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Antimicrobial Management of Febrile Neutropenic Sepsis

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Antimicrobial Management of Febrile Neutropenic Sepsis

[Read in conjunction with PAT/EC 5 Febrile Neutropenic Patients Management Guidelines]

Diagnosis of neutropenic sepsis (as per NICE guidelines Sept 2012) is made in patients having anticancer treatment whose neutrophil count is 0.5 x 10^9/L or lower and who have either a temperature higher than 38^0C OR other signs or symptoms consistent with clinically significant sepsis.

This trust guideline includes patient with the above diagnosis and also includes patients who have a low neutrophil count of between 0.5 and 1.0 x 10^9/L, recent chemotherapy, a temperature of higher than 38^0C and clinically septic

***Table I*:** Details the first line, second line antibiotic therapy and antifungal therapy. Also see flowchart. First line antibiotic should be commenced within one hour in patients with sepsis – see sepsis IPOC. Doses used in renal impairment can be found in appendix 1

***Table II*:** Prophylactic antiviral, antifungal and antibacterial therapy

The initial management should involve a thorough investigation looking for a source for sepsis and include the following:

- Detailed history and examination
- Clinical examination to include skin, mouth, web-spaces , peri-anal area, Hickman line site, chest and abdomen
- Blood cultures – taken from the central venous catheter, if present (through each lumen) and Peripheral cultures; OR via 2 separate venepunctures if no central venous catheter present
- CXR
- MSU/CSU
- Sputum
- Swab from Hickman site/skin lesions/mouth
- Faeces
- CT-sinus, chest, abdomen, pelvis OR brain
- SARS CoV2

  (If clinically indicated)
- FBC, U/E, CRP, liver function tests and Lactate
- During the Flu season – all patients admitted with a temperature should have a throat swab sent for respiratory viruses
- If bronchoscopy performed, send BAL sample for: routine culture and sensitivity, AFB, Pneumocystis, respiratory viruses, fungal culture and galactomannan

Table I : TREATMENT	Category		
	Neutrophil count ≤0.5 x 10^9 /L **AND** Having anticancer treatment **AND** Temperature higher than 38 ^{0}**C OR** other signs and symptoms consistent with clinical sepsis	Neutrophil count of between 0.5 and 1.0 x 10^9/L **AND** Chemotherapy in the preceding 6 weeks **AND** Temperature greater than 38^{0}C Clinical sepsis, no obvious focus of infection	Neutrophil count of between 0.5 and 1.0 x 10^9/L **AND** Chemotherapy in the preceding 6 weeks, **AND** Temperature greater than 38^{0}C Clinically well
FIRST LINE ANTIBIOTIC THERAPY	IV Piperacillin/Tazobactam 4.5g FOUR times daily		Oral Co-amoxiclav 625mg THREE times daily for 5 days
Non life -threatening penicillin allergy OR previous/current ESBL/AmpC carrier	IV Meropenem 1g THREE times daily		Oral Cefaclor MR 375mg TWICE daily + Metronidazole 400mg THREE times daily for 5 days **If previous ESBL/AmpC, contact Microbiologist**
Life-threatening allergy to penicillin	IV Ciprofloxacin 400mg TWICE daily **AND** IV Teicoplanin 400mg TWICE daily for the first 3 doses, then 400mg once daily		Oral Levofloxacin 500mg TWICE daily for 5 days
Previous/current MRSA positive swab OR High suspicion of catheter related infection	**ADD** IV Teicoplanin (see Guidelines for Use of Teicoplanin)		
SECOND LINE	If the temperature persists at 48hrs and clinically stable with no clinical deterioration then continue with the same antibiotic for another 24 hours. If bacterial aetiology is identified, then treat according to the organism identified(if significant) If temperature settles for ≥ 48 and is haemodynamically stable since admission and no bacterial aetiology identified, then stop antibiotics after ≥72hrs, observe for at least 24-48hrs AND re-start IV antibiotics(first or second line as the case may be) if fever recurs If clinical deterioration at 48 hours or patient remains pyrexial after >96hrs of 1st line therapy then switch to second line therapy		
Antibiotic therapy	IV Meropenem 1g THREE times daily (if had Piperacillin/Tazobactam first line). **Following all other first line regimes, discuss with Microbiologist.**		

