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CHEST

The Role of Infection in Interstitial Lung Diseases

A Review

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Interstitial lung disease (ILD) comprises an array of heterogeneous parenchymal lung diseases that are associated with a spectrum of pathologic, radiologic, and clinical manifestations. There are ILDs with known causes and those that are idiopathic, making treatment strategies challenging. Prognosis can vary according to the type of ILD, but many exhibit gradual progression with an unpredictable clinical course in individual patients, as seen in idiopathic pulmonary fibrosis and the phenomenon of "acute exacerbation"(AE). Given the often poor prognosis of these patients, the search for a reversible cause of respiratory worsening remains paramount. Infections have been theorized to play a role in ILDs, both in the pathogenesis of ILD and as potential triggers of AE. Research efforts thus far have shown the highest association with viral pathogens; however, fungal and bacterial organisms have also been implicated. This review aims to summarize the current knowledge on the role of infections in the setting of ILD.

CHEST 2017; 152(4):842-852

KEY WORDS: infection; interstitial lung disease; pulmonary fibrosis

Interstitial lung disease (ILD) comprises a broad and heterogeneous spectrum of pulmonary parenchymal disorders of known and unknown causes. Idiopathic ILDs include idiopathic interstitial pneumonias (IIPs) such as idiopathic pulmonary fibrosis (IPF), idiopathic nonspecific interstitial pneumonia (NSIP), acute interstitial pneumonia, idiopathic lymphoid interstitial pneumonia (LIP), and cryptogenic organizing pneumonia. ILD can also present as a manifestation of an underlying systemic illness, such as in connective tissue disease (CTD) or sarcoidosis, and can also result from occupational, environmental, or drug exposures (pneumoconiosis, hypersensitivity pneumonitis, or drug-induced ILD). Parenchymal lung diseases of infectious nature are generally excluded from the classification of ILDs. However, the potential role of infectious agents in the development of certain ILDs of unknown cause, such as IPF, continues to be of concern and remains to be clarified. Furthermore, it appears likely that the phenomenon of "acute exacerbation" (AE), which can worsen the clinical course of fibrotic ILDs, is in part associated with infections. Diagnostic

ABBREVIATIONS: AE = acute exacerbation; ALI = acute lung injury; CMV = cytomegalovirus; CTD = connective tissue disease; DAD = diffuse alveolar damage; EBV = Epstein-Barr virus; HCV = hepatitis C virus; HHV = human herpesvirus; HSV = herpes simplex virus; IIP = idiopathic interstitial pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LIP = lymphoid interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; PAP = pulmonary alveolar proteinosis; PCR = polymerase chain reaction; PMX = polymyxin B-immobilized fiber column; PPFE = pleuroparenchymal fibroelastosis; TTV = torque teno virus

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DOI: http://dx.doi.org/10.1016/j.chest.2017.03.033

evaluations of patients with suspected ILD also need to consider infections, since they can cause various histopathologic patterns commonly associated with ILDs including NSIP, LIP, organizing pneumonia, and eosinophilic pneumonia, among others (Table 1). This is particularly important, since immunosuppressive agents are commonly used in the treatment of ILDs. Moreover, in recent years, there have been several studies examining the role of antimicrobial therapy in the treatment of ILDs (especially IPF), including in the setting of AE.

Most research looking at the role of infections in the pathogenesis of ILD and as triggers of AE focus on viruses; the role of bacteria is less well studied. Recent microbiological molecular techniques using the 16s sequence of bacteria to identify strains have allowed evaluation of alterations in the lung microbiome and its association with disease processes, including pulmonary fibrosis.[1-3]

In this narrative review, we explore the relevance of infections in the development of ILDs, as triggers of acute exacerbation phenomenon, and in the diagnosis of ILDs.

