Complicated Parapneumonic Effusion and Pleural Empyema in Adults - Microbiology Full Clinical Guideline

Reference number: CG-ANTI/2016/010

Introduction

- The pathogens of pleural infections are most commonly inoculated through a contiguous mechanism of transmission. Another focus of infectious disease (e.g. pneumonia, mediastinitis) disseminates locally and invades the pleural space.
- Less commonly, inoculation is via a haematogenous mechanism of transmission. Another focus of infection culminates in bacteraemia; the microorganism then disseminates via the blood and inoculates the pleural space.
- The pathogens of pleural infection can also be inoculated directly via surgery or trauma; iatrogenic and traumatic mechanisms of transmission, respectively.

- One of the potential outcomes of:
    - Microbial invasion of a pleural effusion; and
    - The subsequent pulmonary inflammatory response

  Is a complicated parapneumonic effusion:
    - Pleural infection without frank pus.
- Another of the potential outcomes is a pleural empyema:
    - Pleural infection with frank pus.

- With local dissemination from pneumonia the most common inoculation method, pleural infections secondary to:
    - Community acquired pneumonia (CAP) are especially associated with the:
        - Gram positive *Streptococcus pneumoniae*.
    - Aspiration pneumonia are markedly associated with the:
        - Gram positive *Streptococcus anginosus* group (formerly *Streptococcus milleri* group): *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*; and
        - Anaerobes: *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella* species.
    - Hospital acquired pneumonia (HAP) are especially associated with the:
        - Gram positive *Staphylococcus aureus*; and
        - Gram negative *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*.

- With the localised dissemination from pneumonia, symptoms and signs of complicated parapneumonic effusion and pleural empyemas may include:
    - Pleuritic pain, breathlessness, purulent cough, haemoptysis; hypoexpansion, increased fremitus, dullness, and bronchial breathing and crackles.
- With the microbial invasion of a pleural effusion, signs may also include:
    - Hypoexpansion, decreased fremitus, ‘stony’ dullness, and decreased breath sounds.
- Temperatures > 38 ° C or < 36 ° C, respiratory rate > 20 breaths/minute, heart rate > 90 beats/minute, and hypotension can denote progression of localised infectious disease into sepsis and septic shock.

Investigation

Radiology

- In general, chest x-ray (CXR) is required initially.
- If there is radiological evidence of pleural effusion, further imaging can be considered:
    - ± Ultrasound (US).
    - ± Computed tomography (CT):
        - Indications for CT chest include clinical suspicion of complicated pleural infection (e.g. loculated infectious disease).

Microbiology and biochemistry

- Before and after radiology, non-invasive investigation can be considered with:
    - ± Sputum culture**:**
        - If purulent cough.
    - ± Blood cultures:
        - If episode(s) of fever.
        - If the differential diagnosis includes bloodstream infection, sepsis, or septic shock.
        - If for initiation of treatment with intravenous antibiotics.
- After radiology, invasive investigation can be considered with:
    - Image-guided (ultrasound) diagnostic/therapeutic pleural aspiration, with fluid for:
        - Biochemistry: glucose, lactate dehydrogenase, and pH; and
        - Microbiology: microscopy (white blood cell [WBC] count, Gram stain, and ± mycobacterial stain) and culture (bacterial, ± mycobacterial, and fungal).

Blood sciences

- Full blood count (FBC), C-reactive protein (CRP), lactate, urea and electrolytes (U&Es), liver function tests (LFTs), and clotting.

Treatment

Medical, radiological, and surgical interventions

- Complicated parapneumonic effusions and pleural empyemas may progress from localised infectious disease into sepsis and/or septic shock.
- Early discussion with the respiratory registrar/consultant on call is recommended.

- Medical/radiological interventions may include:
    - Image-guided (ultrasound) chest drain insertion/drainage.
    - Intrapleural tissue plasminogen activator with deoxyribonuclease.
- Surgical interventions may include:
    - Video-assisted thoracic surgery with debridement or decortication.
- Interventions could enable: (i) reduction of the microbial inoculum; (ii) identification of the causative agent(s); and (iii) restoration of host physiological function.

