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Pathogenesis of pneumonia and acute lung injury

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Abstract

Pneumonia and its sequelae, acute lung injury, present unique challenges for pulmonary and critical care healthcare professionals, and these challenges have recently garnered global attention due to the ongoing Sars-CoV-2 pandemic. One limitation to translational investigation of acute lung injury, including its most severe manifestation (acute respiratory distress syndrome, ARDS) has been heterogeneity resulting from the clinical and physiologic diagnosis that represents a wide variety of etiologies. Recent efforts have improved our understanding and approach to heterogeneity by defining sub-phenotypes of ARDS although significant gaps in knowledge remain. Improving our mechanistic understanding of acute lung injury and its most common cause, infectious pneumonia, can advance our approach to precision targeted clinical interventions. Here, we review the pathogenesis of pneumonia and acute lung injury, including how respiratory infections and lung injury disrupt lung homoeostasis, and provide an overview of respiratory microbial pathogenesis, the lung microbiome, and interventions that have been demonstrated to improve outcomes—or not—in human clinical trials.

Introduction

Pneumonia, acute lung injury, and acute respiratory distress syndrome

Pneumonia, the most common cause of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), is a lower respiratory infection involving lung parenchyma that is most often caused by respiratory viruses, common gram-negative or gram-positive bacteria and, worldwide, mycobacteria. Less frequently, pneumonia results from fungal or parasitic infections, although the risks of these are increased in immunocompromised individuals [1]. Bacterial pneumonia is categorized “Community-acquired” and “Hospital-acquired” pneumonia.

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Author Contribution

M.E.L. and J.C.H. conceptualized the scope, content and organization of the manuscript. M.E.L. drafted the manuscript and researched the field. J.C.H. and R.K.M. provided additional content, oversight and editing. All authors approve of the final manuscript.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Community-acquired pneumonia (CAP) refers to acute lung infections that occur outside of the hospital setting, with clinical presentations ranging from mild pneumonia including fever and cough to severe pneumonia associated with sepsis, acute respiratory failure, and ARDS [1]. Excluding Sars-CoV-2, 1.5 million adults are hospitalized with CAP annually in the U.S.A. [2]. A population survey conducted from 2010 to 2012 indicated an annual incidence of CAP requiring hospitalization of approximately 24.8 cases per 10,000 adults. Of those patients hospitalized for CAP, 21% required intensive care and the overall mortality was 2% [3]. Age is clearly a risk factor for severe CAP requiring hospitalization, as adults aged 65–79 years had an incidence of 63 per 10,000 adults, increasing to 164.3 per 10,000 in those over the age of 80 [3]. Hospital-acquired pneumonia (HAP) refers to pneumonia acquired two or more days after a hospital admission, and ventilator-associated pneumonia (VAP) is an infection acquired more than 2 days following initiation of mechanical ventilation [4]. The burden of HAP has been estimated to affect approximately 1.5% of all hospital admissions in the U.K., though the global burden of HAP is incompletely understood [5].

ARDS represents the clinical manifestation of diffuse, severe ALI characterized by the disruption of the alveolar-capillary barrier due to the death or dysfunction of alveolar epithelial cells and/or pulmonary capillary endothelial cells (Figure 1) [6]. While the operational definition of ARDS has evolved over time with the most recent iteration expressed as the Berlin Criteria (Table 1, adapted from [7]), the fundamental pathophysiologic processes that underlie the clinical syndrome have remained consistent: (1) it is a diffuse process as reflected in bilateral radiographic abnormalities, (2) there is severely impaired gas exchange as reflected by the ratio of measured arterial partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2), and (3) the radiographic and physiologic aberrations are not a primary consequence of heart failure.

ARDS has been estimated to result in ~190,000 cases annually in the U.S.A. (excluding SARS-CoV-2 infections), presenting a high burden on critical care systems globally, with mortality observed into the 40th percentile [6,8]. However, a recent global survey of ICUs suggests that mild ARDS is significantly underdiagnosed [9]. Pneumonia is a leading cause of ARDS, although it is important to recognize that most cases of pneumonia do not lead to ARDS. For example, pneumonia may be multifocal without causing severely impaired gas exchange, or can be anatomically restricted (lobar) and associated with impaired gas exchange. Moreover, ARDS can be the manifestation of a variety of other non-pulmonary infectious and non-infectious systemic processes. The multiple etiologies of ARDS can be categorized by whether there is a “direct” stimulus of injury to lung cells (which may be infectious pneumonia, or non-infectious such as aspiration of gastric contents, pulmonary contusion, toxic or thermal inhalation, or near drowning), or “indirect” stimuli in which the lung injury is part of a systemic inflammatory response triggered outside of the lung (such as sepsis from a non-respiratory infection, nonthoracic trauma, pancreatitis, severe skin burns, drug-induced, blood transfusion, cardiopulmonary bypass, or reperfusion edema following lung transplantation or embolectomy [10]. Pneumonia, aspiration pneumonitis, and sepsis account for the majority ARDS.

Hypoxemia

Disruption of epithelial and/or endothelial barrier function and disease severity differentiates ALI and ARDS from pneumonia. While the host response in pneumonia is contained within the alveolar space, the intact epithelium and alveolar-capillary barrier prevents the flooding of the alveolar space with high molecular weight proteins that characterize the alveolar environment of ARDS. Moreover, intact epithelial function allows removal of intraalveolar fluid and continued production of surfactant, such that it is relatively rare that patients with pneumonia have severe hypoxemia. In contrast, severe hypoxemia is a defining feature of ARDS that is thought to be the consequence of loss of alveolar-capillary barrier function. This disruption permits the accumulation of proteinaceous fluid in the alveolar space coupled with decreased compliance due to loss of surfactant. In many cases, the severe hypoxemia necessitates life-supportive mechanical ventilation and the delivery of high concentrations of supplemental oxygen. This approach, while life-saving, carries with it inherent risks in which the interventions (mechanical ventilation and high-concentrations of oxygen) can exacerbate the underlying lung injury.

Ventilator-induced lung injury

The selection of tidal volume and positive end-expiratory pressure (PEEP) has been clearly shown to affect mortality in patients with ARDS such that the implementation of “lung protective” ventilation strategies have become the standard of care [10]. Use of positive pressure mechanical ventilation is associated with risks of atelectotrauma and volutrama (Figure 2). Atelectotrauma, the cyclical collapse of a lung region at the end of respiration followed by reopening of the region during inspiration, is associated with ventilator-induced lung injury (VILI) in which the mechanical forces imparted to alveolar epithelial cells with the repetitive opening and closing of alveoli can, itself, injure epithelial cells and amplify the problem. For that reason, strategies have evolved to set levels of PEEP above the lower inflection point of the pressure–volume curve of the lung in attempts to minimize that repetitive injury. Of course, the application of PEEP can also have detrimental effects. For one, increasing PEEP can lead to “overdistention” of normally functioning alveoli. This overdistention can also injury epithelium (volutrauma), and in some cases cause a life-threatening pneumothorax. Thus, clinical management of patients with ARDS largely focuses on [1] employing PEEP to avoid microatelectasis, and [2] limiting tidal volumes and minimizing plateau pressures on the ventilator to avoid volutrauma. Within that conceptual framework, a number of approaches have been studied, including use of “driving pressures” to guide management and use of esophageal balloons as a surrogate for pleural pressures to titrate PEEP and optimize trans-pulmonary pressure gradients [11,12].

Pathogens and pneumonia

In the majority of pneumonia cases there is no definitive identification of the causative pathogen. While there are now a variety of culture-based and molecular diagnostic tests to aid in pathogen identification, a recent international study reported that the frequency of pathogen detection in adults hospitalized with CAP was only 36.5% [13]. This was consistent with a frequency of 38% reported in a surveillance study in the U.S.A. [3]. Of the 38% of cases with pathogens identified in the US study, 23% were due to one or

more viruses, 11% were due to bacteria and 3% noted detection of both virus and bacteria. Fungal or mycobacterial species were detected in 1% of patients (Figure 3). The three most commons pathogens positively identified were rhinovirus, influenza, and *Streptococcus pneumonia* [3]. One of the major limitations in this reported distribution is that lower respiratory track samples are not frequently obtained from patients with pneumonia due to the invasive nature of lower respiratory sampling; however, viral infections are commonly identified by PCR done on more easily accessible nasopharyngeal or oropharyngeal swabs.

