Update in Lung Infections and Tuberculosis 2018

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Insights into the Pathogenesis of Pulmonary Infections

The role of the microbiome in lung inflammation continues to gain attention in clinical and experimental studies, with the term "gut–lung axis" referring to the interactions between the lung and intestinal microbiome. Dickson and colleagues reported that lung microbiota in genetically identical healthy mice strongly depend on the cage conditions during breeding and husbandry (1). Strikingly, interanimal differences in the lung microbiome are even larger than in the gut microbiome, and they are more strongly influenced by cohousing than cecal or oral flora. Of several cytokines tested, IL-4 and IL-1α are detectable in healthy lungs and correlate with the composition of local taxa. Thus, differences and dynamic changes of lung microbiota add another layer of complexity to murine experiments and have opened a new area of research (2). It is a well-known clinical observation that antibiotic treatment predisposes to *Pseudomonas aeruginosa* pneumonia, but the underlying cause remained elusive (3). Robak and colleagues found increased outgrowth and dissemination of *P. aeruginosa* in germ-free mice or mice pretreated with antibiotics compared with mice with an intact lung and gut microbiome (4). Further experiments identified decreased levels of pulmonary IgA in these animals and in patients pretreated with antibiotics. In humans and mice, microbiota-depleting antibiotic treatment resulted in reduced levels of a proliferation-inducing ligand and B-cell–activating factor, which are cytokines that, downstream of Toll-like receptor activation, promote production of IgA in the lung. Intranasal application of polyclonal IgA reversed the susceptibility to *P. aeruginosa* infection, offering the possibility for prophylactic or therapeutic interventions. The role of platelet depletion in host defenses and neutrophil recruitment has also been studied (5, 6). Biofilm, which plays a role in propagating pseudomonal and other infections, and its therapeutic implications have been examined recently (7).

Besides *P. aeruginosa*, *Klebsiella pneumoniae* is another important nosocomial pneumonia pathogen. Both organisms can rapidly acquire antibiotic resistance, and some patients reveal coinfection. Jones-Nelson and colleagues discovered that flagellin-induced signaling by (nonviable) *P. aeruginosa* caused prolonged neutrophil recruitment and augmented levels of neutrophil elastase, as well as decreased survival, in an otherwise sublethal *K. pneumoniae* infection model. Therapeutically, these effects in the mixed infection model were reversed by application of sivelestat, an inhibitor of neutrophil elastase; antibodies to flagellin; or specific antibodies to *K. pneumoniae* or *P. aeruginosa* (8). Thus, colocalization of classical nosocomial pathogens not only enables the transmission of plasmid-encoded resistance genes among each themselves but also drives more severe disease (9). With respect to viral–bacterial coinfection, a study from the Dockrell laboratory elegantly demonstrated that alveolar macrophages of patients with HIV infection receiving effective antiretroviral therapy possess reduced killing capacity of *Streptococcus pneumoniae* (10). In a series of *ex vivo* experiments, macrophages from otherwise healthy patients with HIV infection had reduced induction of apoptosis, oxidative phosphorylation, and production of mitochondrial reactive oxygen species compared with macrophages from healthy donors. Gp120, a surface glycoprotein of HIV, prevented apoptosis induction, caspase activation, and increased mitochondrial reactive oxygen species, ultimately leading to reduced bacterial killing. Thus, patients with HIV, regardless of their immune status or the efficacy of antiretroviral treatment, are more prone to pneumonia caused by *S. pneumoniae*.

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The transition from pneumococcal colonization to invasive disease can be mediated by mucosa-associated invariant T cells, influenced by differences in the riboflavin pathway (11), but the impact of these cells on infection outcome needs more study (12). *Pneumocystis jirovecii* pneumonia, also important in HIV infection, may be impacted by the C-type lectin receptor dectin-2, with alveolar macrophage deficiency in this receptor decreasing proinflammatory responses to the organism (13).

An emerging concept of "trained immunity" in the context of sequential infections was examined by Yao and colleagues, who found that alveolar macrophages provide autonomous memory responses after initial infection with adenovirus (14). These memory macrophages developed independently of bone marrow–derived monocytes 7 days after infection, highly expressed major histocompatibility complex class II, and demonstrated an enhanced glycolytic metabolism. Upon reinfection with *S. pneumoniae* or *Escherichia coli*, they produced augmented levels of neutrophilic chemokines, which resulted in improved clearance of bacteria up to 16 weeks after viral infection *in vivo*. From a clinical point of view, it would be interesting to study alveolar macrophage memory in models with more clinically relevant respiratory viruses, such as influenza, respiratory syncytial virus (RSV), or coronaviruses, and their effects on bacteria such as *S. pneumoniae*. This neutrophil response might prove protective against bacterial pneumonia after viral infection but detrimental in other models, such as multipathogen nosocomial pneumonia.

