

**Guideline for the Evaluation and Treatment
of Immunocompromised Pediatric Inpatients with Fever**

NOTE: There is a **separate guideline** on the CG ED website for management of children seen in the ED with Fever and Neutropenia (<https://resources.ssmhealth.com/CGClinicalGuidelines/neutropenic-fever-ED-clinical-practice-guideline.pdf>). Although there is some overlap between the two guidelines, this guideline is oriented towards those children who have been admitted to the inpatient units.

- 1) This guideline was designed for immunocompromised pediatric inpatients where there is concern for infection.
 - a. For the purposes of this guideline, immunocompromised is defined as:
 - i. Currently neutropenic (i.e. absolute neutrophil count < 500/mcL)
 - ii. At imminent risk of developing neutropenia
 - absolute neutrophil count of 500 - 1,000/mcL with anticipated decrease due to myelosuppressive chemotherapy within last three weeks; or
 - in the context of chronic disease states like aplastic anemia or congenital neutropenia
 - iii. Asplenia (including patients with sickle hemoglobinopathies)
 - iv. <1 year s/p stem cell transplant (or later if still receiving immunosuppressive therapy)
 - v. Other patients with primary immune deficiency (e.g., SIFD), those on immune suppression (e.g., chronic steroids for Diamond Blackfan anemia, or patients with chronic immune-mediated cytopenias requiring multiple immune suppressive agents)
 - vi. Calculation of Absolute Neutrophil Count (ANC):
 - $ANC = 10 \times (\text{total WBC, in thousands/mcL}) \times (\% \text{ polys} + \% \text{ bands})$; example:
 - total wbc 5.6 with 34% polys and 2% bands: $ANC = 10 \times 5.6 \times (34 + 2) = 2016$
 - vii. Calculation of Absolute Phagocyte Count (APC):
 - $APC = 10 \times (\text{total WBC, in thousands/mcL}) \times (\% \text{ polys} + \% \text{ bands} + \% \text{ monos})$.
 - Note: significant monocytosis is usually a sign of early marrow recovery and is associated with a decreased risk of invasive bacterial disease, except in patients with myelo-monocytic leukemia that are not in remission
 - b. For the purposes of this guideline, concern for infection is defined as
 - i. Signs or symptoms of infection regardless of temperature; *or*
 - ii. Fever:

- For patients at risk of neutropenia (defined as ANC < 500/mcL), with a central venous catheter, who have anatomic or functional asplenia (including any child with sickle cell disease), or who are s/p stem cell transplant, fever is defined as:
 - a. Single temperature $\geq 101^{\circ}$ F; *or*
 - b. Two temperatures (separated by at least 60 minutes) of $\geq 100.4^{\circ}$ F within last 24 hours
- 2) A separate guideline for children seen in the Emergency Department with fever and neutropenia is available on: <https://resources.ssmhealth.com/CGClinicalGuidelines/neutropenic-fever-ED-clinical-practice-guideline.pdf>

Initial Evaluation:

- 1) Complete physical exam: including vital signs, examination of skin, oral cavity, perineum, central venous access site, etc. **No rectal exams** for patients with suspected/known neutropenia.
- 2) CBC: including differential and platelet count
- 3) Blood cultures from all ports of central venous access device
- 4) Culture of clinically suspected foci (e.g., abscess) if feasible
- 5) Urinalysis and urine culture only if there are symptoms of UTI
- 6) Throat culture with rapid strep testing only if there is sore throat. Not indicated if patient has sore throat as part of oral mucositis following chemotherapy
- 7) Chest radiograph if there are pulmonary symptoms (cough, chest pain, shortness of breath), positive findings on physical exam (rales, rhonchi, wheezes, decreased breath sounds), or decreased oxygen saturation
- 8) NP swab for respiratory PCR panel for all patients with respiratory symptoms

Treatment:

- 1) For patients in the ED, an initial dose of **ceftriaxone** is appropriate pending CBC results; **ceftazidime** may be substituted if the patient is known to be neutropenic from a recent CBC (see drug dosages at bottom of guideline).
- 2) For non-neutropenic patients with suspected or documented infection, the antibiotic regimen will depend on the clinical situation (including decision regarding inpatient vs. outpatient therapy).
- 3) Admit and continue empiric treatment with IV antibiotics based on **any** of the following criteria:
 - a. Child appears ill, regardless of temperature or ANC; *or*
 - b. Child appears well but has an obvious source of infection that requires intravenous therapy; *or*
 - c. Either Tmax $\geq 101^{\circ}$ F *or* Tmax $\geq 100.4 \times 2$ within 24 hours) **and**
 - i. ANC < 500/mcL; *or*
 - ii. History of stem cell transplant in past 12 months; *or*
 - iii. s/p allogeneic stem cell transplant on continued immunosuppressive therapy
- 4) Suggested initial antibiotic coverage for patients with neutropenic fever:
 - a. **Initial therapy** (drug dosages at bottom of guideline)

