Guidance on the initial antibiotic management of adults (18 years and over) with febrile neutropenia OR immunocompromised with sepsis of unknown source

NEUTROPENIA[1] OR IMMUNOCOMPROMISED[2] patient unwell with undifferentiated infection PLUS pyrexia (temperature 38°C or higher), hypothermia (temperature less than 36°C) or other signs or symptoms consistent with sepsis or septic shock (Discuss with infection specialist if HIV positive with fever).

ASSESS national early warning score (NEWS) 2 score within 30 mins of presentation. Categorise as HIGH RISK if NEWS 2 score 7 or higher OR if haematological malignancy (except myeloma) or if receiving cellular therapy [2].

INITIAL MANAGEMENT BEFORE ANTIBIOTICS: Obtain 2 blood culture sets (8-10 ml/ bottle), check lactate, give oxygen to achieve target saturation, monitor urine output and if patient is hypovolaemic, administer IV crystalloid. Consider infection source and review previous microbiology. If in doubt, contact infection specialist. **GIVE IV ANTIBIOTIC(S) WITHIN ONE HOUR TO ALL PATIENTS IRRESPECTIVE OF RISK CATEGORY.**

MASCC score		
Characteristic	**Points**	**Patient score**
Febrile neutropenia with: • no or mild symptoms • moderate symptoms • severe symptoms	 5 3 0	
No hypotension (systolic BP<90mmHg)	5	
No COPD	4	
Solid tumour or haematological malignancy with no previous fungal infection	4	
No dehydration requiring parenteral fluids	3	
Outpatient when developed fever	3	
Age <60 years	2	
Total score for patient (maximum score = 26)		

If MASCC score 21 or higher, CONSIDER starting LOW RISK PATIENT pathway on page 2 FOLLOWING initial antibiotic

MODERATE RISK

NEWS 2 score 6 or less

PENICILLIN or beta-lactam ALLERGY
Confirm type and severity of previous reaction eg rash, anaphylaxis [3]

NO → **IV piperacillin/ tazobactam* 4.5g 6 hourly. No routine IV gentamicin**

YES

Non-severe allergy [3]
IV ceftazidime* 2g 8 hourly **or IV aztreonam*** 2g 6 hourly **PLUS IV teicoplanin or vancomycin** (see local guidelines)

Severe allergy [3]
IV gentamicin or amikacin* (see local guidelines) **or IV aztreonam*** 2g 6 hourly **PLUS IV teicoplanin or vancomycin** (see local guideline)

Oncology patient (non-haematology malignancy) with NEUTROPENIA AND NEWS 2 score of 4 or less - calculate MASCC score

HIGH RISK

NEWS 2 score 7 or higher OR SEPTIC SHOCK OR haematological malignancy or receiving cellular therapy [2]

PENICILLIN or beta-lactam ALLERGY
Confirm type and severity of previous reaction eg rash, anaphylaxis [3]

NO → **IV piperacillin/ tazobactam* 4.5g 6 hourly PLUS IV gentamicin or amikacin** (see local guidelines). **Consider adding IV teicoplanin or vancomycin** (see local guidelines)

YES

Non-severe allergy [3]
IV ceftazidime* 2g 8 hourly **PLUS IV gentamicin or amikacin*** (see local guidelines) **PLUS IV teicoplanin or vancomycin** (see local guidelines)

Severe allergy [3]
IV aztreonam* 2g 6 hourly **PLUS IV gentamicin or amikacin** (see local guidelines) **PLUS IV teicoplanin or vancomycin** (see local guidelines)

*** Use of meropenem (teicoplanin or vancomycin not routinely required empirically with meropenem)**

Use IV meropenem 1g 8 hourly +/- gentamicin or amikacin if:

a. Haematological malignancy or cellular therapy AND sepsis requiring inotropic support or septic shock **OR**

b. Previous or suspected multidrug resistant Gram-negative including ESBL (Extended Beta lactamase producing) infection **OR**

c. Gentamicin or amikacin contra-indicated and alternative treatment not suitable **OR**

d. Aztreonam unavailable. (Patients with penicillin allergy PLUS high risk or 1st line option not suitable)