Recent evidence suggests that polymorphonuclear neutrophils (PMNs) also possess antiinflammatory properties. Tak and colleagues discovered that PMNs suppress inflammation in a CD11b-dependent manner in murine H3N2 influenza virus infection (15). Adoptive transfer of wild-type compared with CD11b-deficient neutrophils normalized the pronounced inflammation in CD11b-knockout animals without affecting the viral load. T-cell depletion abated the antiinflammatory properties of PMNs, suggesting a potential suppression of T-cell activity by CD11b. However, the detailed molecular mechanism needs to be elucidated (16). In contrast, harmful effects of PMNs in acute lung injury are well known, and neutrophil antimicrobial peptides tested in this context demonstrated proinflammatory and organ-damaging effects (17). However, Jayne and colleagues demonstrated that a theta-defensin (RTD-1 [rhesus θ-defensin]), an antimicrobial peptide found in leukocytes of Old World monkeys, reveals antiinflammatory and lung-protective effects and mitigates neutrophil influx after LPS instillation into the lungs (18). These findings are promising with respect to therapeutic applications, but the mechanism of reduced neutrophil influx remains elusive (17). Gross and colleagues also used the model of LPS-induced acute lung injury to study the role of the Sox (SRY [sex-determining region on the Y chromosome]-related high-mobility group box) group F family member, SOX18, in endothelial barrier function in the lung (19). SOX18 increased the expression of the tight junction protein CLDN5 (claudin 5), which inhibited endothelial permeability and lung injury in a series of *in vitro* and *in vivo* experiments. Mechanistically, nuclear factor-κB (p65) was defined as a counterregulator because it bound to the promoter region of SOX18, thereby reducing its expression.

Severe lung injury can also be driven by another important pathogen, *Staphylococcus aureus*. Ziesemer and colleagues showed that the pore-forming hemolysin A or α-toxin of *S. aureus* induces actin filament remodeling in human airway epithelial cells (20). Mechanistically, hemolysin A affected p21-activated kinase 2 and LIM (lin-11, isl-1, Mec-3) protein kinases, which control the activity of the actin-depolymerizing factor cofilin. As the authors speculated, dysfunction of mucociliary clearance in damaged airways might enable outgrowth of *S. aureus* and production of hemolysin A to cause actin rearrangements, which then facilitate the invasion of the bacterium. Another research group elegantly extended *in vitro* evidence of adherence and damage to the alveolar epithelium by the *S. aureus* strain USA300 in *in vivo* models. They showed that the bacterium takes advantage of niches in the microanatomy of the lung by rapidly forming so-called microaggregates in curved but not flat regions of the alveolar wall in human and murine lungs (21). Of note, other bacteria, such as *P. aeruginosa*, *K. pneumoniae*, or the methicillin-susceptible *S. aureus* strain Newman, also formed microaggregates, but these, as opposed to microaggregates of USA300, quickly resolved. The aggregation-promoting factor PhnD was essential for pathogenicity because USA300 strains that lacked PhnD failed to build stable microaggregates. Furthermore, USA300 strains that expressed hemolysin A damaged the alveolar epithelium and induced a calcium flux leading to epithelial dysfunctions spreading to uninfected alveoli. Interestingly, vancomycin given 30 minutes before infection did not improve survival of mice that received wild-type USA300 compared with strains lacking PhnD, demonstrating lack of an antibiotic killing effect toward bacteria that clustered in stable microaggregates, at least in the initial phase of the infection.

Finally, new therapeutic approaches are urgently required to treat respiratory viral infections. Norris and colleagues identified cardiac glycosides as potential drug candidates for RSV infection (22). Manipulating the ion content of the culture medium altered the capacity of glycosides to restrict RSV replication *in vitro*, but actual ion concentrations were not measured, and changes in calcium concentration were not taken into account. Importantly, glycosides lost their antiviral properties if applied 12 hours after infection, and glycosides possess a narrow therapeutic window, limiting their potential use in affected patients. However, because RNA viruses are prone to mutations, host factors might be attractive drug targets, and manipulating intracellular ion concentrations could be one of them (23).