Viral pneumonia

RNA viruses, including influenza and rhinovirus, are frequently implicated in pneumonia, though other viruses such as parainfluenza virus, adenovirus, respiratory syncytial virus, human metapneumovirus, and coronaviruses also cause disease [1]. In 2002, an outbreak of severe pneumonia due to SARS-CoV ("SARS") was associated with a mortality rate of approximately 10% [14]. In 2012, an outbreak of MERS-CoV was identified and has continued to cause severe illness with a mortality of approximately 35% [15]. The 2019 SARS-CoV-2 pandemic (which is ongoing as this manuscript is written) and its recurrent "waves" of infection spurred by emergence of new and challenging variant strains has placed an unprecedented burden on the global healthcare system due to high transmission rates among symptomatic and asymptomatic individuals combined with variable and inconsistent implementation of public health measures. As with other infectious causes of pneumonia, age and immunocompromised status are key risk factors for severe pneumonia and mortality from SARS CoV-2. In addition, obesity or metabolic syndrome has been well described to increase the risk of severe disease due to viral infection including influenza [16] and SARS-CoV-2 [17,18]. Among the coronaviruses causing severe pneumonia with acute lung injury, the case fatality rate of SARS-CoV and MERS-CoV appears much higher than SARS-CoV-2, though whether there are significant differences in the fatality rates due to different SARS-CoV-2 variant strains remains to be fully determined [19]. Regardless, the increased transmissibility and the duration of asymptomatic infectiousness have led to a number of SARS-CoV-2 infected individuals (>500 million worldwide) that is orders of magnitude greater worldwide than was seen with SARS-CoV (8500 total) or MERS-CoV (approximately 2500) [14]. Thus, despite the lower case fatality rate, SARS-CoV-2 infection has been estimated as the third-leading cause of death in the United States in 2020, trailing only heart disease and cancer, while influenza and pneumonia were the ninth leading cause of death [20]. Overall, respiratory viruses will continue to be a significant cause of pneumonia, and viruses with epidemic and pandemic potential retain the ability to significantly disrupt global life.

Bacterial pneumonia

Bacteria, including gram-negative and gram-positive species, are frequent causes of CAP and HAP. The most frequent cause of bacterial pneumonia is infection with the gram-positive *S. pneumoniae.* Vaccination strategies against *S. pneumonia* have resulted in replacement of serotypes colonizing individuals, as there are at least 98 serotypes in circulation [21]. While serotype replacement is a response to prevention strategies, a much larger problem globally is the evolution of anti-microbial resistance (AMR) in a large number of bacterial organisms. AMR-bacterial species pose increasing clinical challenges,

especially in the setting of HAP. While many bacterial species have attained AMR, the World Health Organization designated the ESKAPE pathogens, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species, as a priority of concern [22]. Many of these AMR bacterial species can cause hospital-acquired infections, pose severe risks for immunocompromised individuals, and can cause severe illness as causative agents of VAP.

Bacterial pathogens often have multiple virulence factors that allow them to evade or disrupt host defense mechanisms of the innate immune system. *Pseudomonas aeruginosa,* for example, utilizes a single flagellum and type IV pili that facilitates motility and attachment to epithelial cells. *Pseudomonas aeruginosa* has a type III secretion system (T3SS) encoding the effector proteins ExoS, ExoT, ExoY, and ExoU [23]. Secretion of ExoU into epithelial cells induces rapid cytotoxicity, and *P. aeruginosa* strains expressing ExoU are associated with more severe illness and adverse outcomes in pneumonia [23,24]. *Staphylococcus aureus* also has a variety of toxins that are able to lyse host cells, subvert host defense mechanisms, and contribute to pathology [25–27].

In addition to specific virulence factors of bacteria, whether bacteria are present as planktonic single-celled organisms or biofilm bacterial infections will impact the immune response. All bacterial species are able to form biofilms, which are unique multicellular communities [28]. Bacteria growing in biofilms produce an extracellular polymeric substance (EPS) matrix which consists mainly of polysaccharides, proteins, and extracellular DNA [29,30]. Recent studies have determined that in many bacterial biofilms, the Z-form of extracellular DNA is a key structural feature that imparts DNase-resistance to the biofilm matrix [31,32]. In many biofilms, living bacteria account for a small proportion of the biomass, while the EPS can account for more than 90% of the biomass. The low number of viable organisms and the physical barrier provided by the EPS confers remarkable antibiotic resistance properties to bacterial biofilm communities. Biofilms are more resistant to a variety of host defense mechanisms, including anti-microbial peptides and neutrophil mediated killing. Biofilm formation by *S. aureus* has been demonstrated to prevent phagocytosis by macrophages and modulate the inflammatory response to reduce organism killing by host defense mechanisms. *Staphylococcus aureus* biofilm mechanisms impacting development and potential treatment strategies have been extensively reviewed [30,33]. While biofilms are likely colonizing or present in individuals with pre-existing chronic lung diseases such as cystic fibrosis, abiotic surfaces such as endotracheal tubes serve as surfaces that facilitate bacterial attachment and formation of biofilms [34]. Therefore, biofilm driven pathogenesis is an increasing concern for hospitalized patients who have prolonged requirement for mechanical ventilation.

Secondary bacterial infection following viral pneumonia

While many viral and bacterial organisms are capable of causing severe pneumonia, secondary bacterial infections following a primary viral infection represent a potentially severe complication. Historically, severe influenza infection followed by secondary bacterial pneumonia such as *S. aureus* or *S. pneumoniae* has been a leading cause of morbidity and mortality [35,36]. For example, a predominant cause of mortality during the 1918 pandemic

influenza outbreak was bacterial pneumonia [37], and in studies of the 2009 H1N1 influenza outbreak, approximately one in four individuals had a secondary bacterial infection with the predominant causative agent being *S. pneumoniae* [38]. Viral infections have been found to alter the airway microenvironment to promote bacterial attachment or enhance biofilm formation [39–42]. Influenza A viral infection was recently demonstrated to increase epithelial cell surface expression of GP96 to promote *S. pneumoniae* binding, and influenza infection promotes the degradation and transcriptional repression of cell junction proteins to increase bacterial translocation across the epithelium [43].

Two paradigms of the host defense response, resistance and tolerance, have been used to further understand how viral infection may alter susceptibility to bacterial infection. Resistance refers to the ability to detect and eliminate pathogens, while tolerance describes the ability to facilitate tissue adaptation to a level of pathogen burden [44–49]. To investigate these paradigms, an experimental murine model utilizing *L. monocytogenes* infection following influenza virus infection has been used. These studies uncovered that influenza virus infection increases glucocorticoid production that functions to promote protection from tissue pathology at the expense of suppression of systemic antibacterial host defense mechanisms [50]. Thus, virus-induced changes in the host response may have a protective role in limiting tissue pathology but may also result in increased susceptibility to subsequent infection. Together, the paradigms of resistance and tolerance highlight the complex balance of host immunity and tissue pathology that often exists with complex other confounding factors for individual patients. These examples are only a few of many important factors underlying the pathology of secondary bacterial infections, and additional details of the cellular mechanisms regulating the host response to viral and bacterial infection will be discussed in subsequent sections.

Pulmonary host-defense mechanisms and host-response to pneumonia

In addition to pathogen—driven damage, the innate and adaptive immune responses to infection often drive pathology through excessive inflammation and failure to resolve the inflammatory response to infection. To further understand the pathogenesis of pneumonia and ALI, key aspects of pulmonary physiology and host defense mechanisms will be highlighted so that dysregulation of these mechanisms during pneumonia and ALI/ARDS can be further discussed.

