Editorial (COPM May 2019 volume)

Title:

Towards improving the diagnosis, treatment and prevention of community acquired and nosocomial respiratory tract infections

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Word count: 1,450 words

Keywords: Respiratory tract infections, community, nosocomial, antibiotic resistance, treatment, host-directed therapies, personalized medicine

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Community acquired pneumonia (CAP), Hospital-associated pneumonia (HAP) and ventilator associated pneumonia (VAP) continue to pose a huge burden on healthcare services worldwide and present very significant clinical diagnostic and management challenges. This volume of Current Opinions in Pulmonary Medicine comprises 10 reviews covering a broad range of respiratory infection subject areas.

Transmission of bacterial and viral respiratory tract infections in hospitals and other healthcare environments is a growing problem worldwide. **Wilson and Zumla (Ref)** review recent literature of viruses imported to hospitals from the local community and from abroad, their modes of transmission and measures required to reduce and contain them. They highlight nosocomial outbreaks caused by Influenza A, Influenza B, Parainfluenza, Respiratory syncytial virus A and B, Adenovirus, and two novel zoonotic coronaviruses - the Severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) which are on the 2018 WHO blueprint list of priority pathogens due to their high mortality and epidemic potential. With continuing reports of MERS-CoV transmission to humans in Saudi Arabia, the risk of global spread of MERS-CoV as illustrated by the South Korean outbreak, is ever present due to the estimated 10 million pilgrims who visit Saudi Arabia every year from 182 countries.

Failure of antibiotic treatment of community acquired pneumonia is associated with serious complications such as empyema, lung abscess, broncho-pulmonary fistulae and necrotizing pneumonia (NP). **Simon Tiberi and colleagues (Ref)** remind us that NP was first described in adults in the 1940's and in children fifty years later. Necrotizing pneumonia is characterized by rapid progression of disease from consolidation to necrosis, cavitation and sometimes lung gangrene. They elegantly describe the difficulties in management of NP and its rapid progressive course through examples of two case histories. The rapid course of this lethal condition despite the use of antibiotics has focused attention on adjunctive host-directed therapies.

Markus Maeurer and colleagues (Ref) review the potential of developing adjunct Host-Directed therapies for lung infections where the inflammatory response results in excessive lung damage with long term functional disability. They draw parallels from cell-based, host-directed therapies used in precision cancer therapy and observations from detailed immunological studies, which indicate common protective and tissue destructive and repair pathways. Recent technological advances have allowed the

engineering of T cell receptors (TCR) and chimeric antigen receptors (CARs) targeting pathogen-specific or host-derived mutated molecules for recognition by TCR γδ and NK cells. They suggest their development for adjunct treatment of acute severe lung sepsis and chronic multidrug-resistant tuberculosis (MDR-TB).

A large proportion of patients with respiratory infections present with Community Acquired Pneumonia and are treated as outpatients, where the lack of a rapid, accurate diagnostic test, the uncertainty of the initial etiologic diagnosis and risk stratification, results in empiric antibiotic treatment. Those who do not improve on treatment present to emergency departments or are hospitalized. The symptoms and signs of chest infection and initial imaging with a chest X-ray in emergency departments or in hospitalized inpatients has poor diagnostic accuracy and leads to overdiagnosis of pneumonia, inappropriate antibiotic usage, and delays accurate diagnosis and rendering appropriate treatment. **Virginie Prendki and colleagues (Ref)** review two studies which assessed the diagnostic accuracy of CT-scan in patients suspected of pneumonia. The use of a CT-scan led to a net reclassification improvement of 8 and 18 % of patients and lowered the number of inappropriate antibiotic prescriptions. However, CT scan also defined pneumonia in patients with negative chest radiographs, and for now, these patients need antibiotic therapy, although routine CT scanning for CAP patients is not recommended. Further challenges facing the outpatient management of CAP are reviewed by **Filipe Froes et al**. **(Ref)** and they suggest more evidenced based guidelines for accurate diagnosis, prevention, treatment and in light of recent advances. In addition, they offer the hope that new diagnostic testing and therapies can be extended to improve outpatient CAP management.