Bacterial Pneumonia

Epidemiology

The Centers for Medicare & Medicaid Services coding for community-acquired pneumonia (CAP) did not initially include aspiration pneumonia. Lindenauer and colleagues studied 1,101,892 patients older than 65 years of age from 4,263 hospitals and found that the 17% ($n = 192{,}814$) coded as having aspiration pneumonia were more likely to be older and to have a higher disease burden and a higher 30-day mortality risk (29.4% vs. 11.6%) than those with other forms of CAP (24). Hospitals reporting a high proportion of aspiration pneumonia had a lower risk-adjusted mortality than those with a low coding rate. Thus, accurate reporting of aspiration

pneumonia could improve risk stratification and avoid artificially high reported risk-adjusted mortality associated with undercoding.

In a study of 179 patients with severe CAP, 85% had evidence of myocardial injury with an elevated troponin level during their ICU stay (73% upon admission), possibly as the consequence of altered oxygen supply and demand or infection-related inflammation and coagulation (25). These cardiovascular events could be mitigated by antiinflammatory therapies, including corticosteroids. However, although corticosteroid therapy can have benefit for some patients with bacterial CAP, in patients with viral respiratory infections such as influenza and Middle East respiratory syndrome, it may be harmful, and in one study of 309 patients, corticosteroids delayed Middle East respiratory syndrome coronavirus clearance (26, 27). In a retrospective analysis of 758 patients with CAP, investigators evaluated the role of concurrent corticosteroid treatment and its association with myocardial infarction (28). Using a propensity score, they found that those treated with corticosteroids (32%; $n = 241$) had a lower rate of myocardial infarction (hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.26–0.87) in Cox regression analysis, without a significant difference in overall and cardiovascular-related mortality or stroke. The beneficial effect of steroids was seen predominantly in patients with chronic obstructive pulmonary disease (COPD), but the decision whether to use steroids was up to the treating physician.

A multinational study of 3,702 patients assessed risk factors and characteristics of immunocompromised patients admitted with CAP (29). A total of 652 patients (18%) had at least one or more risk factors for immunocompromise, and they had more frequent *P. aeruginosa*, RSV, *Pneumocystis*, *Aspergillus fumigatus*, and *Nocardia* species infections than immunocompetent patients. In multivariable logistic regression analysis, pathogens not covered by usual CAP therapy were more often associated with COPD, tracheostomy, and severe pneumonia than with the immunosuppressed state. Thus, although almost one in five patients with CAP were immunocompromised, most randomized studies exclude them, which may not be appropriate.

Waterer and colleagues evaluated avoidable factors contributing to CAP-specific short-term mortality using prospective data collected in five U.S. hospitals (30). Overall inpatient mortality was 2.2% (52 of 2,320), but it was higher among patients older than 65 years of age (4%; 33 of 832) and in those with more than three severe comorbidities. Twenty-five percent of the deaths were related to respiratory failure, and 23.1% resulted from septic shock. However, only two patients who died and were to be resuscitated had an identifiable lapse in quality of care, suggesting that CAP-related mortality is unavoidable and determined by older age or comorbidities.

Bacteriology and Diagnosis

Kishore and colleagues reported the bacteriology of pneumonia complicating stroke in 7,968 patients from 15 studies (31). The majority of episodes (78%) occurred within 1 week of stroke, and aerobic gram-negative bacilli (38%) and gram-positive cocci (16%) were frequently isolated. *P. aeruginosa* and *Acinetobacter baumanii* were more commonly isolated in studies from South Asia and Asia than in studies from Western Europe and the United States, and *S. pneumoniae* was less frequently isolated.

Uncertainty regarding ventilator-associated pneumonia (VAP) diagnosis can lead to overtreatment and increased antibiotic use. Walter and colleagues assessed the discriminative capacity of alveolar neutrophilia obtained by bronchoscopic and nonbronchoscopic BAL in predicting bacterial pneumonia from one retrospective and two prospective VAP datasets (32). The majority of patients (>81%) were receiving antibiotics at the time of BAL, and the finding of an alveolar neutrophil percentage less than 50% had a negative predictive value of greater than 90% for VAP in both the derivation and validation cohorts. When combining alveolar neutrophil percentage with negative Gram staining, the negative predictive value improved to greater than 95% in both prospective cohorts. The authors then employed RNA transcriptomic analysis and found 33 differentially expressed genes in resident alveolar macrophages and 24 in recruited macrophages. The cluster of genes strongly associated with bacterial pneumonia was also associated with BAL neutrophilia. As the editorial accompanying that article emphasizes, the simplicity of this approach is elegant, and the lack of contribution of transcriptomics to further enhancing the diagnostic accuracy of this approach reflects the multiple influences on host RNA sequencing in critically ill patients (33).