Pulmonary cell populations

Cellular specialization has been long appreciated in the lung, and recent technological advances have facilitated the identification of previously unappreciated specialized cell subsets, greatly expanding the complexity of cell types present in the lung during health and disease. For example, a recent single-cell RNA sequencing (scRNA-seq) study identified a remarkable 58 unique molecular cell types in the human lung [51]. Among these unique identities are multiple types of epithelial cells, endothelial cells, structural cells (fibroblasts, myofibroblasts, pericytes), and resident immune cells such as alveolar macrophages. Additionally, an array of immune cells patrols the alveolar, interstitial, and vascular niches of the lung. While transcriptional profiles do not delineate the function

of each cell type, our increasing appreciation of complexity of lung tissue during health and disease is further supported by studies employing mass cytometry (Cytometry by time of flight, CyTOF) and advanced histological methods that incorporate spatial information with cellular identity information from either transcriptomic or flow cytometry methods. Additional technologies that have utilized methods to trace and track the origin of cells in tissues have advanced the understanding of the heterogeneity and complexity of tissues. For example, identification of the yolk-sac origin of alveolar macrophages [52] has advanced the understanding of macrophage heterogeneity in disease [53–55]. Further, new epithelial cell types such as the pulmonary ionocyte, which has high expression of the cystic fibrosis transmembrane conductance regulator (CFTR), have been discovered [56,57], and differences in mesenchymal cells and fibroblast phenotypes have recently been recognized [58,59]. While studies demonstrating the differential functions of many of these cell types remain to be performed, there is precedent that infection likely modulates important cellular behaviors. For example, recent evidence has described that respiratory viral infection can result in the induction of different fibroblast activation states that have been described as ECM-synthesizing, damage-responsive, or interferon-responsive [60]. These fibroblast activation states are thought to program the inflammatory and immune response by modifying the lung microenvironment [60]; however, further studies are needed to clarify whether these states are due to distinct fibroblast lineages. Moreover, how these phenotypes are induced in response to different infections remains to be determined. Clearly there are ample gaps in knowledge pertaining to how heterogenous pulmonary cell interactions collectively affect function in health and disease. Increased understanding in this biology will likely yield novel insights into the pathobiology of pneumonia and ALI and identify novel therapeutic targets.

Innate defenses of the pulmonary alveolar and airway spaces

The pulmonary airway and alveolar spaces have multiple mechanisms to protect the host from infection, and airway-specific factors provide a critical defense against infection. Lining the respiratory epithelium is a fluid barrier referred to as the airway surface liquid (ASL), which comprises a mucus layer and a pericellular fluid layer that is in contact with the respiratory epithelium [61]. Ciliated respiratory epithelial cells have coordinated ciliary motion that results in migration of mucus and materials to the pharynx where it is swallowed, a process collectively referred to as mucociliary clearance [61,62]. Some bacteria have evolved mechanisms to disrupt mucus and mucociliary clearance. For example, the *S. pneumonia* proteins neuraminidase A and β-N-acetylglucosaminidase degrade mucus and disrupt mucociliary clearance [21]. In addition to acting as a physical barrier to microbes and foreign particles, the ASL has critical functions in host defense at the apical side of the respiratory epithelium, where cationic antimicrobial proteins selectively target and disrupt the negatively charged microbial membrane [63]. In addition to secreting many of the anti-microbial proteins in the ASL, epithelial cell ion channels contribute to the maintenance of the ASL height and acidity, which are important for maintaining anti-microbial functions. For example, loss of CFTR function results in acidification of the ASL and inhibits antimicrobial function of proteins such as lysozyme [64,65]. Beyond direct killing mechanisms by cationic antimicrobial peptides, host mechanisms that decrease the availability of extracellular iron are important anti-bacterial

defense mechanisms. For example, lactoferrin chelation of iron prevents the ability of *P. aeruginosa* to form biofilms [66]. In addition, the distal lung, specifically alveolar type II epithelial cells, secrete surfactant that not only maintains low-surface activity to stabilize the lung but also releases surfactant-associated proteins, SP-A and SP-D that act as collectins, binding and inhibiting actions of a variety of virulent pathogens [67]. The existence of naturally occurring mutations within these collectins may alter vulnerability to lower tract infection [68]. Overall, whether due to host genetics, environmental factors, or pathogen virulence factors, disruptions in mucociliary clearance, ASL, or surfactant composition creates a microenvironmental niche that can support growth of opportunistic bacterial organisms.

Innate immune pattern recognition receptors (PRR) and the complement system facilitate immune cell recruitment

While mucus, ASL, and surfactant act as physical barriers that contain potent anti-microbial defense mechanisms, respiratory epithelial cells have a host of receptors located on the cell surface and intracellular compartments that are able to detect pathogen-associated molecular patterns (PAMP) and host-derived danger-associated molecular patterns (DAMP). Humans have 10 members of the Toll-like Receptor (TLR) family, which are highly conserved receptors that initiate pro-inflammatory signaling events following ligand binding. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are expressed on the cell surface while TLR3, TLR7, TLR8, and TLR9 detect their ligands within intra-cellular endosomal compartments [69]. Ligand binding of TLRs results in formation of dimer receptor complexes to initiate signaling cascades. While most TLRs form homodimers, TLR2 heterodimers contain either TLR1 or TLR6 based on ligand specificity [70]. Initiation of TLR signaling results in the selected recruitment of the major adaptor proteins MyD88, TIRAP (Mal), TRIF, or TRAM that direct the intracellular signaling cascade and transcriptional response [69]. TLR signaling through these adaptors results in activation of several different kinase pathways, including NFKB, JNK, ERKs, among others, and increased transcriptional activation of target genes [69]. The TLR-pathway dependent increased production and secretion of cytokines and chemokines promotes the recruitment of cells of the innate and adaptive immune system to the site of infection or injury. For example, a *TLR1* polymorphism resulting in increased TLR1 surface expression and increased NFKB pathway activation was associated with worse outcomes in sepsis and acute lung injury [71].

While epithelial cells are often first responders to respiratory pathogens, alveolar macrophages and recruited monocytes also express a robust array of PRRs and serve integral functions in detecting and directing the inflammatory response to pathogens [72–74]. Additional intracellular sensors that detect PAMP and DAMP are the NOD-like receptors (NLRs), RIG-I-Like receptors, and cytosolic DNA sensors such as AIM2 and the cGAS-STING pathway. Detection of PAMP and DAMP by these receptors initiates signaling cascades that stimulate production and secretion of chemokines and cytokines, aid in the recruitment of additional immune cells and in many cases will also initiate cell death mechanisms that will further influence the overall inflammatory response in the alveolar niche.

In addition to these host defense mechanisms, innate immune proteins of the complement pathway family function to directly target microbes for killing via opsonin-mediated lysis or by opsonin-dependent phagocytosis. Opsonization of microbes also promotes recruitment of immune cells by directing chemotaxis toward sites of infection [75]. Despite the multifaceted innate immune functions of proteins comprising the complement system, bacteria have evolved multiple mechanisms to disrupt or evade complement deposition on their surface, and engineering of human antibodies to facilitate opsonization and killing of bacteria is an active area of investigation [76,77].

Mechanisms regulating host cell death during health and infection

Molecular mechanisms regulating cell death are vast, and have been recently reviewed [78]. Two broad categories of cell death that are especially important during pneumonia and ALI/ARDS are caspase-dependent and caspase-independent mechanisms. Caspase-dependent pathways can result in either apoptosis or a more inflammatory type of cell death termed pyroptosis. Apoptosis can be induced by both extrinsic and intrinsic mechanisms, where extrinsic apoptosis, also referred to as receptor-mediated apoptosis, is initiated by ligand-binding death receptors including FAS (CD95) binding to Fas-ligand (FasL) and death receptor 5 (DR5) binding to TNF-related apoptosis-inducing ligand (TRAIL). Death receptor signaling will induce activation of a caspase cascade and ultimate activation of the executioner caspase-3 [78]. As the regulation of cell death pathways are diverse and complex, there are multiple opportunities for host genetics to influence responses to pneumonia or ALI. For example, genetic variants in human *FAS* have been associated with ALI/ARDS [79], and recently described to be associated with soluble Fas levels and organ dysfunction in two cohorts of critically ill individuals [80]. In addition to apoptosis, detection of pathogens through conserved PRR often result in activation of caspase-1 dependent cell death, termed pyroptosis. Studies have demonstrated that *P. aeruginosa*-induced pyroptosis, and lung pathology, is dependent on stimulation of TLR5 and NLR-family CARD domain containing protein 4 (NLRC4) by bacterial flagellin and its type III secretion system [24,81–83]. Pyroptosis results in the activation and secretion of IL-1β, which has fundamental roles in promoting the inflammatory response. Execution of pyroptotic cell death requires the activation of Gasdermin D, which functions to lyse cellular membranes by formation of a large transmembrane pore [84]. Propagation of cell death via transfer of active GSDMD in microparticles may amplify the pyroptotic response to pathogen infection [85–87]; however, additional roles for these mechanisms in pneumonia and ALI/ARDS, and whether they may be therapeutic targets, require further investigation.