Other risk factors affecting treatment	Antimicrobial comment
Myeloma or Myasthenia gravis	**Avoid gentamicin or amikacin (contra-indicated in myasthenia gravis and risk of renal toxicity in myeloma)**
Previous MRSA infection, MRSA colonised (current or previous) OR suspected central line infection	**Add teicoplanin or vancomycin if not already included (as per local guidelines)**
Previous Vancomycin, Daptomycin or Linezolid Resistant Enterococcus (VRE) infection or colonisation	**Discuss with infection specialist**
Consider *C. difficile* risk as well as non-bacterial infection eg COVID-19, influenza, CMV, disseminated fungal infection. Consider other anti-infective agents as appropriate. Discuss with an infection specialist	

- All antibiotic doses are based on normal renal and hepatic function. Refer to BNF and renal drug database, and at earliest opportunity, discuss with ward pharmacist or on call pharmacist
- Refer to local gentamicin, amikacin, vancomycin and teicoplanin guidelines. Maximum gentamicin or amikacin duration 3 or 4 days (see local guidelines)
- Review IV therapy daily. Consider IV to oral switch (IVOST) if clinical improvement (afebrile, reduction in NEWS 2 score, improving sepsis), oral route is reliably available, microbiology results or alternative diagnosis (eg treatment related symptoms) and following discussion with senior or specialist team (see local guidelines)
- Seek early appropriate senior specialist advice and refer patient to specialist acute oncology, haematology or transplant unit or local infection specialist as appropriate

1. Neutropenia - neutrophil count of 0.5 x 10^9/L or less, **OR** 1.0 x 10^9/L or less if recent chemotherapy (usually within 10 days but can be up to 28 days)
2. Immunocompromised - cellular therapy (eg haematopoietic stem cell transplant, CAR-T therapy), haematological malignancy, solid organ transplant, immunotherapy or high dose corticosteroid therapy (eg over 20mg prednisolone for more than 2 weeks)
3. Penicillin allergy severity – determine from history if high probability of previous anaphylaxis or delayed Type IV hypersensitivity reaction or low probability such as intolerance eg gastrointestinal upset.

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Management of LOW-RISK adults (aged 18 years and over) with febrile neutropenia

For assessment and initial management (including empirical IV therapy) see page 1

Patient criteria

- **NEWS 2 score of 4 or less (≤4) WITH MASCC score of 21 or more (≥21) AND can tolerate oral therapy**
- **If not suitable for oral therapy but still low risk, discuss with infection specialist and consider alternative local pathway (eg Outpatient Parenteral Antimicrobial Therapy (OPAT))**
- **Excludes patients with haematological malignancy, cellular therapy and those with previous invasive fungal infection**
- **Use only if the site of infection is unknown. If site of infection is well defined (eg cellulitis, respiratory tract or pneumonia, UTI etc) then treat as per local infection management guidance**

Does the patient have a contraindication to a fluoroquinolone? Consider MHRA warning

No

Continue treatment with oral antibiotic [4]
Oral levofloxacin 500mg 12 hourly [5,6]
Duration: 7 days if no clinical or microbiological focal site identified

Yes or unsure

Discuss with an infection specialist

4. If low risk of pseudomonas infection or high risk of *C. difficile* then consider co-trimoxazole 960mg 12 hourly instead of levofloxacin
5. Levofloxacin - reduced absorption with cations eg calcium, magnesium, iron and zinc
6. Levofloxacin - caution age over 60 years, concurrent corticosteroids and avoid if QTc prolonged. Stop levofloxacin at first sign of adverse reaction eg tendonitis, new neuropsychiatric symptoms

Discharge criteria: Only consider discharge if all the following criteria are met

- Clinically stable and not otherwise requiring ongoing inpatient care
- Has family or carer support in the community and no other medical or social barriers to discharge
- Has a telephone and ready access to an emergency department and lives less than one hour away
- Has follow up arrangements by telephone or in ambulatory setting (for local adaptation)
- Has been given oral and written information on warning signs and symptoms and understands this information and when to seek medical assessment and return to hospital
- For oncology patients, provide the contact telephone number for 24-hour specialist oncology advice (add local number, national phone number 08009177711)
- For haematology patients, contact haematology for follow up
- For solid organ transplant patients, contact transplant team for follow up

Outpatient review: Review daily for a minimum of 3 days to monitor fever resolution, clinical progress and outstanding microbiology results

Plan follow up review according to ongoing clinical assessment and progress. Hospital admission should be considered after 48-72 hours of initial empirical antimicrobial treatment for patients:

- With continued febrile neutropenia
- Who re-present with new signs or symptoms of infection or clinical deterioration
- Where oral therapy is inappropriate (eg vomiting)
- Where a change of antimicrobial therapy is indicated based on changing diagnosis or microbiology results

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