Typical or atypical pneumonia and severe acute respiratory symptoms in PICU

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Abstract

Background and Aims: Mycoplasma pneumoniae (MP) is a common childhood pathogen associated with atypical pneumonia (AP). It is often a mild disease and seldom results in paediatric intensive care (PICU) admission. In 2003, World Health Organization (WHO) coined the word SARS (severe acute respiratory syndrome) in patients with severe acute respiratory symptoms (sars) for an outbreak of AP in Hong Kong due to a novel coronavirus. In 2012, another outbreak of coronavirus AP occurred in the Middle East. Confusing case definitions such as MERS (Middle East respiratory syndrome) and SARI (severe acute respiratory infections) were coined. This paper aims to present a case of MP with sars, ARDS, pneumonia and pleural effusion during the MERS epidemics, and review the incidence and mortality of severe AP with MP.

Methods: We presented a case of MP with sars, acute respiratory distress syndrome (ARDS), pneumonia and pleural effusion during the MERS epidemics, and performed a literature review on the incidence and mortality of severe AP with MP requiring PICU care.

Results: In early 2013, an 11-year-old girl presented with sars, ARDS (acute respiratory distress syndrome), right-sided pneumonia and pleural effusion. She was treated with multiple antibiotics. Streptococcus pneumoniae was not isolated in this girl with 'typical' pneumonia by symptomatology and chest radiography, but tracheal aspirate identified MP instead. The respiratory equations are computed with PaO_2/FiO_2 consistent with severe lung injury. Literature on the incidence and mortality of severe AP with MP requiring PICU care is reviewed. Six, 165 and 293 articles were found when PubMed (a service of the U.S. National Library of Medicine) was searched for the terms 'mycoplasma' and 'ICU', 'mycoplasma' and 'mortality', and 'mycoplasma' and 'severe'. Mortality and PICU admission associated with MP is general low and rarely reported. Experimental and clinical studies have suggested that the pathogenesis of lung injuries in MP infection is associated with a cell-mediated immune reaction, and high responsiveness to corticosteroid therapy has been reported especially for severe disease. Management of severe mycoplasma infection in the PICU includes general cardiopulmonary support and specific antimicrobial treatment. Macrolide resistance genotypes have been detected.

Conclusion: We urge health organizations to refrain from the temptation of coining unnecessary new terminology to describe essentially the same conditions each and every time when outbreaks of AP occur.

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Key words
atypical pneumonia – immuniztions – MERS – *Mycoplasma pneumoniae* – pleural effusion – pneumococcus – MERS – severe acute respiratory syndrome

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Conflict of interest
K. L. Hon has received travel and conference sponsorship from Pfizer and Wyeth.

Case

A previously healthy 11-year-old girl became dyspneic and critically ill with pneumonia and pleural effusion. There was no significant past history of respiratory illness. She had been on-and-off febrile (maximal body temperature 40°C) with worsening productive cough of yellow sputum for 2 weeks despite visiting her general practitioner twice and a course of Augmentin (GlaxoSmithKline UK, Middlezex, UK; standard dosage of 914 mg/10 mL, twice daily for 1 week). She had post-tussive vomiting and her appetite poor. Her immunizations were up to date except for pneumococcal vaccination. She travelled to Shenzhen in Mainland China and was hospitalized and treated with intravenous medication, but her symptoms persisted. Therefore, the patient was taken back to a hospital in Hong Kong the next day. At the emergency department, her vitals were: heart rate 131/min, respiratory rate 20/min, blood pressure (BP): 103/60 mmHg, tympanic temperature 38.6°C and SaO_2 90% in room air. Percussion notes were dull and air entry to the right lung decreased. Chest radiography showed patchy right-sided consolidations with pleural effusion (Fig. 1). She was immediately treated with oxygen (4 L/min via nasal cannula), intravenous cefotaxime and oral azithromycin to cover pneumococcus and atypical pathogens. Cloxacillin was added to cover possible *Staphylococcus aureus* infection.

Because of further desaturations (SpO2 down to 89%) and borderline BP (90/60 mmHg), the girl was transferred to a pediatric intensive care unit (PICU) for further care. On admission to the PICU, temperature 36.5 °C, pulse 117/min, respiratory rate 28/min, BP 133/82 mmHg and SaO_2 95% with 100% oxygen by non-rebreathing mask. Blood gas analyses showed that her lowest PaO_2/FiO_2 was 46.5, and arterio-alveolar gradient 616 mmHg (Table 1), consistent with very severe lung injury and impaired diffusion and ventilation/perfusion mismatch. As the child remained critically ill, cloxacillin was changed to high-dose penicillin G and vancomycin added to cover for potentially resistant *Streptococcus pneumoniae* and *S. aureus.* An ultrasound-guided pigtail catheter was placed by the radiologist, which yielded blood-stained pleural fluid.