- With regard to radiology:
    - Interventional radiology requires:
        - Written (an electronic request) and verbal communication; and
        - Informed consent for the procedure (https://derby.koha-ptfs.co.uk/cgi-bin/koha/opac-detail.pl?biblionumber=774); and

        - An up-to-date platelet count and clotting (https://derby.koha-ptfs.co.uk/cgi-bin/koha/opac-detail.pl?biblionumber=1577) to be completed by the referring team.
    - Please note, in general, local Trust policy requires omission of antiplatelets (e.g. clopidogrel for 5-7 days) and anticoagulants (e.g. warfarin for 5 days, apixaban or rivaroxaban for 48 hours) before radiological intervention.
    - Possible exceptions – wherein the clinical condition dictates drainage or omission is contraindicated – require consultant to consultant discussion, regarding potential benefits and risks of intervention.

Empiric, intravenous antibiotics: community acquired (including CAP associated with aspiration)

- First line:
    - Metronidazole 500 mg 8 hourly; **and**
    - Amoxicillin 1 g 8 hourly.
- Second line, if non-immediate without systemic involvement penicillin allergy:
    - Metronidazole 500 mg 8 hourly; **and**
    - Cefuroxime 1.5 g 8 hourly.
- Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
    - Metronidazole 500 mg 8 hourly; **and**
    - Co-trimoxazole 960 mg 12 hourly.
- Fourth line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy and if co-trimoxazole is contraindicated:
    - Metronidazole 500 mg 8 hourly; **and**
    - Levofloxacin 500 mg 12 hourly.
- Fifth line, if penicillin allergy and if metronidazole is contraindicated:
    - Clindamycin 600 mg 8 hourly.

Empiric, intravenous antibiotics: hospital acquired (including HAP associated with aspiration)

- First line:
    - Piperacillin tazobactam 4.5 g 6 hourly; **±**
    - If there are clinical concerns regarding the risk of methicillin resistant *Staphylococcus aureus* (MRSA), glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l.
- Second line, if non-immediate without systemic involvement penicillin allergy:
    - Metronidazole 500 mg 8 hourly; **and**
    - Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l; **and**
    - Ceftazidime 2 g 8 hourly.
- Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
    - Metronidazole 500 mg 8 hourly; **and**
    - Ciprofloxacin 400 mg 8 hourly; **and**
    - Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l.
- Fourth line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy and if ciprofloxacin is contraindicated:

    - Metronidazole 500 mg 8 hourly; **and**
    - Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l; **and**
    - Aztreonam 2 g 6 hourly.
- Fifth line, if penicillin allergy and if metronidazole is contraindicated:
    - Clindamycin 600 mg 8 hourly; **and**
    - Aztreonam 2 g 6 hourly.

Directed, intravenous antibiotics (with susceptibilities)

- *Streptococcus pneumoniae*, according to susceptibilities:
    - First line:
        - Benzylpenicillin 1.2 g 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefuroxime 1.5 g 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Clindamycin 600 mg 8 hourly.
- *Streptococcus anginosus* group (formerly *Streptococcus milleri* group; *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*), according to susceptibilities:
    - First line:
        - Amoxicillin 1 g 8 hourly; **and**
        - Metronidazole 500 mg 8 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefuroxime 1.5 g 8 hourly; **and**
        - Metronidazole 500 mg 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Clindamycin 600 mg 8 hourly.
- Anaerobes (e.g. *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella* species), according to susceptibilities:
    - First line:
        - Penicillin; narrowest spectrum of benzylpenicillin, amoxicillin, or co-amoxiclav standard dosage.
    - Second line, if penicillin allergy:
        - Metronidazole 500 mg 8 hourly.
    - Third line, if penicillin allergy and if metronidazole is contraindicated:
        - Clindamycin 600 mg 8 hourly.
- *Staphylococcus aureus*, according to susceptibilities:
    - First line:
        - Flucloxacillin 2 g 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefuroxime 1.5 g 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l.
- *Enterobacterales* (e.g. *Escherichia coli*, *Klebsiella* species), according to susceptibilities:

    - First line:
        - Penicillin; narrowest spectrum of amoxicillin or co-amoxiclav or piperacillin tazobactam standard dosage.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cephalosporin; narrowest spectrum of cefuroxime or ceftriaxone standard dosage.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Co-trimoxazole 960 mg 12 hourly.
- *Pseudomonas aeruginosa*, according to susceptibilities:
    - First line:
        - Piperacillin tazobactam 4.5 g 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Ceftazidime 2 g 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Ciprofloxacin 400 mg 8 hourly.
- Other bacteria, fungi, and parasites:
    - Collaborate with the microbiology team.