In addition to the caspase-dependent molecular mechanisms regulating apoptosis and pyroptosis, caspase-independent programmed cell death mechanisms also exist. Receptor interacting protein kinase 1 (RIPK1) and RIPK3 are central to programmed necrosis, also termed necroptosis [88]. RIPK1 and RIPK3 facilitate the activation of mixed lineage kinase domain-like pseudokinase (MLKL), which forms homo-oligomer structures and inserts into the plasma membrane. Similar to GSDMD, the results in a transmembrane pore formation and cell death [89,90]. The necroptosis pathway has important functions in regulating responses to pulmonary infection and injury. For example, critically ill patients receiving mechanical ventilation had higher plasma levels of RIPK3, but not RIPK1 or MLKL,

and a in a murine model of ventilator-induced lung injury, RIPK3 knockout animals were protected from lung injury compared with wild-type mice [91]. Additional functional roles of necroptosis in regulating pulmonary diseases and their potential as therapeutic targets has recently been reviewed in depth [92]. Overall, lung infection and injury have the potential to initiate multiple pathways of programmed cell death that influence the severity of disease.

Interferon programming of antiviral responses

In addition to the recruitment of cells of the innate and adaptive immune system, detection of viral PAMP by infected cells (including epithelial cells and a number of immune cells depending upon the virus) results in secretion of type I and type III interferon to induce potent antiviral responses in neighboring cells. Type I and III interferon also increase activation of dendritic cells that migrate to lung-draining lymph nodes to initiate activation of effector cells of the adaptive immune system [93]. Therapies targeting type I and type III IFN responses have been the subject of much investigation, as it is postulated that activation of these critical antiviral responses may reduce pneumonia severity. In a recent clinical trial, treatment with IFN-β-1a and the antiviral compound Remdesivir, compared with Remdesivir alone, did not improve outcomes in adults hospitalized with COVID-19. In fact, the addition of IFN-β-1a was associated with worse outcomes in patients on high-flow oxygen [94]. In contrast with type I IFN, type III IFN also has important antiviral effects and is thought to be less inflammatory, partially due to more restricted receptor expression compared with the receptors for type I IFN [93,95]. Additionally, while both type I and type III IFN signal via the JAK/STAT signaling cascade and NFKB, differential downstream transcription factor usage and downstream gene activation may occur following type III IFN signaling compared with type I IFN, but this is an area of active research [96,97]. The therapeutic use of peginterferon lambda is currently under investigation as an antiviral therapeutic, and a single subcutaneous injection within the first seven days following confirmation of SARS-CoV-2 infection accelerated viral clearance [98]. Whether peginterferon lambda has therapeutic utility during severe viral pneumonia or ARDS is unknown. Type I and III interferon also have important functions by stimulation of both resident and recruited cells of the innate and adaptive immune systems during lung injury and infection. Notably, while type I and III interferon responses have key roles in driving the host response to bacterial infections, therapeutic interventions to induce interferon responses during bacterial pneumonia are generally not thought to be beneficial [99].

Neutrophils balance the host defense response

Cytokine and chemokine secretion, and activation of complement cascade, results in activation of the innate and adaptive immune response. Neutrophils, innate immune cells that have potent anti-microbial effector functions, are often the first cells to be recruited to the site of infection or injury. Neutrophil migration out of circulation and into tissues occurs by highly regulated chemotaxis mechanisms, and neutrophil-to-neutrophil communication results in extravascular swarming behavior, mediated, in part, by leukotriene B4 (LTB4) [100], which coordinates a robust inflammatory response. Neutrophil swarming is also controlled by G-protein-coupled receptor desensitization mechanisms that limit neutrophil recruitment to prevent excessive tissue destruction [101]. A therapeutic intervention antagonizing the LTB4 receptor (LTB4R) was investigated in the context of cystic fibrosis

(CF), where chronic infection and neutrophil recruitment contributes to lung pathology. However, the human trial of this compound was halted due to increased pulmonary exacerbations [102], and subsequent murine studies showed that while this compound reduced neutrophil recruitment during *P. aeruginosa* infection, it also impaired bacterial clearance and resulted in increased bacteremia and lung inflammation [103]. In murine models of influenza infection, depletion of neutrophils at the time of infection increases mortality; however, neutrophil depletion at late time points was protective in aged mice [104,105]. These studies highlight the critical role of neutrophils in balancing clearance of organisms and limiting tissue pathology while also emphasizing the time-dependent differential effects that inflammatory cells can exert during the evolution and resolution of lung infection.

Neutrophils release multiple serine proteases, such as neutrophil elastase (NE), which have anti-microbial functions, but also indiscriminately cause tissue injury. While potentially pathological roles of NE are well appreciated, NE also has important roles in protection against gram negative bacteria and *S. pneumonia,* and cleaves multiple PRRs to decrease pro-inflammatory signaling [106]. Recognizing the potential benefit of limiting non-specific tissue damage, pharmacologic inhibitors of NE have been the subject of much investigation [107] and other strategies have aimed to more broadly inhibit neutrophil degranulation [108]. For example, “Nexinhibs” are small molecule inhibitors that target the interaction between Rab27a, an essential regulator of neutrophil exocytosis, and the protein JFC1, a Rab27a effector. Nexinhibs are able to prevent neutrophil exocytosis without altering phagocytosis abilities or formation of neutrophil extracellular traps (NETs, as discussed in the following section) [109]. Recently, the compound Nexinhib20 was formulated in a novel nanoparticle embedded microgel system to enhance delivery to the lower airways, demonstrating beneficial anti-inflammatory effects in murine lung injury models [110]. Whether application of Nexinhib containing therapeutics have the ability to alleviate host driven pathology in pneumonia or ALI without impairing host defense remains to be determined.

Formation of NETs, characterized by the activation-induced release of extracellular DNA, histones, NE, and other neutrophil proteins such as myeloperoxidase (MPO), represents another important host defense mechanism of neutrophils [111]. As with other neutrophil defense mechanisms, the protective function of NETs can be offset by their ability to also contribute to tissue damage [112]. Patients with VAP and ARDS had higher alveolar concentrations of MPO-DNA and cell-free DNA, biomarkers of NET formation than patients with ARDS alone. Notably, increased levels of NETs correlated with bacterial burden and levels of IL-8 [113]. Extracellular DNA increases mucus viscosity, potentially contributing to impaired mucociliary clearance [114]. To reduce and degrade extracellular DNA, recombinant DNase I has been utilized as a routine therapy for patients with CF [115] and for pediatric critically ill patients to reduce mucus plugs and atelectasis [116,117]. Despite use in pediatric patients and in adults with CF, only few case reports of DNase therapy in adults without CF have been reported [118]. The use of recombinant DNase I in patients with ARDS secondary to COVID-19 pneumonia has been reported, suggesting that treatment may improve oxygen saturation [119]. A key step in NET production is regulated by proteins of the peptidyl arginine deiminase (PAD) family that

are critical for histone citrullination. The essential role of PAD proteins in regulating NET formation and antibacterial immunity have been established in studies using PAD4 knockout mice [120], and additional studies have described roles for PAD2 in modulating NETs or the response to NETs [121–123]. Pharmacologic inhibitors to PAD2 and PAD4 have been developed, although they have not been tested in human pneumonia or ALI. Additional immune cell types, including monocytes [124], macrophages [125], and T-cells [126–128] also form extracellular traps, but their relevance in the context of pulmonary infection has not been clearly established. Overall, neutrophils are key immune effectors whose functions are critical for elimination of pathogens, but these cells can also drive deleterious tissue-damaging inflammation. Neutrophils and their secreted products remain the focus of investigation to limit host-mediated lung pathology during infection and ALI. While neutrophil accumulation has the potential to cause severe tissue damage, neutrophil extravascular migration also contributes to subsequent recruitment of monocytes to the site of infection or injury through coordination of CCL2 and CCL3 driven chemotaxis [129].

