EMPYEMA: MANAGEMENT

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- Empyema is an uncommon complication of pneumonia but it is a significant source of morbidity.
- The most frequent causative organisms include Streptococcus pneumonia, Streptococcus pyogenes, Staphylococcus aureus and Methicillin Resistant Staphylococcus aureus (MRSA).
- Empyema should be suspected in any child with pneumonia with persisting fevers despite 48 hours of intravenous (IV) antibiotics.
- Chest X-ray (AP or PA) should be performed in all children with suspected empyema. Chest ultrasound is indicated to differentiate pleural fluid from lung consolidation in suspected cases.
- There is no role for routine CT scans in the management of empyema.
- Pleural fluid sampling (diagnostic thoracocentesis) is rarely indicated or performed in children.
- 1st line antibiotic combination is IV cefotaxime and clindamycin.
- 2nd line antibiotics are considered (vancomycin or linezolid) if a poor treatment response is seen.
- All inpatients diagnosed with empyema, complicating a pneumonia, requiring drainage should have their care transferred to the respiratory physician on call.
- The indication for pleural fluid evacuation is an effusion causing significant lung compression with respiratory compromise and/or persisting fever spikes. In this instance the respiratory team should be consulted. Management options include small bore percutaneous drain insertion and intrapleural urokinase instillation into the pleural cavity, or Video Assisted Thoracoscopic Surgery (VATS). The respiratory team will liaise with interventional radiology and thoracic surgical teams in deciding whether intervention is required, and if so what choice of intervention is most suitable.

Related documents:

- Intrapleural Urokinase in Empyema Drug Protocol:
- (Nurse) Administration if Intrapleural Urokinase in Empyema Local Work Procedure

Approved by:	SCHN Policy, Procedure and Guideline Committee	
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Team Leader:	Staff Specialist	**Area/Dept:** Respiratory

CHANGE SUMMARY

- Updated February 2022 to include updated references from the medical literature
- Additional section on Approach to renal impairment in Empyema
- Expanded discussion on criteria for screening for underlying immunodeficiency
- Addition of specific section discussing risk factors when considering intervention
- **20/06/23:** minor review – updated dose of albumin, see page 11.

READ ACKNOWLEDGEMENT

- All clinical staff who may care for children with empyema should read and acknowledge they understand the contents of this guideline.

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1 Introduction

1.1 Background

Empyema is an uncommon complication of pneumonia and represents an accumulation of infected fluid in the pleural space. It is a significant source of morbidity. British thoracic guidelines were published in 2005[1] and more recently local Australian guidelines were published in 2011[2]. These Australian guidelines were produced to address recently reported significant variation in practice[3 4]. The recommendations of this protocol are largely based on the recommendations contained within the Thoracic Society of Australia and New Zealand (TSANZ) position paper, but also incorporate local practice and experience[5 6].

1.2 Epidemiology

- Incidence of hospitalization for empyema in children in Australia is 1.8 per 100,000, or 1.5% of childhood pneumonias[6]. It is most common in children of preschool age (1-4 years old)[6].
- Increasing prevalence has been demonstrated across a number of countries
- Most frequent causative organisms include *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus,* including Methicillin Resistant *Staphylococcus aureus* (MRSA)[6].
- Other organisms to consider include *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and anaerobes. *Mycoplasma pneumoniae* is a rare cause of empyema, and recent data confirmed the low incidence of this organism in true empyema (<1%)[3 6].
- Evidence of increasing isolation of non-vaccine *S. pneumoniae* serotypes since the introduction of the 7-valent, and subsequently 13-valent, pneumococcal conjugate vaccine, has been confirmed by recent local Australian and New Zealand data[3 6]. However, vaccine serotypes remain prevalent: serotype 3 (present in 7-valent) remains the predominant cause and 19A is also a leading cause (present in 13-valent)[6].

