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Review

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Mycoplasma pneumoniae: A Potentially Severe Infection

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Abstract

Mycoplasma pneumoniae infections remain one of the most common etiologies of community-acquired pneumonia (CAP). The clinical presentation and manifestations vary widely and can affect all organs of the body. Diagnosis is challenging because there are no constant findings in physical exams or laboratory or radiological assessments that indicate *Mycoplasma pneumoniae* pneumonia, and specific diagnostic tools are not readily available. Extrapulmonary manifestations and severe pulmonary manifestations can lead to long-term sequelae. The increasing emergence of *Mycoplasma pneumoniae* that is resistant to macrolides in some areas of the world and increased world travel could add to the difficulty of controlling and treating *Mycoplasma pneumoniae* infections. We present a concise and up-to-date review of the current knowledge of *Mycoplasma pneumoniae* pneumonia.

Keywords: *Mycoplasma pneumoniae*; Atypical pneumonia; Mycoplasma IgM

Introduction

Pneumonia, despite significant advances in infection prevention and antibacterial armamentarium, still results in significant mortality. The World Health Organization estimates that lower respiratory tract infection is the most common infectious cause of death in the world, with almost 3.5 million deaths yearly (The top 10 causes of death. Geneva: World Health Organization, 2013; http://www.who.int/mediacentre/factsheets/fs310/en/index.html).

The prevalence of infection with *Mycoplasma pneumoniae* (MP) is widely underestimated, as most patients infected with MP are seldom symptomatic and they rarely seek medical attention. MP infection is considered one of the common etiologies of community-acquired pneumonia (CAP). The non-specific clinical and radiological characteristics and lack of accurate diagnostic modalities make the diagnosis not only difficult, but often controversial. *Mycoplasma pneumoniae* pneumonia (MPP) is often called "walking pneumonia" because of its presumed benign nature. The overall mortality of MP infection is low, but mortality of up to 30% has been reported in the literature, especially among the elderly [1-3]. Fulminant MPP accounts for 0.5-2% of all MPP cases and primarily affects young, healthy individuals [4]. This review focuses on new developments and research findings with regard to resistant strains of MP and its modern diagnostic techniques.

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Epidemiology

Pneumonia is the most clinically important manifestation of MP infection, as MP has been reported in 10-40% of CAP cases, with children and young adults as the most susceptible group. The reported incidence of sporadic MP in adults ranges from 4% to 8% of community-acquired bacterial pneumonias which increases up to 20% and 70% during epidemics [4-7].

The rate of hospitalization among the adult population in the USA due to MPP is approximately 100,000 hospitalizations per year. MPP remains largely underdiagnosed because of its presumed benign nature, lack of diagnostic tests with good sensitivity and specificity, and other infections that either co-exist or mimic MP [5, 8]. Although current evidence suggests that the incidence of MPP is high in children older than 4 years and adolescents, the true impact on adults, the elderly population and public health remains unclear [5, 8-10].

The geographic distribution of MP infections remains widespread [5]. Japanese studies have demonstrated an association of MP infections with climate changes, especially with elevated atmospheric temperatures and humidity during summer months. One study showed a 17% increase in MPP cases with every increase of 1 °C and a 4% increase for every 1% increase in humidity [11]. Onzuko et al propose that these associations can be used as early warning signs for MP epidemics [11, 12]. The incidence of MPP has been found to be higher in patients with underlying bronchial asthma (BA) or chronic obstructive pulmonary disease (COPD) [13-16].

The Center for Disease Control and Prevention (CDC) has reported several recent outbreaks among children and adults [17]. These outbreaks have occurred in schools, colleges and nursing homes. Few subjects suffered severe illness requiring prolonged hospitalization with intensive care and/or life threatening cutaneous or neurological diseases [18-20]. An outbreak in a nursing home in Nebraska resulted in a mortal-

ity of 13% among 55 affected patients [21, 22]. Spread of MP infections among family members has also been reported [23, 24]. However, the ability of the bacteria to reside and persist in humans as a carrier remains controversial, as no test is able to differentiate a carrier state from an infection [25].

