Review on paediatric necrotising pneumonia and its pulmonary co-morbidities

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Abstract
Necrotising pneumonia (NP) is defined as destruction of normal lung parenchyma with the presence of areas of decreased contrast-enhancement +/- small air or fluid cavitations. Apart from the complication of sepsis, it can also be associated with other pulmonary co-morbidities including parapneumonic effusion/empyema, bronchopleural fistula and lung abscess. Most literature have reported *Streptococcus pneumoniae* and community-acquired methicillin resistant *Staphylococcus aureus* as the commonest pathogens. *Mycoplasma pneumoniae*, however, is becoming another important causative agent, especially in the setting of increased prevalence of macrolide-resistant strain. Contrasted computer tomography thorax remains the gold standard for the diagnosis of NP, but its role may be substituted in the near future by thoracic ultrasonography with no concern of radiation risk. Intravenous antibiotic is the main line of treatment and surgery has only ancillary role in managing the complications. Though NP has significant morbidity in its acute stage, which usually leads to prolonged hospitalisation, extended course of antibiotics or even necessity of surgical intervention, its long-term prognosis is found to be excellent with low mortality, based on full clinical recovery and minimal residual changes in follow-up imaging. More studies are however required to have better assessment on the functional outcomes of children affected.

Keywords: Child, necrotising, pneumonia

Introduction
Nowadays, dramatic increase in incidence of paediatric necrotising pneumonia (NP), after the introduction of 7 polyvalent pneumococcal conjugate vaccine (PCV-7) followed by the selection of more virulent non-vaccine serotypes of *Streptococcus pneumoniae*, was reported as well as the worldwide epidemic of community-acquired methicillin resistant *Staphylococcus aureus* (C-MRSA). Though paediatric community-acquired pneumonia has good prognosis in general, the same situation may not be true in severe NP. In this article the relevant publications on paediatric necrotising pneumonia will be reviewed.

Definitions of necrotising pneumonia, parapneumonic effusion and empyema and pulmonary complications
In nearly all studies, necrotising pneumonia was defined mostly by findings in the computer tomography (CT) of thorax. Different studies had minor variations in their working definitions but the main features are similar as follows,2-6:
- Areas of consolidation without loss of volume
- Destruction of normal parenchyma with the presence of areas of decreased contrast-enhancement
- Plus or minus presence of multiple small air or fluid cavities
- Excluding abscess, the features of which include prominent rim of contrast-enhancement in the periphery

Parapneumonic effusion and empyema are actually within a continuum. Parapneumonic effusion (PPE) is the presence of pleural effusion in association with the underlying pneumonia.6 Empyema is usually defined when there is macroscopic appearance of purulent pleural fluid, but in broader definition it also includes the condition in which bacteria is identified in the pleural fluid.6

Bronchopleural fistula (BPF) is defined as the presence of persistent communication between the pleura and the underlying necrotic lung tissue.7 Pneumatocele is a
thin-walled, air-filled cyst inside the lung parenchyma. Finally lung abscess is defined as the well-delineated area of intrapulmonary fluid density or cavity with air-fluid level, with thick (>2 mm) enhancement wall.

**Epidemiology and incidence**

Reports on necrotising pneumonia in children were scanty before 1990s with the first case report published in 1994. Since then the publications have been accumulating but they were mainly case reports or retrospective studies of small patient number. Tables 1a and 1b have listed some important findings extracted from the relevant published articles on necrotising/ necrotizing pneumonia limited to paediatric population (birth-18 years).

It can be seen that there is no prospective study on population basis to evaluate the true incidence of NP. Nevertheless, several retrospectives studies indicated the rise in the incidence, especially after the launch of PCV-7. Data from one Taiwan tertiary university hospital showed that there was gradual growth in the annual number of pneumococcal pneumonia from 1995 to the peak in 2000 followed by modest slip to to 2002. However, the percentage of complicated pneumonia, defined as the presence of empyema or necrotising pneumonia, showed rapid rise from 25% in 1995 to 70% in 2002. Another study in Children’s Hospital Boston on their confirmed NP also saw a drastic increase in case number from three cases per year in the interval 1993-1996 to 14 cases per year in 2003-2004. The strongest evidence demonstrating an increase in both the number of culture-positive pneumococcal pneumonia and the percentage of paediatric NP actually came from the study in Utah when data in pre- and post-PCV-7 era were compared. The authors divided the study period into two groups, 1997-2000 and 2001-2006, separated by the demarcation line of the year 2000 when PCV-7 vaccine was first launched in the United States. Over the total study period of around nine years, 124 cases of culture-positive paediatric pneumococcal pneumonia were retrieved. A significant escalation in the percentage of NP was detected from 5 of 39 cases (13%) in the earlier time to 28 of 85 cases (33%) in the post-PCV-7 period, with odd ratio (OR) 3.34 [95% confidence interval (95% CI) 1.11-12.03].

A recent French study in one tertiary Paediatric Hospital provided a better estimate on their local incidence of necrotising pneumonia. Between May 2006 and April 2011, there were 4859 consultations of pneumonia in their Paediatric Emergency Department. Six hundred and thirty-five patients (13%) required hospitalisation and 41 (0.8%) children was later diagnosed to have NP. Furthermore the percentage of pneumonia complicated with NP actually doubled from 4.5% to 9% when comparing the two periods 2006-2009 and 2009-2011.

