that most deaths occur. No clinical trials have yet examined lung-specific interventions to support patients through this vulnerable stage, but there is a substantial body of work on reversing the systemic state of immunosuppression. This article focuses on the use of immunostimulatory cytokines and checkpoint inhibition, but see van der Poll and colleagues for more on the topic.

Granulocyte-macrophage colony–stimulating factor (GM-CSF) promotes granulocyte production, survival, phagocytic function, and extravasation into tissue. It also reverses the downregulation of (human leukocyte antigen, antigen D related (HLA-DR), an important contributor to and biomarker of immunoparalysis in advanced sepsis. The potential efficacy of GM-CSF was shown in a double-blind multicenter trial in which 38 patients with low HLA-DR expression (most of whom presented with pneumonia) were randomized to receive GM-CSF or placebo. The treatment arm showed complete normalization of HLA-DR expression, restored responses to TLR stimulation, improved APACHE (Acute Physiology And
Chronic Health Evaluation) scores, and decreased duration of mechanical ventilation and ICU stay, without significant side effects. This biomarker-guided (ie, theranostic) immunomodulatory approach represents an important example of personalized treatment of pneumonia and a model for future studies. Of note, a related cytokine that similarly stimulates granulocyte production, granulocyte colony–stimulating factor (G-CSF), has been studied in the context of neutropenic pneumonia, but evidence is accumulating to show that the resultant neutrophil reconstitution can precipitate ARDS and therefore G-CSF should be avoided in these patients.

IFNγ, the quintessential T helper 1 (Th1) cytokine, exerts potent stimulatory effects on granulocytes to promote clearance of bacterial and fungal pathogens. Human studies have mostly been limited to case reports and results have been mixed, but administration is generally well tolerated and there is some evidence for efficacy. For instance, Dignani and colleagues described complete resolution of antimicrobial-refractory pulmonary aspergillosis in 3 patients after administration of IFNγ; similar success was seen in 2 cases of invasive aspergillosis and 1 of candidiasis, all involving the lung. In select patients, this may prove a valuable adjunctive therapy for pneumonia; further insights are sure to be generated by an RCT examining its role in the treatment of patients with septic shock (https://clinicaltrials.gov/ct2/show/NCT01649921).

IL-7 predominantly affects adaptive immunity, promoting T cell proliferation, activation, survival, and trafficking to infected tissue. It has shown promise in preclinical models of pneumonia, and is currently the focus of a multicenter clinical trial in septic patients (https://clinicaltrials.gov/ct2/show/NCT02960854).

Checkpoint inhibitors, as applied to sepsis, have been studied mostly in mice, but they may find use in severe pneumonia given the evidence of T-cell exhaustion in a postmortem examination of septic patients (more than half of whom had evidence of lung infection) and evidence for improved pathogen clearance following checkpoint blockade in preclinical models of acute pneumonia. Although some of the trials discussed earlier used a biomarker-based determination of candidates for immunostimulation, selection of patients for therapy may be improved by a more comprehensive immunophenotyping, such as through gene expression signatures or multimarker protein assays, which may improve not only prediction of response but also tailoring of therapy to individuals’ specific immune defects. As shown by only 11% of postsepsis deaths being attributable to secondary infection, not all patients require immune stimulation. More sophisticated diagnostics should at the least distinguish patients needing immunosuppression (as discussed in relation to phase III), from those who need stimulation.

Protection and Restoration of Microbiome

The iatrogenic toll of antimicrobials continues to be underestimated, as described in relation to phase III, but nowhere more so than in the gut. In addition to predisposing to CDI, antibiotics select for resistant bacteria and create a state of dysbiosis, which has several harmful consequences. These consequences derive in part from the eradication of commensals, which normally function to protect against outgrowth of pathobionts, a phenomenon termed colonization resistance. Also, through metabolism of dietary fiber, healthy gut microbiota synthesize short-chain fatty acids, which positively influence systemic immune function and maintenance of gut epithelial integrity. Compromise of these mechanisms caused by dysbiosis promotes gut translocation of bacteria and PAMPS, which exacerbates the prolonged, smoldering inflammation of sepsis and in some cases produces frank infection.