Idiopathic Pulmonary Fibrosis

The pathogenesis of IPF, the most common form of ILD, is largely unknown. IPF is characterized by the histopathologic pattern of usual interstitial pneumonia, which manifests as a temporally and geographically heterogeneous pattern of parenchymal fibrosis.[4] Many experts theorize that repeated episodes of alveolar injury in a predisposed host with dysfunctional healing mechanisms are central to the development and progression of IPF.[5,6] Environmental factors that are thought to contribute include dust, particulate exposures, aspiration of gastric contents, and infection.[5-7]

TABLE 1] Histopathologic Patterns of Lung Injury Encountered in Both Interstitial Lung Diseases and Lung Infections

Nonspecific interstitial pneumonia
Organizing pneumonia
Diffuse alveolar damage
Lymphoid interstitial pneumonia
Pleuroparenchymal fibroelastosis
Granulomatous inflammation
Eosinophilic pneumonia
Alveolar hemorrhage
Alveolar proteinosis

No definitive evidence exists to support the causal role of infections in the pathogenesis of IPF. Moreover, during AEs, infectious triggers are identified in only a minority of patients (possibly due to limitations of testing methods). In the setting of IPF and IPF with AE, we present evidence that supports a possible association with infection that does not necessarily imply cause and effect. Moreover, many of the studies presented further on were carried out in an era when immunosuppressive agents (such as systemic corticosteroids) were commonly used in the treatment of ILDs, and thus the data with respect to infections must be interpreted accordingly.

Viruses

Several studies have pointed toward an association between viruses and IPF, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenovirus, and hepatitis C virus (HCV). It has been theorized that these viruses provide a persistent antigenic stimulus in predisposed hosts, leading to fibrosis. Evidence from animal (murine) models shows that infection with gamma-herpesvirus can induce fibrosis and exacerbate established fibrosis, evidenced by increased total lung collagen, acute lung injury (ALI), histopathologic diffuse alveolar damage (DAD), and reduced lung function.[8,9]

The most frequently identified virus appears to be EBV.[10,11] Egan et al[12] showed in vivo EBV replication (localized to pulmonary epithelial cells) in 70% of patients with IPF vs 9% of control subjects. Importantly, the patients evaluated were classified as immunocompetent, and the majority had not received IPF-targeted therapy at the time of the biopsy procedure. Tang et al[11] attempted to show the association between chronic viral infection and IPF. Using polymerase chain reaction (PCR) techniques, they found one or more herpesviruses more frequently in patients with IPF vs control subjects (97% of the 33 patients with IPF vs 36% of control subjects ($P < .0001$)). These viruses included CMV, EBV, human herpesvirus-7 [HHV-7], and HHV-8. They found that herpesviruses were found more frequently in patients with sporadic cases of IPF than in familial cases ($P < .05$), supporting the role of these viruses as triggers or in the pathogenesis of IPF.[11]

Yonemaru et al[13] studied patients with ILD (43 cases of IPF, seven cases of CTD-ILD, 22 cases of sarcoidosis) and emphysema (17 cases) and compared CMV, EBV, herpes simplex virus (HSV), adenovirus, and parainfluenza serologies. They showed that CMV IgG,

complement fixation, and EBV IgG titers were significantly higher in patients with IPF and CTD-ILD compared with the other groups. In contrast, adenovirus and parainfluenza titers demonstrated no significant difference among the groups. Interestingly, in these patients, increased CMV IgG and complement fixation suggests that latent CMV infection may be more prominent in ILD, giving further credence to the theory that such pathogens act as a chronic antigenic stimulus for lung injury.[13]

Some speculate that the pathogen load required to trigger the cascade of inflammation and ultimately fibrosis may be too small for our tests to identify. To test this hypothesis, Santos et al[14] used immunohistochemical analysis in 37 patients with IIPs who underwent open lung biopsy procedures. CMV and measles were detected in patients with both IPF and NSIP and histopathologic DAD.