**Microbiology**

**Streptococcus pneumoniae**

As shown in the Table 1a, as well as the local experience, *Streptococcus pneumoniae* is the most important pathogen causing necrotising pneumonia. Furthermore the non-PCV-7 serotypes including serotypes 3, followed by 19A, have become the important serotypes causing the disease after the start of PCV-7 vaccination.

In Utah’s study, after the launch of the universal immunisation of PCV-7, serotype 3 has become the most important strain of Streptococcus pneumonia causing NP with OR 14.67 (95% CI 3.39-86.25). Furthermore the serotypes 3 was also found to have higher risk in developing empyema (OR 5.38, 95% CI 1.11-51.14), requiring chest tube insertion (OR 5.0, 95% CI 1.03-47.57), and undergoing surgical procedure (OR 3.59, 95% CI 0.90-13.28, p=0.025). A letter to the Editor from Texas’ researchers also reported 4 cases of NP all caused by the more virulent serotype 19A. When compared with the 7 NP in the control group, all of which were retrieved from the past hospital record with no pathogens identified, the serotype 19A led to more complicated disease with longer hospital stay (19 days versus 13 days), prolonged duration of intravenous antibiotics (19.2 days versus 17 days), more admission to intensive care unit (75% versus 29%) as well as higher intubation rate (75% versus 29%).

One Taiwan’s study also compared the PCV-7 and non-PCV-7 strains on their role in all paediatric invasive pneumococcal disease (IPD) over 12 year at the time when the compliance of PCV-7 was still poor in Taiwan. Serotype 14, covered by PCV-7, remained the most important strain identified in IPD (23.8%), followed by serotypes 6B (19.0%) and 23F (16.2%). The serotype 3, not included in PCV-7, ranked the fourth causing IPD (13.3%). Second commonest member in the non-PCV-7 group associated with IPD was serotype 19A (3.8%). When compared with PCV-7 group, the non-PCV-7 serotypes had more pulmonary manifestation (63.4% versus 38.7%), but also their pneumonia were mostly complicated with necrotising pneumonia or empyema.
### Table 1a. Summary of published articles on necrotising pneumonia (NP) in children

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Year</th>
<th>Type</th>
<th>Number</th>
<th>Age</th>
<th>Premorbid</th>
<th>Pathogens</th>
<th>Duration of fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerem (Israel)</td>
<td>2</td>
<td>1994</td>
<td>Case report</td>
<td>4</td>
<td>1.3yr, 1.5yr, 2.9yr, 7.5yr</td>
<td>Normal immunity except one IgG2 deficiency</td>
<td>SP</td>
<td>9-20 days</td>
</tr>
<tr>
<td>McCarthy (USA)</td>
<td>40</td>
<td>1999</td>
<td>Case report</td>
<td>3</td>
<td>1.3yr, 2yr, 7yr</td>
<td>Healthy</td>
<td>SP</td>
<td>ND</td>
</tr>
<tr>
<td>Wong (Taiwan)</td>
<td>3</td>
<td>2000</td>
<td>Retrospective review</td>
<td>21</td>
<td>Mean 28.3mth +/- 15.1(SD)</td>
<td>Healthy</td>
<td>3 SP, 2 SA, 2 HIB, 2 MP, 13 culture-negative</td>
<td>ND</td>
</tr>
<tr>
<td>Congiz (Turkey)</td>
<td>26</td>
<td>2004</td>
<td>Case report</td>
<td>1</td>
<td>7 yr</td>
<td>Healthy</td>
<td>GAS</td>
<td>ND</td>
</tr>
<tr>
<td>Wang (Taiwan)</td>
<td>23</td>
<td>2004</td>
<td>Case report</td>
<td>5</td>
<td>3yr, 4yr, 6yr, 6yr, 14yr</td>
<td>Healthy</td>
<td>MP</td>
<td>3-20 days</td>
</tr>
<tr>
<td>Hsieh (Taiwan)**</td>
<td>10</td>
<td>2004</td>
<td>Retrospective review</td>
<td>40</td>
<td>Mean 52.3mth (9-144mth)</td>
<td>5 asthma, 4 heart disease, 2 genetic, 2 malignancy, 1 haemolytic anaemia, 1 metabolic</td>
<td>SP</td>
<td>13.5 days +/- 8.2 days(SD)</td>
</tr>
<tr>
<td>Hacimustafaoglu (Turkey)</td>
<td>4</td>
<td>2004</td>
<td>Prospective study</td>
<td>36</td>
<td>Mean 3.8yr (9mth-14yr)</td>
<td>Healthy</td>
<td>1 GAS, 3 gram positive diplococci in pleural fluid</td>
<td>8.9 days +/- 4.3 days(SD)</td>
</tr>
<tr>
<td>Tseng (Taiwan)</td>
<td>20</td>
<td>2005</td>
<td>Case report</td>
<td>1</td>
<td>2yr</td>
<td>Healthy</td>
<td>C-MRSA</td>
<td>15 days</td>
</tr>
<tr>
<td>Chiu (Taiwan)</td>
<td>22</td>
<td>2006</td>
<td>Case report</td>
<td>1</td>
<td>7yr</td>
<td>Healthy</td>
<td>MP</td>
<td>Around 30 days</td>
</tr>
<tr>
<td>Hsieh (Taiwan)###</td>
<td>31</td>
<td>2006</td>
<td>Retrospective review</td>
<td>15</td>
<td>Mean 49mth (9-85mth)</td>
<td>Healthy</td>
<td>SP</td>
<td>Median 9 days (4-30 days)</td>
</tr>
<tr>
<td>Sawicki (USA)</td>
<td>5</td>
<td>2008</td>
<td>Retrospective review</td>
<td>80</td>
<td>Median 3.6yr (IQR 2.4-6.2yr)</td>
<td>53 healthy, 2 immunocompromised</td>
<td>18 SP (22%), also MSSA/MRSA, 42 culture-negative (52%)</td>
<td>Median 6 days (IQR 3-9 days)</td>
</tr>
<tr>
<td>Obando (Spain)</td>
<td>27</td>
<td>2009</td>
<td>Case report</td>
<td>1</td>
<td>12yr</td>
<td>Healthy</td>
<td>C-MRSA + H1N1 flu A</td>
<td>23 days</td>
</tr>
<tr>
<td>Kalaskar (USA)</td>
<td>12</td>
<td>2009</td>
<td>Case report</td>
<td>4</td>
<td>2.8-4.1yr</td>
<td>1 asthma, 3 healthy</td>
<td>4 SP serotype 19A</td>
<td>ND</td>
</tr>
<tr>
<td>Pascual (Switzerland)</td>
<td>30</td>
<td>2010</td>
<td>Case report</td>
<td>1</td>
<td>15yr</td>
<td>Healthy but sexually active</td>
<td>Mycoplasma hominis</td>
<td>ND</td>
</tr>
<tr>
<td>Yazer (Canada)</td>
<td>28</td>
<td>2011</td>
<td>Case report</td>
<td>1</td>
<td>5yr</td>
<td>Mild asthma</td>
<td>SP+ H1N1</td>
<td>ND</td>
</tr>
<tr>
<td>Moreira Silva (Portugal)</td>
<td>29</td>
<td>2012</td>
<td>Case report</td>
<td>1</td>
<td>28mth</td>
<td>Healthy</td>
<td>Acinetobacter Iwofii</td>
<td>ND</td>
</tr>
<tr>
<td>Wang (China)</td>
<td>24</td>
<td>2012</td>
<td>Case report</td>
<td>5</td>
<td>3yr, 4.5yr, 5yr, 5yr, 9yr</td>
<td>ND</td>
<td>MP</td>
<td>Up to 20 days</td>
</tr>
<tr>
<td>Lematre (France)</td>
<td>11</td>
<td>2013</td>
<td>Retrospective review</td>
<td>41</td>
<td>Median 14mth (1mth-16yr)</td>
<td>Not immunocompromised</td>
<td>13 C-MRSA, 7 SP</td>
<td>Median 7 days (1-25 days)</td>
</tr>
</tbody>
</table>