As explained in relation to phase III, dysbiosis is likely to increase risk of pneumonia. Several microbiome-protective strategies, besides minimizing unnecessary antimicrobial exposure, have been proposed. One creative solution involves coadministration of activated charcoal with antibiotics, which decrease intestinal but not plasma antibiotic levels, thus protecting the gut microbiota. More attention has been given to the literature on oral probiotics, which shows both a trend toward lowering incidence of VAP and a significant delay in acquisition of Pseudomonas aeruginosa respiratory colonization. Meta-analyses have differed in their conclusions regarding these data, but there does seem to be a substantial clinical effect, amounting to an approximate 20% reduction in VAP as estimated by Siempos and Ntaidou. This effect was confirmed as significant by the most recent meta-analysis on the subject. Even stronger data support the use of probiotics in mitigating the risk of CDI in patients receiving antibiotics: a Cochrane analysis showed a number needed to treat of only 12 in patients with a CDI risk greater than 5%. Thus, especially when treating pneumonia in a patient with high risk of CDI, probiotics should be strongly considered.

Prevention of Future Infection

Vaccines have been called the most effective medical intervention ever devised because of their
low cost, ability to prevent disease, and continued efficacy in the presence of drug resistance.237 They remain the mainstay in the prevention of pneumonia, as exemplified by the highly effective antipneumococcal and antinfluenza agents. Although in some ways the antithesis of personalized medicine, because they are given to huge populations with minimal stratification, vaccine development and delivery must be improved to decrease the burden of preventable illness and reduce antibiotic use.232

With regard to personalized prevention of pneumonia, Evans and colleagues233–235 have developed a provocative pharmacologic approach wherein inhaled TLR agonists (specifically TLR2/6 and TLR9 ligands) are used to induce a state of tissue resistance; this has been shown to protect mice from both influenza and bacterial pneumonia. Numerous potential applications can be envisaged for such technology, including prophylaxis in patients with hematologic malignancies after myelosuppressive therapy that induces prolonged neutropenia. This prophylactic strategy is currently under investigation as part of a phase I clinical trial (https://clinicaltrials.gov/ct2/show/NCT03097796) and warrants further study.

**Sequelea of Pneumonia**

Although primarily a lung infection, pneumonia should be considered a systemic illness,236 with manifestations in numerous extrapulmonary organs, including heart, kidneys, and brain (reviewed by Restrepo and colleagues237). As mentioned earlier, premorbid compromise in these systems decreases the patient’s physiologic reserve and acute ability to survive infection. However, there is also an increasing appreciation of the longer-term consequences of pneumonia. In addition to the well-described architectural distortion that may compromise necrotizing pneumonia, as well as the bronchiectasis that may result from repeated infection (exemplified by patients with cystic fibrosis), there is an increased risk of developing obstructive disease in patients who have an episode of pneumonia in early life.238

Outside the lung, there is a strong association with cardiovascular events, including an increased 30-day incidence of heart failure (~15%), arrhythmia (~5%), and acute coronary syndrome (~5%).239 Up to 20% of deaths from CAP are attributable to these complications.240 Furthermore, although cardiovascular risk is highest immediately after pneumonia, it remains increased for 10 years.241 The mechanisms underlying increased cardiovascular risk in pneumonia include inflammation-associated endothelial dysfunction and thrombophilia, as well as microbe-specific processes such as the pneumolysin-induced myocyte injury and microabscesses observed in S pneumoniae infection.242,243

A strong body of literature suggests that pneumonia can precipitate cognitive decline as well. For instance, one study showed that one year after hospitalization for CAP, one-third of patients over 65 had moderate to severe impairment, and an additional third showed mild impairment.244 The relationship was shown to be bidirectional, in that premorbid cognitive dysfunction predisposes to pneumonia (likely because of increased risk of aspiration), and pneumonia in turn leads to cognitive impairment.245 Functional status, quality of life, and mood also decline substantially after an episode of pneumonia.246,247

Renal dysfunction frequently complicates sepsis associated with pneumonia by mechanisms relating to systemic inflammation and hemodynamic compromise that are only now becoming clear248; however, to our knowledge, the long-term risk of CKD postpneumonia has not been studied. Thirty-day readmission rates are greatly increased after pneumonia (7%–12%),249,250 as is long-term mortality (40% vs 25% for those hospitalized for other conditions).251,252 Thus, long-term sequelae both within the lung and without can be severe and represent important opportunities for personalization (eg, treating with aspirin or high-dose statin to prevent major cardiovascular events in patients with vascular risk factors).