1.3 Definition and staging

- The presence of pus in the pleural space.
- Empyema evolves through the following stages[7]:
  - Sterile phase (termed “Exudative”)
  - Pus is present within the pleural fluid (termed “Fibrinopurulent”)
  - A final “organized” phase with thick exudate and heavy sediment (ultrasound or CT appearance or direct visualization)

1.4 When to suspect Empyema

Empyema should be suspected in any child with:

- Pneumonia with persisting fevers despite 48 hours of intravenous (IV) antibiotics
- This *may* be accompanied by
    - signs of increasing respiratory distress – e.g. increased respiratory rate, increased oxygen requirement
    - changes on examination consistent with fluid collection (dullness to percussion, decreased air entry, decreased vocal and tactile fremitus) and worsening pneumonic consolidation/collapse (crepitations, bronchial breathing, dullness to percussion).
    - Abdominal pain, or even acute abdomen, in cases with lower lobe pleurisy.

2 Investigations

2.1 Initial Investigations

1. Chest X-ray (AP or PA)
    - Should be performed in all children with suspected empyema
    - Areas of consolidation may be difficult to differentiate from a pleural effusion. Contralateral Mediastinal shift (i.e. away from the affected side) is a feature of a large effusion and should be treated emergently.
    - There is no role for lateral decubitus CXRs due to the availability of chest ultrasound.
2. Chest Ultrasound
    - Able to differentiate pleural fluid from lung consolidation
    - Estimates of volume of fluid are not accurate.
    - Demonstrates fibrinous septations within the pleural fluid collection which indicate a complicated effusion.
3. Blood tests (performed at baseline)
    - Aerobic and anaerobic blood cultures, prior to initiation of antibiotics. Refer to SCHN Blood Culture Collection Practice Guideline for volumes.
    - Consider early pneumococcal PCR on EDTA blood especially if signs suggesting bacteraemia or sepsis.
    - FBC, CRP, EUC, LFTs, clotting studies.
    - Comments regarding specific results that may be encountered:
        - Hypoproteinaemia (low serum albumin) is a relatively common finding but rarely requires specific treatment.

- Secondary thrombocytosis (platelet count >500 x 10^9/L) is common but benign. Anti-platelet therapy is not required.

- Other, rarer, complications which can occur with empyema that may influence the blood tests requested include:
  - haemolytic uraemic syndrome with empyema caused by *S. pneumoniae.*
  - Syndrome of inappropriate ADH secretion (SIADH).

4. Sputum, where available for MC&S.
5. Pleural fluid to be sent for MCS
   - a separate PCR panel for pneumococcus, MSSA/MRSA, and *Streptococcus pyogenes* should be considered and can be requested from microbiology.
6. Anterior nose (nares) swab for MRSA/MSSA culture (ideally prior to initiation of antibiotics)

2.2 Other investigations

1. Chest CT scan
   - No role for routine CT scanning in the management of empyema [8].
   - Indicated if
     - surgical intervention is required to guide surgical approach, after consultation with the surgical team (see later section)
     - complicated pneumonia and failure to respond to further treatment to look for co-existing pathology such as abscess formation, underlying tumour etc.
2. Pleural fluid sampling (diagnostic thoracocentesis)
   - Rarely indicated or performed in children. Pleural fluid is sent at the time of pleural drain placement, if performed (see below).
3. Diagnostic bronchoscopy
   - Not indicated unless there is concern of an inhaled foreign body or unusual history.