Monocyte recruitment during infection

Blood monocytes are a heterogeneous cell population derived from bone marrow precursors. Monocytes are capable of responding to inflammatory signaling and migrating to tissue sites of infection or injury by directed chemotaxis. Circulating monocytes in mice and humans have been categorized into different subsets by surface marker expression that correlates with their abilities to respond to chemotactic signals and their functions. In mice, the two predominant subsets are designated as $Ly6C^{hi}$ or $Ly6C^{low}$ monocytes, with $Ly6C^{hi}$ having high expression of CCR2 and $Ly6C^{low}$ cells having high expression of CX_3CR1. In humans, circulating monocyte subsets can be identified based on differential CD14 and CD16 expression. $CD14^{+}CD16^{-}$ monocytes, also referred to as classical monocytes, share features with murine $Ly6C^{hi}$ monocytes and are recruited by CCR2-mediated chemotaxis [130,131]. Human CD16+ monocytes can be further subdivided into $CD14^{+}CD16^{++}$, also referred to as non-classical monocytes and comparable to murine $Ly6C^{low}$ patrolling monocytes, or $CD14^{++}CD16^{+}$ intermediate monocytes [132]. Monocytes secrete cytokines that augment responses of both innate and adaptive immune cells in the response to bacterial, fungal, and viral infections in the lung [133]. Further, monocyte interactions with T cells during influenza infection drive differentiation of lung resident memory CD8 T cells, demonstrating critical roles in programming long-term immunity [134]. However, monocyte recruitment to the lung can further enhance pathology, in part, by expressing the apoptosis-inducing ligand TRAIL. For example, the CCR2-dependent recruitment of monocytes following influenza pneumonia and *S. pneumoniae* secondary infection results in increased epithelial cell damage and increased bacterial growth, which can be inhibited by blocking TRAIL-induced apoptosis [135]. In addition to recruitment during inflammation, recent studies in mice have demonstrated that there are at least two distinct subpopulations of long-lived, non-alveolar resident tissue monocyte-derived macrophages in the lung, collectively referred to as interstitial macrophages [136]. Further studies utilizing human lung tissue explants may yield additional insight into the identification of function and spatial localization of monocyte populations and their relevance to the pathogenesis of pneumonia and ALI.

Alveolar macrophages

Bacterial and viral organisms that evade the host defense mechanisms of the upper airways and transition to the alveolar spaces encounter additional cellular and acellular host defense mechanisms beyond those described above. Resident alveolar macrophages are a unique immune cell population derived from different embryonic precursor cells compared with other tissue macrophages and monocytes that function to clear organisms and debris from alveoli [52]. During inflammation, these cells are able to proliferate and repopulate so that they are not depleted following cell death [137]. *In vivo* imaging studies show that alveolar macrophages patrol multiple alveoli and migrate to bacteria to phagocytose and clear the organisms, thus limiting neutrophil recruitment and the amplification of inflammation [138]. Interestingly, influenza infection decreases the ability of alveolar macrophages to patrol alveoli and clear bacteria, providing insight into the mechanisms of post-viral secondary bacterial infection [138]. Macrophages that are unable to kill ingested bacteria can serve as a niche for pathogen survival and replication, as has been reported for *S. aureus* [139–141]. Single-cell transcriptional analyses from healthy adults identified multiple subsets of airway macrophages, most of which aligned with resident alveolar macrophage origin while some data suggest derivation from circulating monocytes [53]. Monocytes and monocyte-derived macrophages have plasticity and incorporate a range of environmental cues to program their cellular phenotype. These phenotypes, often termed macrophage polarization, are often oversimplified into a M1 and M2 phenotypes based on *in vitro* experimental conditions [142]. However, this spectrum of macrophage polarization states does influence the immune response and is associated with Th1 and Th2 immune programming [143] which can be manipulated by therapeutic interventions in murine models of infection and ALI [144,145]. Interestingly, macrophage polarization or reprogramming may be long lasting following infection. In a murine model of *S. pneumoniae* infection, alveolar macrophages regionally localized to an affected lobe with pneumonia, maintained differential expression of cell surface markers 6 months following infection. Moreover, changes in their metabolomic and transcriptomic profiles were identified one month following infection [146]. In humans, assessment of BAL macrophage polarization by transcriptomic profiling or cell surface markers may also serve as biomarkers associated with outcomes in ALI/ARDS [54]. The diversity of macrophage populations and their central importance as regulators of pulmonary health positions these cells as significant drivers of detrimental host immune responses that can potentially be targeted to alleviate pathology in ALI and promote resolution of inflammation [147]. Overall, application of multidimensional data acquisition and analysis techniques to characterize monocyte and macrophage subtypes will continue to yield new insights into the mechanisms regulating pulmonary inflammation and its resolution.

Surfactant homeostasis

As stated above, surfactant is a composition of both lipids and proteins, each with important properties that are essential for normal lung function. In addition to the host defense mechanisms of the alveolar macrophage populations, surfactant proteins, particularly SP-A and SP-D, present in the alveolar space have direct anti-microbial functions and can promote microbial phagocytosis by resident or recruited phagocytes. However, the primary role of surfactant is to prevent the collapse of the alveolar space during respiration by lowering surface tension at the air-liquid interface in alveoli through actions of the

major lipid dipalmitoyl-phosphatidylcholine and the key hydrophobic proteins, SP-B and SP-C. Surfactant is depleted or altered in pneumonia and ARDS, and altered surfactant homeostasis, with resultant deficiency or excess, can lead to disease. We recently reviewed detailed roles of surfactant in lung disease and host defense [148]. Of note, viral and bacterial infections resulting in type II alveolar epithelial cell death can disrupt surfactant production. In contrast, excess surfactant accumulation, as seen in pulmonary alveolar proteinosis, can impair gas exchange. Hereditary and acquired conditions that disrupt GM-CSF signaling impair the ability of alveolar macrophages to process and degrade surfactants, highlighting a critical function of alveolar macrophages in maintaining homeostasis of the lung [149]. Surfactant deficiency causes respiratory distress syndrome in preterm infants and can be prevented by treatment with surfactant [150,151]. In contrast with neonatal respiratory distress, direct delivery of surfactant proteins has not shown benefit in adults with ARDS [152,153]. Nevertheless, new research indicates that treatment with liponucleotides, essential precursors for surfactant phospholipid synthesis, can attenuate influenza virus induced ALI in mice [154], demonstrating that modulation of surfactant might hold promise in the clinical management of ALI/ARDS.

Contribution of adaptive immunity to host defense and pathology

In addition to innate immune host defense mechanisms, the adaptive immune system aids in regulating the balance between infection control/clearance and tissue pathology. B cells are critical for generating antibody responses to pathogens and T cells program the immune response and also serve to eliminate infected cells in the lung [155]. CD4+ T cells have important roles in helping B cells mount antibody responses (T follicular helper cells, T_{FH}) or secrete interferon-gamma (Th1) and IL-17 (Th17) depending on their programming to enhance macrophage and neutrophil bactericidal functions and to modulate epithelial responses [156,157]. While neutralizing antibodies are important, CD8 T cell responses are required for clearance of primary respiratory virus infections such as influenza virus and SARS-CoV-2 infections [158]. Further, memory CD8 T cells can mediate protection in settings when infection avoids neutralizing antibody responses [93]. In contrast with protective CD8 T-cell functions, memory CD8 T-cells have also been reported to contribute as drivers of lung pathology following RSV infection [159], demonstrating that T cells can have both protective and detrimental roles during infection. Further, host factors such as obesity have large impacts on decreasing the effectiveness of vaccination, in part, through impairing development of effective T cell immunity. Obesity is a major risk factor associated with increased risks of infection and hospitalization [16,160]. Protective and detrimental roles of gamma-delta T cells have been described during *S. aureus* pneumonia, where mice lacking this specialized T cell subset have attenuated bacterial clearance but also less lung tissue damage [161]. Decreased levels of CD4+ and CD8+ T cells in HIV infection both increase risk of bacterial pneumonia [162–165], further highlighting the important antibacterial role of T cells in the lung. Overall, these multifaceted roles for adaptive immunity in balancing pathogen clearance versus pathology during respiratory pathogen infection are still not well understood and active areas of investigation.

The lung microbiome

A traditional paradigm in pulmonary biology historically suggested that the lung microenvironment was sterile. Application of culture-independent methods, however, have conclusively demonstrated that the lung has a microbiome and that the composition of the microbiome changes during disease [166–172]. While the bacterial burden of the lung microbiome is comparatively much lower than some other anatomical sites, it is likely that interactions of the lung microbiota, pathogenic organisms, and the host immune system are important in directing the outcomes of pneumonia and ALI. Ongoing challenges to better understanding of the role of the lung microbiota in health and disease are the inability to culture many of the bacterial organisms detected by culture-independent methods, and barriers to sample collection from the lower airways of patients with severe respiratory failure [173]. Other unresolved questions are whether regional changes in lung microbiota occur during pneumonia and ALI, and if they do, how they impact disease outcome. For example, during chronic infection in CF, heterogeneity in the evolution of *P. aeruginosa* was observed based on regional isolation in the lung and this may promote one mechanism by which *P. aeruginosa* avoids elimination by antibiotics. Incorporation of culture-independent methods to pneumonia and ALI/ARDS research should continue to inform how the microbiota interacts with the host response to infection to impact disease outcomes.