Recent epidemiological studies indicate an association between acute respiratory tract bacterial and viral infections and increased risk of subsequent cardiovascular events, such as cardiac failure, acute coronary syndrome and strokes occurring weeks to years after recovery. The evidence base from epidemiological and basic science research studies is reviewed by **Martin Witzenrath and colleagues (Ref)**. In murine and non-human primate studies. *Streptococcus pneumoniae* appears to be able to invade and damage the cardiac myocytes leading to the development of scarring although the underlying pathogenesis of subsequent consequences remain to be defined. However, the findings emphasize that CAP may have long term health effects, and that its consequences may be far more than as a short-lived acute infection. Cardiac troponin or coronary artery calcium appear useful biomarkers for predicting risk of cardiac involvement during and after pneumonia.

Specialty society guidelines for management of pneumonia in hospitalized patients were recently updated in light of the increasing number of infections with multi-antibiotic resistant bacterial infections, and changes in the therapeutic options for HAP and VAP. **Ignacio Martin-Loeches et al (Ref)** compare two major guidelines for the management of nosocomial pneumonia: The International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator associated pneumonia and the American guidelines for Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia. They point out that despite several differences between the European and American guidelines, both guidelines concur on promoting prompt and appropriate empiric treatment guided by local microbiological data, followed by an adequate de-escalation protocol based on culture results, often with a one-week course of treatment. The conflicting views in regard to the optimum method of diagnosis, the risk factors used to stratify patients, the number of patients needing empiric broad-spectrum therapy, the use of biomarkers, the benefit of pharmacokinetic-guided antibiotic dosing, the use of clinical scoring systems and the various antibiotic classes used are also reviewed.

The past few years have witnessed an increasing number of patients with Multi-drug resistant (MDR-), tuberculosis. The WHO 2018 annual TB report **(Ref WHO 2018)** states there were nearly half a million cases of MDR-TB worldwide and only 50% of those who receive treatment are cured. Also increasing are pulmonary diseases due to non-tuberculous mycobacteria (NTM) *Mycobacterium avium* complex (MAC which include *M. intracellulare* and *M. chimaera*), *M. kansasii, M. abscessus* and M. *fortuitum*. **Marc Lipman and colleagues (Ref)** review recent progress in new drug and drug regimen development. They suggest that a regimen based on appropriate NTM-specific drug susceptibility testing should be a cornerstone of treatment for NTM as it is for *Mycobacterium tuberculosis* treatment, thus all new drugs should also be tested for activity against NTM.

Bronchiectasis is a chronic respiratory disease associated with numerous bacterial species and heterogeneous clinical manifestations and varied treatment outcomes. Identifying clinical phenotypes could help in improving management of patients with bronchiectasis through a personalized medicine approach. **Eva Polverino et al (Ref)** review the current literature focused on stratifying bronchiectasis phenotypes according to etiology, microbiology or other associated comorbidities and conclude that there is a need to further investigate the host-related factors (endotype) and their effects on diseases

severity and management outcomes. This is particularly true for patients with COPD and asthma, where bronchiectasis can co-exist, and its presence may have an impact on the approach to therapy.

Lung infections in cystic fibrosis patients have been successfully treated with inhaled antibiotics administered directly to the lung tissue, allowing for high antibiotic levels in the lung parenchyma , and avoiding systemic toxicities. This success has led to studies of inhaled antibiotics for treating patients with ventilator associated pneumonia. **Andrew Shorr and Matthew Schreiber (Ref)** review the results of 3 recent randomized studies which investigated aerosolized antibiotics for gram-negative pneumonia in ventilated patients. One single center, non-blinded investigation suggested a benefit with inhaled amikacin for resistant gram-negative infections while, two multicenter, blinded trials found no benefit to adjunctive nebulized amikacin for severe gram-negative pneumonia. They conclude that while there is no overwhelming evidence for the use of inhaled amikacin there may be a potential role for aerosolized antibiotics when other options are limited. However, as pointed out, a number of design issues in the negative trials, suggest that future trials will need to have a new methodologic approach.

The World Health Organisation **(WHO 2019)** global health observatory data (WHO, 2018) indicate that lower respiratory tract infections remain among the top three global causes of death, coming third after ischaemic heart disease and strokes. The early diagnosis and treatment of community acquired and nosocomial respiratory tract infections in both immunocompetent and immunocompromised individuals is becoming more difficult with the global increase in infections due to antibiotic resistant organisms. With better understanding of the host-pathogen interactions and disease pathogenesis, and limited antibiotic options, investments into developing adjunct host-directed therapies towards a more personalized medicine approach to management of RTIs is a key to improving management in the future.

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Financial support and sponsorship: None

Conflicts of interest: Alimuddin Zumla and Michael Nederman are editors of this volume of COPM