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CONTEMPORARY CONCISE REVIEW

Contemporary Concise Review 2018: Respiratory infections and tuberculosis

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INTRODUCTION

Respiratory tract infections (RTI), such as community-acquired pneumonia (CAP) and tuberculosis (TB), are important causes of morbidity and mortality. The ongoing outbreaks of Middle East respiratory syndrome coronavirus (MERS-CoV) infection and epidemic waves of avian influenza A(H7N9) since their emergence in 2012 and 2013, respectively, have raised global concern in recent years. The huge clinical burden of common respiratory viruses, such as respiratory syncytial virus (RSV) and seasonal influenza, on healthcare resources and utilization highlights the importance for developing more effective treatment modalities in order to reduce morbidity and mortality. In this contemporary concise review, articles related to these common respiratory infections and TB published recently in *Respirology* and selected articles published in other journals that highlight advances in knowledge are summarized.

RESPIRATORY INFECTIONS

Pneumonia

RSV is an important cause of acute RTI in early life. High bacterial loads colonizing the upper RT are often observed during RSV infections in children. Brealey *et al.*[1] identified an association between co-detection of RSV and *Streptococcus pneumoniae* and more severe disease in a Brisbane-based cohort of young children aged under 2 years with acute RTI, suggesting the bacteria may play a pathogenic role in these young children. Their findings may potentially have major implications for the management of young children with acute RTI in determining whether hospitalization is required and in directing the appropriate use of antibiotics, in addition to understanding factors involved in the development of asthma and new pathways of immunomodulation.[2]

KEY POINTS

- **In tropical countries, the spectrum of pathogens with pneumonia includes diseases such as melioidosis, scrub typhus, leptospirosis, hanta virus, chikungunya, dengue and parasitic pneumonias.**
- **Up to 30% of patients hospitalized for CAP develop cardiovascular complications.**
- **Further clinical and mechanistic studies are required to define the role of vascular endothelial growth factor (VEGF)-A as a marker of resolution of lung inflammation in ventilator-associated pneumonia (VAP).**
- **The provision of procalcitonin assay results to emergency department and hospital-based clinicians did not result in less use of antibiotics than did usual care among patients with suspected lower RTI.**
- **β-Lactam and macrolide in combination reduced the 30-day mortality compared with β-lactam alone in patients with low drug-resistant pathogen (DRP) risk.**
- **Systemic corticosteroid therapy was associated with delay in MERS-CoV RNA clearance in critically ill patients.**
- **Early treatment of patients with avian influenza A(H7N9) within 2–5 days from illness onset with a neuraminidase inhibitor (NAI) can reduce mortality.**
- **Baloxavir marboxil is a selective inhibitor of influenza virus cap-dependent endonuclease that is effective in the treatment of uncomplicated influenza.**
- **The role of adjunctive immunomodulating agents for patients with severe influenza deserves further investigation.**

The complex interaction of climate change, socio-economic factors and human migration patterns has led to changing patterns of respiratory infections in tropical climate but also increasingly in temperate countries. Tropical and poorer countries, especially South East Asia, account for almost one-third of the global burden of TB pandemic. In addition to TB, Lim and Siow[3] have emphasized that in tropical countries, the spectrum of

pathogens with pneumonia includes diseases such as melioidosis, scrub typhus, leptospirosis, hanta virus, chikungunya, dengue and parasitic pneumonias. Clinicians must be aware of the possible aetiology of pneumonia in the locality of practice and not solely dependent on published treatment guidelines.[4]

Up to 30% of patients hospitalized for CAP develop cardiovascular complications (such as new onset or worsening cardiac failure or arrhythmias, myocardial infarctions and cerebrovascular accidents) in the acute phase and even up to 10 years thereafter. Cardiac complications result from complex interactions between co-morbid conditions, upregulation of the sympathetic system, relative ischaemia, systemic inflammation and direct pathogen-mediated damage to the cardiovascular system. These mechanisms could provide the target of future therapeutic intervention to reduce incidence of cardiovascular complications and improve outcomes in patients with CAP.[5]