Epithelial cell regeneration and mechanisms of alveolar-capillary barrier disruption

The mechanisms regulating local versus diffuse injury in pneumonia remain unclear, though they likely involve both host and pathogen factors, with multiple routes that can result in breakdown of the alveolar-capillary barrier. Direct infection of epithelial cells by viruses or bacteria will result in epithelial cell death, and many human genetic determinants of epithelial infection have been recently reviewed [174]. Disruption of the epithelial cell barrier presents an opportunity for microorganisms to invade new locations, where they may encounter different structural cells in addition to endothelial cells. Similar mechanisms of cell infection, invasion, and lysis by microbial secreted factors may disrupt the integrity of the endothelial cell layer. For example, influenza virus replicates in ciliated respiratory epithelial cells as well as type I and type II alveolar epithelial cells and club cells, demonstrating the capability to disrupt the epithelial barrier in multiple locations and to disrupt critical functions of type II epithelial and club cells that maintain surfactant properties and the alveolar fluid balance [175–178]. The recruitment of neutrophils and monocytes have the capacity to induce epithelial and endothelial cell death by multiple mechanisms that include secretion of toxic effector molecules, NETs, or the activation of epithelial cell death receptors. Bacterial species have numerous secreted factors and toxins that are able to induce cell death or lysis. Following damage to the epithelial cell barrier, alveolar epithelial regeneration of type I and type II epithelial cells occurs by proliferation of type II cells and transdifferentiation into ATI cells, through multiple mechanisms recently described and reviewed [179–183]. The balance of epithelial injury and epithelial repair is influenced by the pathogen and the host immune response and is a central regulator of the recovery from pneumonia and development of ALI/ARDS.

Clinical phenotypes, biomarkers, and ALI and ARDS outcomes

While the interplay of host-pathogen interactions likely dictates the duration and outcome following pneumonia, significant gaps in knowledge remain in understanding the mechanisms of regulation and resolution of infection and inflammation during pneumonia and severe disease that progresses to ALI/ARDS.

Heterogeneity of ARDS and response to clinical interventions

Clinical responses in individuals with ARDS are heterogeneous, often difficult to predict, and are likely the result of complex host, pathogen and environmental factors. A main hypothesis in the field is that ARDS due to direct lung injury, such as pneumonia or aspiration, is associated with higher biomarkers of epithelial cell injury compared with indirect ARDS (e.g., due to sepsis), which is hypothesized to have higher levels of endothelial injury [184]. Several clinical cohorts were used to measure plasma biomarkers indicative of lung epithelial or endothelial injury to evaluate this hypothesis. The results indicate that biomarkers of epithelial injury, such as surfactant protein D were significantly higher in patients with direct ARDS, and biomarkers of endothelial injury, such as angiopoietin-2, were significantly elevated in individuals with indirect ARDS [184]. These findings highlight that there are different biological mechanisms of ARDS, and that clinical interventions specifically targeting pathways depending on the underlying driver of injury would likely provide benefit. Further, clinical studies have identified that the four plasma biomarkers, interleukin-6, interferon gamma, angiopoietin 1/2, and plasminogen activator inhibitor-1 can predict ARDS mortality with either an uninflamed or reactive sub phenotype [185]. In addition to ARDS, recent analyses of two independent ICU cohorts further suggest that patients with acute hypoxemic respiratory failure (HRF) defined by invasive mechanical ventilation with a PaO_2-to-FIO_2 ratio ≤ 300 who did not resolve on day three after ICU admission had elevated levels biomarkers of inflammation (IL-6 and IL-8) and endothelial dysfunction (antiopoietin-2) in blood [186]. These data indicate that in critically ill populations requiring mechanical ventilation but not meeting the diagnoses of ALI/ARDS, similar mechanisms of epithelial and endothelial cell damage may be occurring and may be identified by disease biomarkers. Common clinical research techniques have utilized bulk transcriptomic analysis of whole blood or peripheral blood mononuclear cells to investigate the gene expression signatures that may be associated with outcomes in pneumonia or ALI/ARDS. However, one limitation of this method is that the transcriptional signatures of peripheral blood cells may not reflect the inflammatory process occurring in the alveolar space [187]. While difficult to employ in collection of samples from large clinical cohorts, application of methods including single-cell RNA-seq from blood and bronchoalveolar lavage will likely continue to expand our understanding of the cellular and molecular mechanisms driving ARDS and its resolution. Further understanding on the mechanisms by which mechanical ventilation exacerbates pneumonia pathogenesis are needed.

Hyperoxia-induced lung injury and dysregulation of the lung microbiome

As understanding of the lung microbiome has increased, it has increasingly been appreciated that interventions employed for patients with pneumonia, including administration of

antibiotics, supplemental oxygen, and mechanical ventilation that can alter the microbiome and, thereby, impact host responses. We have noted that delivery of supraphysiologic oxygen concentrations is frequently necessary in the life-supportive care of patients with ARDS. However, recent studies suggest that hyperoxia alters lung and gut bacterial communities, and it has been hypothesized that these changes in microbiota contribute to oxygen-induced lung injury [188]. In one study, protection from oxygen-induced lung injury in mice was observed in mice reared under germ-free protocols; however, delivery of systemic antibiotics increased measures of inflammation and oxygen-induced lung injury in non-germ-free mice [188]. These data suggest that alterations in microbial communities and their relationship to pathology are complex. Interestingly, changes in lung bacterial communities were observed 24 h following hyperoxia exposure, whereas lung injury from this model was not detectable until 72 h following hyperoxia [188]. This suggests that microbial responses may be driving hyperoxia-induced lung injury and that the microbial community could be harnessed to identify additional biomarkers that associate with clinical outcomes or lung injury phenotypes.

Microbiome changes are likely also important in driving responses during ALI/ARDS. In a small cohort of critically ill patients, culture-independent methods were used to show that bacterial burden and presence of gut-associated bacteria were associated with fewer ventilator-free days and ARDS [189]. An additional report utilizing the murine cecal ligation and puncture (CLP) model of sepsis reported detection of gut bacteria in the lung on day five following injury that had cleared by two weeks following injury. In this study, direct lung injury from intratracheal administration of LPS did not induce translocation of gut bacteria to the lung, however in a systemic LPS-induced shock model translocation of gut bacteria to the lung was observed [190]. In contrast, a separate LPS-induced lung injury model, also using intratracheal LPS delivery did report altered lung microbiota [191]. What accounts for the discrepancy in these findings of the murine LPS-ALI model remains unclear. In a small cohort of ARDS patients and healthy controls that measured 16S RNA copy numbers from bronchoalveolar lavage fluid, it was shown that bacterial copy numbers were increased in ARDS [192]. These data suggest that ratios between pathogenic and commensal bacteria in the lung could be utilized as a biomarker of illness severity in ARDS. Overall, additional preclinical and clinical studies are required to further examine the relationship between lung commensal organisms and the presence of typical respiratory pathogens in addition to translocation of organisms from the gut.