THIRD LINE	If temperature persists and patient continues to deteriorate after a further 5 days of 2nd line antibiotic therapy and no bacterial pathogen has been identified, repeat examination and investigate for fungal infections(see below) **OR** Where antifungal therapy is necessary because of possible invasive fungal infection, THEN consider antifungal therapy AND stop antibiotics after at least a total of 10 days (unless deep-seated infection) and continue to closely observe the patient and to re-start them if the patient deteriorates. Patients not responding to first line anti-fungal agents should be investigated for invasive aspergillosis and other fungal infections **AND** discussed with the Microbiologist • Bronchoalveolar lavage • Serum galactomannan assay & 1,3 β-D Glucan (may be repeated after 1 week if initially negative) • HRCT – halo sign and air-crescent sign • Transthoracic percutaneous biopsy	
Antifungal therapy **Invasive aspergillosis suspected**	Caspofungin 70mg loading dose , then 50mg once daily if <79kg or 70mg once daily if >80kg Administered by slow intravenous infusion over approximately one hour. Voriconazole IV 6mg/kg TWICE daily for 2 doses, then 4mg/kg TWICE daily **OR** Voriconazole orally 400mg TWICE daily for 2 doses, then 200mg TWICE daily Check trough level after 5 to 7 days and monitor LFTs	
Antiviral therapy	**Agent**	**Comments**
Suspected herpes simplex virus lesions	IV Aciclovir 5mg/kg THREE times daily	Use IBW for dosing if overweight (i.e. if >20% above IBW) Send swab in viral transport medium
Suspected varicella-zoster virus (chickenpox/shingles) infection	Aciclovir 10mg/kg 8-hourly by IV infusion	Use IBW for dosing if overweight (i.e. if >20% above IBW) Exposure to chickenpox/shingles – see Policy for management of chickenpox/shingles PAT/IC 15 v2

Comments

Suspected CMV infection- discuss investigation with Microbiologist

If RSV positive consider treatment with aerosolised Ribavirin

Table II : PROPHYLAXIS			
		AGENT	**CAUTION**
AML patients and Myelodysplastic Syndrome receiving intensive chemotherapy	**First line**	Posaconazole 100mg tablets **Dose:** 300mg TWICE daily on first day then 300mg once daily thereafter	Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with posaconazole should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm3.
	Second line (if patient not tolerating the tablets)	Posaconazole suspension 200mg/5ml **Dose:** 200mg THREE times daily The syrup should ideally be taken with food to increase absorption	
Haematological malignancy where patients are receiving severely immunosuppressive chemotherapy		Oral Aciclovir 400mg TWICE daily OR 200mg FOUR times daily	
AML patients receiving intensive chemotherapy with neutrophil count of 0.5 x 10^9/L or less and continue until resolution of neutropenia		Oral Ciprofloxacin 500mg TWICE daily	High risk of *Clostridium difficile* infection - if diarrhoea develops consider stopping

Appendix 1: Drug Dosing in Renal Impairment:

DRUG AND DOSE IN NORMAL RENAL FUNCTION	DOSE IN RENAL IMPAIRMENT
IV Piperacillin/Tazobactam 4.5g FOUR times daily	if CrCl = 20 to 40mls/min, reduce dose to 4.5g THREE times daily if CrCl ≤20ml/min, reduce dose to 4.5g TWICE daily
IV Meropenem 1g THREE times daily	if CrCl = 10 to 25mls/min, reduce dose to 1g BD if CrCl ≤10ml/min, reduce dose to 1g OD
IV Ciprofloxacin 400mg TWICE daily	if CrCl ≤10ml/min, reduce dose to 200mg TWICE daily
IV Teicoplanin 400mg TWICE daily for three doses then once daily	– see Guidelines for Use of Teicoplanin
IV Aciclovir 10mg/kg THREE times daily	If CrCl = 25 to 50mls/min, reduce dose to 10mg/kg TWICE daily If CrCl = 10 to 25ml/min, reduce dose 10mg/kg ONCE daily If CrCl < 10ml/min, reduce dose to 5mg/kg ONCE daily
IV Aciclovir 5mg/kg THREE times daily	If CrCl = 25 to 50mls/min, reduce dose to 5mg/kg TWICE daily If CrCl = 10 to 25ml/min, reduce dose 5mg/kg ONCE daily If CrCl < 10ml/min, reduce dose to 2.5mg/kg ONCE daily
Caspofungin	No dosage adjustment is necessary in renal impairment

Fig 1. Flow chart for first and second line antimicrobial management of febrile neutropenic sepsis