3 Management

Also see Empyema Management Flowchart

3.1 Managing team

- All children with parapneumonic effusion or empyema should be admitted to hospital[1]. Children admitted to hospital with pneumonia who remain unwell or pyrexial at 48hrs of admission should have parapneumonic effusion or empyema excluded.
- All inpatients diagnosed with empyema requiring drainage should have their care transferred to the respiratory physician on call.
- In children presenting, or being transferred from another hospital, with an empyema which is likely to need drainage, admission should be under the on call Respiratory Physician. There should be early consultation with the interventional radiologist and surgical team on-call, depending on availability, for any planned/anticipated procedure (see later section 3.6).
- Children referred from other hospitals should be transferred (preferably at an early stage) to the appropriate tertiary level paediatric centre (CHW or SCH) if:
  - Suitable investigations to clarify the presence of empyema are not available
  - An empyema is confirmed on suitable investigations and if the need for further intervention is suspected.
  - No ability to insert and manage intercostal chest catheter

3.2 Supportive therapy

- Oxygen to maintain saturations ≥95%.
- Antipyretics.
- Adequate analgesia.
  - Adequate pain relief will have beneficial effects on mobilization and chest expansion and will reduce the risk of hypoventilation-induced atelectasis complicating the speed of recovery.
  - Compensatory scoliosis and shallow breathing may indicate inadequate pain control.
- Fluid management – The strategy used for fluid requirements should be driven by the clinical status of the child. Refer to fluid management guidelines.

3.3 Antibiotic therapy*

Refer to Meds4Kids or AMH Children's Dosing Companion

1st line:

IV cefotaxime 50 mg/kg/dose (max 2 g) q8h

AND IV clindamycin 15 mg/kg/dose (max 600 mg) q8h

Recent data suggests a low incidence of Mycoplasma pneumoniae causing empyema.[3] If suspected, azithromycin may be given in addition - *IV azithromycin 10 mg/kg/dose (max 500 mg) q24h.

**Another alternative 1st line to cefotaxime would be IV amoxicillin-clavulanic acid 25 mg/kg/dose (max 1 g) q6h)

Poor treatment response, defined as:

- Continuing clinical deterioration despite 1st line antibiotics
- Failure to defervesce as anticipated, taking into account the likely clinical course for the organism isolated.

Generally represents a failure of source control rather than antibiotic failure and (re-)drainage should be considered a first priority. These cases should be discussed with Infectious Diseases and Microbiology services prior to changes in antibiotic regimen.

2nd line antibiotics may include:

ADD IV vancomycin 15 mg/kg/dose q6h

OR IV linezolid 10 mg/kg/dose q8h (if >12 years old q12h)

2nd line antibiotics should also be added if the child develops signs of sepsis

Refer to:

- At SCH Vancomycin Guideline or
- At CHW Vancomycin Dosing and Therapeutic Drug Monitoring Guideline
- Australasian Neonatal Medicines Formulary (ANMF)

- *The above box displays standard dosing, but more detailed dosing based on age and specific situations (e.g. renal impairment, intensive care support) may be needed.
- In those with clinically suspected/reported drug allergies to the recommended antibiotic, please contact the Infectious diseases team for advice regarding an alternate regimen.
- Whilst there is some evidence to preference oral rather than intravenous antibiotics for community acquired pneumonia these recommendations do not extend to parapneumonic effusion or empyema and IV antibiotics are recommended as initial treatment [9].
- Antibiotic therapy should be adjusted if/when identification of the infecting organism and its sensitivities are confirmed by the laboratory.
- Antibiotic therapy should cover the most commonly encountered organisms. In a recent Australian-based study these were *Streptococcus pneumoniae, Streptococcus pyogenes, and Staphylococcus aureus,* including MRSA [6].

- *Staphylococcus aureus*; more common in infants (<12months) and Indigenous populations [5].
- *Streptococcus pyogenes*; may present with more severe respiratory compromise and with shorter duration of illness than *Streptococcus pneumoniae*. Higher rates of PICU admission prior to intervention [10 11].

- Risk factors for MRSA infection include:
  - Aboriginal or Torres Strait Islander ethnicity
  - previous history of MRSA isolation/colonization or skin lesions (e.g. boils)
- Rationalise IV antibiotic choice based on culture isolates and sensitivity patterns as they become available.
- Convert to oral antibiotics once afebrile for 24 – 48 hours. Whilst the table below is a guide, the choice should be driven by susceptibility results where available.