Kuwano et al[15] studied the presence of adenovirus DNA in patients with CTD-ILD and IPF. They used molecular techniques to identify the adenovirus genome in transbronchial biopsy specimens from 19 patients with IPF, 10 patients with CTD-ILD, and 20 patients with sarcoidosis. Adenoviral DNA was present in 16% of patients with IPF, 50% of patients with CTD-ILD, and 10% of patients with sarcoidosis. Patients who had received corticosteroids were more likely to be positive for the adenovirus DNA, suggesting that the immune status of the host plays a significant role and that adenovirus is not truly associated with the pathogenesis of ILD or as a trigger of AE.[15]

HCV causes liver fibrosis, and a number of case reports have suggested the possibility of its role in the development of IPF. Ueda et al[16] studied 66 patients with IPF and showed that 28% had positive serum antibodies to HCV vs 3% of control subjects (9,464 healthy volunteers). Arase et al[17] studied a cohort of 6,150 patients with HCV and 2,050 patients with hepatitis B virus. In the HCV group, they noted a 10- and 20-year cumulative incidence of IPF of 0.3% and 0.9%, respectively, compared with zero cases of IPF in the hepatitis B virus group. The study concluded that age, smoking, and liver cirrhosis enhance the development of IPF in HCV-positive patients.[17] However, a number of other studies have failed to replicate this association.[18] The lack of a consistent signal among various cohorts suggests that HCV is unlikely to be an important trigger for the development of IPF.[2]

Bacteria

Bacteria have been less well studied in the realm of IPF. Richter et al[19] demonstrated positive BAL cultures for pathogens such as *Haemophilus* species, *Streptococcus* species, and *Pseudomonas* species in eight of 22 stable patients with IPF.[19] It is currently difficult to determine whether patients with IPF are more susceptible to infection or colonization due to abnormal lung parenchyma, associated traction bronchiectasis, and immunosuppressive medications (which historically have been commonly used for treatment of ILDs), or whether bacteria are involved as triggers of AE or in the pathogenesis of IPF.

A 1989 study from Israel found that the incidence of pulmonary tuberculosis in chronic ILD (mostly IIP) was $4^1/_2$ times higher than in the general population, and corticosteroid therapy was not found to be a confounding factor.[20] This finding is thought to be related to an increased susceptibility to atypical infections as a result of abnormal lung parenchyma, rather than a trigger in the evolution of ILD.

The lung microbiome has also been an area of research in relation to various respiratory conditions.[2] Molyneaux and Maher[21] analyzed BAL samples from 25 patients with IPF using culture-independent metagenomic analysis. They found the phylum Firmicutes (*Streptococcus* and *Veillonella* species), Proteobacteria, and Bacteroidetes were most commonly encountered. Such data demonstrate that the lower airways (once thought to be sterile) are colonized with microbial communities that can possibly be involved in the pathogenesis or progression of lung injury and ultimately fibrosis.[21] The same authors were able to show by longitudinal analysis of patients with IPF serum and BAL samples that specific genes, some of which coded for antimicrobial peptides, were present in patients with IPF and such expression increased over time, supporting the theory that pathogens may provide chronic antigenic stimuli in patients with IPF.[22]

Fungi

Even less information is available about the potential role of fungi in the pathogenesis of IPF or in AE of IPF. On occasion *Pneumocystis jirovecii* is detected as a factor associated with acute deterioration.[23] Other studies have also suggested that a significant rate of colonization with *P jirovecii* occurs in patients with IPF and other ILDs. For instance, Vidal et al[24] documented a

38% colonization rate with *P jirovecii* in patients with IPF.

Other Idiopathic Interstitial Pneumonias

Infectious causes need to be considered in the diagnostic evaluation of patients with suspected IIP, since the histopathologic patterns of lung injury underlying some IIPs can also be seen in pulmonary infections (Table 1).[25] These patterns include NSIP, organizing pneumonia, DAD, lymphoid (lymphocytic) interstitial pneumonia (LIP), and pleuroparenchymal fibroelastosis (PPFE). Thus, it is imperative that infection be excluded in diagnosing these forms of IIP.

