Recommendation for management of febrile neutropenia in AML

Febrile neutropenia in AML is a high-risk medical emergency and individualisation of management is often warranted. This recommendation is to be viewed as a guideline and a safeguard for adequate work-up, monitoring and treatment but cannot replace the careful monitoring and judgement of the patient by an experienced pediatric oncologist. The recommendations can also be applied to other high-risk febrile neutropenias such as those occuring during intensive treatment for ALL or in patients undergoing stem cell transplantation.

The recommendations have been made by the Nordic AML group.

Febrile neutropenia in AML is a medical emergency

Goal to start iv therapy within 30 minutes in septic patients else in 60 minutes*

Fever ≥ 38,5 once or sustained ≥ 38 one hour
Don't wait for neutrophil results in high-risk patients

Vital parameters
SpO_2, blood pressure, respiratory rate, heart rate, capillary refill
Blood count, electrolytes, creatinine, inflammatory parameter, lactate
Cultures blood, urine (no delay)
In septic patients blood gas, tests for DIC, liver function
consider need of fluid bolus (20 ml/kg) immediately

Broad-spectrum antibiotics
Very careful monitoring the first 4-6 hours

* Fletcher M et al Prompt administration of antibiotics is associated with improved outcomes in febrile neutropenia in children. Ped Blood & Cancer 2013 60:1299

Choice of first antibiotic

- Antipseudomonal ß-lactam (APP) or meropenem as monotherapy* (Lehrnbecher et al JCO 2012) (1A)**

- Meronem 20 mg/kg q4 (max dose 1g)
  OR
- Piperacillin/tazobactam most commonly used APP
  Dose Pip/Taz 80 (-100) mg/kg q4 (max dose 4g/dose)

- Cefepime and ceftazidime inferior***

- Never use older generation cephalosporins

* Lehrnbecher T et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation. J Clin Oncol 2012 30:4427
** Parentheses indicate GRADE strength of recommendation (1, strong; 2, weak) and quality of evidence (A, high; B, moderate; C, low or very low).
*** Paul M et al. Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. Cochrane Database Sys Rev 2010 Nov 10

Addition of antibiotics

- **In clinically unstable patients** -
  Add aminoglycoside and/or glycopeptide already initially (also when a resistant disease is suspected) (1B)

- The second drug can be discontinued in patients who improve after 24-72 hours if cultures or clinical evaluation don't give reason to continue (1B)

- Persisting fever in stable and well patients does not necessitate addition (1C) but in unstable patients coverage against resistant G+, G- and anaerobic infection should be added (1C)

- If suspicion of clostridium infection add metronidazole

- Note that viridans streptococci may have reduced sensitivity to ß-lactams*

- Vancomycin can be given as 20 mg/kg q3

- Aminoglycoside as single dose is effective and allows excellent monitoring by serum concentrations after 8 hours

* Shelburne SA et al. In vitro killing of community-associated methicillin resistant Staphylococcal aureus with drug combinations. Clin Infect Dis 2014 59:223. Freifeld AG et al. Viridans group streptococci in febrile neutropenic cancer patients. What should we fear? Clin Infect Dis 2014 59:231.

Addition of antifungal therapy

- All AML patients are high-risk for invasive fungal infection.
- Start empiric therapy with agent active against molds if fever persists 72-96 hours.
- Liposomal amphotericin B or caspofungin recommended
- Galactomannane in serum, blood culture for fungi in all
  Consider computed tomography of lungs
- U-arabinitol can help in *Candida albicans* infections
  Beta-D-glucan can be of value but false positives common.
  Beta-D-glucan very sensitive test for *Pneumocystis Jiroveci*.

Monitoring of an episode

- Very important to early detect clinical deterioration. Scheduled monitoring of vital parameters including diuresis.

- Assess clinical signs of focality at least daily

- Careful homeostasis beneficial including fluid status, electrolytes, glucose. Consider albumin substitution if edema, low urinary output and hypoalbuminemia. Measure lactate and blood gas frequently in unstable patients

- Monitor inflammatory parameters (CRP, procalcitonin and/or cytokines).

- Assess kidney and liver function and coagulation abnormalities regularly

- Physiotherapy to all with respiratory compromise. Early consultation with pediatric anaesthesiologist in patients with increasing oxygen requirement. Consider high-flow nasal prong therapy.

- Monitor drug concentrations of aminoglycosides and glycopeptides

Further investigations

- **Repeat blood cultures** in febrile patients. Maintain good cooperation with the microbiology laboratory to ensure rapid culture results. Be prepared to add coverage (eg Colistin) for ESBL/carbapenemase producing bacteria.

- Chest X ray not routinely required but should be done in all with respiratory signs and in those with persistent fever. CT recommended if fungal infection suspected.

- Test for bacteria, viruses and chlostridium in stools in those with abdominal symptoms
  Test for viruses, *Pneumocystis Jiroveci*, atypical bacteria in nasal swabs for those with respiratory signs
  Consider viral testing in mucositis

- In cases with abdominal pain consider CT (ultrasound + plain Xray) to detect typhlitis

- Echocardiography in unstable patients

- In prolonged episodes or patients with rash and/or abnormal liver tests check for CMV, EBV and adenovirus in blood

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