IV antibiotic		Oral antibiotic
cefotaxime	**Convert to**	amoxicillin-clavulanate 22.5 mg/kg/dose (max 875 mg) q12h*
clindamycin		clindamycin 10 mg/kg/dose (max 450 mg) q8h
vancomycin		clindamycin 10 mg/kg/dose (max 450 mg) q8h
azithromycin		azithromycin 10 mg/kg/dose (max 500 mg) q24h

*additional amoxicillin 25 mg/kg/dose (max 1g) at midday for children with large parapneumonic effusion or empyema may be considered.

- Duration of antibiotics is individualized depending on source control and clinical response. Total duration of combined IV and oral antibiotics of at least 7 days is required (usually 2-4 weeks is adequate, rarely up to 6 weeks). If azithromycin is given, it should be given for 5 days in total [12-15].

3.4 Indication for evacuation of pleural fluid

- The indication for pleural fluid evacuation is:
  - An effusion causing significant lung compression with respiratory compromise and/or fever.
  - Defining exact criteria for intervention is challenging, but the merits of intervention on all pleural effusions with a rim of fluid >2cm on ultrasound examination should be carefully considered.
- In smaller pleural effusions with minimal respiratory impact, evacuation may be of minimal clinical benefit and should be avoided.
- Evacuation may be indicated for diagnostic or therapeutic purposes if defervescence does not occur despite prolonged, either anticipated or culture determined, appropriate IV antibiotics.

3.5 Recommended treatment options for evacuation

- **Small bore percutaneous drain insertion and intrapleural urokinase instillation into the pleural cavity**
  - Small bore percutaneous intercostal catheter (ICC) inserted by interventional radiology or paediatric surgery using ultrasound guidance under general anaesthetic.
    - Evidence suggests that small bore drains (8-12F) are just as effective as large bore and are more comfortable, less invasive and encourage better mobilization and coughing. This is associated with a better recovery and shorter hospital admissions.
  - A CXR should be performed after ICC insertion.
  - The ICC should be clamped for one hour after the first 10 mL/kg is drained to reduce the risk of re-expansion pulmonary oedema [16].
  - The ICC to be fitted with a 3-way tap at the time of insertion.
  - All children receiving an ICC for drainage of suspected or confirmed empyema should receive intrapleural urokinase (see 3.8 below). There is no role for chest drainage without fibrinolytics in this setting.
- **Video Assisted Thoracoscopic Surgery (VATS)**
  - VATS may be considered as the preferred initial therapy if
    - dense fibrinous septations visible at empyema diagnosis which are deemed unlikely to respond to ICC drainage and intrapleural urokinase therapy (note: based on anecdotal evidence alone, as empyema staging has not been shown to affect outcome) [8].
  - It should also be considered as 2nd line evacuation therapy if there is significant effusion with evidence of mass effect causing persisting or worsening significant respiratory compromise and/or fever *despite* ICC drainage, IV antibiotics and intrapleural urokinase therapy.
  - If VATS is being considered the case should be directly discussed with the on-call surgeon.
  - A CT chest may be requested by the on-call surgeon but is not recommended in this situation.
  - Lower rates of reintervention following VATS have been reported than Chest drain and Fibrinolytic (10.2% vs. 23.9%, respectively) [17]. A 10% failure rate with ICC and fibrinolytics is reported in the literature [18].

3.6 Risk factors for consideration when considering intervention

- The decision regarding intervention and preferred method of intervention (i.e. ICC insertion or VATS) should ideally be made through a three-way conversation between the on-call Respiratory Medicine, Surgical and Interventional radiology staff

(fellow/consultant level). Workload challenges at the time may mean that a three-way conversation is not always possible, and discussions may need to be sequential in nature. The Respiratory consultant on-call should give final approval for the decision made.