NSIP is characterized histopathologically by varying degrees of interstitial chronic inflammation or fibrosis (or both) that appears temporally homogeneous with inconspicuous or absent fibroblastic foci.[4,25] This pattern of lung injury can be encountered in various clinical contexts. The diagnosis of idiopathic NSIP requires exclusion of identifiable causes. For example, NSIP is the most common form of ILD found in patients with CTDs, that is, as a form of CTD-associated ILD.[26] In their initial description of NSIP, Katzenstein and Fiorelli[27] postulated that this form of lung injury may represent a result of prior ALI including infections. It has been known that NSIP can be encountered in HIV-positive patients with or without *P jiroveci* pneumonia.[28,29] NSIP has also been encountered as a pattern of lung involvement in viral infections such as human T-cell lymphotropic virus type 1.[30]

Organizing pneumonia is a nonspecific response to a wide array of lung injury including infections. It is histopathologically characterized by the presence of organizing polypoid intraluminal plugs of granulation tissue within the alveolar spaces and ducts with varying degrees of bronchiolar involvement.[4,25] Similar to idiopathic NSIP, the diagnosis of cryptogenic organizing pneumonia entails exclusion of potential causes, including infections, aspiration and other inhalational injuries, drugs, CTDs and other systemic inflammatory disorders.[4,31-34] In a retrospective study of 254 cases of organizing pneumonia pattern confirmed on lung biopsy specimens, 59 cases (23%) were related to pulmonary infections.[31] An organizing pneumonia pattern of lung injury can be seen with many forms of pulmonary infections, including bacterial, viral, fungal, and parasitic.[33-35] It seems likely that even some cases diagnosed as cryptogenic organizing pneumonia that have a self-limited clinical course represent resolving pulmonary infection.[36]

DAD is the histopathologic pattern underlying an acute form of IIP—acute interstitial pneumonia—and most cases of ARDS.[4,25,37] It is characterized histopathologically by the presence of hyaline membranes, along with diffuse alveolar septal thickening, septal edema, and interstitial fibroblast proliferation. This pattern can be encountered in patients with various forms of ALI.[4,37,38] Acute interstitial pneumonia (Hamman-Rich syndrome) refers to DAD occurring in the absence of an identifiable cause.[4,37,38] In one study looking at patients with DAD, the majority of cases were thought to have potential triggers identified. In this study of 58 consecutive cases of DAD confirmed by surgical lung biopsy results, 13 cases (22%) were thought to be infection related, most commonly viral pneumonias.[38]

Idiopathic LIP is currently classified as a rare form of IIP along with idiopathic PPFE.[25] Histopathologically, LIP manifests diffuse infiltration of the alveolar septa with mostly lymphocytes and varying numbers of plasma cells.[4] The idiopathic form of LIP is indeed rare and outnumbered by those cases associated with disorders of immunodeficiency, CTDs, and other autoimmune disorders.[4,25,39-41] Similar to NSIP, LIP can be seen in HIV-positive patients and has also been associated with several viral infections, including EBV, HHV-8, and human T-cell lymphotropic virus type 1.[42-47]

PPFE is a recently delineated entity and is characterized histopathologically by elastotic fibrosis involving the pleura and adjacent subpleural parenchyma.[25] This process predominantly affects the upper lobes, in contrast to IPF. Several underlying disease processes have been implicated in cases of PPFE, including infections (eg, *Mycobacterium* and *Aspergillus*). A history of recurrent infections has been described in some patients with PPFE, raising the possibility that it may result from infection-related lung injury. PPFE can also be seen as a rejection phenomenon in recipients of allogeneic lung or hematopoietic stem cell transplantation, drug or occupational exposures (asbestos, aluminum), chemotherapy, radiation, underlying autoimmune disease, and hypersensitivity pneumonitis. Idiopathic PPFE is a very rare form of IIP and may be associated with a genetic predisposition as a form of familial interstitial pneumonia.[25,48-54]

Sarcoidosis

Sarcoidosis is a granulomatous inflammatory disorder of unknown cause and is diagnosed by a combination of

clinical, radiographic, and histopathologic findings. Infection has been proposed as a trigger leading to an aberrant inflammatory cascade in a predisposed host. Given the lack of histopathologic specificity in diagnosing sarcoidosis and the wide spectrum of its clinical manifestations, it is difficult to identify a common cause in such a diverse disorder.[55,56]