** Abbreviation: SP, Streptococcus pneumoniae; SA, Staphylococcus aureus; MSSA, methicillin-sensitive SA; MRSA, methicillin-resistant SA; C-MRSA, community acquired MRSA; MP, Mycoplasma pneumoniae; GAS, Group A Streptococcus; HIB, Haemophilus influenzae type B; BPF, bronchopleural fistula; PPE, parapneumonic effusion; AB, antibiotic; CD, chest drain; VATS, video-assisted thoracoscopic surgery; PFT, pulmonary function test; ND not documented; FU, follow-up; IQR, interquartile range; SD, standard deviation; yr, year; mth, month.

** Study on complicated pneumonias (with empyema or NP) out of 71 pneumococcal pneumonias.

# Study on NP out of 56 pneumococcal pneumonias. @ Days of fever from hospital admission.
<table>
<thead>
<tr>
<th>Study</th>
<th>Hospitalisation day</th>
<th>Complications</th>
<th>Duration of relevant AB</th>
<th>Other treatments</th>
<th>Mortality</th>
<th>Outcome</th>
<th>FU time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerem (Israel)</td>
<td>12-26 days</td>
<td>PPE, empyema</td>
<td>6 weeks</td>
<td>2 CD</td>
<td>Nil</td>
<td>Full recovery except 1 CXR with pleural thickening</td>
<td>Up to 12mth</td>
</tr>
<tr>
<td>McCarthy (USA)</td>
<td>10-15 days</td>
<td>PPE, abscess, BPF</td>
<td>20-22 days</td>
<td>2 decortication, 1 abscess debridement+ decortication+closure of BPF</td>
<td>Nil</td>
<td>CT done at 6 weeks in 1 patient: small pneumatocele and residual pleural thickening</td>
<td>ND</td>
</tr>
<tr>
<td>Wong (Taiwan)</td>
<td>ND</td>
<td>Empyema, loculations, pneumothorax, BPF, lung absscess</td>
<td>14-35 days</td>
<td>9 VATS, 2 segmentectomy, 2 abscess debridement</td>
<td>Nil</td>
<td>19 normal CXR, 2 with small residual pneumatocele</td>
<td>6mth</td>
</tr>
<tr>
<td>Congiz (Turkey)</td>
<td>8 days</td>
<td>Empyema</td>
<td>8 days</td>
<td>CD</td>
<td>Death</td>
<td>Death on 8th day</td>
<td>Nil</td>
</tr>
<tr>
<td>Wang (Taiwan)</td>
<td>ND</td>
<td>PPE (Massive), multiple abscess</td>
<td>3 weeks in 1 patient</td>
<td>CD</td>
<td>Nil</td>
<td>3 full recovery, 2 residual lung damage (1 pneumatocele, 1 partial atelectasis of left lingular)</td>
<td>Some up to 8mth</td>
</tr>
<tr>
<td>Hsieh (Taiwan)**</td>
<td>25.2 days+/- 12.0 days (SD)</td>
<td>1/40 NP alone, 12/40 NP+empyema</td>
<td>ND</td>
<td>24/40 thoracotomy</td>
<td>3/40 (7.5%)</td>
<td>ND except 7.5% mortality</td>
<td>ND</td>
</tr>
<tr>
<td>Hacimustafaoglu (Turkey)</td>
<td>9 days (SD)</td>
<td>Empyema/PPE (94%), BPF (55%)</td>
<td>ND</td>
<td>66% requiring lung excision, fistula repair, or decortication</td>
<td>6%</td>
<td>5.5% Mortality, others fully recovered</td>
<td>2mth</td>
</tr>
<tr>
<td>Tseng (Taiwan)</td>
<td>8 days</td>
<td>Empyema</td>
<td>8 days</td>
<td>CD</td>
<td>Death</td>
<td>Death on day 8th</td>
<td>Nil</td>
</tr>
<tr>
<td>Chiu (Taiwan)</td>
<td>22 days</td>
<td>PPE (massive)</td>
<td>10 days</td>
<td>VATS, decortication, CD</td>
<td>Nil</td>
<td>Full recovery</td>
<td>ND</td>
</tr>
<tr>
<td>Hsieh (Taiwan)##</td>
<td>Median 18 days (5-40 days)</td>
<td>Empyema (93%)</td>
<td>16-38 days</td>
<td>93% CD, 53% VATS</td>
<td>1 death</td>
<td>FU CXR in 10 patients: 2 total resolution, 7 minimal fibrosis, 1 cicatrizing atelectasis</td>
<td>1-6mth</td>
</tr>
<tr>