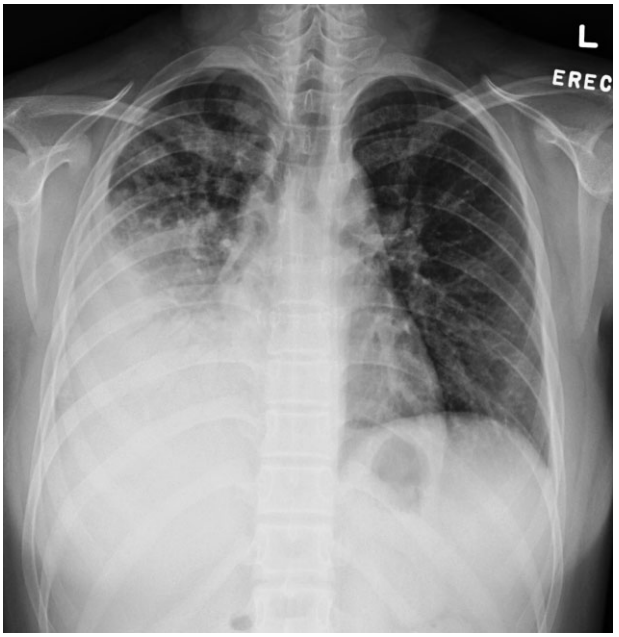

Figure 1. Chest X-ray shows patchy consolidation in both upper and lower zones of right lung associated with massive right pleural effusion.

Table 1. Pediatric index of mortality 2 and respiratory indices

Parameters	Data	Remarks
Pediatric index of mortality 2	1.7%	Predicted mortality (http://www.sfar.org/scores2/pim22.html)
Ventilation index	N/A	Prognostic marker of lung injury (http://www.users.med.cornell.edu/~spon/picu/calc/ventindx.htm)
Alveolar-arterial oxygen gradient	615.9	Impaired diffusion or shunting (http://www.users.med.cornell.edu/~spon/picu/calc/aagrad.htm)
Oxygenation index	21.5	Denotes risk of treatment (http://www.users.med.cornell.edu/~spon/picu/calc/oxyindex.htm)
PaO_2/FiO_2 ratio	46.5	Severity of lung injury: ALI <300, ARDS <200 (http://easycalculation.com/medical/ALI.php)
Qs/Qt	2.1%	Intrapulmonary shunt and V/Q mismatch, normally <5% (http://www.medfixation.com/classic-shunt-equation-qsqt-calculation/)

$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2)$. The oxygen content of mixed arterial blood (CaO_2) is determined by the content of oxygen in the blood that reached ventilated alveoli (CcO_2), the content of oxygen in blood that bypassed ventilated alveoli (CvO_2) and the proportion of the two. CcO_2 is the content of oxygen in pulmonary capillary blood and is estimated by plugging in 100% as the saturation because the PcO_2 (pulmonary capillary PO_2) can be assumed to be high enough to assure 100% saturation.

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

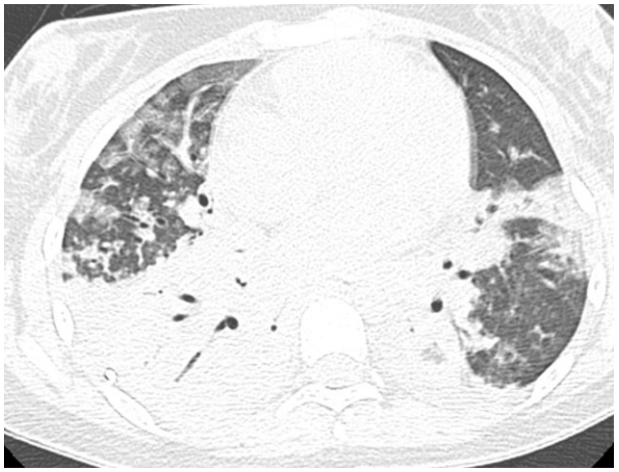

Figure 2. High-resolution computed tomography (HRCT) thorax shows consolidation with air bronchogram in bilateral lower lobes, more severe on the right side. There are also patchy ground glass opacifications in the right middle lobe. Overall features are compatible with acute pneumonia.