Mycobacterium is the most commonly implicated species. Although *Mycobacterium* has not been demonstrated in sarcoid granulomas by culture or acid-fast stains, immunohistochemical studies have shown remnants of the mycobacterial cell wall within sarcoid specimens.[57-59] In addition, PCR and nucleic acid testing have demonstrated mycobacterial nucleic acid in up to 80% of sarcoid specimens. A meta-analysis found that mycobacterial DNA/RNA was identified in 26% of sarcoid tissues, which was significantly higher than in nonsarcoid tissues of control subjects.[58,60,61]

Propionibacterium has also been implicated in sarcoidosis and has been cultured in up to 78% of sarcoid specimens.[58,62] It is important to note that *P acnes* is a commensal bacterium and has been cultured in a large proportion of healthy control subjects. Eishi et al[62] found *Propionibacterium* through real-time PCR in 106 of 108 patients with sarcoidosis but also found the species in up to 60% of control subjects. A systematic review of 58 studies (> 6,000 patients) found a link between sarcoidosis and both *P acnes*, and mycobacteria.[63] Herpesvirus has also been implicated, although viruses have not been known to trigger granulomatous reactions.[64] Various other pathogens studied, including *Borrelia*, *Rickettsia helvetica*, *Chlamydia pneumoniae*, EBV, and retroviruses, were not associated with sarcoidosis. These studies support, but do not confirm, the theory that various antigens can stimulate granulomatous inflammation in a predisposed host and that the microorganism acting as the trigger can vary.[63]

Currently available antibiotics can target enzymes encoded by microbial genes found to be present in sites of granulomatous inflammation in sarcoid specimens.[58,65] A randomized placebo-controlled trial in patients with chronic cutaneous sarcoidosis who were randomized to receive concomitant levofloxacin, ethambutol, azithromycin, and rifampin vs placebo for 8 weeks demonstrated reduced diameter of sarcoid skin lesions and overall clinical improvement in the treatment arm.[66] The same regimen was used in 15 patients with chronic pulmonary sarcoidosis with encouraging outcomes, including improved FVC, functional capacity, and quality of life.[67] The same group is pursuing this regimen in a larger cohort of patients to confirm their findings (ClinicalTrials.gov NCT01169038). Use of antimicrobial agents directed against target enzymes may be an innovative treatment alternative.[68]

There is also evidence that sarcoidosis may be transmissible; bone marrow transplants from donors with sarcoidosis have resulted in granuloma formation in recipients.[69,70] Although this does not directly support infection, it supports the theory of an antigenic stimulus leading to granuloma formation.

Whether sarcoidosis is a result of active or latent infection or is an abnormal response to remnants of a cleared or partially cleared infection are theories that continue to be debated. Infections may act simply as a stimulus for an aggressive inflammatory reaction in a predisposed host. In such predisposed hosts, there can be more than one type of antigenic stimulus leading to the clinical manifestations of sarcoidosis.

Other ILDs

There are other less common forms of ILD in which the role of infection deserves mention. Acute eosinophilic pneumonia is generally thought of as an acute respiratory illness of unknown cause.[71-73] In recent years, cigarette smoking and medications have been identified as the inciting agents in a subset of patients with acute eosinophilic pneumonia.[74-76] It should also be recognized that acute eosinophilic pneumonia can be of infectious origin, as seen in fungal pneumonias—for example, coccidioidomycosis, and parasitic infections.[74,76] Since corticosteroids are frequently used in the treatment of idiopathic acute eosinophilic pneumonia, it is crucial for a possible infectious origin to be considered.

Interstitial pneumonia with autoimmune features is a recently described entity that comprises a cohort of patients with ILD and features of autoimmunity (extrapulmonary and serologic) but do not meet criteria for established CTDs. Such patients pose a difficult question with respect to the role of immunosuppressive therapy. Little is known about the pathogenesis of interstitial pneumonia with autoimmune features or indeed the role of infection in this patient population.