A significant increase in human blood VEGF-A is associated with early resolution of VAP; VEGF-A was an independent predictor of resolution despite disease severity. Experimental chronic pulmonary infection by *Pseudomonas aeruginosa* in the mice model led to increased VEGF-A concentrations in the lungs and yet a reciprocal reduction of pro-inflammatory cytokines and myeloperoxidase activity. Further clinical and mechanistic studies are required to define the role of VEGF-A as a marker of resolution of lung inflammation in VAP.[6]

The standardized approach to treatment makes CAP a target for comparative performance and outcome measures. Hadfield and Bennet[7] discussed clinical- and patient-reported outcomes, including endpoints such as the time to clinical stability and patient satisfaction, and strategies to improve these outcomes including use of a risk stratification tool, local antimicrobial guidelines with antibiotic stewardship and care bundles to include early administration of antibiotics and early mobilization. Interestingly, the provision of procalcitonin assay results to emergency department and hospital-based clinicians did not result in less use of antibiotics than did usual care among patients with suspected lower RTI in a randomized controlled trial (RCT) involving 14 hospital sites in the USA.[8]

There are limited published data evaluating the effects of antibiotic in CAP according to the DRP risk. In a post hoc analysis of a prospective multicentre cohort of patients with CAP, Okumura *et al.*[9] have shown that β-lactam and macrolide in combination reduced the 30-day mortality (adjusted odds ratio: 0.28, 95% CI: 0.09–0.87) compared with β-lactam alone. In addition, among patients at low risk for CAP-DRP, independent host factors associated with mortality included high arterial carbon dioxide ($PaCO_2$) level, non-ambulatory status, leucopenia, low haematocrit, older age, tachypnoea, low serum albumin level and low body temperature. These factors should be evaluated in future clinical trials in patients with low CAP-DRP risk for stratification to assess antibiotic effects. In an accompanying editorial, Waterer[10] emphasized the importance of starting a macrolide early followed a short time later by a third-generation cephalosporin, preferably all within 2 h of presentation to hospital.

Middle East respiratory syndrome

MERS-CoV infection of humans first emerged in 2012 in Saudi Arabia (Fig. 1). Nosocomial outbreaks are a major hallmark of MERS-CoV infection. In 2015, the largest outbreak outside the Middle East occurred in South Korea following the return of a businessman to Seoul from a trip to Qatar, UAE, Saudi Arabia and Bahrain, resulting in a total of 186 confirmed cases with 38 deaths. The risk factors for primary, household and nosocomial transmission are listed in Table 1.[11]

Another businessman returned to Seoul from Kuwait on 28 August 2018 with atypical presentation of MERS-CoV infection including diarrhoea and weakness without respiratory symptoms. With improved infection control awareness and disease surveillance after the major outbreak in 2015, the patient was isolated by the health authority quickly without causing any outbreak.[12]

Treatment of MERS-CoV infection is mainly supportive at present. An RCT is in progress in Saudi Arabia comparing lopinavir/ritonavir (400 mg/100 mg) bd for 14 days, recombinant interferon-β1b [0.25-mg/mL subcutaneous (SC) injections on alternate days for 14 days] and standard supportive care versus placebo and standard supportive care in patients with laboratory-confirmed MERS requiring hospital admission.[13] In a study of 309 patients in 14 intensive care units (ICU) in Saudi Arabia, systemic corticosteroid therapy was associated with delay in clearance of MERS-CoV RNA [adjusted hazard ratio (HR): 0.35, 95% CI: 0.17–0.72, $P = 0.005$][14] while a retrospective study of the same ICU cohort has shown that macrolide therapy is not associated with a reduction in 90-day mortality or improvement in MERS-CoV RNA clearance.[15]
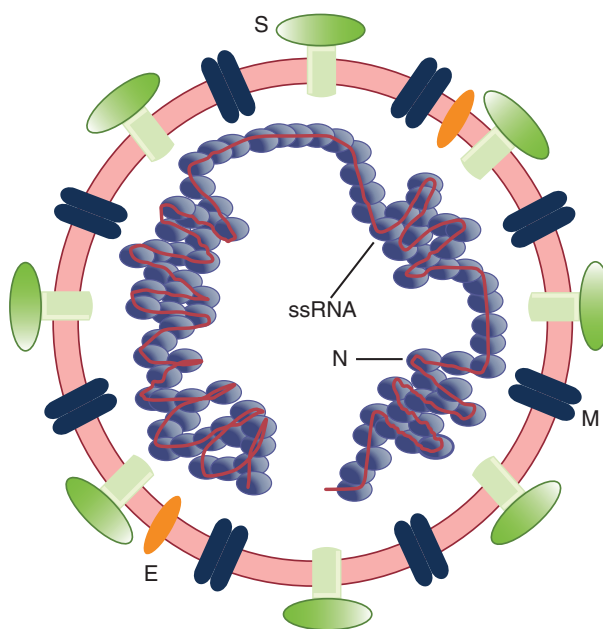