The girl had further desaturations down to 87% in 100% oxygen. Bilevel positive airway pressure support was started.

Investigations showed hemoglobin 11.1 g/dL, white cell count 5.8×10^9/L, platelet 156×10^9/L, elevated C-reactive protein (highest 316.5 mg/L), pleural fluid total protein/blood total protein ratio was 0.53 and pleural LDH/blood LDH ratio was 2.22 (i.e. exudative and non-empyema).

Nasopharyngeal aspirates yielded *Mycoplasma pneumoniae* [MP; by polymerase chain reaction (PCR)]. Blood, pleural fluid, sputum and nasopharyngeal aspirates did not yield any other pathogens. Interferon gamma release assay (quantiFERON, Qiagen, Valencia, CA, USA) was negative. Fungal, tuberculosis, *Pneumocystis carinii* and viral infections were rule out [negative modified Toluidine Blue O stain (Sigma-Aldrich, St. Louis, MO, USA), Mantoux, Ziehl–Neelsen stain, adenosine deaminase, fungal, mycobacteria, pneumocystis and viral cultures].

Urgent contrast computed tomography (CT) with high-resolution CT (HRCT) reconstruction showed extensive collapse/consolidation of bilateral lower lobes with air bronchogram. On addition, patchy ground glass opacities and consolidative changes were scattered throughout the right upper, right middle and left upper lobes, consistent with acute pneumonia (Fig. 2). There was no definite nodule or tree-in-bud appearance to suggest endobronchial tuberculosis. Echocardiography showed no pericardial effusion.

The patient was jointly managed in the PICU with pulmonology and cardiothoracic surgery consultations. Initial clinical response was poor with azithromycin. A 7-day course of intravenous ciprofloxacin was also added in view of potential mycoplasma resistance to azithromycin. She gradually improved and was discharged to the general pediatric ward 6 days later. Macrolide resistance pattern was not routinely tested at our center. Mycoplasma serology rose from (<10) to (≥160).

The patient defaulted follow up for lung function or imaging after discharge. Three months later, she presented to the emergency department of another hospital with hair loss. The emergency department record documented no respiratory symptoms and a normal respiratory rate for age.

Discussion

MP is one of the most common agents of community-acquired atypical pneumonia (AP) in children and young adults. The epidemiologic characteristics, including periodic epidemics, and some clinical characteristics of MP are similar to those observed in systemic viral infections (1). AP caused by MP has been called 'walking pneumonia' because it usually affects older children and seldom results in PICU admission (2–11). Nevertheless, the pathogen can occasionally cause severe acute respiratory symptoms (sars) (4, 7, 9, 11). Rarely, mycoplasma can co-infect children and result in very severe and even fatal disease (12). Literature on the incidence and mortality of severe AP with MP requiring PICU care is reviewed. Six, 165 and 293 articles were found when PubMed (a service of the US National Library of Medicine) was searched for the terms 'mycoplasma' and 'ICU', 'mycoplasma' and 'mortality', and 'mycoplasma' and severe', with limits activated (ages: birth to 18 years), respectively, as of March 2013. These publications are used to address the clinical questions as to the epidemiology of MP, PICU admission and mortality. Mortality and PICU admission associated with MP is general low and rarely reported (3, 4, 8). One study indicated that patients with MP-associated encephalitis are predominantly pediatric, and they frequently require intensive care with prolonged hospitalizations (5). In a large Chinese study on etiology and epidemic characteristics of hospital-acquired pneumonia in children, mycoplasma was only reported in 0.4% (3, 4, 8). Nevertheless, recent MP infections play a significant role in exacerbations of asthma and occurrence of status asthmaticus in children (4). A retrospective review of all patients

admitted to PICU over a 12-month period with status asthmaticus showed evidence of recent mycoplasma infection [by Immunocard Mycoplasma Enzyme Immunoassay for detection of MP immunoglobulin M antibodies (Meredian Diagnostics, Inc., Cincinnati, OH, USA)] in 42% (3, 4, 8). There were no statistically significant differences in length of hospitalization, ICU days, duration of continuous albuterol aerosol, days on oxygen or white blood cell counts between the two groups. However, patients who were mycoplasma positive were treated with a macrolide antibiotic in addition to their standard asthma therapy. Patients with evidence of recent MP infection were more likely to have one or more infiltrates on their chest radiography. The authors reported no mortality reported in the series. Full respiratory recovery and ICU discharge has been reported despite persistent acute respiratory distress syndrome, respiratory impairment and hypoxia in a patient with Down syndrome (3, 4, 8).