Pulmonary alveolar proteinosis (PAP) is a diffuse lung disease characterized by an alveolar filling process with amorphous lipoproteinaceous surfactant-like material. Most cases of PAP represent an autoimmune disease

mediated by the development of anti-granulocyte macrophage-colony stimulating factor neutralizing antibodies.[77,78] These antibodies induce a functional deficiency of granulocyte macrophage-colony stimulating factor, which is a critical mediator of surfactant protein and lipid homeostasis in the alveoli. A minority of PAP cases are considered secondary forms, caused by exogenous agents or hematologic disorders. Nocardiosis is a well-recognized infection that can complicate the course of patients with PAP.[79] In addition, *P jiroveci*, mycobacteria, and CMV have also been reported to induce PAP.[77-79]

Acute Exacerbation in ILDs

The natural course of patients with ILD is not fully understood and, in part, depends on the type of underlying ILD. Especially in the fibrotic ILDs, AE accounts for significant morbidity and mortality.[80-82] Although no consensus definition for AE-ILD exists, the generally accepted criteria are extrapolated from the IPF population given the similarities in presentation. AE is generally characterized by acutely (typically $<$ 1 month) worsening dyspnea and parenchymal infiltrates on imaging. It can occur in many forms of ILD and is histologically characterized by DAD in most cases.[83,84] Such episodes are an important cause of ILD-related mortality, with a 3-month survival of $<$ 50% in patients with IPF.[81,85,86] The various populations studied, evolving definitions of AE, and the retrospective design of the majority of studies make it difficult to assess the true frequency and sequelae of respiratory worsening in these patients. The theory that infection plays a role in the pathogenesis of the underlying disease, as well as in triggering AEs, has not been fully evaluated, but there is some data to support this concept in the current literature.

The true incidence of AE by any definition is unclear, and reports range from 4% to 30% per year.[81] Differences in definitions and in the cohorts studied largely explain this variation. Most of the current data are derived from retrospective studies, and most clinical trials estimate a lower incidence of AE (4%-15%), perhaps due to more strict definitions used for inclusion.[81,85]

The definition of AE in IPF has been broadened in the most recent expert recommendations.[81,87] Historically, AE excluded those with infection and other "reversible" conditions (ie, heart failure, venous thromboembolism). Despite advancements in diagnostic methods, infection in patients with ILD remains difficult to diagnose. Bronchoscopy, although quite specific in diagnosing infection, is relatively insensitive, particularly in the context of recent antibiotic use.[88,89] Given our inability to definitively rule infection in or out, it is not practical to define AE by the exclusion of infection. Thus, the newly accepted definition includes AE with or without an identifiable trigger such as infection (Table 2). In the majority of patients with respiratory decline, no trigger can be identified, and the progression of the underlying ILD remains the most likely cause. However, the host response to an external stimulus may be important. Specifically, infections as antigens may play a role in triggering some fraction of exacerbations.[81] Additionally, the histopathologic finding of DAD in patients with AE leads to the natural correlation with ALI/ARDS. The causes of ALI (histopathologic DAD) are numerous and are also thought to include infection, aspiration, toxins, transfusion, and surgery.[4,38] Many of these triggers may lead to events that are indistinguishable from idiopathic exacerbations of ILD.[81]

The role of bronchoscopy should be a clinical decision made on a case by case basis. Those with AE may have a tenuous respiratory status, and bronchoscopy may risk worsening this. In the setting of empirical antibiotic therapy and extensive laboratory investigations looking for identifiable triggers, bronchoscopy specifically looking for infection may not be necessary in all patients with AE. The risk of the procedure in this population, when weighed against the uncertain yield, makes it difficult to recommend for every patient, since its effect on outcomes remains unclear. The current evidence also does not support mandating other investigations when searching for possible triggers of AE (eg, specific blood

TABLE 2] Revised Definition of Acute Exacerbation of IPF[81]

Acute clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality
Diagnostic criteria
Previous or concurrent diagnosis of IPF
Acute worsening of dyspnea (within 1 mo)
CT evidence of diffuse infiltrates/ground glass/ consolidation on a background of UIP pattern
Deterioration not fully explained by heart failure/fluid overload

IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

work or serologic tests), clinical judgment must be used to determine appropriate and exhaustive testing looking for reversible triggers of AE, for example, testing for opportunistic pathogens in patients receiving immunosuppressive agents or testing for endemic pathogens.