Figure 1 Major structural proteins of the MERS-CoV, with viral RNA structural proteins spike (S), envelope (E), matrix (M) and nucleocapsid (N). The S glycoprotein is the critical component for binding the host-cell receptor, dipeptidyl peptidase 4 (DPP-4), in order to initiate infection. (Reproduced from Zumla *et al*,[54] with permission)

Table 1 Risk factors for primary, household and nosocomial transmission of MERS-CoV infection (Reproduced from Hui *et al*,[11] with permission)

Primary MERS-CoV infection

(a) Significant risk factors include:
- Camel training
- Milking camels
- Workers with respiratory symptoms requiring overnight stay in hospital
- Contact with camels' waste
- Poor hand hygiene before and after animal task

(b) Independent factors associated with primary MERS-CoV illness:
- Direct dromedary exposure in the 2 weeks before illness onset (adjusted OR: 7.45, 95% CI: 1.57–35.28)
- Diabetes (adjusted OR: 6.99, 95% CI: 1.89–25.86)
- Heart disease (adjusted OR: 6.87, 95% CI: 1.81–25.99) or currently smoking tobacco (adjusted OR: 6.84, 95% CI: 1.68–27.94)
- Direct physical contact with dromedaries in the previous 6 months (adjusted OR: 14.59, 95% CI: 2.38–89.55)

Household transmission
- Sleeping in an index patient's room (RR: 4.1 (1.5–11.2))
- Removing patient's waste (urine, stool and sputum) (RR: 3.2 (1.2–8.4))
- Touching respiratory secretions from an index patient (RR: 4.0 (1.6–9.8))

Nosocomial transmission
- Exposure of patients, HCW and visitors to contaminated and overcrowded healthcare facilities especially emergency departments, inpatient wards and dialyses units
- Exposure to symptomatic MERS patients or healthcare workers caring for them
- Poor compliance with MERS-specific infection control guidelines
- Poor compliance with appropriate personal protective equipment when assessing patients with febrile respiratory illness
- Application of potential aerosol-generating procedures (e.g. resuscitation, CPAP and nebulized drugs)
- Lack of proper isolation room facilities, bed distance <1 m
- Frequent shifting of healthcare-seeking behaviour from hospital to hospital/emergency department to another
- Friends and family members staying as caregivers in overcrowded healthcare facilities

CPAP, continuous positive airway pressure; HCW, healthcare workers; MERS, Middle East respiratory syndrome; MERS-CoV, MERS coronavirus; OR, odds ratio; RR, risk ratio.

Influenza

It is difficult to forecast the timing, size and severity of influenza seasons despite advances in surveillance system.[16] NAI has been the mainstay of treatment for seasonal and avian influenza but its effectiveness is limited by delay of patient presentation for management.[17] Early treatment of patients with avian influenza A(H7N9) in Zhejiang, China, within 2–5 days from illness onset with an NAI can reduce mortality.[18] Of the 20 patients, 3 (15%) patients who had received NAI within 2 days died versus 12 of 52 (23.1%) patients who received treatment within 2–5 days versus 33 of 88 (37.5%) patients who were treated after 5 days ($P < 0.05$). The median durations of viral shedding from NAI therapy initiation was 4.5 days (interquartile range (IQR): 3–9 days) for patients who took NAI within 2 days, which was significantly shorter than that for those who took NAI within 2–5 days (7.5 days (IQR: 4.25–12.75 days)) or after 5 days (7 days (IQR: 5–10 days)) ($P < 0.05$).[18] Introduction of a bivalent H7/H5 vaccination of poultry in mainland China in October 2017 has resulted in better control of A(H7N9) outbreaks, with detection of only three human cases from October 2017 to September 2018, and a corresponding reduction of A(H7N9) viruses detected in poultry and environmental samples of A(H7N9) in China.[19]