Immune modulation in the management of pneumonia and ARDS

The diagnosis and treatment of pneumonia is largely based on empiric treatment with antibiotics or antiviral therapies based on the context, severity, and pathogen-specific information as detailed by ATS and IDSA guidelines [193]. Adjunctive therapies targeting host-inflammatory pathways, remain an enticing area of active investigation. Broad-spectrum immune suppression with routine use of corticosteroids is not recommended in non-severe or severe influenza pneumonia [1,193–195]. However, recent analyses of 17 randomized controlled trials assessing the efficacy and safety of corticosteroids as an adjunct to antibiotics demonstrates that corticosteroid therapy reduced mortality in adults with severe CAP but did not have a survival benefit for non-severe CAP [196]. In viral

pneumonia, previous clinical trials from influenza, SARS-CoV, or MERS-CoV suggested no benefit of corticosteroids or even deleterious effects of corticosteroid use [194,197–200]. Experimental models utilizing primary human airway epithelial cell *in vitro* infection with either rhinovirus or influenza A virus demonstrated that glucocorticoid treatment reduced cellular antiviral mechanisms and allowed increased viral replication [201]. Further, in a mouse model of influenza A virus infection, glucocorticoid treatment starting 48 h prior to infection significantly increased viral load, illness and mortality compared with mice receiving vehicle control treatment [201]. Despite these potential harmful effects of steroids during viral infections, corticosteroid treatment during SARS-CoV-2 infection has been investigated by multiple large multi-center RCTs and a meta-analysis sponsored by the World Health Organization [202–207]. For example, the RECOVERY trial found that dexamethasone treatment reduced mortality by 33% in patients on mechanical ventilation and by 20% in patients requiring treatment with supplemental oxygen [204]. Steroids have also been evaluated as a therapy in ARDS for several decades with conflicting results. For example, one large sentinel study [208] showed no clear benefit in mortality (and increased mortality with treatment starting after 14 days of ARDS) but did show a benefit in physiologic parameters and a reduction in ventilator-free days. In a more recent trial, treatment with dexamethasone showed promising results with reduced mortality and increased ventilator free days, although the trial was stopped early due to poor enrollment [209]. There have been a vast array of emerging therapies entering clinical trials for ARDS, especially since the onset of the SARS-CoV-2 pandemic. These therapies, many which have immunomodulatory properties or target defined cellular responses, have recently been reviewed [210]. Overall, the role of immune modulation as a treatment for lower respiratory tract infections and ARDS continues to evolve.

Summary and future outlook

Pneumonia and ALI/ARDS are major disease burdens globally and account for significant morbidity and mortality worldwide. There are multiple tools and best practices available to reduce the global burden of disease caused by pneumonia including prevention of severe disease by vaccination, antimicrobial stewardship and surveillance, and maintenance of strong clinical trial networks to provide timely and quality evaluation of emerging therapeutic approaches. When infection has progressed to severe pneumonia and ALI/ARDS, therapeutic interventions are limited and imperfect, as supportive care including oxygen therapy and mechanical ventilation have the potential to increase pathology. Detrimental host responses to infection are often drivers of severe disease, and there are no host-response targeted therapies that can alleviate disease. New approaches to target viral and bacterial co-infections are needed, especially with growing antimicrobial resistance strains of bacteria. These are global problems that will likewise require international collaboration to find sustainable solutions. Beyond pathogen-specific targeted approaches as currently being investigated using bacteriophages, precision therapies aimed at modulation of the host-response remains an enticing possibility for the future. Given the heterogeneity of the immune response and the variable phenotypes of ARDS, there is an urgent need to improve our understanding of host–pathogen interactions to identify mechanistic biomarkers that may be used to guide precision therapy in a context- and time-specific manner.

Utilizing preclinical models that incorporate mechanical ventilation in addition to infectious organisms will likely yield more insight into the underlying pathogenesis of disease [211].

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Data Availability

Not applicable.

Abbreviations

ALI	acute lung injury
ARDS	acute respiratory distress syndrome
ASL	airway surface liquid
CAP	community-acquired pneumonia
CF	cystic fibrosis
CLP	cecal ligation and puncture
HAP	hospital-acquired pneumonia
HRF	hypoxemic respiratory failure
LTB4	leukotriene B4
NET	neutrophil extracellular trap
PAD	protein-arginine deiminase
PEEP	positive end-expiratory pressure
VAP	ventilator-associated pneumonia

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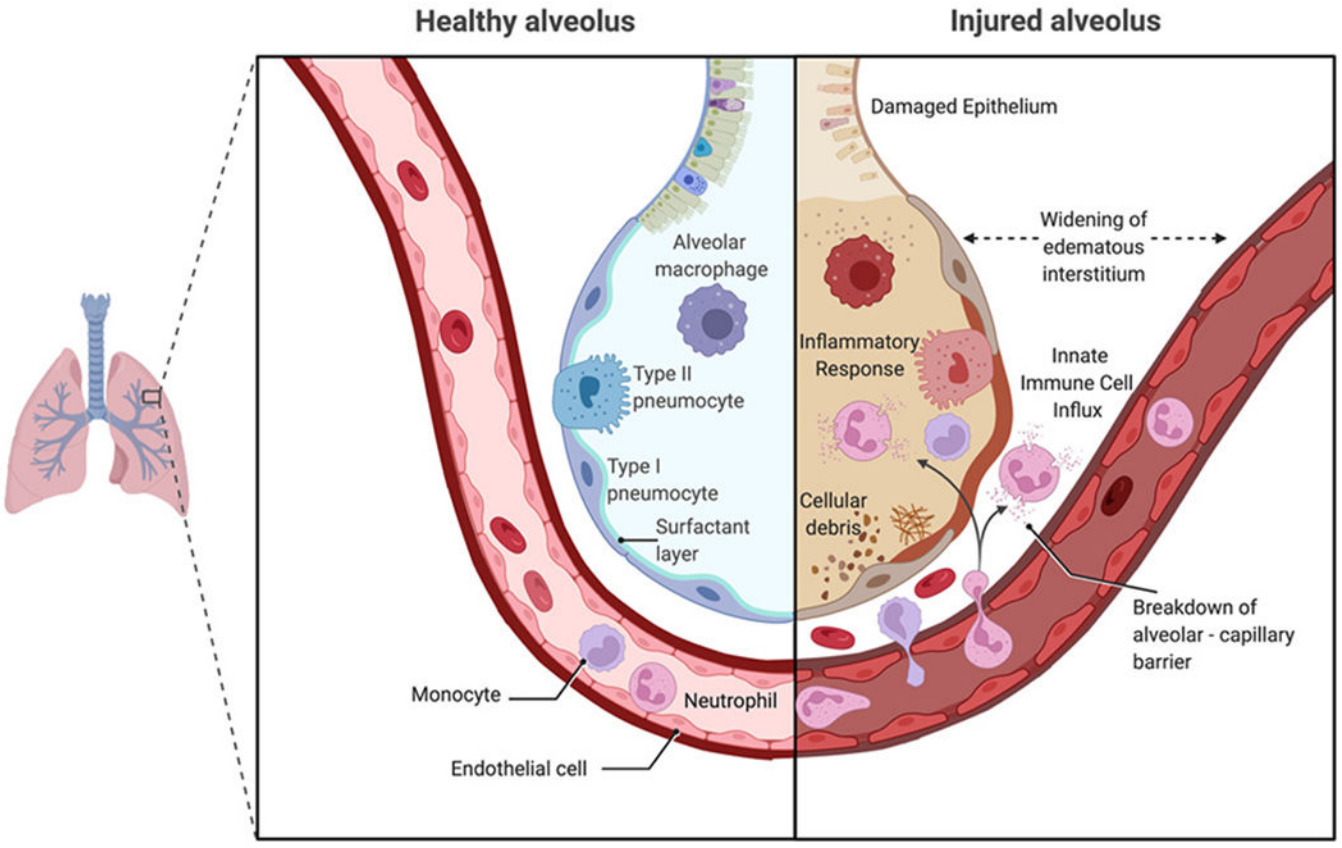

Figure 1. Alveolar changes during acute respiratory distress syndrome

An uninjured healthy lung contains an intact respiratory epithelial layer and alveolar space patrolled by resident alveolar macrophages. Type I and type II pneumocytes contribute to regulation of alveolar contents, including surfactant, and maintain the integrity of the alveolar-capillary barrier. Following infection or injury, an influx of innate immune cells such as neutrophils and monocytes migrate from the circulation into the interstitial and alveolar spaces, During ARDS, damage to the epithelial and endothelial layers results in breakdown of the alveolar-capillary barrier and accumulation of edematous fluid and debris in the alveolar spaces. Pro-inflammatory and destructive functions of alveolar macrophages, monocytes, and neutrophils contribute to disease pathology. Figure was created in Biorender.