Intravenous to per oral step down, or outpatient parenteral antimicrobial therapy

- After 2-3 days of intravenous antibiotics, if the patient is afebrile, observations stable, and inflammatory markers downward trending, collaborate with the respiratory team ± microbiologist regarding: (i) per oral step down; or (ii) outpatient parenteral antimicrobial therapy (OPAT).
- After ≥ 7 days of systemic antibiotics, if the patient is febrile, observations unstable, and/or inflammatory markers upward trending, collaborate with the respiratory team ± radiologist ± microbiologist regarding: (i) ± re-imaging; (ii) ± further medical/radiological intervention; (iii) ± referral for surgical intervention; and (iv) continue systemic therapy.

Directed, per oral antibiotics (with susceptibilities)

- *Streptococcus pneumoniae*, according to susceptibilities:
    - First line:
        - Amoxicillin 500 mg 8 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefaclor 500 mg 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Clindamycin 300 mg 6 hourly.
- *Streptococcus anginosus* group (formerly *Streptococcus milleri* group; *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*), according to susceptibilities:
    - First line:
        - Amoxicillin 500 mg 8 hourly; **and**
        - Metronidazole 400 mg 8 hourly.
    - Second line, if penicillin allergy:
        - Clindamycin 300 mg 6 hourly.
    - Third line:

        - Collaborate with the microbiology team.
- Anaerobes (e.g. *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, and *Prevotella* species), according to susceptibilities:
    - First line:
        - Penicillin (narrowest spectrum of amoxicillin or co-amoxiclav) standard dosage.
    - Second line, if penicillin allergy:
        - Metronidazole 400 mg 8 hourly.
    - Third line, if penicillin allergy and if metronidazole is contraindicated:
        - Clindamycin 300 mg 6 hourly.
- *Staphylococcus aureus*, according to susceptibilities:
    - First line:
        - Flucloxacillin 1 g 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefalexin 1 g 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy
        - Clindamycin 300 mg 6 hourly.
- *Enterobacterales* (e.g. *Escherichia coli*, *Klebsiella* species), according to susceptibilities:
    - First line:
        - Penicillin; narrowest spectrum of: (i) amoxicillin 1 g 8 hourly; or (ii) co-amoxiclav 625 mg 8 hourly plus amoxicillin 500 mg 8 hourly.
    - Second line, if penicillin allergy:
        - Co-trimoxazole 960 mg 12 hourly.
    - Third line, if penicillin allergy and if co-trimoxazole is contraindicated:
        - Ciprofloxacin 500 mg 12 hourly.
- *Pseudomonas aeruginosa*, according to susceptibilities:
    - Ciprofloxacin 750 mg 12 hourly.
- Other bacteria, fungi, and parasites:
    - Collaborate with the microbiology team.

Directed, outpatient parenteral antibiotic treatment

- Collaborate with the OPAT consultant.

Empiric, per oral or outpatient parenteral antibiotic treatment

- If diagnoses of complicated parapneumonic effusion or pleural empyema, and microbiology negative, collaborate with the microbiology team regarding empiric options.

Duration of antibiotics

- Before discharge to the community, collaborate with the respiratory/radiology team(s) regarding the modality and timeframe for follow-up imaging.
- If for per oral step down or OPAT, monitor bloods (FBC, CRP, U&Es, and LFTs) weekly-fortnightly.
- Complicated parapneumonic effusion:
    - Courses of antibiotics 2-3 weeks:
        - If (i) medicine or radiology or surgery have intervened and (ii) if the patient is afebrile, observations are stable, inflammatory

markers have resolved, and follow-up imaging is satisfactory: 2 weeks, from the date of intervention.
        - If neither medicine nor radiology nor surgery have intervened: 3 weeks, if the patient is afebrile, observations are stable, inflammatory markers have resolved, and follow-up imaging is satisfactory.