Baloxavir marboxil is a selective inhibitor of influenza virus cap-dependent endonuclease, with therapeutic activity in preclinical models of influenza A and B virus infections, including strains resistant to current antiviral agents. Early treatment with a single-dose baloxavir was superior to placebo in alleviating influenza symptoms (in patients 20–64 years of age (median difference: 25.6 h) and among those 12–19 years of age (median difference: 38.6 h)). In addition, baloxavir was superior to both oseltamivir and placebo in reducing the viral load 1 day after initiation of treatment in patients aged 12–64 years with uncomplicated influenza, although there was no significant difference in the median time to alleviation of symptoms between baloxavir and oseltamivir recipients. However, there was emergence of mutant viruses with the development of decreased susceptibility to baloxavir after treatment in a small percentage of cases.[20] The therapeutic role of baloxavir in older or immunocompromised patients with severe seasonal or avian A(H7N9) influenza especially with some time delay in administration of the drug later in the clinical course of the infection or in combination with an NAI requires investigation.[21]

Lee *et al*.[22] have found significant anti-inflammatory effects with adjunctive macrolide treatment in adults with severe influenza infections, although virus RNA decline was unaffected. The role of adjunctive immunomodulating agents for patients with severe influenza deserves further investigation.[23]

TUBERCULOSIS

Progress in global TB control

According to estimates by the World Health Organization, 10 million incident TB cases and 1.6 million TB deaths occurred in 2017.[24] The estimated TB incidence declined only by 2% from 2016 to 2017,[24] barely higher than the 1.7% annual decline in TB mortality in the United Kingdom before the availability of effective treatment.[25] Social inequities continue to hamper TB control in many parts of the world, and major gaps remain in reaching, diagnosing and effectively treating TB patients, especially in resource-limited settings.[26] On 26 September 2018, heads of state and government meeting at the United Nations General Assembly committed to mobilize US\$ 13 billion to implement TB prevention and care, and US\$ 2 billion for research on an annual basis by 2022.[27] Hopefully, this important political commitment and additional funding support will promote universal health coverage and social protection, facilitate access to quality TB care and accelerate the development of better tools to meet the targets of the End TB Strategy by 2035.[26]

KEY POINTS

- **Major gaps remain in reaching, diagnosing and effectively treating TB patients in many parts of the world.**
- **Xpert MTB/RIF adds to conventional microbiological methods for TB diagnosis in thoracoscopic biopsy and bronchoscopic evaluation with tracheobronchial lesions.**
- **Levofloxacin/moxifloxacin, bedaquiline and linezolid are to be prioritized for use in the treatment of multidrug-resistant (MDR) TB, especially in presence of bacillary resistance to fluoroquinolones.**
- **Shorter rifamycin-based regimens, for example weekly rifapentine plus isoniazid for 12 weeks and daily rifampicin for 4 months, are proving safe and effective alternatives to isoniazid.**
- **A subunit vaccine, M72/AS01E, showed 54% protection against active pulmonary TB in HIV-negative adults with a positive interferon-gamma release assay (IGRA) in a recent phase IIb trial.**