**SUMMARY**

The practical implementation of personalized pneumonia management depends heavily on the clinical setting, which spans from the ambulatory clinic to the academic ICU, where there are vastly different levels of patient acuity and available resources (Fig. 4). For instance, ambulatory providers do not have access to advanced diagnostics such as next-generation sequencing on BAL but should also not need them for the management of mild CAP. The focus in that context should be on developing tools that quickly and reliably discriminate between bacterial pneumonia, viral pneumonia, and noninfectious disease, perhaps using qPCR-based host response profiling. Because of the impracticality of waiting for culture data to guide antibiosis in this setting, pathogen characterization will be limited to rapid assays such as viral PCR on upper airway specimens, mass spectrometry on sputum, and/or pathogen-associated biomarkers such as the pneumococcal
The principal goal is to identify and treat patients with antimicrobial-sensitive infections and spare those without, thus reducing the massive overuse of antibiotics in the clinic and spread of resistance.

In contrast, for sicker patients in the ICU, more elaborate testing should be considered. For instance, it may be justifiable to perform a several-thousand-dollar host transcriptomic analyses to identify candidates for targeted immunomodulation, because even steroids (a fairly crude form of such therapy) are known to reduce the length of stay in the ICU, the daily costs of which are commensurate with such studies. Furthermore, the use of bacteriologic NGS may be considered in such patients to facilitate institution of highly selective antimicrobials, especially as sequencing costs decrease and antimicrobial susceptibility prediction improves.

Conceptually, a well-designed personalized treatment plan consisting of both antimicrobials and immunomodulation would reduce the hysteresis usually observed during the course of severe pneumonia; that is, the deviation from the resilience curve depicted in Fig. 5A, B. This hysteresis often derives from the immunopathologic consequences of infection, which include ARDS, renal failure, and CARS (the downward curve in Fig. 5A). Thus, even when the offending pathogen is cleared, the patient may be left with significant debility and increased risk for secondary infection. Meanwhile, excessive immunosuppression may seem to improve a patient’s clinical status but also impairs pathogen clearance and increases susceptibility to infection (see Fig. 5B). The ideal therapeutic regimen would therefore involve selective antimicrobials with minimal toxicities to the host, plus tailored immunomodulation that offsets the downward deviation from the curve; the combination should be designed to return patients directly to their premorbid states (Fig. 5C).

Ultimately, this may require a multiomic diagnostic platform that deeply characterizes the host, pathogen, and their interaction alongside a comprehensive suite of antimicrobial therapeutics (comprising not only antibiotics but also inhibitors of virulence factors and promoters of host resistance mechanisms) as well as immunomodulators that offset maladaptive host responses to infection and promote...
resolution of inflammatory responses. Biomarkers should be developed to guide subsequent cessation of antibiotics. Complementary strategies for preventing secondary infections and restoring microbiomic homeostasis should also be developed. In short, the goal is to not only improve survival from pneumonia but also limit the possible systemic and long-term consequences of infection.

Although a lofty vision, the obstacles to the realization of this goal are less technical than practical. Much of the necessary technology, including host transcriptomics, pathogen NGS, and multiplex protein analyses, already exists. What is needed now is a recognition both within the field and beyond of the clinical burden of pneumonia and the hazards of overuse of antibiotics; this should drive further research into the mechanisms of pneumonia, development of diagnostics and therapeutics, streamlining of technology to reduce costs, and methods for effective clinical implementation.

REFERENCES


133. Gautam et al.


