

Management of Haematology/Oncology & Blood and Marrow Transplant (BMT) Patients with Fever

These guidelines apply to the management of patients:

- with fever and neutropenia as a result of a known or suspected malignancy or the use of antineoplastics;
- BMT patients who present with fever or evidence of infection within 6 months of their transplant, regardless of their actual neutrophil count, and
- BMT patients who continue to receive immunosuppressant agents after transplant, regardless of their actual neutrophil count.

These guidelines may also be appropriate for children with fever or evidence of infection who are receiving antineoplastics or who have completed cancer therapy within 6 months **even though they are not neutropenic**. The necessity of initiating empiric antibiotic therapy in such cases is gauged by the severity of the presenting signs and symptoms, the results of initial investigations and the presence/absence of a central venous catheter (CVC). **CVC cultures (all lumens) must be drawn as part of this assessment.**

EMERGENCY DEPARTMENT MANAGEMENT

1. Obtain CBC and differential. Obtain blood cultures from all lumens of indwelling venous lines **AND** a peripheral site. Delay in antibiotic administration due to delay in obtaining peripheral cultures is not to be tolerated.
2. Consider antibiotic treatment as per Guidelines for Initial Empiric Antibiotic Therapy in Hospitalized Children (page _)if:
 - **absolute neutrophil count (ANC = sum of mature polymorphs and band forms) $\geq 0.5 \times 10^9/L$ and expected ANC nadir following antineoplastic administration has already been reached, or**
 - **patient is >6 months post BMT and is not taking immunosuppressant agents.**Follow subsequent protocol if:
 - **ANC $< 0.5 \times 10^9/L$, or**
 - **ANC $> 0.5 \times 10^9/L$ and expected ANC nadir following antineoplastic administration has not yet been reached, or**
 - **patient is < 6 months post BMT, or**
 - **patient is > 6 months post BMT and continues to take immunosuppressant agents.**
3. Stop all antineoplastics until discussed with the staff oncologist. Consider holding cotrimoxazole prophylaxis.
4. Start IV and give fluids at about 1.5 x maintenance rate.
5. Order a chest x-ray (if clinically warranted), renal function tests (creatinine, urinalysis) and the following cultures (in addition to CVC and peripheral cultures as noted above):
 - a) urine
 - b) any apparent site of infection

6. Always consider the patient's past history regarding resistance patterns of **previously cultured organisms** and clinical status (eg septic shock) when selecting antibiotics. Standard initial antibiotics for the stable patient as given below may not be appropriate in a patient who has a history of serious infection due to an antibiotic-resistant organism.
7. Catheter associated infection may present as fever related to manipulation of the CVC, infection at the catheter exit site or as infection along the subcutaneous course of the catheter. If this is the case, antibiotics directed at this site of infection (usually vancomycin) should be initiated IN ADDITION to the broad spectrum empiric antibiotic regimen below. If CVC cultures confirm infection, a full course of antibiotics, alternated through all lumens, is indicated. Removal of the catheter is often required. Consultation with Infectious Diseases is recommended to facilitate this decision.
8. Administer ANTIBIOTICS STAT (should be given prior to patient transfer to any other area and prior to administration of blood products):

STABLE PATIENTS:

No significant beta-lactam allergy:

TAZOCIN® (piperacillin-tazobactam)* 80 mg piperacillin/kg/dose IV q8h
(Max single dose: 4g) AND
GENTAMICIN <9 years: 10mg/kg/dose IV q24h
9 to <12 years: 8mg/kg/dose IV q24h
≥ 12 years: 6mg/kg/dose IV q24h

* Adjust dose for renal impairment.

- The combination of Tazocin® and gentamicin usually provides adequate empiric coverage against Gram positive organisms including viridans streptococci. However, if additional coverage against Gram positive organisms is desired, the addition of clindamycin is recommended. Consider discontinuation of clindamycin once culture and susceptibility results are available.

Significant beta-lactam allergy (ie anaphylaxis):

CIPROFLOXACIN* 10 mg/kg/dose IV q12h (Max single dose: 400mg)
GENTAMICIN dose as per above AND
CLINDAMYCIN 8 mg/kg/dose IV q8h (Max: 600mg/dose).

* Adjust dose for renal impairment.

- Consider discontinuation of clindamycin once culture and sensitivity results are available.

UNSTABLE PATIENT INCLUDING SEPSIS SYNDROME:

No significant beta lactam allergy:

MEROPENEM* 20 mg/kg/dose IV q8h (Max single dose: 1g)
GENTAMICIN dose as per above AND
VANCOMYCIN* 15 mg/kg/dose IV q6h (Max single dose: 1g)

* Adjust dose for renal impairment.

Significant beta lactam allergy (ie anaphylaxis):

CIPROFLOXACIN* 10 mg/kg/dose IV q12h (Max single dose: 400mg)

AMIKACIN 20 mg/kg/dose IV q24h AND

VANCOMYCIN* dose as above

* Adjust dose for renal impairment.

- Consider anaerobic coverage in patients who have signs of perirectal infection if not already receiving Tazocin® or meropenem.
- Consider discontinuation of vancomycin once culture and sensitivity results are available.

9. **Vital signs q1h until stable and then q4h and/or as indicated.**

10. Acetaminophen is the preferred antipyretic agent. Ibuprofen is not generally recommended for neutropenic patients.

11. Please contact the Haematology/Oncology fellow on call to discuss the patient. If the patient is stable this can wait until the next day.