TB diagnostics

Molecular diagnostic tools are increasingly utilized to diagnose TB and detect drug resistance for both pulmonary and extrapulmonary diseases.[24,28] In a study by Christopher *et al.*,[29] Xpert MTB/RIF assay on the thoracoscopic biopsy gave a substantially higher yield of 45% than biopsy culture (39%), pleural fluid culture (17%) or pleural fluid Xpert MTB/RIF (14%) among 73 patients with TB confirmed by histopathology on thoracoscopic biopsy. Among 61 cases of endobronchial TB diagnosed on bronchoscopic features, histology and positive sputum or tissue TB cultures in another study by Zhang *et al.*,[30] Xpert MTB/RIF performed on bronchoscopic brushing and biopsy had sensitivities of 57% and 64%, respectively, as compared to 13.1%, 32.8%, 36.1% and 68.9% for sputum smear, bronchial brush smear, sputum culture and tissue culture, respectively. With its short turnaround time of less than 2 h and additional ability to detect rifampicin resistance, Xpert MTB/RIF adds to conventional microbiological methods for TB diagnosis in thoracoscopic biopsy and bronchoscopic evaluation with tracheobronchial lesions.[31]

Drug susceptibility test

Unlike other bacterial infections, a single critical concentration that inhibits the growth of 99% of phenotypically wild type strains is used to classify phenotypic susceptibility or resistance to TB drugs.[28,32] However, this may not reflect the achievable serum drug level or clinical response of a mutant strain.[28] Clinical breakpoint (minimal inhibitory concentration at or below which the relevant strain is likely to respond to treatment) may be more informative for isoniazid, rifampicin, fluoroquinolones and other drugs that can be used at higher doses. The target drug coverage of commercial rapid molecular tests suitable for direct application to clinical specimens is still too limited to guide the formulation of individualized treatment regimens for MDR-/rifampicin-resistant (RR-) TB.[28,33] Whole-genome sequencing holds promise for revolutionizing the predictive power of genotypic drug susceptibility test,[34] but cost, throughput, facility requirement, background noises and replicative errors are important hurdles to overcome before its direct application to clinical specimens.[27]

Drug-resistant TB

Bacillary resistance to TB drugs continues to emerge. About 3.5% of new TB cases and 18% of previously treated cases in 2017 were MDR-/RR-TB, while 8.5% of MDR-TB cases were extensively drug-resistant (XDR-)TB.[24] Standardized treatment regimens, while having facilitated programmatic implementation, could have inadvertently accelerated the development of MDR-TB and XDR-TB through progressive selection of resistant mutants.[33,35] The standardized 9- to 12-month shorter MDR-TB regimen showed marginally less favourable outcome (78% vs 81%) than the conventional 18- to 24-month regimen in the preliminary results of the STREAM Stage 1 Trial.[36] In some MDR-TB hotspots such as Eastern Europe, South East Asia, Pakistan and Brazil, the high prevalence of resistance to one or more of the drugs used in the shorter regimen may render 50–96% of MDR-TB patients ineligible for the regimen by the strict drug susceptibility criteria.[33] Partly based on an updated meta-analysis of observational data in the treatment of MDR-TB,[37] the World Health Organization proposed reclassification of TB drugs used in the longer conventional regimen for MDR-TB into three different categories in August 2018.[38] Group A drugs, including levofloxacin/moxifloxacin, bedaquiline and linezolid, are to be prioritized. Group B drugs, including clofazimine and cycloserine/terizidone, are to be added next. Group C drugs (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin/streptomycin, ethionamide/prothionamide and p-aminosalicylic acid) are included when drugs from Groups A and B cannot be used. With the favourable outcomes achievable by the optimized background regimens in the treatment of MDR-TB in both the STREAM Stage 1 Trial (81%)[36] and Delamanid Trial 213 (78%),[39] the need for the relatively toxic drug, linezolid, and the expensive new drug, bedaquiline, with very short and incompletely established safety record, remains to be established, at least for fluoroquinolone-susceptible MDR-TB.[27]