<td>Sawicki (USA)</td>
<td>Median 12 days (IQR 9-17 days)</td>
<td>PPE, BPF</td>
<td>Median 27days (range 3-95)</td>
<td>CD, VATS, open thoracotomy/ decortication, partial lung resection</td>
<td>Nil</td>
<td>Full clinical recovery; 12 with FU PFT: 4 mildly deranged</td>
<td>Median 174 days (IQR77-360 days)</td>
</tr>
<tr>
<td>Obando (Spain)</td>
<td>28 days</td>
<td>Empyema, pneumothorax</td>
<td>3 weeks</td>
<td>VATS, CD</td>
<td>Nil</td>
<td>Full recovery except CXR: multiple small pneumatoceles and residual pleural thickening</td>
<td>ND</td>
</tr>
<tr>
<td>Kalaskar (USA)</td>
<td>15-28 days</td>
<td>ND</td>
<td>23-35 days</td>
<td>VATS</td>
<td>Nil</td>
<td>Full recovery</td>
<td>ND</td>
</tr>
<tr>
<td>Pascual (Switzerland)</td>
<td>19 days</td>
<td>PPE, pericardial effusion</td>
<td>2 weeks</td>
<td>CD, pericardiectomy</td>
<td>Nil</td>
<td>Full recovery</td>
<td>ND</td>
</tr>
<tr>
<td>Yazer (Canada)</td>
<td>ND</td>
<td>Empyema, BPF</td>
<td>ND</td>
<td>CD</td>
<td>Nil</td>
<td>Minimal respiratory symptoms</td>
<td>ND</td>
</tr>
<tr>
<td>Moreira Silva (Portugal)</td>
<td>ND</td>
<td>Empyema, BPF</td>
<td>ND</td>
<td>CD</td>
<td>Nil</td>
<td>Full recovery</td>
<td>2yr</td>
</tr>
<tr>
<td>Wang (China)</td>
<td>17-35 days</td>
<td>PPE</td>
<td>Up to 4 weeks</td>
<td>CD</td>
<td>Nil</td>
<td>ND but one with persistent consolidation in CXR up to 180 days after FU</td>
<td>Up to 180 days</td>
</tr>
<tr>
<td>Lematre (France)</td>
<td>Median 16 days (7-43 days)</td>
<td>Empyema, pneumothorax, hydro pneumatocele</td>
<td>Median 42 days (31-60 days)</td>
<td>3 CD+ later VATS, 3 VATS at outset</td>
<td>Nil</td>
<td>No deaths</td>
<td>ND</td>
</tr>
</tbody>
</table>

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@ Days of fever from hospital admission.
(78.9% compared with 55.2%). Importantly, serotype 3 was identified to carry the highest risk of developing complicated pneumonia (necrotising pneumonia or empyema) with OR 8.8 (95% CI: 1.024-75.59). The serotype 19A also caused more complicated pneumonia than uncomplicated one (12.9% versus 0%), though not reaching the statistical significance (p=0.282). According to the authors, the emergence of serotype 19A was rather related to selection of more resistant-strains after extensive antibiotic usage. It should be reminded that the results in this study should be interpreted cautiously as none of the IPD patients were reported to have received prior PCV-7.

One local study also analysed the change in serotypes involved in IPD for all ages (from less than 5 to greater than 65 years) after initiation of PCV-7 immunisation.14 Serotype 14 declined from 36% to 15.7% (p<0.01) whereas 19A rose exponentially from 0 to 12.9% (p<0.01). For those younger than 5, the proportion of PCV-7 covered serotypes decreased from 89.5% to 65.7%, but those serotypes included in PCV-13 remained similar (from 91.4-93.2%). Furthermore 19A was associated with penicillin/erythromycin resistance. Another similar study in China analysed all hospitalised children <5 years with pneumococcal pneumonia from February 2006 to February 2008.15 The most predominant serotype was 19F (55.6%), followed by 19A (13.9%). The 19A serotype was also found to have the highest drug resistance.

