Neutropenic Sepsis in Adults - Microbiology Full Clinical Guideline

Reference number: CG-T/2024/059

Definitions

- Locally, in the University Hospitals of Derby and Burton:
  - (1) Neutropenia: absolute neutrophil count ≤ 1.0 x 10^9 neutrophils/L.
- Nationally, including the National Institute for Health and Care Excellence (NICE):
  - (2) Sepsis: life threatening organ dysfunction caused by a dysregulated host immune response to infection.

Introduction

- The human body and the environment harbour microorganisms including bacteria, fungi, and viruses. Notable reservoirs include the gastrointestinal tract.
- In haematology and oncology patients, cytotoxic chemotherapy may mediate injury to the mucosa. Disruption of the mucosal integrity of the gastrointestinal tract enables translocation of bowel flora from the luminal surface and localised invasion into submucosal tissues and layers.
- The immunodeficiencies of haematology pathologies, and/or the immunosuppressive nature of the haematology/oncology therapies, facilitate microbial dissemination.
- The commonest causes of infectious disease in neutropenic patients are bacteria. Gram positive causative agents include *Enterococcus*, *Staphylococcus*, and *Streptococcus* species; Gram negative pathogens include *Enterobacterales* (e.g. *Enterobacter, Escherichia*, and *Klebsiella* species) and *Pseudomonas aeruginosa*.
- Other less common causes include fungi (e.g. *Candida* species) and viruses (e.g. herpes simplex virus [HSV]-1, HSV-2, and varicella-zoster virus [VZV]).
- The risk of infectious disease in haematology/oncology patients is directly proportional to the degree and duration of neutropenia.
- Early intervention reduces the risk of neutropenic sepsis progressing into septic shock, organ dysfunction, or death.

Differential diagnosis

- The immunocompromising nature of haematology/oncology pathologies and therapies can dampen host inflammatory responses. This, in turn, mutes the typical symptoms and signs of infectious disease.
- Therefore, low levels of suspicion for investigating and treating infection are recommended by physicians regarding patients with:
  - Past medical histories of haematology/oncology disease and other immunodeficiencies; and/or
  - Drug histories of immunosuppression.
- Infective complications include bloodstream infection, sepsis, septic shock, organ dysfunction, and death.
- If the differential diagnosis/diagnosis includes suspected/confirmed infection, both NICE and the United Kingdom Sepsis Trust (UKST) outline low levels of suspicion to screen for sepsis:
  - For example, the NICE suspected sepsis: recognition, diagnosis and early management guideline includes:

        - "Suspect neutropenic sepsis in people who become unwell and:
            - Are having or have had systemic anticancer treatment within the last 30 days
            - Are receiving or have received immunosuppressant treatment for reasons unrelated to cancer. Use clinical judgement (based on the person's specific condition, medical history, or both, and on the treatment they received) to determine whether any past treatment may still be likely to cause neutropenia."
    - For example, the UKST clinical tools include:
        - "Recent chemotherapy / risk of neutropenia".

Classification

National Early Warning Score 2 (NEWS2)

- The development of infective sequelae can be recognised, in part, through the multi-system parameters of the NEWS2.
    - Measurements of consciousness, temperature, respiratory rate, oxygen saturation, supplemental oxygen, systolic blood pressure, and heart rate facilitate early recognition of pathology severity, including infection.

High risk of severe illness or death from sepsis

- **Neutropenia* and symptoms/signs of sepsis**; **or**
- **Neutropenia* and temperature > 38°C**; **or**
- Suspected/confirmed infection and NEWS2 ≥ 7; **or**
- Suspected/confirmed infection, NEWS2 5 or 6, **and** 1 of:
    - Mottled or ashen skin.
    - Non-blanching purpuric rash.
    - Cyanosis of skin, lips, or tongue.
    - Single NEWS2 parameter score of 3.
    - Lactate > 2 mmol/L.
    - Acute kidney injury.
    - Clinical deterioration from last NEWS2.
    - Clinical deterioration from last intervention.
- *** Or high pre-test probability of neutropenia**.

Investigation: past

- If possible, review the past microbiology for cultures - especially blood cultures - of bacteria with resistance to initial, empiric intravenous antibiotic options.

Investigation: present

Blood sciences

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

Microbiology

- If possible, before starting antibiotics, blood cultures (8-10 ml of blood into an aerobic bottle and 8-10 ml of blood into an anaerobic bottle) ≥ × 1*.
    - * If central venous catheter in situ, centrally and peripherally.
- Urine culture.
- If localising symptoms and/or signs, extra investigations as per hospital guidelines.

Radiology

- Chest x-ray (CXR).
- If there are localising symptoms and/or signs, in collaboration with the senior, consider further imaging.

Treatment

Empiric antibiotics

- With regard to high risk of severe illness or death from sepsis:
    - The NICE suspected sepsis: recognition, diagnosis and early management guideline outlines:
        - "Broad-spectrum intravenous antibiotic treatment, within 1 hour of calculating the person's NEWS2 score on initial assessment in the emergency department or on ward deterioration."