Radiographic diagnosis of CAP is both nonspecific and sometimes not sensitive, whereas computed tomography (CT) can provide more information. In a study of 2,250 hospitalized adults with CAP, 66 had CT-only pneumonia (3%), and compared with those with radiographic pneumonia, they had similar pathogens (bacterial, 12% and 13.6%, respectively; viruses, 30.3% and 26.1%, respectively) and similar clinical outcomes, including disease severity, death, need for ICU admission, vasopressor use, or invasive mechanical ventilation (34). Patients with CT-only pneumonia had a lower proportion receiving antibiotics within 6 hours than those with radiographic pneumonia (59% vs. 83%; $P < 0.01$). Thirty patients with radiographic pneumonia did not have pneumonia based on a CT scan, most likely owing to lymphadenopathy, pulmonary edema, or fibrosis.

Samanta and colleagues collected blinded mini-BAL to measure α-amylase levels in 154 patients with suspected VAP within 48–72 hours of intubation to identify microaspiration (35). Microbiologically confirmed VAP was present in 65%, and the median α-amylase level was significantly higher in VAP than in non-VAP (287 vs. 94 U/L; $P = 0.001$). α-Amylase levels greater than 163 U/L had a sensitivity and specificity of 73% and 68%, respectively, for VAP diagnosis, and higher levels were seen in parallel with an increasing number of aspiration risks. An endotracheal tube with subglottic secretion drainage above the tube cuff has been used to interrupt microaspiration, but the subglottic space can incubate pathogenic bacteria in an inflammatory milieu (36, 37). With ventilation, mucin hypersecretion occurs and can impair host neutrophilic function, leading to the proliferation of a microbiome with reduced diversity that can further intensify local inflammation (36, 37). Mucolytic agents can reverse phagocytic impairment, thus enhancing the effect of subglottic drainage of aspirated secretions (36).

Biomarkers

Pulmonary vascular hyperpermeability in CAP results from direct toxic effects of

bacteria and an uncontrolled host immune response. Angiopoietins (Ang1 and Ang2) bind tyrosine kinase Tie2 receptors, with Ang2 promoting vascular neogenesis, permeability, and inflammation as an antagonist to Ang1 at Tie2. Gutbier and colleagues studied endogenous Ang2 in severe pneumococcal pneumonia from two independent pneumonia cohorts (38). In patients with CAP from the CAPNETZ (Competence Network for Community Acquired Pneumonia) study, they observed an increased Ang2/Ang1 ratio compared with healthy control subjects (0.12 vs. 0.04) and a higher level of Ang2 in nonsurvivors from both the CAPNETZ ($n = 75$) and PROGRESS (Study of Progression of Community Acquired Pneumonia in the Hospital; $n = 395$) cohorts. Combination of Ang2 with CURB-65 score (confusion of new onset [defined as an Abbreviated Mental Test Score ≤8], blood urea nitrogen >7 mmol/L [19 mg/dl], respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or diastolic blood pressure ≤60 mmHg, and age ≥65 yr) had the highest predictive power for 28-day mortality (area under the curve, 0.797; 95% CI, 0.703–0.891). Postmortem analysis showed Ang2 and Tie2 proteins exclusively localized in pulmonary blood vessels. In an associated murine pneumococcal pneumonia model, Ang1 therapy attenuated inflammation and vascular permeability, demonstrating a protective role.

Procalcitonin (PCT), an inflammatory hormokine, is elevated in patients with bacterial but not viral infection. In the ProACT study (Procalcitonin Antibiotic Consensus Trial), investigators randomized 1,656 emergency department patients with suspected lower respiratory tract infection from 14 U.S. centers to PCT guidance ($n = 826$) versus usual care ($n = 830$) (39). Of the 47.2% ($n = 782$) of patients hospitalized, 71.2% had COPD/asthma exacerbations, but only 19.9% had CAP. Adherence to the PCT protocol was 64.8% ($n = 513$), and intention-to-treat analysis showed no difference in antibiotic exposure between the PCT and usual care groups (4.2 vs. 4.3 d) or in the percentage of patients receiving any antibiotics (57% vs. 62%). This finding could be related to the case mix of enrolled patients, the low CAP rate, and the high antibiotic use rate in both groups.