- i. Hemodynamically stable: **ceftazidime**
 - ii. Hemodynamically unstable or ill appearing: **meropenem ± vancomycin ± amikacin**
 - 1. Note: Based on our local antibiogram, there is a modest benefit of amikacin when compared to other aminoglycosides for gram negative coverage
- b. **Special Considerations** (drug dosages at bottom of guideline)
- i. **Mucositis**
 - 1. Antibiotic regimen should include increased anaerobic coverage. Suitable regimens include:
 - a. monotherapy with **piperacillin/tazobactam** OR
 - b. monotherapy with **meropenem** OR
 - c. combination therapy with either **cefepime/metronidazole** or **cefepime/clindamycin**
 - 2. Consider need for coverage of *Candida* spp., *Aspergillus* spp., and/or HSV
 - 3. Specific length of therapy has not been established for mucositis
 - ii. **Typhlitis** (neutropenic colitis)
 - 1. Suitable antibiotic regimens include:
 - a. **piperacillin/tazobactam** OR
 - b. **meropenem** OR
 - c. **cefepime/metronidazole**
 - d. **NOTE:** if possible, avoid using piperacillin/tazobactam with other nephrotoxic drugs (e.g. vancomycin, IV contrast)
 - 2. **Metronidazole** should be part of regimen if there is evidence of *C. difficile* colitis
 - 3. Length of therapy should continue 2 weeks after recovery from neutropenia
 - 4. Consider switch to oral **ciprofloxacin PLUS metronidazole** after recovery of neutropenia
 - iii. **Vancomycin** should be added to initial therapy (as above) to provide additional gram-positive coverage for any of the following scenarios:
 - 1. Cellulitis or abscess
 - 2. Proven or suspected meningitis or CNS shunt infection
 - 3. History of treatment with high dose Ara-C within the last three weeks (due to increased risk of infection with alpha-hemolytic streptococci)
 - iv. If prior infection or colonization with *Stenotrophomonas* spp., consider adding **TMP-SMX** to the initial therapy regimen (as above)
 - v. If prior infection or colonization with VRE, consider adding **linezolid** to the initial therapy regimen (as above) Caution: risk of myelosuppression with linezolid
 - vi. **Fluconazole** (IV or PO) is recommended for patients with oral candidal lesions, or with esophageal candidiasis either documented by endoscopy or suspected on clinical grounds (e.g., significant dysphagia in the absence of oral mucositis).

- vii. **Acyclovir** should be given to patients with suspected or documented HSV or VZV infections, e.g. those with blistering eruptions.
 - b. If possible, antibiotics should be rotated among all lumens of multi-lumen central venous catheters.
- 4) Modifications of therapy
- a. ***When should antifungal therapy be added?***
 - i. Positive culture for yeast/mold;
 - ii. If persistent fever and neutropenia after 96 hours and **high risk neutropenic fever** (AML, relapsed ALL, highly myelosuppressive chemo or long-term corticosteroids, post allogeneic stem cell transplant);
 - iii. Consider adding empiric antifungal therapy if:
 - 1. new or continued hemodynamic instability despite antibiotics (i.e., critically ill patients)
 - 2. imaging or exam suggestive of fungal disease
 - 3. persistent fever and neutropenia after 96 hours and **low risk** (defined as any patient who does not meet the above-mentioned high-risk criteria)
 - 4. positive galactomannan assay (or other non-culture based fungal diagnostic test)
 - b. ***Which antifungal agent should be added?***
 - i. Start **micafungin** if concern for candidemia
 - ii. Voriconazole should be started if concern for *Aspergillus* spp. (high risk neutropenic fever, s/p allogeneic stem cell transplant, anticipated duration of neutropenia >2 weeks)
 - iii. Consider starting **liposomal amphotericin B** if
 - 1. already on an azole or micafungin for home prophylaxis
 - 2. clinical or imaging concern for *Mucor* spp.
 - iv. **NOTE:** we do not recommend the routine combination of an echinocandin and an azole for empiric antifungal treatment. However, double coverage may be necessary until it can be demonstrated that the azole has reached a therapeutic level.
 - c. ***When should the empiric antibiotic regimen be broadened?***
 - i. ***When should ceftazidime be broadened to meropenem?***
 - 1. If hemodynamically unstable (or ill appearing): switch to **meropenem**, strongly consider addition of **vancomycin and/or amikacin**
 - 2. If a culture is positive for an organism that requires **meropenem**
 - 3. If concern for intraabdominal infection or typhlitis (see above section of guideline)
 - 4. **NOTE:** we do not recommend routinely broadening to meropenem based on prolonged fever alone, however certain high risk patients may require a broader antibiotic regimen.