To summarise all the studies, the immunisation of Prevnar-7 has actually selected the two more virulent non-vaccine serotypes 3 and 19A, which has supported the concept of serotype replacement.14 The serotype 3 also results in more necrotising pneumonia or empyema, as well as the necessity of surgical treatment. On the other hand, the emergence of serotype 19A has posed a threat of multiple antibiotic resistance. Fortunately, most of the common serotypes reported to cause NP nowadays are still protected by the newer 13-valent pneumococcal conjugated vaccine.

**Staphylococcus aureus**

The second commonest bacteria causing necrotising pneumonia in the literature is *Staphylococcus aureus*, especially community acquired methicillin resistant *Staphylococcus aureus* (C-MRSA), which carries the gene for Panton-Valentine leukocidin (PVL).16-20 From the French single center study on 41 children with NP, 13 cases were caused by C-MRSA followed by 7 children with Streptococcus pneumoniae.15 From Taiwan's study in 2000 including 21 cases, two out of eight culture-positive NP were caused by *Staphylococcus aureus*, one being methicillin-sensitive whereas another methicillin-resistant.3 Tseng et al also reported one fatal case of C-MRSA with severe sepsis and necrotising pneumonia.20 With respect to the local incidence, the only article published in 1993 stated that *Staphylococcus aureus* ranked the third of the commonest bacteria in childhood pneumonia, following *Haemophilus influenzae* and *Streptococcus pneumoniae*.21 No recent articles in the literature have reported the current local situation of paediatric *Staphylococcus aureus* pneumonia, nor are there any case reports of paediatric NP caused by C-MRSA in Hong Kong. However from the author's experience, few necrotising pneumonia are caused by C-MRSA.

**Mycoplasma pneumoniae**

*Mycoplasma pneumoniae* (MP), on the other hand, has become an important cause of NP around this region. In Wong's study, two cases of necrotising pneumonia were caused by MP.3 Subsequently two further case reports from Taiwan22,23 and one from China24 also described NP related to this bacteria, though the total number of cases remained small. The three case reports however revealed the clinical features quite different from the usual self-limiting atypical pneumonia. First, it predominantly affected the younger age, down to the age of three.22,23 Second, prolonged fever occurred up to 20 days even after starting erythromycin and there was long hospital stay ranged from 17-35 days.24 Third, though no mortality was reported so far, the massive parapneumonic pleural effusion actually required chest drain insertion24 and video-assisted thoracoscopic surgery (VATS) with decortication.22 Furthermore, there was a recent article reporting an increase in the prevalence of macrolide-resistant MP in Hong Kong.25

**Miscellaneous pathogens**

Other pathogens reported in the literature also included group A Streptococcus,25 co-infection with human swine influenza (H1N1),27,28 as well as those rare bacteria including *Acinetobacter species*29 and *Mycoplasma hominis*.30

**Pathogenesis of necrotising pneumonia**

It is still debatable about the pathogenesis of necrotising pneumonia in paediatric population. Panton-Valentine leukocidin-positive *Staphylococcus aureus*, has been showed to induce extensive necrotic ulcerations of the tracheal and bronchial mucosa, as well as massive haemorrhagic necrosis of inter-alveolar septa in one
post-mortem study. However it is still unclear how *Streptococcus pneumonia* causes tissue destruction and it has been postulated to be related to one unknown virulent factor secreted. Furthermore, the same authors performed the autopsy in their only mortality case and identified pulmonary gangrene in the right middle lobe and intravascular thrombi in the pulmonary artery draining to the infarcted region. They postulated that pulmonary gangrene might be infrequently associated with pneumococcal NP. The gangrene subsequently evolved to liquefaction of pulmonary parenchyma and then cavitations.

In another article, lung resection was performed in 12 patients with necrotising pneumonia complicated with bronchopleural fistula. Coagulation necrosis was detected in 11/12 cases. Eight of those twelve patients were also detected with co-existent suppurative necrosis. Furthermore vasculitis and thrombosis formation were identified histologically in 33.3% (4/12) and 66.7% (8/12) respectively. These findings further support the theory of macroscopic pulmonary gangrene and microscopic ischemic necrosis.

**Risk factor for the development of necrotising pneumonia/complicated pneumonia**

Only one study investigated the potential risk factors leading to the complicated pneumococcal pneumonia, which was defined to be culture-positive and associated with necrotising pneumonia or empyema. Out of 71 confirmed pneumococcal pneumonia in their 8-year retrospective review, 40 developed parenchymal necrosis or empyema. Univariate analysis identified 5 characteristics associated with complicated pneumonia as tabulated (Table 2).

However further multivariate analysis only isolated the latter three conditions, namely no-underlying diseases, presence of immature PMN and elevated CRP, to be risk factors. The identification of the above three conditions actually supports the notion that the host inflammatory towards the pathogens, as exhibited by left-shifted neutrophilia and elevated CRP, is probably the key element for the tissue injury. Furthermore, as shown in Table 1a, most children with NP were healthy without impaired immunity. It further supports the postulation that NP is developed out of the exaggerated cytokine-immune response from the host toward the pathogens, leading to parenchymal destruction. Nonetheless, two rather contradictory findings from that retrospective study was that neither the serotypes of *Streptococcus pneumonia*, nor the penicillin resistant strains were found to have significant difference between the complicated pneumonia and lobar pneumonia. Actually the predominant serotype isolated in that study was serotype 14 and none of the cases was caused by serotype 3.