Initial, empiric intravenous antibiotic options

- This antibiotic section includes fluoroquinolone usage.
- The Medicines and Healthcare products Regulatory Agency (MHRA) - with input from the Commission on Human Medicines (CHM) - have reviewed and published drug safety updates regarding systemic fluoroquinolones.
- Ciprofloxacin is hyperlinked to the British National Formulary.
- For NHS medicines and MHRA information for healthcare professionals on ciprofloxacin, click here and here, respectively.
- For MHRA printable information for patients on fluoroquinolones, click here.

Option 1	
Piperacillin tazobactam	4.5 g 6 hourly
± Tobramycin	Stat dose as per hospital guidelines for haematology patients, with the exception/exclusion of myeloma patients. NB Tobramycin doses thereafter require collaboration with the haematology senior, within the next week day or weekend review
± Teicoplanin	If clinical concerns regarding the risk of central venous catheter infection or methicillin resistant *Staphylococcus aureus* (MRSA), add teicoplanin, dose as per hospital guidelines

Option 2, if non-severe penicillin allergy (i.e. non-immediate without systemic involvement penicillin allergy)	
Ceftazidime **AND**	2 g 8 hourly
Teicoplanin	Dose as per hospital guidelines
± Tobramycin	Stat dose as per hospital guidelines for haematology patients, with the exception/exclusion of myeloma patients. NB Tobramycin doses thereafter require collaboration with the haematology senior, within the next week day or weekend review
± Metronidazole	If the differential diagnosis includes an abdomen pelvis focus of infection, add metronidazole 500 mg 8 hourly

Option 3, if severe penicillin allergy (i.e. immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy)	
Ciprofloxacin **AND**	400 mg 8 hourly
Teicoplanin	Dose as per hospital guidelines
± Tobramycin	Stat dose as per hospital guidelines for haematology patients, with the exception/exclusion of myeloma patients.

	NB Tobramycin doses thereafter require collaboration with the haematology senior, within the next week day or weekend review
± Metronidazole	If the differential diagnosis includes an abdomen pelvis focus of infection, add metronidazole 500 mg 8 hourly

- NB If the differential diagnosis includes (i) candidiasis, aspergillosis, or mucormycosis, or (ii) pneumocystosis, please note invasive fungal disease and *Pneumocystis jirovecii* hospital guidelines, respectively.

Stabilisation of respiration

- ± Administer oxygen as per hospital guidance on Sepsis Management in Non-Pregnant Adult Patients (page 7).
- If hypoxia is persisting after the administration of high concentrations of inspired oxygen (FiO_2 90-100%), liaise with the team senior regarding an intensive care unit (ICU) referral ± transfer of care for respiratory support.

Restoration of perfusion

- ± Administer fluids intravenously as per hospital guidance on Sepsis Management in Non-Pregnant Adult Patients (page 9).
- If hypotension (SBP < 90 mmHg or mean arterial pressure < 65 mmHg) or metabolic acidosis (e.g. lactate > 4 mmol/L) are persisting after the administration of fluids intravenously, liaise with the team senior regarding an ICU referral ± transfer of care for cardiovascular support.

Monitoring of fluid input and output

- ± Monitor fluid input and output as per hospital guidance on Sepsis Management in Non-Pregnant Adult Patients (page 10).
- If the urine output is < 0.5 ml/kg/h, liaise with the team senior regarding an ICU referral ± transfer of care.

Haematology/Oncology intervention and reviews

- If the drug history includes immunosuppressants, withhold the immunosuppressive chemotherapy whilst awaiting speciality consultation.
- With regard to haematology reviews:
    - Contact the haematology registrar or consultant on call, via switchboard, for a telephone consult ± review, regarding every haematology patient with neutropenic sepsis.
- With regard to oncology reviews:
    - In Burton, 0900-1700, Monday to Friday: contact the acute oncology team, via switchboard, for a telephone consult ± review, regarding every oncology patient with neutropenic sepsis.
    - In Derby, 0900-1900, Monday to Friday: contact the oncology registrar or consultant on call, via switchboard, for a telephone consult ± review, regarding every oncology patient with neutropenic sepsis.
    - In Burton 1700-0900 and in Derby 1900-0900, Mondays-Sundays:
        - In general, the medical team is to proceed with the empiric antibiotic guidance, and liaise with the oncologist within the next working day. However, if the medical consultant requests a specialty consult, then the medical team is to liaise with the oncology registrar or consultant on call.

± Surgical intervention

- Neutropenic sepsis necessitates medical ± intensive care.
- Infectious disease may also warrant surgical intervention to remove foci of infection and restore the function of tissues, organs, and systems.