- ii. ***When should vancomycin be added to regimen?***
 1. If patient develops cellulitis, abscess or evidence of central line site infection (tunnel infection)
 2. If culture is positive for an organism that requires vancomycin, or if a gram stain shows an organism that may require vancomycin (e.g. gram positive cocci in clusters)
 3. If hemodynamically unstable (or ill appearing), as above, along with consideration of adding Amikacin and switching to meropenem
 4. Proven or suspected meningitis or CNS shunt infection
 5. History of treatment with high dose Ara-C within the last three weeks
 6. NOTE: some experts recommend adding **vancomycin** to the antibiotic regimen in patients that have received fluoroquinolones in the past 72 hours given increased risk of alpha-hemolytic streptococci (Allen et al.)
 7. In patients with surgical site/prosthetic infections, or in patients with recent orthopedic or neurosurgery procedures.
- d. ***When should therapy be deescalated or narrowed after it has previously been broadened?***
 - i. For patients whose coverage has been broadened from ceftazidime to meropenem, de-escalation back to ceftazidime should be considered after 48 hours if:
 1. no specific disease process has been identified that requires meropenem; *and*
 2. no specific organism has been identified that requires meropenem
 3. NOTE: certain high risk patients (particularly those with possible typhlitis), may require prolonged empiric meropenem if improvement is seen after broadening therapy
 - ii. For patients started on empiric amikacin for critical illness, this drug should be discontinued at the same time as meropenem is de-escalated to ceftazidime (see iv. below)
 - iii. For patients who are started on empiric vancomycin, this drug should generally be discontinued after 48-72 hours if no evidence of gram positive infection
 - iv. **NOTE:** for patients on multiple broad-spectrum antibiotics, it may be prudent to discontinue or change one antibiotic at a time
- e. ***When should all IV antibiotics be discontinued or stepped down to oral therapy?***
 - i. **Neutropenic patient:**
 1. Patient is afebrile (<101° F) for ≥ 24 hours; *and*
 2. At least the initial set of cultures have been negative for ≥ 48 hours; *and*
 3. ANC is rising
 4. If ANC is not rising, for selected patients, consider discontinuation with overnight observation after patient is afebrile for ≥ 48 hours and all cultures are negative for ≥ 72 hours.
 - ii. **Non-neutropenic patient:**

1. patient is afebrile (<101° F) for ≥24 hours; *and*
 2. At least the initial set of cultures have been negative for ≥ 48 hours
 3. If fevers persist but cultures are negative and the patient is clinically stable, consider discontinuation and overnight observation after 72 hours
 4. Note: clinically stable non-neutropenic patients with a low clinical risk for bacteremia and reliable social situation can be considered for earlier discharge after a second dose of ceftriaxone, ± continued oral therapy
- iii. Choice of oral antibiotic: levofloxacin is preferred due to its broader gram positive coverage when compared to ciprofloxacin. The latter may be used if insurance does not cover levofloxacin.
- 5) Pediatric Infectious Disease consultation should be considered in patients with:
- a. Positive blood cultures, especially with unusual organisms
 - b. Hemodynamic instability
 - c. Suspected or documented opportunistic infections
 - d. Allergy to front-line antibiotics
 - e. Signs or symptoms of CNS infection or complex focal infection
- 6) Additional evaluation and treatment considerations:
- a. Repeat central blood cultures should be obtained for patients who:
 - i. Have a temperature spike of ≥101° F (once per 24 hour period unless there are specific signs of symptoms of bacteremia as defined below), *or*
 - ii. A fever <101° F with signs and symptoms of bacteremia (e.g. shaking chills, new murmur, embolic phenomenon, hypotension, etc.)
 - b. Bronchoalveolar lavage should be considered in neutropenic patients with pulmonary infiltrates or with persistent/unexplained respiratory symptoms in order to look for opportunistic infections (*Pneumocystis jiroveci* pneumonia, *Legionella*, fungus). Empiric coverage with azithromycin, voriconazole, and/or amphotericin B pending results of the lavage should be considered, depending on the patient's clinical status. TMP/SMX can also be considered if patient has not been compliant with PJP prophylaxis, but myelosuppression limits use in this context. Consider a Pediatric Infectious Disease consult in these situations.
 - c. Other diagnostic studies to consider in persistently febrile or critically ill patients may include ophthalmologic exam, cardiac ultrasound, and CT scan of abdomen/chest/sinuses to look for foci of infection.
 - d. Removal of central venous access catheters is indicated for:
 - i. Fungal bacteremia or sepsis
 - ii. Persistent bacteremia despite adequate intravenous antibiotic therapy
 - iii. Porta-Cath pocket infection
 - iv. Significant tunnel infections of Hickman/Broviac catheters
 - v. Removal should be considered in a critically ill patient with presumptive sepsis unresponsive to initial therapy