Méndez and colleagues studied the timing of biomarker measurement in two different prospective CAP cohorts (derivation $n = 541$ and validation $n = 398$) (40). Patients were either early presenters (<3 d) or not, based on time since onset of self-reported symptoms. C-reactive protein levels were higher after 3 days (18 vs. 13.2 mg/L, $P = 0.005$ in derivation cohort; 18.8 vs. 13.6 mg/L, $P = 0.006$ in validation cohort), whereas PCT was higher in early presenters (0.5 vs. 0.3 ng/ml, $P = 0.023$; 0.9 vs. 0.4 ng/ml, $P = 0.028$), together with IL-6 and IL-8 levels. The findings were not affected by prior antibiotic use and suggest that there is a risk of underestimation of inflammation in CAP clinical trials, depending on the biomarker used and when it was measured.

Therapy

The 2016 Infectious Diseases Society of America/American Thoracic Society guidelines for nosocomial pneumonia were based on risk factors for multidrug-resistant (MDR) pathogens. Ekren and associates assessed the predictive performance of these guidelines, using prospective observations in 316 patients with ICU-acquired pneumonia (31% hospital-acquired pneumonia and 69% VAP) (41). Ninety-four percent of patients with VAP and 85% of patients with hospital-acquired pneumonia had at least one MDR risk factor from the guideline; yet, only 34% had these organisms present. In clinical practice, patients were treated according to the guideline 19–40% of the time but received adequate antibiotics 83% of the time and 61% of the time if MDR pathogens were present. If the Infectious Diseases Society of America/American Thoracic Society guideline had been followed, only 3% of patients would have been undertreated, and 37% would have received appropriate therapy, but 60% would have been overtreated. Thus, the guideline algorithm would have led to widespread use of unnecessary broad-spectrum therapy because of its sensitive but not specific MDR risk factors.

Aminoglycoside use, as part of dual antipseudomonal therapy, is limited by potential toxicities and decreased local antibiotic concentrations. Hassan and associates randomized 133 postcardiothoracic surgery patients with MDR gram-negative pneumonia to intravenous piperacillin/tazobactam plus either intravenous amikacin 20 mg/kg once daily or amikacin nebulized 400 mg twice daily, excluding patients with creatinine clearance less than 30 ml/min or those in whom only monotherapy was indicated (42). Clinical cure rates were significantly higher in the nebulized than in the intravenous group (91.8% vs. 70.2%; $P = 0.002$). Although mortality was similar between the groups, patients with nebulized amikacin had fewer days of mechanical ventilation, shorter ICU length of stay, lower serum trough levels, and less deterioration of kidney function. The findings show efficacy for inhaled antibiotics in selected (but not all) patients with nosocomial pneumonia. In the future, the limited antibiotic efficacy against *P. aeruginosa* could be supplemented by biologic therapies directed at the organism's pathogenic mechanisms, including quorum sensing, flagella, pili, LPS, and the type III secretion system with the use of immunomodulatory agents, neutralizing antibodies, or bacteriophages (43).

Inappropriate intravenous antibiotic use in the ICU leads to antibiotic resistance, but awareness of this problem can also lead to antimicrobial overuse. In a cluster-randomized crossover trial in eight European ICUs, cycling of antibiotics every 6 weeks versus a mixing strategy whereby antibiotics are changed after each consecutive patient is treated had no impact on the mean prevalence of antibiotic-resistant gram-negative organisms, which was 23% with cycling and 22% with mixing (44).

Prevention

In a study of the impact of pneumococcal conjugate vaccine (PCV) on pneumonia and non–pneumonia-related hospitalizations in Canada, investigators evaluated five intervals: prevaccine, availability of PCV7 for private purchase, public funding of PCV7, replacement of PCV7 with PCV10, and replacement of PCV10 with PCV13 (45). Hospitalization rates and costs for pneumonia began diverging in the postvaccination period, with the greatest benefit in the PCV13 period. The effect was more prominent for groups older than 65 years and younger than 1 year, but indirect benefits were also seen among those ineligible to receive the vaccine.