Pathogenesis

MP is broadly divided into two genetic groups, subtype 1 and subtype 2, which are differentiated based on repetitive elements of RepMP2/3 and RepMP4 in the P1 protein gene [26]. MP epidemics are likely a consequence of the interplay between the two subtypes, each emerging after the other induces transient herd immunity [27].

The most important intrinsic virulence factors of MP include cyto-adherence and mobility. The main anchor proteins that enable adherence are P30 and P1 that are attached to the polar terminal organelle of the pathogen. One of the most important virulence factors responsible for negative outcomes of MPP is an ADP-ribosyltransferase exotoxin called community-acquired respiratory distress syndrome (CARDS) toxin that causes vacuolation and ciliostasis of the host cells. CARDS toxin is also responsible for production of free radicals that further cause cytotoxicity [28, 29].

MP infection is associated with elevated mRNA levels of cytokines, including interleukin (IL)-8, tumor necrosis factor-α and IL-1β, which lead to the recruitment of inflammatory cells [5, 30, 31]. Medina et al proved a temporal association between the CARDS toxin and airway hyperactivity, histological changes and deterioration of lung function. CARDS toxin produces an allergic-type reaction in animals. CARDS toxin also exponentially stimulates the expression of Th-2 cytokines (IL-4 and IL-13) and Th-2 chemokines (CCL17 and CCL22) resulting in a mixed inflammatory response of eosinophilia, accumulation of T cells and B cells, and mucous metaplasia [32, 33]. Some strains of MP release free radicals that are potential virulent factors [34].

Major mechanisms of MP infection include: 1) direct infection with evidence of the MP organism at the site of inflammation and activation of local cytokines; 2) indirect infection by modulation of the immune system that may involve cross-reactivity between bacterial and human cells. These include cold agglutinins to I-antigen of human red blood cells [35]; 3) vasculitis and/or thrombosis [36].

Clinical Presentation

The clinical presentation of MPP is non-specific and can be classified as pulmonary or extrapulmonary. Similarly, symptoms are non-specific and resemble prodromal symptoms of a viral infection involving the respiratory tract; however, exudates or lymphadenopathy are seldom seen in MPP [5, 37, 38]. Experimental evidence suggests that symptom severity increases with the amount of bacterial burden and with a lack of pre-existing antibody [13, 39]. Most commonly, patients present with fever, cough, myalgias and/or gastrointestinal symptoms.

Physical exams and vital signs can be normal during MPP, and abnormal findings depend on which organs are involved. Rarely, pulse-temperature dissociation can be found during MP infection. Relative bradycardia is less common when compared with other atypical agents such as typhoid fever, Legionellosis, psittacosis and rickettsial infection. The fever range for MPP is broad, including low- to high-grade fevers such as 39 °C [40].

Laboratory assessments of patients with MPP are similarly non-specific. Leukocytosis develops in approximately 25% of patients, but white cell counts are typically normal or low. An elevated erythrocyte sedimentation rate (ESR) can be present. No specific abnormalities of hepatic or renal function are likely to occur; however, occasionally there is an increase in serum creatinine phosphokinase or serum lactate dehydrogenase [41, 42].

Pulmonary

Productive or dry coughs secondary to tracheobronchitis remains the most common manifestation of MP infection. Pulmonary symptoms range from mild viral-like symptoms to more severe presentations, such as exacerbation of obstructive airway diseases with bronchospasm or pneumonia symptoms. Fulminant presentation with acute respiratory distress syndrome (ARDS) or diffuse alveolar hemorrhage has been reported [5, 13, 37-39].

Extrapulmonary

There is a myriad of extrapulmonary manifestations of MP infection that can involve any organ. Extrapulmonary manifestations are not only directly related to the infection process, but are usually due to auto-immune or vascular complications. Table 1 presents a summary of extrapulmonary manifestations of MP infection [36, 43].