MANAGEMENT ON THE NURSING UNIT

Antibiotic Management

- Continue antibiotic initiated in the Emergency Department or see Emergency Department management for antibiotic selection and dosing guidelines.
- Patients with **multi-lumen CVC's** should have their antibiotic therapy alternated among all lumens for the duration of antibiotic therapy.
- If **initial blood cultures (peripheral or central) are positive**, then repeat cultures should be drawn when this result becomes known. Antibiotics specifically directed toward the identified organism should ordinarily be **added to** the broad spectrum therapy if the initial antibiotics do not provide adequate coverage. Alternatively, the antibiotic regimen may be adjusted to provide BOTH broad-spectrum AND organism-specific coverage. **Broad spectrum coverage must not be replaced by organism-specific antibiotic(s) alone in the neutropenic patient.**
- Patients who remain febrile after initiation of appropriate antibiotic therapy ordinarily should have CVC cultures drawn no more than once daily. Peripheral cultures are of limited value at this point in therapy and should not be routinely drawn under most circumstances.

Gentamicin/Amikacin Concentration Monitoring

- "Special" concentrations should be ordered 3 hours and 6 hours after the FIRST dose of gentamicin or amikacin. The target back-extrapolated maximum concentration at the end of the infusion (C_{max}) is 20-25mg/L for gentamicin and 60-80mg/L for amikacin. A drug-free interval (DFI; period during which the gentamicin concentration is <2mg/L or the amikacin concentration is <4mg/L) of at least 4 hours should be targeted.
- Subsequently, "special" concentrations 3 hours and 6 hours after the dose should be ordered once weekly to verify that the target C_{max} and DFI continue to be achieved. If the patient is receiving concurrent nephrotoxic drugs (e.g. amphotericin, acyclovir) or has unstable renal function, assessment of "special" concentrations twice weekly may be warranted.

- The sample for the 3 hour concentration must be either a peripheral sample or, for patients who have a multi-lumen CVC, a sample from the lumen not used to give the aminoglycoside dose. The sample for the 6 hour concentration may be taken from the CVC.

Alternative Antibiotic Management

- **PATIENTS WHO ARE PERSISTENTLY FEBRILE** but **STABLE** should continue to receive the initial empiric antibiotic regimen described above. If the patient's condition indicates evolving infection at a particular site (e.g. abdominal pain, severe mucositis, pneumonia), antibiotics directed toward possible causative organisms should be added to the broad spectrum coverage. After 5 to 7 days of persistent fever, consider the addition of **AMPHOTERICIN**.
- **PATIENTS WHO DETERIORATE** (become hemodynamically unstable) or appear to be progressively deteriorating should be brought to the immediate attention of the Haematology/Oncology Fellow or Staff on-call. Please also request an Infectious Disease consult.

The empiric antibiotic regimen of these patients should be changed to:

No significant beta lactam allergy:

MEROPENEM* 20 mg/kg/dose IV q8h (Max single dose: 1g)

AMIKACIN 20 mg/kg/dose IV q24h AND

VANCOMYCIN* 15 mg/kg/dose IV q6h (Max single dose: 1g)

* Adjust dose for renal impairment

Significant beta lactam allergy (ie anaphylaxis):

CIPROFLOXACIN* 10 mg/kg/dose IV q12h (Max single dose:400mg)

AMIKACIN dose as above AND

VANCOMYCIN* dose as above

* Adjust dose for renal impairment

- Consider the addition of **AMPHOTERICIN** after 5 to 7 days of persistent fever.

DURATION OF ANTIBIOTIC THERAPY

PATIENT PARAMETERS	PLAN
Afebrile, ANC > 0.5 x 10 ⁹ /L, cultures negative	DISCONTINUE antibiotics
Afebrile, ANC < 0.5 x 10 ⁹ /L, cultures negative, IV antibiotic duration ≥ 48 hours	CONSIDER <i>discontinuing antibiotics</i> (see criteria in Management on Discharge section)
Afebrile, ANC < 0.5 x 10 ⁹ /L, cultures negative, IV antibiotic duration > 7 days	CONSIDER discontinuing antibiotics
Afebrile, ANC > 0.5 x 10 ⁹ /L, cultures positive	CONSIDER discontinuing broad spectrum coverage, CONTINUE specific therapy

DISCHARGE CONSIDERATIONS

After a minimum of 48 hours of IV antibiotic therapy, it may be reasonable to consider stopping antibiotics and discharging patients who meet the following criteria, even though the ANC is less than 0.5 x 10⁹/L:

1. not on induction therapy for a malignancy known to significantly involve the bone marrow;
2. did not present with clinical sepsis;
3. negative blood cultures (CVC and peripheral);
4. afebrile for a minimum of 24 hours;
5. fever did not persist beyond 96 hours;
6. clinically well and not in need of other inpatient care;
7. evidence of bone marrow recovery: increased monocyte, increased neutrophil or increased platelet counts; and
8. no known or suspected non-compliance with follow-up instructions.

Discharge of patients with **localized sites of infection** and who meet the above criteria should be considered on a case by case basis.

NOTE: It is not necessary to keep the patient in hospital for 24 hours following discontinuation of IV therapy. Families must be advised to continue strict follow-up with their treatment team. Any recurrence of fever should be approached as a *de novo* fever in an immunocompromised host and requires immediate evaluation.

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