- Pleural empyema:
    - Courses of antibiotics 4-6 weeks:
        - If (i) medicine or radiology or surgery have intervened and (ii) if the patient is afebrile, observations are stable, inflammatory markers have resolved, and follow-up imaging is satisfactory: 4 weeks, from the date of intervention.
        - If neither medicine nor radiology nor surgery have intervened: 6 weeks, if the patient is afebrile, observations are stable, inflammatory markers have resolved, and follow-up imaging is satisfactory.

Management (1 of 2)

Clinical concerns re complicated parapneumonic effusion/pleural empyema

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Investigation:

- Radiology:
  - Initially, CXR
  - If there is radiological evidence of pleural effusion, consider US ± CT in collaboration with the respiratory team
- Microbiology:
  - ± Sputum culture (e.g. if purulent cough)
  - ± Blood cultures (e.g. if episode[s] of fever; if the differential diagnosis includes bloodstream infection, sepsis, or septic shock; if for initiation of treatment with intravenous antibiotics)
- Blood sciences:
  - FBC, CRP, lactate, U&Es, LFTs, and clotting

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Consultation with the respiratory registrar/consultant on call

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Investigation and treatment

- Image-guided (ultrasound) diagnostic/therapeutic pleural aspiration (or chest drain insertion/drainage), with pleural fluid for:
  - Biochemistry: glucose, lactate dehydrogenase, and pH
  - Microbiology: microscopy (WBC count, Gram stain, ± mycobacterial stain) and culture (bacterial, ± mycobacterial, fungal)
- If clinically unstable or symptom onset is acute (day[s]) in nature:
  - Start empiric intravenous antibiotics before the pleural aspiration (or chest drain insertion/drainage)
- If clinically stable and symptom onset is subacute (weeks) in nature:
  - Start empiric intravenous antibiotics after the pleural aspiration (or chest drain insertion/drainage)

NB Please note Management (2 of 2) regarding empiric intravenous antibiotic regimens

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Treatment; medical, radiological, or surgical intervention

- In collaboration with the respiratory ± thoracic team(s):
  - ± Image-guided (ultrasound) chest drain insertion/drainage
  - ± Intrapleural tissue plasminogen activator with deoxyribonuclease
  - ± Video-assisted thoracic surgery with debridement or decortication

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Treatment; antibiotics

- Directed with culture and susceptibilities

Management (2 of 2)

Empiric intravenous antibiotics: community acquired (including CAP associated with aspiration)

First line	Metronidazole 500 mg 8 hourly **and** Amoxicillin 1 g 8 hourly
Second line, if non-immediate without systemic involvement penicillin allergy	Metronidazole 500 mg 8 hourly **and** Cefuroxime 1.5 g 8 hourly
Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy	Metronidazole 500 mg 8 hourly **and** Co-trimoxazole 960 mg 12 hourly
Fourth line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy and if co-trimoxazole is contraindicated	Metronidazole 500 mg 8 hourly **and** Levofloxacin 500 mg 12 hourly
Fifth line, if penicillin allergy and if metronidazole is contraindicated	Clindamycin 600 mg 8 hourly

Empiric intravenous antibiotics: hospital acquired (including HAP associated with aspiration)

First line	Piperacillin tazobactam 4.5 g 6 hourly **±** If there are clinical concerns regarding the risk of MRSA, glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l
Second line, if non-immediate without systemic involvement penicillin allergy	Metronidazole 500 mg 8 hourly **and** Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l; **and** Ceftazidime 2 g 8 hourly
Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy	Metronidazole 500 mg 8 hourly; **and** Ciprofloxacin 400 mg 8 hourly; **and** Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l
Fourth line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy and if ciprofloxacin is contraindicated	Metronidazole 500 mg 8 hourly; **and** Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 15-30 mg/l; **and** Aztreonam 2 g 6 hourly
Fifth line, if penicillin allergy and if metronidazole is contraindicated	Clindamycin 600 mg 8 hourly; **and** Aztreonam 2 g 6 hourly

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Document control

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