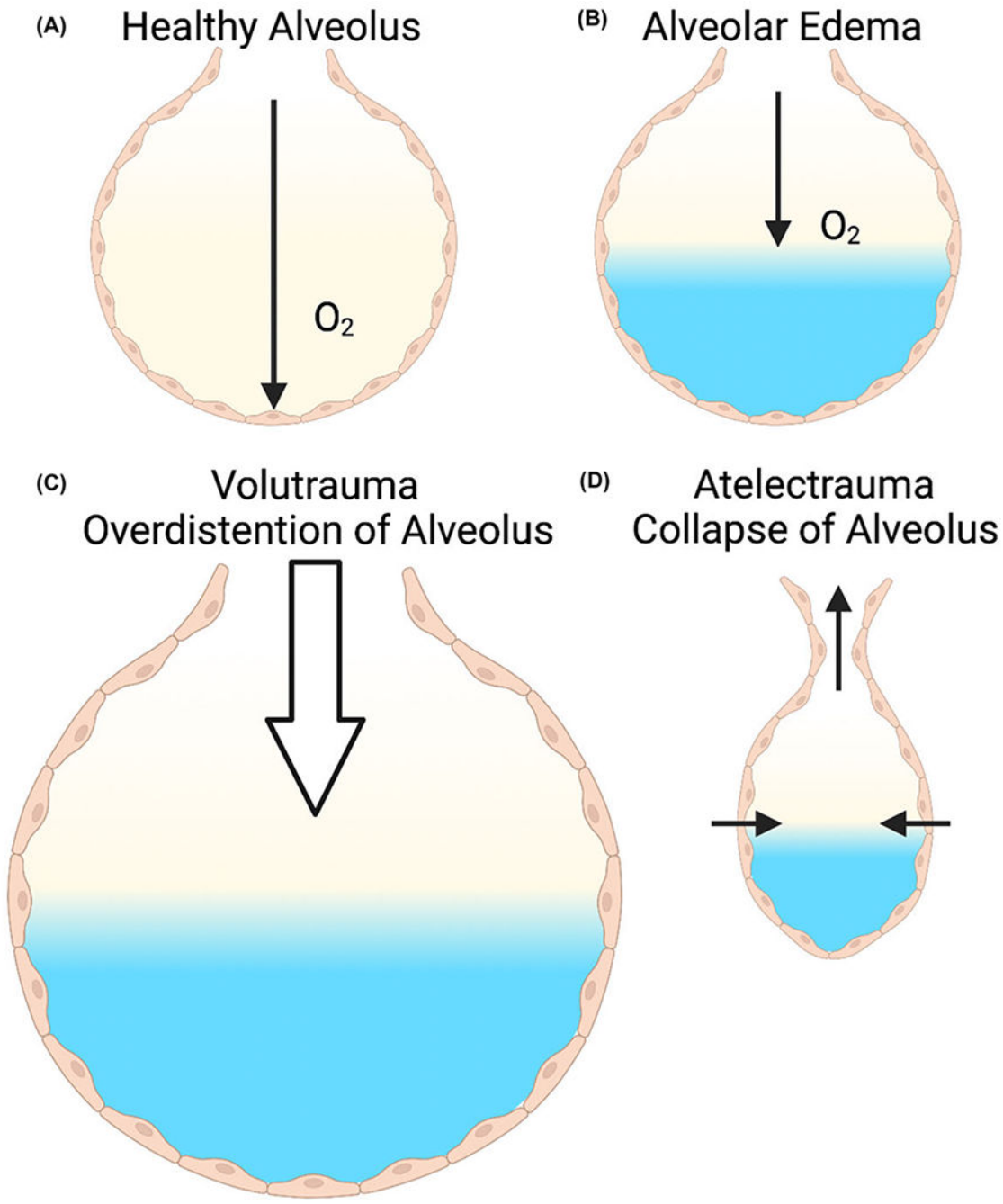

Figure 2. Physiologic mechanisms of ventilator induced lung injury

Under normal homeostatic conditions (**A**), the alveolar epithelium is lined by a thin layer of surface liquid. Surfactant reduces surface tension at the air-liquid interface preventing alveolar collapse thereby optimizing compliance of the lung throughout the respiratory cycle while facilitating gas exchange. (**B**) In the setting of acute lung injury, breakdown of the alveolar-capillary barrier allows proteinaceous fluid into the alveolar space with disruption of gas exchange. (**C,D**) With mechanical ventilation and positive end expiratory pressure (PEEP) to provide oxygenation support in patients with life-threatening lung injury, clinical

management rests on strategies to maintain low tidal volumes and to titrate PEEP to avoid overdistention (C; volutrauma) of compliant alveoli while ensuring that the epithelium of less compliant alveoli are not subjected repetitive cycles of opening and collapse (D; atelectrauma). Figure was created in Biorender.

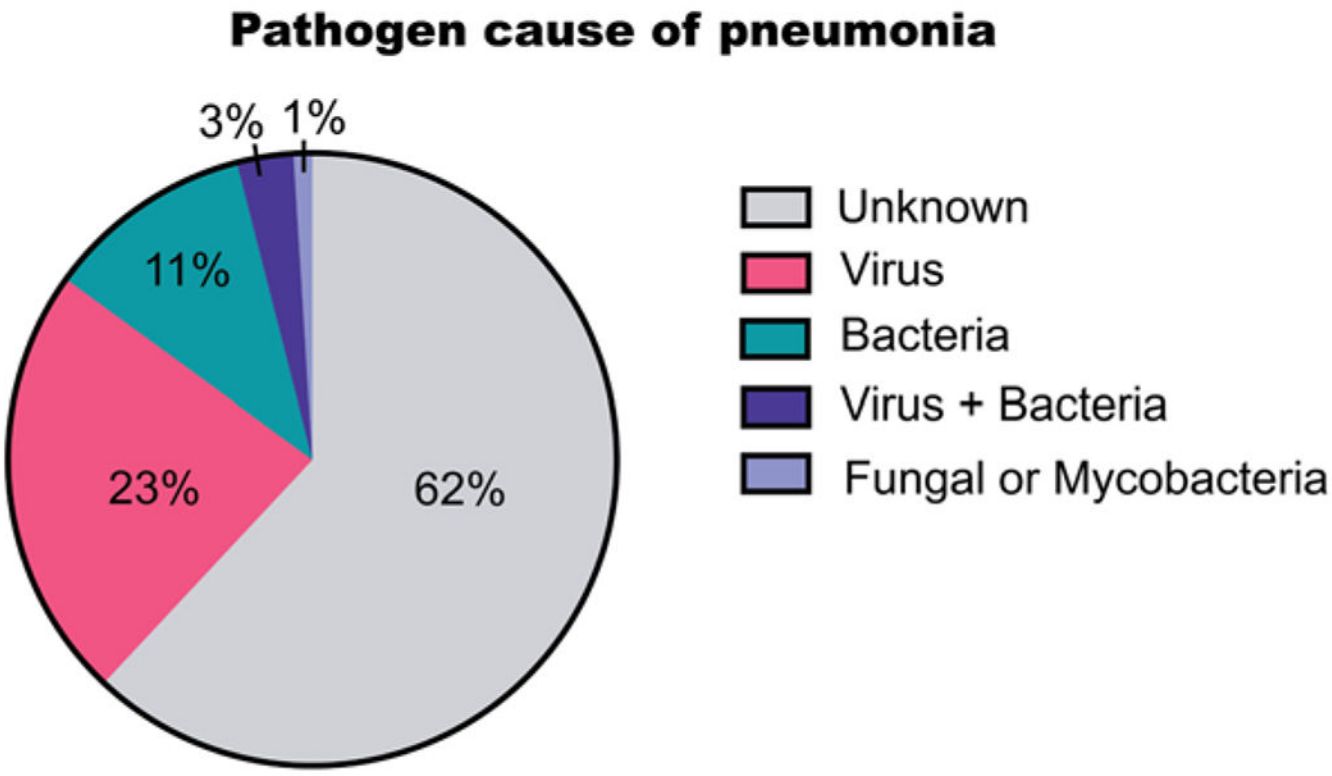

Figure 3. Most cases of pneumonia are from unidentified aetiology

Diagnostic tests utilizing both culture-based and molecular methods have identified a large and diverse number of etiologic agents as causes of pneumonia. However, a large gap in knowledge remains due to the high percentage of unknown causes of pneumonia. Factors that may contribute to the unknown or unidentified causes of pneumonia include limited access to timely testing, and barriers to obtaining samples from lower airways and alveolar spaces due to the invasive methods required, such as bronchoalveolar lavage. Previously reported data were utilized to create this graphical representation [3].

Table 1

Berlin definition of acute respiratory distress syndrome

Timing	Occur within 1 week of clinical insult/or new or worsening symptoms
Chest imaging	Bilateral opacities
Origin of edema	Respiratory failure of non-cardiac or fluid overload origin
Severity	**Oxygenation**
Mild	200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP
Moderate	100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP
Severe	PaO_2/FiO_2 ≤ 100 mm Hg with PEEP