Neurological

One of the most important extrapulmonary manifestations of MP infection is neurological sequelae, which is reported in up to 10% of patients and is more common in children. A frequent neurological manifestation is encephalitis. Late-onset encephalitis can have false-negative results in polymerase chain reaction (PCR) assessments of MP infections [44, 45]. Fatal forms of encephalitis include acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalitis, aseptic meningitis and early-onset transverse myelitis secondary to local invasion. Vascular injury can further lead to stroke, striatal necrosis, and psychological disorders [36, 45]. Immune dysregulation secondary to MP infection can lead to cerebellar dysfunction, late-onset transverse myelitis, peripheral nerve involvement, cranial nerve palsies and Guillain-Barre paralysis; however, MP is occasionally isolated from the cerebrospinal fluid [46-50]. Poor correlations between serology and PCR assessments

Table 1. Pulmonary and Extrapulmonary Manifestations of *Mycoplasma pneumoniae* Infection

Organ involvement	Manifestation
Pulmonary	Asthma/chronic obstructive pulmonary disease (COPD) exacerbation Tracheobronchitis Pneumonia: lobar and multi-lobar infiltrates Diffuse alveolar hemorrhage
Gastrointestinal	Nausea, vomiting, abdominal pain, anorexia Diarrhea Transaminitis
Cardiovascular	Myocarditis, pericarditis Cardiac arrhythmias Thrombotic events
Neurological	Meningitis, encephalitis, optic neuritis Guillain-Barre syndrome
Renal	Acute tubular necrosis, glomerulonephritis, interstitial nephritis
Musculoskeletal/skin	Erythema nodosum, cutaneous leukocytoclastic vasculitis Erythema multiforme, Stevens-Johnson syndrome MP-associated mucositis Myopathy, arthritis, and rhabdomyolysis
Thrombotic	Pulmonary embolism Splenic artery and left atrium and right ventricle thrombosis Aortic thrombosis/renal artery thrombosis
Other	Vasculitis (positive antineutrophil cytoplasmic antibodies) Cytopenias, cold agglutinin-induced autoimmune hemolytic anemia, sickle cell disease, idiopathic thrombocytopenic purpura-like syndrome Kawasaki disease

for MP infections in patients with neurological manifestations make the diagnosis difficult, especially because it prevents identification of the convalescent phase [5]. A long-term follow-up study of children with MP infections reported cases of significant neurological disability [51].

Dermatology

Stevens-Johnson syndrome (SJS) is the most common and serious dermatological manifestation of MP infection. As the clinical course, distribution and milder presentations of SJS associated with MP infections differ from the usual drug-induced SJS, it has been suggested to be a separate entity. Anecdotal case studies have found MP in SJS skin blisters, suggesting direct invasion from the blood stream. Other dermatological manifestations, such as urticaria, anaphylactoid purpura and erythema multiforme, are most likely immunologically mediated [36, 52, 53].

Hematological

Hematological symptoms range from rather vague thrombocytosis or thrombocytopenia to fatal hemolytic anemia secondary to cold agglutinins, thrombotic thrombocytopenic purpura and disseminated intravascular coagulopathy. The occurrence of cold agglutination can be even more dangerous in patients with sickle cell disease [41, 54-56].

Cardiac

Cardiac symptoms are uncommon in MP infections, have variable prognoses and often present without evidence of pneumonia. The cardia symptoms can include pericarditis, cardiac tamponade, myocarditis, myopericarditis and endocarditis. Few reports of direct detection by PCR of MP in cardiac tissue or pericardial fluid exist; however, an autoimmune component to the cardiac pathogenesis cannot be ruled out [36, 57].

Musculoskeletal

Musculoskeletal symptoms of MP infection include septic arthritis and rhabdomyolysis. Rhabdomyolysis often co-exists with neurological or pulmonary manifestations, but can be an isolated finding in MP infections. One or more of the mechanisms (direct invasion, immunological reactions or vascular occlusion) may be responsible for these symptoms [36, 57-59].

Gastrointestinal

There are sparse data and a general lack of evidence on gastrointestinal manifestations of MP infections. It is speculated

that early-onset hepatitis from MP infections is due to direct invasion and injury to hepatocytes, while late-onset hepatitis may result from immunological reactions and vascular occlusion or injury [36].

Renal

Acute glomerulonephritis, including nephrotic syndrome, interstitial nephritis and immunoglobulin (Ig)A nephropathy, has been associated with MP infections and is presumed to be secondary to immune complex formation [5]. There are reports documenting detection of the MP organism itself by PCR and immunoperoxidase staining from kidney tissue [60, 61].