"Synbiotics"—a combination of probiotics (*Lactobacillus* and *Bifidobacterium*) and prebiotics—may preserve the gut microbiome and reduce infectious complications in ventilated patients with sepsis. In a single-blind study, 72 ventilated patients were randomized to either the synbiotic arm (initiated within 3 d after admission; $n = 35$) or the control

arm ($n = 37$) (46). There were fewer infectious complications, including enteritis and VAP, in the treatment arm at 28 days (28.6% vs. 67.6%; $P < 0.05$), with a VAP incidence of 14.3% compared with 48.6% in control subjects. The study may have overdiagnosed VAP, but conceptually it suggests that modulating the gut microbiota can affect innate immunity and sepsis-related infectious complications.

Pulmonary Infections in Immunocompromised Patients

Several studies have characterized the epidemiology of pneumonia, the leading cause of acute respiratory distress syndrome (ARDS), in the immunocompromised host; identified risk factors and predictors of poor outcomes; provided insights into potential mechanisms; and evaluated management strategies. In LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure), 584 (20.8%) patients were immunocompromised (47); pneumonia (71%) and nonpulmonary sepsis (16%) were the two most common risk factors for ARDS in immunocompromised patients, who had higher in-hospital mortality than immunocompetent patients (52% vs. 36%; $P < 0.0001$).

In the prospective, multinational TAVeM study (International Multicenter Study of Ventilator Associated Tracheobronchitis) of 663 immunocompromised and 2,297 immunocompetent patients from 114 ICUs, ICU mortality was similarly higher in the population with ventilator-associated lower respiratory tract infection (VA-LRTI) and immunocompromise compared with the population without VA-LRTI (54% vs. 30%; $P < 0.0001$). Surprisingly, the incidence of VA-LRTI in immunocompromised compared with nonimmunocompromised patients was lower (HR, 0.65; 95% CI, 0.53–0.80; $P < 0.0001$) (48). However, the frequency of MDR bacteria (72% vs. 59%; $P = 0.011$) was significantly higher in immunocompromised patients. Whether the reduced incidence of VA-LRTI was the result of decreased identification of LRTI in patients with a reduced inflammatory response or a result of the protective effects of greater exposure to antibiotics is unclear.

The LUNG SAFE study (47) provided insight into managing ARDS in immunocompromised patients, finding that these patients were more likely than immunocompetent patients to receive noninvasive ventilation as an initial ventilatory strategy. However, immunocompromised patients had a significantly higher incidence of noninvasive ventilation failure than immunocompetent control subjects, raising questions about the optimal ventilatory strategy for them. A study by Schmidt and colleagues (49) described 6-month outcomes in 203 immunocompromised patients treated with extracorporeal membrane oxygenation at 10 international ICUs. Bacterial, viral, and *Pneumocystis* pneumonia (PCP) infections accounted for the majority of reasons for ARDS (54% combined). Outcomes were poor, with only 42% successfully weaned off extracorporeal membrane oxygenation, and survival was 30% at 6 month. Mortality was significantly higher in patients with hematological malignancies, but those with a new diagnosis of immunodeficiency within the preceding 30 days had better outcomes.

The lung microbiome can impact pulmonary complications after hematopoietic stem cell transplant (HCT). Using a murine model of HCT, O'Dwyer and colleagues found that HCT and viral infection independently altered the composition of the lung microbiota, but individually they had no effect on microbial diversity (50). When HCT and viral infection were combined, the lung microbiome demonstrated altered composition as well as significantly decreased diversity, and pathology showed histologic pneumonitis. The human lung microbiota in BAL fluid from 43 HCT recipients showed an increased presence of Proteobacteria phylum in association with worse pulmonary function. This was the first study evaluating lung dysbiosis in HCT and builds on prior data associating gut dysbiosis with pulmonary complications in HCT (51).

PCP

One of the most common causes of pneumonia and respiratory failure in immunocompromised patients is PCP (also called "PJP" for *P. jirovecii* pneumonia). The incidence of PCP is increasing in non-HIV populations, and the clinical presentation of PCP varies with the type of immunodeficiency (52). Using clinical and radiographic data, Azoulay and colleagues developed and validated a multivariable model for predicting the risk of PCP in ICU patients with hematologic malignancies and acute respiratory failure (53). Variables associated with PCP were lymphoproliferative disease, absence of PCP prophylaxis, more than 3 days between respiratory symptom onset and ICU admission, and a nonalveolar pattern on radiographs. Variables associated with lower likelihood of PCP were age older than 50 years, shock, and pleural effusion. The predictive model had a mean area under the curve of 0.80 in the derivation cohort and 0.83 in the validation cohort, with an 87% sensitivity and 68% specificity for a score of 3 or greater for PCP risk factors. With a PCP prevalence of 10%, the negative predictive value was 97% in the validation cohort, making this a potentially useful initial screen to help rule out the diagnosis of PCP. Future studies could evaluate this tool in other immunocompromised populations and could include biomarkers such as lactate dehydrogenase and β-D-glucan. *Pneumocystis* cytochrome *b* A144V mutations can be a risk for PCP, and in heart transplant recipients, it was present in patients who developed PCP in spite of atovaquone prophylaxis (54).