- Factors influencing the decision will include, but are not exclusive to:
  - A risk-benefit evaluation of the different intervention procedures available based on the clinical condition of the child.
  - The experience, availability and workload of the Interventional radiology and Surgical teams at the time an intervention is clinically indicated.
  - The response to previous intervention(s)

Note: A recent retrospective analysis of 129 empyema cases managed with ICC and urokinase showed that the initial ultrasound appearance of the effusion was not predictive of subsequent need for re-intervention[19], and therefore the density/amount of loculations is not listed as a risk factor here.

3.7 Additional points to consider

1. *Pleural fluid sampling at the time of evacuation*
   - Pleural fluid should be sent for
     - cytology
     - MC&S including smear and culture for Acid Fast Bacilli (AFB) and TB PCR and TB culture if *Mycobacterium tuberculosis* is suspected.
     - LDH, albumin.
     - Respiratory PCR panel: primarily for *Streptococcus pneumoniae, Haemophilus influenzae +/- Mycoplasma pneumoniae.* Request separately *Streptococcus pyogenes* and *Staphylococcus aureus* (including MRSA) PCR if available.
2. *CVAD insertion (PICC/midline)*
   - All children with empyema having a general anaesthetic should have a CVAD (PICC/midline) inserted at the same time.
3. *Patient or Nurse Controlled Analgesia (PCA or NCA, respectively).*
   - Pain team consult and PCA/NCA in all children where an ICC is left in situ.
   - This should be continued for the duration that the percutaneous drain is in situ.
   - A PCA/NCA should be started before leaving Recovery and should remain in situ until the ICC drain is removed.
4. *Physiotherapy*
   - The role of physiotherapy is to support:
     - early mobilization
     - encouragement of deep breathing and airway clearance techniques to aid resolution/prevention of atelectasis and/or consolidation.

- Chest-directed physiotherapy should be delayed in the following situations:
  - Prior to evacuation of pleural fluid.
  - Radiological evidence of necrotizing pneumonia.
  - Bronchopulmonary fistula.

3.8 Urokinase administration

- Refer to:
  - Intrapleural Urokinase in Empyema Drug Protocol AND
  - (Nurse) Administration of Intrapleural Urokinase in Empyema Local Work Procedure
- **Note:** the instructions for the preparation of urokinase provided by pharmacy must be checked and followed due to varying brands of urokinase being available.

3.9 Approach to renal impairment in Empyema

- Acute renal impairment: requires regular review to assess volume status, fluid balance, blood pressure, urine output and clinical assessment for features of pulmonary oedema (inspiratory crepitations, tachycardia, tachypnoea, increasing oxygen requirement).
- Common for low albumin state in empyema and this may be associated with third spacing of intravascular fluid and so reduced renal perfusion pressure.
- Approach to this involves:
  - Cautious fluid resuscitation. Particularly important to monitor urine output (strict fluid balance and daily weights).
  - Consider albumin replacement in patients with non-dependent oedema, concerns of pulmonary oedema contributing to respiratory compromise, albumin replacement is usually not considered if >20 g/L.
  - Dose of albumin is albumin 20% 0.5 - 1 g/kg given over 4 hours ± Furosemide. Albumin should not be given to patients with decreased urine output (oliguria or anuria).
- Other Complications of empyema associated with renal impairment include:
  - Post streptococcal glomerulonephritis
  - Haemolytic uraemic syndrome (HUS)[20]; An important cause of HUS is *S. pneumoniae* infection and is thought to represent ~15% of cases. An Australian case series of HUS reported 82% of cases required renal replacement therapy. Diagnostic criteria include:
    - Hb <100g/L (blood film; fragmented RBCs),
    - Thrombocytopenia (PLT <130 $x10^9$/L),
    - Acute renal impairment (elevated creatinine and oliguria).
- Suggest review with Nephrology team if not consulted prior.