Chest Imaging

Radiological assessments of MP infection also result in nonspecific presentations. Normal chest-roentgenograms (CXR) are reported in approximately 5% of MPP patients. The four most common patterns in CXRs of MPP patients are peribronchial and perivascular interstitial infiltrates (49%), airspace consolidation (38%), reticulonodular opacification (8%) and nodular or mass-like opacification (5%). Uncommon findings include pleural effusion, cavitary disease and hilar lymphadenopathy [62].

Findings in chest computed tomography (CT) assessments of MPP patients include airspace consolidation, ground glass opacification and pleural effusions. Reittner and colleagues found airspace consolidation and ground glass attenuation to be the most common pattern among 28 patients with MPP undergoing high-resolution chest CT [62]. In the pediatric population, focal or bilateral reticulonodular opacification has been reported to be most suggestive of MPP [63-65].

Diagnosis

Diagnosis of MP infections can be challenging because mycoplasmas are not visible by Gram staining due to the lack of a cell wall. Cellular responses in sputum are typically mononuclear. Approximately 75% of MPP patients have a cold agglutinin titer of at least 1:32 by the second week of illness, which is typically resolved after 6 - 8 weeks. This is not a specific test for MP infection, but the greater the cold agglutinin titer (> 1:64) is in a patient with pneumonia, the more likely the cold agglutinins are due to MP [5].

Current diagnostic modalities include various direct PCR assays, serology and culture. The accuracy of PCR assays depends on the technique and the sample size. PCR assays and serology are not always concordant, especially in patients of extreme ages; infants and the elderly may have insufficient immunological responses towards MP infections at the time of testing. Additionally, MP infection becomes undetectable by PCR sooner than by serological analysis once antibiotic therapy is initiated [5].

The gold standard for serological diagnosis is a four-fold change in antibody titers over time (IgM antibody titers rise earlier than do IgG antibodies). The sensitivity of IgM assays increases with the duration of symptoms, approaching more than 70% after 16 days of symptoms. The positive predictive value of IgM approximates 80% [66]. Although evidence of concordance is more concrete in children, both PCR and serology have been shown to correlate well in adults as well. The use of both techniques improves the reliability and accuracy of MPP diagnosis [25, 38, 67].

Cross-reactivity with Epstein-Barr virus (EBV) is common. Cold agglutinins help to confirm the diagnosis of MP infection as they are elevated in 50-60% of MPP patients; however, cold agglutinins may be present in EBV, cytomegalovirus or *Klebsiella* infections. Anti-I-specific IgM-cold-agglutinin is more specific for diagnosis. Cold agglutinins are positive in 50% of patients infected with MP [68]. PCR and serological analyses could be a good combination screen for reliable and accurate diagnosis of MP infection. Bacterial cultures are usually time-consuming and not readily available [38].

The Japanese Respiratory Society's scoring system for atypical pneumonias can diagnose MPP with 88.7% sensitivity and 77.5% specificity. The presence of more than four out of six of the following parameters provides the clinician with a strong suspicion of MP: 1) age < 60 years; 2) absence of or only minor underlying diseases; 3) stubborn cough; 4) positive findings in chest auscultation; 5) absence of sputum; or 6) identifiable etiological agent by rapid diagnostic testing and serum white blood cell counts < 10×10^9/L [5, 26, 38, 67, 69-71].

Other modern diagnostic techniques that lack widespread validity include Nanorod array-surface-enhanced Raman spectroscopy (NA-SERS) and matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) [5].

Treatment

Spontaneous resolution of MP infections in 7 - 10 days is not uncommon [66]. However, treatment is often necessary. Mycoplasma does not have a cell wall, which makes the choice of antibiotics restricted to those that act on the bacterial ribosome to inhibit protein synthesis. These antibiotics include macrolides, ketolides, streptogramins and tetracyclines. Azithromycin remains the macrolide of choice, with better tolerance and a longer half-life than the others, which allows for a shorter course of treatment. Macrolides and ketolides bind to specific nucleotides of the 23S rRNA in the 50S bacterial ribosomal subunit, blocking protein synthesis by causing premature dissociation of peptidyl-tRNA from the ribosome [5, 72]. The anti-inflammatory and bacteriostatic potential of macrolides will act synergistically [5].