Management

Haematology/Oncology disease or other history of **immunocompromise**

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Suspected/confirmed infection

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≥ 1 of the sepsis flags that include:

- "Looks unwell" to clinicians/carers
- **Recent chemotherapy*/immunotherapy**
- NEWS2 trigger (e.g. ≥ 5)
- Lactate > 2 mmol/L

* **With regard to recent chemotherapy, NICE outlines within the last 30 days**

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Screen for sepsis:

- Doctor (FY2 or more senior) or equivalent healthcare professional review stat
- NEWS2 repeat
- Lactate

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High risk of severe illness or death from sepsis

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If high risk of severe illness or death from sepsis

Investigate

- Past: if possible, review the past microbiology for cultures - especially blood cultures - of bacteria with resistance to initial, empiric intravenous antibiotic options
- Present:
  - Blood sciences: FBC, CRP, U&Es, clotting, LFTs; blood gas (glucose, lactate)
  - Microbiology: if possible, before starting antibiotics, blood cultures (8-10 ml of blood into an aerobic bottle and 8-10 ml of blood into an anaerobic bottle) ≥ × 1 (if central venous catheter in situ, centrally and peripherally); urine culture; if there are localising symptoms and/or signs, extra microbiology investigations as per hospital guidelines
  - Radiology: CXR; if there are localising symptoms and/or signs, in collaboration with the senior, consider further imaging

Treat (**after blood cultures [if possible] - asap - ≤ 1 hour - awaiting other investigative findings**)

- Empiric antibiotics intravenously (pages 3-4)
- ± Administer oxygen; Sepsis Management in Non-Pregnant Adult Patients page 7
- ± Administer fluids intravenously; Sepsis Management in Non-Pregnant Adult Patients page 9
- ± Monitor fluid input and output; Sepsis Management in Non-Pregnant Adult Patients page 10

Monitor/Escalate

- NEWS2 repeats every 30 minutes
- Inform the haematology/oncology registrar (or equivalent healthcare professional) stat (page 5)
  - Haematology/oncology registrar (or equivalent healthcare professional) review within 1 hour if no improvement
- If no improvement within 1 hour:
  - Inform the haematology/oncology/medical consultant on clinical duty/on call
  - ± ICU referral ± transfer of care (page 5)

Management: ongoing neutropenic sepsis

Investigation[1]

- If neutropenia and sepsis are persisting after 48-72 hours:
    - Repeat the blood cultures ≥ × 1*:
        - * If central venous catheter in situ, centrally and peripherally.
    - If there are localising symptoms and/or signs, extra microbiology investigations as per hospital guidelines.
    - If there are no localising symptoms and/or signs, in collaboration with the senior, consider imaging of the abdomen pelvis.

Treatment: empiric intravenous antibiotics

- Noting that NICE outlines "do not switch initial empiric antibiotics in patients with unresponsive fever unless there is clinical deterioration or a microbiological indication ":
    - If neutropenia and sepsis are persisting after 48-72 hours, in collaboration with the medical senior, consider modifying empiric intravenous antibiotics:

If the drug history includes the initial administration of piperacillin tazobactam or ceftazidime for neutropenic sepsis	
Meropenem	1 g 8 hourly
± Teicoplanin	If clinical concerns regarding the risk of central venous catheter infection or MRSA, add teicoplanin, dose as per hospital guidelines

If the drug history includes the initial administration of ciprofloxacin for neutropenic sepsis and severe penicillin allergy (i.e. immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy)	
Aztreonam **AND**	2 g 6 hourly
Teicoplanin	Dose as per hospital guidelines
± Metronidazole	If the differential diagnosis includes an abdomen pelvis focus of infection, add metronidazole 500 mg 8 hourly
Or, in collaboration with the medical and microbiology consultants	
Colistin **AND**	9 million unit loading dose; 4.5 million units 12 hourly thereafter
Teicoplanin	Dose as per hospital guidelines
± Metronidazole	If the differential diagnosis includes an abdomen pelvis focus of infection, add metronidazole 500 mg 8 hourly

Investigation[2]

- If there are ongoing clinical concerns regarding neutropenic sepsis, after initial ± modified antibiotics (or before [if risk factors, symptoms, signs, etc.]), consider both fungal and viral aetiologies:
    - The combination of (1) *Candida* species colonising the skin and mucosa, (2) *Aspergillus* environmental niches, (3) immunocompromise, and (4) cytotoxic chemotherapy mediation of mucositis, can cause invasive fungal disease.
        - Candidiasis, aspergillosis, mucormycosis, and pneumocystosis infectious disease may require consideration. Please note hospital guidelines regarding invasive fungal disease and *Pneumocystis jirovecii*.
    - The reactivation of latent virions can exacerbate the immunocompromise of haematology/oncology patients.
        - Adenovirus, Epstein-Barr virus, and cytomegalovirus may also require consideration.

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Document control

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Version:	2
Approval date:	AMSG 16.07.2024 CDCS 06.08.2024
Changes from previous version:	Definitions: reworded (minor). Introduction: reworded (minor). Differential diagnosis: reworded (major). Classification (new). Investigation: reworded (minor). Treatment: reworded (minor) and reformatted (minor). Management: reworded (major) and reformatted (major). References: updated (minor).
Date uploaded:	07/08/2024
Next review date:	August 2027
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