Ageing and co-morbidities

Yew *et al.*, in their review of the epidemiological, clinical and mechanistic perspectives of TB in older people, highlighted the increasing clinical and public health challenge posed by TB in the ageing population in many Asian countries.[40] The complex interactions among oxidative stress, mitochondrial dysfunction and immunological dysfunction may contribute to the development of TB in the geriatric population and worsen the disease outcomes, especially in presence of co-morbid conditions such as smoking and diabetes mellitus. In a 1:1 propensity score-matched analysis of data from a longitudinal health insurance database in Taiwan, Lin *et al.* showed 76% reduction in TB risk

among 5026 diabetic patients put on metformin as compared with 5026 non-metformin users, after adjusting for co-morbidities, diabetic complications, anti-diabetic therapy type and statin use.[41] In another longitudinal study from the same locality,[42] metformin users were associated with 44% reduction in mortality during TB treatment despite their higher haemoglobin A1c level. The protective effect of metformin therefore appears independent of diabetic control. While the sizeable protective effects of metformin in the above-mentioned studies suggest a potential role of the drug as host-directed therapy in the treatment of latent TB infection and active TB, randomized trials are need to delineate its exact role(s) before introduction into clinical practices.[43] Park et al. retrospectively reviewed the data of 1784 patients with chronic obstructive pulmonary disease (COPD) in the Korean COPD Subtype Study cohort.[44] The COPD assessment test (CAT) scores, total St George's Respiratory Questionnaire for COPD (SGRQc) scores and exacerbation prevalence were significantly higher, and lung function was significantly poorer in COPD patients with prior TB than those without, both at the baseline and on follow-up over 3 years. Poorer lung function was observed among patients with prior TB, irrespective of whether they had visible lung lesions on chest radiographs.

Latent TB infection

Despite the introduction of IGRA using more specific antigens to avoid interference by prior BCG (Bacillus Calmette-Guerin) vaccination, all existing tests for latent TB infection[45] and predictive biomarkers for future disease development[46] are subject to a generic limitation imposed on their positive predictive value by the generally low absolute disease risks.[27] Shorter rifamycin-based regimens (e.g. weekly rifapentine plus isoniazid for 12 weeks[47] and daily rifampicin for 4 months[48]) are proving safe and effective alternatives to 9 months of isoniazid, especially in terms of lower risk of hepatotoxicity. However, the risks of other adverse effects (e.g. systemic or hypersensitivity reactions to rifamycins)[47–49] remain considerable relative to the number of TB cases averted. A targeted approach is therefore necessary to optimize the benefit versus risk ratio at the expense of reduced population coverage.[27] Despite the higher risk of TB infection among household contacts, household transmission accounts only for a small portion of the overall transmission in the ongoing TB epidemic.[50] The safety of rifapentine in pregnancy remains to be established even though no excess risks of foetal loss or congenital anomalies were observed among pregnant women inadvertently exposed to either isoniazid or isoniazid plus rifapentine in two clinical trials.[51]

Novel TB vaccines

Novel TB vaccine candidates being developed include whole-cell vaccines, adjuvanted protein subunit vaccines, viral vector-delivered subunit vaccines, plasmid DNA vaccines, RNA-based vaccines etc.[52] Vaccines are useful as a first-line tool in controlling infectious diseases because they are more readily applied on a population scale.[25] Unlike preventive treatment, the protective effects of vaccines will not be nullified by reinfection after the intervention. However, with the high global burden of latent TB Infection, vaccines capable of preventing pulmonary TB in infected individuals will be needed to reduce TB incidence quickly.[27] At least 12 novel TB vaccine candidates are now in clinical trials.[52] A subunit vaccine, M72/AS01E, showed 54% protection against active pulmonary TB in HIV-negative adults with a positive IGRA in a recent phase IIb trial.[53] This proof-of-concept study brings fresh hopes for new and possibly transformative TB vaccines in the near future.

Abbreviations: bd, twice daily; CAP, community-acquired pneumonia (CAP); DRP, drug-resistant pathogen; HIV, human immunodeficiency virus; ICU, intensive care unit; IGRA, interferon-gamma release assays; IQR, interquartile range; MDR, multidrug-resistant; MERS, Middle East respiratory syndrome; MERS-CoV, MERS coronavirus; NAI, neuraminidase inhibitor; RCT, randomized controlled trial; RR, rifampicin-resistant; RSV, respiratory syncytial virus; RTI, respiratory tract infection; TB, tuberculosis; VEGF, vascular endothelial growth factor; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

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