With respect to PVL-positive *Staphylococcus aureus* necrotising pneumonia, the French researchers investigated PVL-positive *Staphylococcus aureus* necrotising pneumonia in 50 patients with median age 14.5 years (range 1 month - 78 year). The risk factors identified in deceased group when compared with the survived group included airway haemorrhage and leukopenia. Multivariate analysis further calculated that the adjusted relative hazard associated with death for total WBC count >1000-3000 /ml and 0-1000 were 7.99 (95% CI 1.66-38.43) and 7.38 (95% CI 1.60-34.02) respectively. Six year later from the same French institution, another paper was published and it included larger population of 148 patients with median age of 22 years (interquartile range 3.0-43.7 years). Severe leukopenia (<3000/ml) increased the mortality with adjusted hazard ratio 4.5 (95% CI: 2.38-8.51). The presence of prior influenza illness increased the risk of severe leukopenia with adjusted odd ratio 4.45 (95% CI 1.67-11.88).

### Table 2. Risk factors associated with complicated pneumonia

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age &gt;36 months</td>
<td>2.81 (1.05-7.56)</td>
<td>0.038</td>
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<tr>
<td>Thrombocytopaenia</td>
<td>8.71 (1.04-73)</td>
<td>0.035</td>
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<tr>
<td>No underlying disease</td>
<td>7.79 (1.96-30.99)</td>
<td>0.01</td>
</tr>
<tr>
<td>Presence of immature polymorphs in peripheral blood</td>
<td>5.14 (1.79-14.74)</td>
<td>0.002</td>
</tr>
<tr>
<td>C-reactive protein &gt;12 mg/dL</td>
<td>5.83 (1.64-20.70)</td>
<td>0.04</td>
</tr>
</tbody>
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OR: odd ratio; CI: confidence interval.
Tool of diagnosis

Role of CT for the diagnosis of NP

In most studies, necrotising pneumonias were diagnosed by CT. Some papers also used chest X-ray (CXR) for diagnosis in the presence of multiple cavities on the background of consolidation. In a Switzerland's study on 9 children, when CXR findings were compared with those of contrasted CT, there was a delayed detection of cavitary necrosis in three children by 5-9 days. In evaluation of detection of the associated complications, CXR also missed 2 cases of parapneumonic effusion in 5 children confirmed by CT. Three cases of BPF were only identified in that series and all was diagnosed by CT solely.

Though CT thorax should be the investigational tool of choice in diagnosing necrotising pneumonia, its routine use for all suspected cases is not recommended in view of its considerable radiation dose especially in children who still have higher number of active dividing cells than adult. There is no study on the role of CT thorax guiding on the management of isolated necrotising pneumonia. However in treating empyema, the United Kingdom randomised controlled trial on conservative approach versus video-assisted thoracoscopic surgery (VATS) on paediatric empyema suggested that additional findings obtained from CT thorax did not alter the management plan nor provide any prognostic value. In that study, out of 25 patients with CXR abnormality showing simple opacification in lung parenchyma only, CT was more sensitive in detecting one additional cavitation, one more pneumatocele and four extra cavity-necrosis, but no lung abscess were detected by CXR and CT. Those additional CT findings, according to the authors' comments, could still be managed conservatively. Thus they concluded that there was no additional role for CT when those children with empyema were already managed with combination of chest tube drainage with intrapleural urokinase. It can always be argued that the results may be biased as the subtle findings of CXR might only be picked up by the very experienced paediatric radiologists in that tertiary children hospital, the Great Ormond Street Hospital for Children. However as the Table 1b has pointed out, necrotising pneumonia mostly has an excellent prognosis with full clinical recovery, even the confirmation of NP by CT-findings will usually not alter the conservative approach for management on those patients.

Growing potential of thoracic ultrasonography

Ultrasoundography (USG) of thorax has gained a more important role nowadays in the management of pneumonia, especially in the management of co-existing complicated pleural effusion/empyema. In British Thoracic Society (BTS) guidelines on the management of pleural infection in children, thorax ultrasonography is indicated to differentiate consolidation/parapneumonic effusion (PPE), simple versus complicated PPE, and to guide the algorithm into different management approach: antibiotic alone, chest tube drainage plus intrapleural fibrinolytic, or even surgical intervention. Its role on the diagnosis of NP has not been well established currently. Only one case report from Taiwan showed that the presence of peripheral hypoechoic spaces (PHES) was specific sonographic features for childhood NP with the specificity and positive predictive values both of 100%. However the low sensitivity of 35% of PHES could not exclude NP in its absence.

Nevertheless, there was an adult study (aged 33-79 years) proving the usefulness of thoracic ultrasound in differentiating between empyema and lung abscess for peripheral pulmonary air-fluid lesions. The study showed that the ultrasound findings of complex-septated effusions and passive atelectasis both were specific (specificity 100%) for empyema, but with low sensitivity of 40% and 47% respectively. However when the additional Colour Doppler technique was applied, the identification of vessel signals in pericavitary consolidation was found excellent in diagnosing peripheral lung abscess with sensitivity 94%, specificity 100%, positive predictive value 100% and negative predictive value 94% respectively. Thus with the vast advancement in the field of thoracic ultrasonography, it may be in near future widely utilised as the primary tool for investigating the suspected NP and detecting other pulmonary complications.