Several studies evaluated risk factors for poor outcomes in PCP. A retrospective, single-center cross-sectional analysis of 240 patients with PCP (52% of whom had HIV) found that treating with less than 15 mg/kg body weight of trimethoprim-sulfamethoxazole was associated with a mortality HR of 1.80 (95% CI, 1.10–3.44; $P = 0.02$) (55). In multivariable regression models, lactate dehydrogenase above 495 U/L predicted in-hospital mortality (55). Overall, HIV-infected patients with PCP had lower mortality (13%) than patients with non-HIV immunocompromise (30–45%), and patients who required ICU admission were more likely to die.

Although PCP is treated similarly for HIV and non-HIV immunocompromised patients, the benefit of corticosteroids remains less certain in non-HIV populations. In a single-center retrospective review of 323 non-HIV immunocompromised patients with PCP, Wieruszewski and colleagues found no difference in mortality, ICU admissions, or need for mechanical ventilation between steroid recipients and nonrecipients (20%),

including in severity- and propensity-adjusted analyses (56). Thus, adjuvant corticosteroids may not provide the same benefit in non-HIV populations that we have come to expect in the HIV population.

Lung Health and HIV

Although pulmonary complications of HIV have been reduced with the advent of antiretroviral therapy, patients with HIV infection frequently have a high burden of respiratory symptoms and abnormal lung function. Gingo and colleagues investigated the impact of respiratory symptoms and lung function on outcomes in 396 patients with HIV infection in a multicenter cohort study (57). Patients with airflow obstruction (HR, 2.47; 95% CI, 1.10–5.58) and impaired D_{LCO} of less than 60% had an independent increase in all-cause mortality (HR, 2.28; 95% CI, 1.08–4.82) over a 6-year follow-up period. These results are consistent with work by Triplette and colleagues that also demonstrated an increased mortality risk associated with impaired lung function and radiographic emphysema in patients with HIV (58).

Mycobacterial Infections

Treatment of Drug-Resistant TB

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are an ongoing global health threat (59). Günther and colleagues reported results of a prospective cohort study of 380 patients treated for MDR-TB and XDR-TB from 2010 to 2014 across 16 European countries (59). They found that patients from high-incidence countries (vs. low- and middle-incidence countries) were treated more frequently with standardized regimens, experienced more delayed initiation of treatment tailored to drug susceptibility testing (DST), developed more drug resistance, and had increased mortality. These results emphasize the importance of increasing access to DST and second-line TB drugs to individualize MDR-TB and XDR-TB treatment regimens (59, 60). Recent data also showed a strong association between whole-genome sequencing–based genotypic and phenotypic predictions of TB drug susceptibility, and thus increased access to rapid genotypic DST may assist in developing more individualized treatment plans (61).

Dheda and colleagues, through evaluation of drug concentrations in blood and within resected TB cavities from 14 patients without HIV infection who had MDR-TB or XDR-TB, found large concentration–distance gradients for each drug, with low concentrations in the cavity center for most of the drugs studied (62). Notably, location-specific concentrations inversely correlated with minimum inhibitory concentrations, indicative of acquired drug resistance. These results have considerable clinical and pharmacologic relevance with respect to MDR-TB drug selection, route of delivery, and future efforts to prevent acquired drug resistance (62). Reassuringly, Salindri and colleagues found that patients with isoniazid-monoresistant TB have microbiologic and clinical outcomes similar to those of patients with drug-susceptible TB (63).

Treatment of Drug-Susceptible TB

Velásquez and colleagues conducted a phase II randomized controlled trial, testing rifampin at doses of 10 (standard dose), 15, and 20 mg/kg during the first 8 weeks of treatment among 180 adults in Peru with newly diagnosed drug-susceptible pulmonary TB (64). Notably, only 33% of patients in the 10-mg/kg group achieved therapeutic drug target concentrations, compared with 81% in the 20-mg/kg group (64, 65). Higher rifampin doses (and area under the concentration curve) increased the rate of sputum bacillary clearance; rifampin-related adverse events were similar across dosing arms. Reinforcing prior data, this study supports the safe use of high-dose rifampin for treatment of drug-susceptible TB (64, 65). Highlighting the importance of maximizing therapeutic drug concentrations, Colangeli and colleagues reported that among patients with drug-susceptible TB, those with higher pretreatment minimum inhibitory concentrations for either isoniazid or rifampin were associated with an increased risk of disease relapse (66).