4 Percutaneous ICC – ongoing management and removal

- All ICC should be connected to a unidirectional flow drainage system (e.g. underwater seal bottle) which must be kept below the level of the child's chest at all times.
- Once urokinase administration course has finished, twice daily flushes of sodium chloride 0.9% 10 mL should be prescribed on EMM, commenced and continued until the ICC is removed.
    - 20 mL should be administered as 10 mL up from the 3 way tap, 10 mL down from the 3 way tap.
- Consider removal once pleural fluid output falls to below 1-2 mL/kg/day.
    - Ensure that the ICC is not blocked
- A period of clamping prior to removal is not recommended.
- Refer to chest drain policy for details of removal technique.
- Consider earlier removal if evidence of pneumatocoele or necrotic pneumonia near to chest drain tip to minimise the associated risk of bronchopulmonary fistula formation.
- A chest x-ray is not routinely required following ICC removal if the child remains clinically stable.
- Once ICC is removed, mobilization and exercise is recommended.
- The primary team contacted for ICC issues should be the Respiratory team, who will then liaise with the interventional radiology and surgical teams as required (with preference to consult the team who initially inserted the ICC if available).

5 Discharge and further management

- Discharge is appropriate once tolerating oral antibiotics for a 24-hour period without re-emergence of fever.
- Generally to complete 2-4 weeks of antibiotics, including IV antibiotic course administered in hospital.
- Review in respiratory clinic at 4 weeks post discharge. The CXR may not return to baseline for 4-6 months. For regional and rural patients, in most cases, this follow up can be performed through their local paediatrician.
- Although most children with empyema are otherwise healthy, first-line investigations for primary immune deficiency should be performed.
    - The first-line primary immune deficiency screen should include FBC and blood film (for asplenia), and immunoglobulins (IgG, IgA, and IgM)
    - Second line investigations for primary immune deficiency should be considered in those with:

- pneumococcal empyema secondary to vaccine-associated strains (in vaccinated individuals),
- other unusual causative micro-organisms (e.g., salmonella, fungus),
- recurrent episodes and/or protracted clinical courses,
- a history of recurrent sinopulmonary infection (sinusitis, otitis media or pneumonia) with purulent discharge