Important role of CT thorax in equivocal/complicated cases and pre-operative assessment

Despite the above discussion, CT thorax still has its unique role for more difficult cases. USG is not easily performed in uncooperative children. Presence of pneumothorax will also hinder the detailed lung imaging beneath the air layer. Moreover, the pathology which is situated in areas not easily accessible by USG (e.g. adjacent to scapula) cannot be identified. Finally, some surgeons still prefer to request CT scan as a road-map before they proceed to VATS/decortication.
Pulmonary complications/co-morbidities

Most patients diagnosed to have necrotising pneumonia usually suffer from other complications, as showed in Table 1b. In addition to those secondary to severe sepsis (septic shock, disseminated intravascular coagulopathy, acute renal failure/fluid-electrolyte disturbance, acute respiratory distress syndrome), there are important pulmonary complications that needed to be managed simultaneously, including parapneumonic effema, bronchopleural fistula, pneumatoceles and lung abscess.

Parapneumonic effusion and empyema

PPE and empyema are within a continuum. Necrotising pneumonia is nearly universally associated with PPE/empyema. In the earliest paediatric report including 4 patients, two patients had PPE while empyema was found in the remaining two children both with positive pleural culture of Streptococcus pneumoniae.  In Taiwan's study in 2000, from the 11 out of 21 NP successfully treated conservatively with antibiotics, nine patients had chest-drain inserted also for PPE and two of the 9 patients had complicated PPE. One-third (7/21) of the patients needed surgical intervention for the empyema. From Boston's study including 80 cases of paediatric NP, 86% were found to have appreciable pleural effusion. Nineteen cases (24%) had bacteria cultured from pleural fluid and 5 cases was positive for pneumococcal antigen in pleural fluid. In a French study on paediatric NP, the percentage of empyema in NP was 63% (26/41 cases).

Bronchopleural fistula

The presence of bronchopleural fistula actually implies the extension of tissue necrosis from the lung parenchyma to the adjacent pleura. This complication should be suspected when the pneumothorax exists in the background features suggestive of necrotising pneumonia. The definitive diagnosis depends on contrast CT thorax. From the Turkey study, 55% of patients with NP had BPF. Twenty percent resolved on conservative management (with small fistula) while 80% required surgical intervention. In another study, out of 112 children with culture-confirmed pneumococcal pneumonia, 18 of them (16%) were detected to have BPF. All of them also had empyema and necrotising pneumonia concurrently. The prognosis in that study was not satisfactory as 15 patients with BPF required surgery, including lung resection in 12 cases. On the contrary, the data from the Boston study showed a better outcome. Twenty-one percent (10/47) on pleural drainage developed BPF. Those with BPF, when compared with no-BPF group, had longer duration of pleural drainage (median 14 versus 6 days, p=0.0007), and prolonged hospitalisation (median 19 versus 13 days, p=0.001). Nevertheless all BPF could be treated successfully by chest drainage without surgery.

Pneumatoceles

Pneumatoceles are thin-walled, air-filled cysts inside the lung parenchyma, resulted from alveolar and bronchiolar necrosis, which allow unilateral air entry into the interstitial tissue through the check-valve effect. It is well known to be associated with Staphylococcus aureus pneumonia. With respect to necrotising pneumonia, a study investigated the 394 children admitted to one Brazilian university hospital with the diagnosis of pneumonia complicated with empyema and/or pneumatocele. 8.3% (33/394 cases) were found to have pneumatoceles with diameter ranging from 5 mm to 90 mm. The authors did not describe which pathogens were more commonly associated with the pneumatoceles, though in that study the most commonest three bacteria in all culture-positive pleural fluid were Streptococcus pneumoniae (18%), Staphylococcus aureus (10%) and Gram negative bacteria (7%). Twenty-eight children had their pneumatoceles resolved spontaneously but four cases including one tension pneumatocele and three ruptured cysts required drainage.

Pneumatoceles can be detected as early complication or late sequel. In the literature review as shown in Table 1, pneumatoceles as an acute complication was only reported in one article. Out of 41 cases in the French study, pneumatoceles were present in 4 (9.7%) patients. Staphylococcus aureus was the predominant pathogen (13/21 cases) in all positive culture in NP followed by Streptococcus pneumoniae (7/21 cases). On the other hand, pneumatoceles as small and residual findings in the follow-up chest X-rays were relatively common as mentioned in 4 reports.

Lung abscess

In most studies investigating necrotising pneumonia, abscess was excluded and was treated as a separate disease entity. However, in many patients suffered from "complicated" pneumonia, both conditions co-existed simultaneously. Further from one case report, the authors suggested that multiple small lucent lesions coalesced to lung abscess over 3-4 days.
Management of necrotising pneumonia and pulmonary co-morbidities

The management of NP including treating the pneumonia itself, together with the associated pulmonary complications. The management can be divided into medical versus surgical interventions.

Antibiotic treatment

The main treatment for NP remains to be medical therapy with intravenous antibiotics. No randomised control trial is available to guide the evidence-based recommendation on this disease management. Thus the duration of antibiotic treatment is still controversial. Both British Thoracic Society (BTS) and Infectious Diseases Society of America (IDSA) did not state clearly how long the antibiotics are required for NP in their latest guidelines on management of community-acquired pneumonia in children. From BTS statements, it only mentions that prolonged course of intravenous antibiotic may be required until the fever settles. IDSA does not discuss the antibiotic strategy for NP. In contrast, the recommendation on the antibiotic duration for empyema was written explicitly. BTS suggests that intravenous antibiotics are continued until the child is afebrile or at least until the chest drain is removed. Then oral antibiotics are continued on discharge for 1-4 more weeks, but longer if there is residual disease. IDSA gives similar recommendation of 2-4 weeks’ duration of antibiotics for empyema, or at least 10 more days after resolution of fever.