Fluoroquinolones are also useful for MPP treatment as they inhibit DNA replication. Fluoroquinolones have the potential to eradicate infections due to their bactericidal action. When serology is used for diagnosis, determination of eradication remains a challenge, leading to inaccurate efficacy measurements [5].

Regarding minimal inhibitory concentrations (MICs) of antibiotics, Azithromycin remains one of the most potent drugs against MP infection [38]. Fluoroquinolones are as effective as macrolides, but with higher MICs. Tetracyclines, which are protein synthesis inhibitors, are used in neurological manifestations of MP infection [5, 73, 74].

All extrapulmonary manifestations must be treated with antibiotics as direct invasion of the organisms cannot be ruled out and decreasing overall bacterial loads can dampen the robust host immune system.

The emergence of macrolide resistance has been reported, leading to the development of new investigational antimicrobial agents such as Lefamulin, Solithromycin, Nafithromycin, Omadacycline and Zoliflodacin [5]. Widespread macrolide-resistant MP (MRMP) was first reported in Japan during the early 2000s and eventually spread through Asia and North America [5, 75]. The resistance pattern predominates in almost 90% of all mycoplasma isolates in Japan and China [76-78]. Reports of MRMP in Europe show wide disparities from less than 1% in Slovenia and the Netherlands to close to 30% in Italy and Israel [79, 80]. In the USA and Canada, MRMP accounts for approximately 10% of all MP infections [17, 81, 82].

Prior administration of macrolides is associated with MRMP [5, 83] and several studies suggest that the widespread use of macrolides may be responsible for MRMP [5, 84-90]. This supports the highest incidence of MRMP in Japan because macrolides account for 30% of all oral antibiotics prescribed in the country [91]. Multilocus variable-number tandem-repeat analysis (MLVA) of the P1 adhesion gene has shown no evidence of an association with macrolide resistance, indicating a polyclonal origin for MRMP. This suggests that the resistance develops *de novo* during treatment rather than from person to person [92-97]. However, the specific MLVA type 4-5-7-2 was reported to have increased macrolide resistance during an epidemic in Hong Kong [98].

In addition to antibiotics, there are anecdotal and conflicting reports regarding benefits of steroids, plasmapheresis and intravenous immunoglobulin therapy. These therapies are usually reserved for severe and life-threatening manifestations of MP infections, especially in patients with neurological involvement or dermatological complications such as SJS [67, 70, 99-101].

Youn et al reported rapid resolution of infection in 86 out of 90 children with complicated MPP who received systemic steroids [102]. Prednisolone appears to be the most effective corticosteroid in the adjunctive therapy of CAP, as it inhibits platelet activation *in vitro* by a non-genomic mechanism not shared with other types of corticosteroids [103]. Use of steroids could lead to earlier clinical and radiological resolution than antibiotics alone [104]. A recent large multicenter retrospective study in Japan identified 2,228 adult patients with MPP. The effects of low-dose and high-dose corticosteroid therapies on mortality, hospital length of stay (LOS), drug costs and hyperglycemia requiring insulin treatment of MPP were evaluated. However, adjunctive corticosteroid therapy did not decrease 30-day mortality. In addition, both low-dose and high-dose corticosteroid therapies were associated with increases in LOS. Furthermore, hyperglycemia requiring insulin treatment and drug costs increased with corticosteroid use [105]. Therefore, currently, the benefits of treating MPP patients with steroids needs further study. It has shown positive effects in children but outcomes in adults are controversial.

Identification of MRMP considering the recent increased rates of macrolide resistance has gained clinical significance. One study that defined clinical efficacy as the rate of symptom resolution showed that clinical efficacy was 91.5% in patients with macrolide-sensitive MP as compared to 22.7% in patients with MRMP [106]. Kawai et al also showed that the number of MP organisms was higher in patients with MRMP [107]. MRMP is associated with more extrapulmonary symptoms and more serious radiological findings and pneumonias than is macrolide-sensitive MP [108]. It is speculated that severe presentations of MRMP may result from a more robust host immune response with inflammatory cytokines and ILs [109-111].