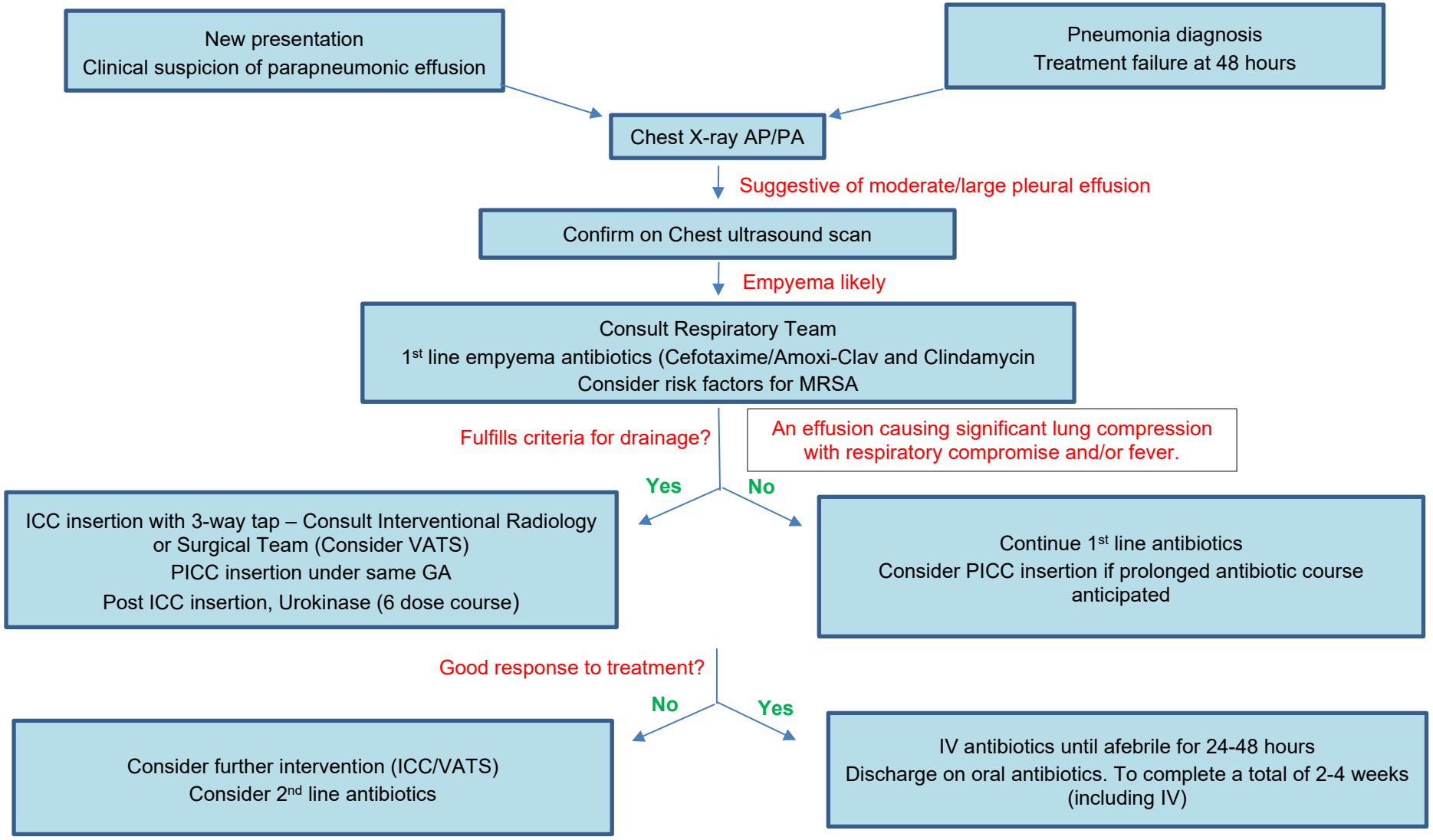
  - Second line immune investigations may include T and B cell subsets, response to vaccinations (baseline pneumococcal*, Haemophilus influenzae type B,* diphtheria and tetanus antibodies, repeated a month after booster vaccination), IgE and CH50 as well as other tests and formal immunology consultation, as indicated.
  - Although approximately 10% of children with invasive pneumococcal disease will have an associated immunodeficiency[21], the rates of immunodeficiency with isolated empyema may be significantly less (Hilliard et al ADC ref).

- The child should be followed in the outpatient clinic until they have recovered completely and the CXR has returned to near normal.

6 Further Pneumococcal vaccine booster dose

- There are over 90 different serotypes of *Streptococcus pneumoniae* (pneumococcus), and vaccines only cover against a selection of the commonly encountered serotypes.
- Vaccinations commonly used in NSW are:
  - 7-valent pneumococcal conjugate vaccine *(Prevenar 7)* covers serotypes 4, 6B, 9V, 14, 18C, 19F & 23F: this is no longer available, having been replaced in 2011 by *Prevenar 13* made by the same manufacturer
  - 13-valent pneumococcal conjugate vaccine *(Prevenar 13)*: additionally covers 1, 3, 5, 6A, 7F, and 19A
  - 23-valent polysaccharide Pneumovax vaccine: additionally covers serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F but does not cover 6A.
- At present use of booster doses are not recommended following empyema in either national or international guidelines, nor is there data to suggest the risk of empyema recurrence is sufficient to warrant this. Please check that all vaccinations are up to date in patients admitted with empyema.
  - See the NSW Health fact sheet on pneumococcal disease and current vaccination recommendations
- All *S. pneumoniae* isolates from culture-positive cases of invasive disease are routinely sent for serotype identification for public health purposes. The results are usually available after one month.

7 Flowchart for Empyema Management



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