Data from small retrospective studies report an infectious cause as a trigger for 10% to 30% of AEs in patients with non-IPF fibrotic lung diseases.[85] One larger study of 220 patients with ILD (100 cases of IPF, 120 cases of non-IPF) showed that 20% of patients were diagnosed with infection in the setting of acute respiratory worsening.[82] There are also postmortem studies examining this issue: One such study of 42 patients with IPF who underwent autopsy showed that 15% had an infection identified (including fungal, bacterial, and viral).[90] Another study found that 28.8% of patients with AE had bronchopneumonia (fungal; 13.5%; CMV, 11.5%; and bacterial, 9.6%) identified postmortem and not diagnosed clinically.[91] Such studies highlight difficulties in diagnosing infection in this clinical setting and further support the recent revisions to the definition of AE.

Although, infectious causes are found in 10% to 30% of patients with AE, identifying infection has not yet been demonstrated to affect outcomes.[85] For example, Blivet et al[23] reported that in six of 10 patients with confirmed treatable pathogens (including *Staphylococcus aureus*, *Streptococcus pneumoniae*, influenza A, and *P jiroveci*), outcomes were not affected and mortality remained high despite antibiotics targeting these organisms. Of the two patients in whom *P jiroveci* was identified, only one patient's condition improved with antipneumocystis therapy.[23] The patients who did the best in this cohort were those with noninfectious reversible causes of respiratory worsening, that is, pneumothorax and complications of anesthesia.

Wootton et al[92] also failed to clearly identify an infectious trigger for AE in the majority of the patients they studied. BAL and serum from patients with AE of IPF, IPF without AE, and those with evidence of ALI (without IPF) were tested for viral nucleic acid using multiplex PCR testing, pan-viral microarray, and high-throughput cDNA sequencing. Of the 43 patients with AE, only four had evidence of common respiratory viruses (parainfluenza [n = 1], rhinovirus [n = 2], and coronavirus [n = 1]). No viruses were detected in the BAL of stable patients with IPF. Additional pan-viral microarrays revealed evidence of nonrespiratory viruses in 15 patients with AE: HSV (n = 1), EBV (n = 2), and torque teno virus (TTV) (n = 12). TTV was significantly more common in patients with AE and ALI compared with stable control subjects. Overall, the presence of a common respiratory virus was not detected in most patients with AE; however, the presence of TTV in a significant minority of the AE and ALI cohort may be important and an area for future study.[92] The results suggest that the presence of TTV is not specific for AE but may be associated with ALI in general. Konishi et al[93] also failed to identify gene transcription profiles that would be expected in viral infections in both patients with IPF and patients with IPF with AE.[2,93]

Chlamydophila pneumoniae infection has been known to cause exacerbation of asthma and COPD. A prospective study was conducted to investigate the possible role of *C pneumoniae* infection in triggering AE of IPF. Sputum, blood cultures, and acute and convalescent serologic tests for *C pneumoniae* IgG and IgA (ELISA) were performed prospectively in 27 patients over a 5-year period. Only two patients had an antibody response suggestive of acute or reactivated infection, suggesting that *Chlamydophila* is an unlikely trigger for AE of IPF.[94]

Although existing data do not support the role of infection/viruses in all cases of AE, or even in a majority, the possibility of viruses as a trigger remains to be explored.[87,92] Unlike other respiratory conditions in which exacerbations are truly acute events, the onset of an AE in ILD is generally more insidious. It is possible, therefore, that by the time of clinical presentation, any triggering viruses would no longer be detectable.[2] Moreover, a significant proportion of patients with AE may have occult infection despite a vigorous clinical workup.[95]

There is also some epidemiologic support for infectious causes of AE, which comes from studies that demonstrate AE occurring more frequently in winter and spring months[96] and in patients taking immunosuppressive medications. Song et al[86] showed in their study of patients with IPF that there was an increased risk of opportunistic infections, possibly attributable to prior treatment with chronic corticosteroid therapy or other immunosuppressive agents.[86]