Outcomes

Morbidity and mortality

Despite MPP been considered a "benign" infection, reports suggest that there is significant morbidity and mortality associated with it. A study looking at all patients admitted with MP infections from 2007 to 2012 at the Hadassah-Hebrew University Medical Centre identified 416 patients, of which 68 (16.3%) required intensive care unit (ICU) admission. ICU care was required for 18% of adult patients aged 19 - 65 years and 46.6% for older patients. The hospital mortality for the MP-infected patients admitted to the ICU was 29.4% [3]. A small review of 46 patients admitted with MPP showed that younger males who are smokers are most susceptible to fulminant MPP. The authors proposed that strong immune responses of the young male smokers to the infection could have led to the adverse outcome [4]. Severe forms of MP infection have heterogeneous clinical presentations from diffuse alveolar hemorrhage, cavitary lesions and ARDS [1].

The importance of early administration of antibiotics for MPP patients was reinforced in a study of 227 MPP patients. The 13 (6%) patients that required admission to ICUs for acute respiratory failure did not receive appropriate antibiotics until approximately 10 days after diagnosis [112]. ICU care for elderly patients has been reported at approximately 9% with almost a third of those patients requiring mechanical ventilation.

Obstructive airway disease

The data remain controversial, but MP infection has been associated with the development or exacerbation of obstructive airway disease [5, 32, 69, 113]. A study by Lieberman et al showed that among 100 asthmatics hospitalized for exacerbation, MP infection was present six times more often than in the control group that was composed of adult trauma and surgical patients with no evidence of active or recent past infections and no lung disease [21].

A large epidemiological study of 7,955 adults from Tai-

wan's national database compared 1,591 patients with MP infections with 6,364 without MP infections. Patients with MP infections had a higher risk of developing asthma, which was further augmented by co-existing atopy disease [114]. The prevalence of MP infections in adults with refractory asthma is approximately 50-65% [115, 116].

Few studies have examined the prevalence of MP in chronic asthma. In a small study of 55 patients with chronic stable asthma, 42% of the patients were positive for MP as determined by PCR [117]. Two other similar small studies found a lower prevalence rate of MP at approximately 10%; however, those studies collected oropharyngeal and nasopharyngeal samples for MP identification [118, 119].

Kraft et al showed that among asthmatics, a subgroup of patients with MP infections showed improved lung function when treated with 6 weeks of Clarithromycin [68]. The mechanism of this positive outcome is unclear, though macrolides have anti-inflammatory effects that may play a significant independent role toward improving lung function [5].

Animal studies show that exposure to MP can increase airway hyperreactivity and that allergic airway inflammation downregulates the action of the host immune system towards MP infection [120-122]. Administration of purified recombinant CARDS toxin to model animals reproduces substantial features of MPP, including increased cytokine production, eosinophilia and airway hyperreactivity that closely resembles asthma [29, 32, 33].

Evidence of an association between MP infections and COPD is also vague with mixed results. Smith et al evaluated the association of viral and MP infections in acute respiratory illness among 150 patients with COPD. During an 8-year period, the frequency of acute respiratory illnesses was three times higher among patients with viral or MP infections [13]. Among 242 hospitalizations for acute exacerbation of COPD (AECOPD) in a 17-month period, 14% of patients were serologically positive for MP infection. A confounder is that the study included patients with positive titers for IgM, IgG and IgA. There was no association with any clinical outcome [14]. Other studies have found a seroprevalence for MP infection in 10-20% of patients with obstructive airway disease [15, 16].

Conclusions

MP infection carries significant morbidity and mortality, especially in patients at the extreme of ages. Prompt serological diagnosis and treatment is advisable with aggressive supportive care. Presumptive early antibiotic treatment is advised, especially in patients with poor prognostic features, such as severe underlying illness, old age and hospitalization requirement.

We have seen many advances that help us to better understand the pathophysiology and mechanisms of MP infections, including genome sequencing and molecular methods for strain typing. However, MP infections are widespread and affect all age groups, especially the vulnerable. Much work is still required to develop an improved and readily available test for accurate and rapid diagnosis. Diagnostic tools are imperative due to the emergence of antibiotic resistance that can potentially make MPP a very difficult disease to contain.

Another area for future MP research is vaccine development. MP vaccine development was attempted in the 1960s - 1970s, but was technically difficult. If we consider the worldwide burden of obstructive airway diseases and the potential association with MP infections, prevention of MPP could subsequently improve control of COPD and asthma.

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