Preventing and Predicting Incipient TB and TB Mortality

Van Der Meeren and colleagues reported results of a phase II randomized clinical trial evaluating a novel vaccine, M72/$AS01_E$ (two *Mycobacterium tuberculosis* proteins and $AS01_E$ adjuvant) in preventing active TB among roughly 3,500 adults without HIV infection with latent tuberculosis infection (LTBI) in South Africa, Kenya, and Zambia (67). Although further mechanistic and clinical studies are needed to better evaluate its performance, the vaccine's reported efficacy of 54% is promising. In the absence of an available vaccine, improved identification of patients with LTBI at highest risk for progression to active disease is needed. Suliman and colleagues used host transcriptomics to identify a four-gene signature associated with progression to active TB among a cohort of HIV-negative household TB contacts from South Africa, the Gambia, and Ethiopia, as well as among a cohort of South African adolescents with LTBI (68, 69). Also, Beavers and colleagues developed a scoring system to identify those at highest risk for TB-related mortality (70).

TB Immunology

Little is known about the host immune response in MDR-TB and XDR-TB. Davids and colleagues applied flow cytometry and immunohistochemical methods to determine the host immunologic profile in patients with XDR-TB in South Africa (71). Compared with patients with drug-susceptible TB and LTBI, patients in whom XDR-TB treatment failed had increased proportions of regulatory T cells ($CD4^+CD25^+FoxP3^+$) that suppress T-cell proliferation, identifying these pathways as potential targets for host immunotherapeutics (72).

Bénard and colleagues demonstrated that B cells may play important roles in the immune response to TB, most notably as a source of type I IFN (73, 74). Fox and colleagues also demonstrated that multiple platelet and platelet-associated markers were upregulated in plasma of patients with TB and that platelets may promote TB-related tissue destruction through induction of matrix metalloproteases (75, 76). They also showed evidence that platelets may enhance mycobacterial survival through mediation of monocyte production of IL-1α and IL-10 (75, 76).

Diagnosing LTBI in Pediatric Populations

Kampmann and colleagues reported results of a prospective cohort study of nearly 400 children in the United Kingdom with household exposure to active TB (77, 78). Children were followed for 24 months and evaluated with tuberculin skin testing and an IFN-γ release assay (IGRA). Reinforcing prior data about IGRA's substantial utility for diagnosing LTBI, no incident TB cases

were found among the 15 untreated children who had positive tuberculin skin testing results but persistently negative IGRA results (77, 78).

Nontuberculous Mycobacterial Disease

Although treatment success rates for *Mycobacterium avium* complex (MAC) have historically been poor, results of a phase III randomized controlled trial (CONVERT [Concurrent Once-Daily versus Twice-Daily Radiotherapy]) of a novel formulation of amikacin liposome inhalation suspension (ALIS), published by Griffith and colleagues, suggest that this paradigm may be shifting (79, 80). Among 336 patients with amikacin-susceptible MAC lung disease, with sputum cultures persistently positive for MAC after 6 months of guideline-based therapy, the addition of ALIS (vs. continued guideline-based therapy alone) resulted in a significant improvement in culture conversion at 6 months (29.0% vs. 8.9%) (79, 80). On the basis of results of the CONVERT trial and its predecessors, the Food and Drug Administration has approved ALIS for treatment-refractory MAC lung disease.

Jhun and colleagues addressed a fundamental question for clinicians (81): Why, despite prolonged exposure to macrolides, do patients with refractory MAC infections infrequently develop macrolide resistance? Among 72 patients with refractory MAC disease, macrolide resistance developed in 22% after treatment for a median of 33 months. Interestingly, of 49 patients with banked pre- and post-treatment isolates, genotyping demonstrated that reinfection by different MAC strains occurred in a very high proportion (73%) of patients with refractory MAC, with only 27% having persistent infections with original strains (81, 82). Also, Liu and colleagues identified an increased risk of pulmonary nontuberculous mycobacterial infection among patients who used high-dose inhaled corticosteroids (83). ■

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