Experimental and clinical studies have suggested that the pathogenesis of lung injuries in MP infection is associated with a cell-mediated immune reaction, and high responsiveness to corticosteroid therapy has been reported especially for severe disease (1, 13–16). Management of severe mycoplasma infection in the PICU includes general cardiopulmonary support and specific antimicrobial treatment (3, 4, 8, 17).

Macrolide resistance in MP has been investigated in a number of publications. Some patients with MP infection are clinically resistant to antibiotics such as erythromycin (EM), clarithromycin or clindamycin. The relationship between the point mutation pattern of EM-resistant strains and their resistance phenotypes to several macrolide antibiotics was investigated in a Japanese study, which isolated MP from patients and found that one of three isolates showed a point mutation in the 23S ribosomal RNA (rRNA) gene (18, 19). Furthermore, 141 EM-sensitive clinical isolates of MP were cultured in broth medium containing 100 microg/mL of EM. Among 11 EM-resistant strains that grew in the medium, point mutations in the 23S rRNA were found in three strains at A2063G, five strains at A2064G and three strains at A2064C. During an outbreak of MP infections in southern Italy in 2010, 48 clinical specimens from 43 pediatric patients hospitalized for lower respiratory tract infections were analyzed for macrolide resistance (18, 19). The mutations associated with resistance (A2063G and A2064G) and MP subtypes were detected by sequencing the targeted domain V region of the 23S rRNA gene and a region in the MPN528a gene, respectively. Macrolide resistance genotypes were detected in 11 (26%) of the 43 MP-positive children. The A2063G mutation was identified in seven patients, and the A2064G mutation was identified in the remaining four. Upon admission, the isolates from three patients showed a susceptible genotype but subsequently acquired the A2063G mutation. Genotyping revealed MP subtype 1 in 33 of 40 sequenced strains and subtype 2 in the remaining 7. There was no association between macrolide resistance or susceptibility and the MP subtypes. Locally, Lung *et al.* reported that macrolide-resistant MP accounted for 33% (3 out of 10 patients) of the PCR-confirmed cases (20). A recent Hong Kong study identified A2063G macrolide-resistant MP quasispecies populations in 78.8% of the respiratory specimens (21).

Evidenced-based guidelines for management of infants and children with community-acquired pneumonia (CAP) were prepared by an expert panel comprising clinicians and investigators representing community pediatrics, public health and the pediatric specialties of critical care, emergency medicine, hospital medicine, infectious diseases, pulmonology and surgery (22). Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool-aged children with mild to moderate CAP suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *S. pneumoniae*, the most prominent invasive bacterial pathogen. Macrolide antibiotics (such as azithromycin) should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with CAP caused by atypical pathogens (23). There is no need to change macrolide use in the case of mild to moderate disease, but tetracyclines or fluoroquinolones should be considered if the symptoms persist or there are signs of a clinical deterioration, especially in countries in which macrolide-resistant MP strains are very common (24). Laboratory testing for MP should be performed if available in a clinically relevant time frame. Empiric combination therapy with a macrolide (oral or parenteral), in addition to a beta-lactam antibiotic, should be prescribed for the hospitalized child for whom MP and *Chlamydia pneumoniae* are significant considerations; diagnostic testing should be performed if available in a clinically relevant time frame. Co-infections by viral and bacterial agents in critically ill patients have been reported (25–28). These pathogens are known to cause pneumonia on their own and both are not commonly carried by healthy young persons (22, 26).

AP is an interesting albeit confusing disease entity. In 2003, World Health Organization (WHO) coined the word SARS (severe acute respiratory syndrome) in patients with severe acute respiratory symptoms for an

outbreak of AP in Hong Kong due to a novel coronavirus. In 2012, another outbreak of coronavirus AP occurred in the Middle East. Confusing case definitions such as MERS (Middle East respiratory syndrome) and SARI (severe acute respiratory infections) were coined. Our case occurred during the MERS or SARI epidemic. We urge health organizations to refrain from the temptation of coining unnecessary new terminology to describe SARS when outbreaks of AP occur.

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