A polymorphism of the mucin (*MUC5B*) gene has been associated with both familial and sporadic IPF and is essential in mucosal immune defense.[97] In healthy individuals, the mucociliary escalator constitutes an

important innate pulmonary defense mechanism. In contrast to cystic fibrosis in which impaired mucociliary clearance predisposes to AEs, mucociliary dysfunction of the peripheral airways has not been directly shown to cause AE-ILD, even though recent studies implicate the mucin gene in the pathogenesis of several ILDs.[98,99]

Attempts to implicate specific pathogens in the etiopathogenesis of AE have not often been successful; no association has been shown between AE and any specific organism.[84] Accumulating evidence suggests a multiple-hit hypothesis leading to progressive deterioration of lung function,[100] with infections being possible contributors to such "hits." The prognostic implications of AE are profound; data suggest that up to 46% of deaths from IPF are preceded by an AE.[81] The median survival of patients with IPF who experience an AE is approximately 3 to 4 months,[81] so further research in this area is crucial, both to clarify the role of infection in respiratory worsening/AE and to evaluate the role of the lung microbiome and chronic infectious stimuli in the pathogenesis of ILDs.

Antimicrobial Treatment Studies

Although bacteria have been less commonly implicated in the pathogenesis of ILDs, they have been studied in the setting of AE as well as in antimicrobial trials. Most experts would agree with empirical antibiotic treatment in the setting of AE given the potential benefit and minimal risk to the patient,[101] as occult infection remains a possibility.

The efficacy of azithromycin in treating IPF was studied in a prospective open-label study: 20 patients with AE received azithromycin in addition to high-dose pulse steroid therapy. Outcomes were compared with a historical cohort treated with fluoroquinolone agents ($n = 56$). The primary end point of mortality at 60 days was significantly lower in patients treated with azithromycin (mortality, 20% vs 70%; $P < .001$), and no serious adverse events were observed.[102] Whether these findings are attributable to azithromycin's anti-inflammatory effects, antimicrobial effects, or a combination of both, cannot be ascertained from such studies and remains an area to be investigated.

A placebo-controlled study evaluated the prophylactic use of co-trimoxazole for 12 months compared with usual care for patients with fibrotic IIP. Although there were significant dropouts in the co-trimoxazole arm (30% vs 8% in placebo arm), post hoc analysis suggested that co-trimoxazole led to a reduction in infections and mortality.[103] There are ongoing clinical trials looking at co-trimoxazole therapy in IPF (ClinicalTrials.gov NCT01777737).

Polymyxin-B-immobilized fiber column (PMX) helps remove endotoxins and is used for the treatment of endotoxemia. Several studies from Japan have reported an improvement of oxygenation in patients with ALI/ARDS treated with PMX.[104,105] Given that DAD is the most common pathologic finding in ALI/ARDS and in AE, treatments targeting ALI/ARDS may have relevance in the management of AEs. A retrospective study aimed at clarifying this in patients with IPF with AE showed a significant improvement in the Pao_2 to Fio_2 ratio with PMX treatment.[106] However, the improvements in oxygenation did not translate into a survival benefit, as 1- and 3-month survival rates (70% and 34%, respectively) of patients with IPF with AE remained low.[106] A more recent retrospective Japanese study suggests that survival in those patients who received PMX may have been improved.[107] PMX is not a currently accepted treatment for AE-ILD, but such research may support the role of infections as antigenic stimulus in the setting of AE.

Conclusions

The role of infection in the pathogenesis of ILD and AE-ILD remains unclear and needs further exploration. The current literature suggests that infections may play a role in the complex interaction between a susceptible host and the environment, leading to the development or progression of ILD. Given the overlap in histopathologic manifestations of infections and ILDs, infectious causes should always be considered in a patient with suspected ILD prior to institution of immunosuppressive therapy. Moreover, infections become a more significant concern when patients with ILD receive chronic immunosuppressive medications as treatment for their ILD. Recent studies suggest a potential role for antimicrobial therapy in the treatment of AE as well as ILD itself.

Acknowledgments

Financial/nonfinancial disclosures: None declared.

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