As the NP and empyema usually co-exist, the usual practice in my institution is to give a similar duration of antibiotics to treat both conditions as follows:

A total of 4 weeks, or 2 weeks after the patient is afebrile and has improved clinically.

Role of surgery on NP

It has already been a generally accepted approach that surgical intervention for NP per se should be avoided as NP usually has an excellent outcome in children. This is also in accordance with the recommendations from IDSA and American Pediatric Surgical Association (APSA). The suggestion is based on the evidence that drainage of necrotic lung tissue actually led to the development of bronchopleural fistula. Nevertheless, in some uncommon circumstances when the sepsis cannot be controlled after appropriate antibiotic, excision of the necrotic tissue, in the form of segmentectomy, lobectomy or even bilateral lobectomy, may be performed as the last resort.

Consequently, the role of surgery in the management of necrotising pneumonia is mainly to treat the associated pulmonary complications. The main indications for the surgical intervention include decortication for local empyema causing atelectasis, the surgical excision of diseased lung with persistent bronchopleural fistula, or excision of large pneumatocele which imposes heavy pressure effect on the adjacent healthy lung tissues, imaging-guided aspiration or insertion of drainage catheter for lung abscess in non-responding patients treated with intravenous antibiotics.

Adjunctive treatment for empyema thoracis

There has been no change in the approach of the management of empyema since the publication of the BTS guidelines in 2006. Conservative management through chest drain insertion plus intrapleural fibrinolytic should be considered first, and the VATS will only be proceeded in those failed cases. The APSA also adopts the same approach and recommends that the chemical debridement is the first line treatment and surgical debridement will be reserved for those failed cases as the last resort.

Prognosis

The prognosis of the necrotising pneumonia is usually excellent with very low mortality and minimal morbidity.

In the literature review, the mortality of NP was found to be very low. Apart from those isolated case reports, only two relative large studies including 36-40 children reported the mortality from 5.5% to 7.5%. The causes of death were not discussed in details in both reports. In another article focusing on invasive pneumococcal disease, the mortality was 6.7% and all the death had concurrent bacteremia.

With respect to the morbidity, all recovered clinically up to the follow-up period of 12 months in the first paediatric case report. Out of the four patients, one had follow-up CXR done at 2 months, which still detected pneumatoceles but the lesions resolved in 6 months after discharge. CXR at 2 months in another patient only detected pleural thickening with no parenchymal abnormalities. One patient had pulmonary function test (PFT) showing decreased lung volume during the acute illness, but subsequent PFT at 2 months’ time had normalised.
Based on the Boston's study, all 80 children had full clinical recovery, as well as normal CXR. Only a few had follow-up CT thorax, which also revealed complete resolution. In Taiwan's study, follow-up CXR films within 1-3 months showed complete resolution or only minimal fibrotic changes in all nine patients with the imaging performed.

It is still arguable that clinical and radiological resolution are not equivalent to absence of functional pulmonary deficit. Furthermore, CXR is not sensitive enough to detect residual structural lesions. In Switzerland study on radiologic imaging, CT still detected pneumatoceles in 25% (2/8) of the patient. In another study including five patients suffering from necrotising pneumonia caused by *Mycoplasma pneumoniae*, two patients had residual lung damage detected by follow-up CT thorax 6-8 months after the illness, one with pneumatocele while another with persistent atelectasis. All the above studies have already suggested that CXR may not be a appropriate tool for detecting permanent lung damage. However too liberal use of CT thorax as evaluation is also discouraged in view of the profound radiation risk.

Pulmonary function test is definitely a better measurement in assessing the functional status but it can only be performed for those older and cooperative children. Out of 80 patients studied in Boston's study, only 12 patients had PFT done in their follow-up. Normal PFT was found in 8 patients, mild obstructive pattern in 3 patients and mild restrictive pattern in 1 patient. DLCO study was not performed in that study.

To summarise, necrotising pneumonia can impose a significant morbidity on paediatric population in terms of acute complications. The current evidence, however, suggests an excellent outcome with full clinical recovery, normal follow-up CXR as well as normal to mildly deranged pulmonary function tests. However, without the longer-term follow up, the better imaging technique such as CT with low radiation dose protocol, as well as better modalities of pulmonary function tests for the appropriate age group (including preschoolers), it is still too earlier to predict the long-term pulmonary capacity of those children recovered from NP.

**Conclusions**

Necrotising pneumonia can have significant morbidity during its acute stage, which may lead to prolonged hospitalisation, extended course of antibiotics or even necessity of surgical intervention. However in long run, its prognosis is suggested to be excellent with low mortality. The most common pathogen, in this locality, is *Streptococcus pneumoniae* with potential serotypes already covered by PCV 13 currently. *Mycoplasma pneumoniae* is another important bacteria, especially in the setting of emergence of macrolide-resistant strains. Ultrasonography of thorax has gained an important role in the management of empyema and necrotising pneumonia and will probably replace CT as the primary investigation. Intravenous antibiotic treatment is still the first line treatment for NP and surgery is reserved for managing its complications. More studies are required to have better understanding on the functional outcomes on this disease.

**References**