- vi. For a more comprehensive approach to central line infections see the IDSA guideline (Mermel et al. 2009)
- 7) **Patients with documented bacteremia** should be treated with intravenous antibiotics for a total of 10 - 14 days. Choice of antibiotics should be guided by identification of organism and sensitivities. Clearance of bacteremia should be confirmed with surveillance cultures obtained ≥ 24 hours after the initiation of appropriate antibiotic coverage; surveillance cultures should be repeated following completion of antibiotic therapy if the patient's CVL (or other foreign body, such as VP shunt) is left in place. Persistent/recurrent bacteremia usually mandates removal of CVL.
- 8) Patients with suspected or documented fungal infections or other non-bacterial opportunistic infections should receive therapy for a duration as recommended by Pediatric Infectious Diseases.

References

- 1) Allan R. Tunkel, Kent A. Sepkowitz; Infections Caused by Viridans Streptococci in Patients with Neutropenia, *Clinical Infectious Diseases*, Volume 34, Issue 11, 1 June 2002, Pages 1524–1529, <https://doi.org/10.1086/340402>
- 2) Alison G. Freifeld, Eric J. Bow, Kent A. Sepkowitz, Michael J. Boeckh, James I. Ito, Craig A. Mullen, Issam I. Raad, Kenneth V. Rolston, Jo-Anne H. Young, John R. Wingard; Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America, *Clinical Infectious Diseases*, Volume 52, Issue 4, 15 February 2011, Pages e56–e93, <https://doi.org/10.1093/cid/cir073>
- 3) Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update Thomas Lehrnbecher, Paula Robinson, Brian Fisher, Sarah Alexander, Roland A. Ammann, Melissa Beauchemin, Fabianne Carlesse, Andreas H. Groll, Gabrielle M. Haeusler, Maria Santolaya, William J. Steinbach, Elio Castagnola, Bonnie L. Davis, L. Lee Dupuis, Aditya H. Gaur, Wim J.E. Tissing, Theo Zaoutis, Robert Phillips, and Lillian Sung. *Journal of Clinical Oncology*. 2017 35:18, 2082-2094
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Antimicrobial Dosing Table

Dosing does not apply to the neonatal age group. Consult Neofax for appropriate neonatal dosing

Drug	Dose	Maximum	Comments
Ceftriaxone	50 –100 mg/kg/day q12-24h	2 g per dose; 4 g per day	Caution in patients with TPN or Calcium containing fluids or elevated bilirubin levels
Ceftazidime	150 mg/kg/day divided q8h	2 g per dose	Dose adjustments required for renal impairment (GFR <50 mL/min/1.73 m ²)
Cefepime	150 mg/kg/day divided q8h	2 g per dose	Dose adjustments required for renal impairment (GFR <50 mL/min/1.73 m ²)
Piperacillin/tazobactam	300 mg/kg/day of piperacillin divided q8h >40 kg: 3 g piperacillin q6h	3 g per dose	Dose adjustments required for renal impairment (GFR <50 mL/min/1.73 m ²)
Meropenem	60 mg/kg/day divided q8h	2 g per dose	Dose adjustments required for renal impairment (GFR <50 mL/min/1.73 m ²)
Metronidazole	30-40 mg/kg/day IV divided q8h	500 mg per dose	Renal dose adjustment if GFR <10 mL/min/1.73m ²
Clindamycin	40 mg/kg/day IV divided q8h	Usual max 600 mg per dose	No renal dose adjustments
Vancomycin	Dose per Pharmacy Protocol (usual initial dosing 15-20 mg/kg/dose q6-8h)	Initial max 1500 mg per dose	Dose adjustments required for renal impairment (GFR <50 mL/min/1.73 m ²) Therapeutic drug monitoring required; nephrotoxic agent
Ciprofloxacin	30-40 mg/kg/day IV divided q12h Adults: 400 mg IV q8h	400 mg per dose	Dose adjustments required for renal impairment (GFR <30 mL/min/1.73 m ²)
Sulfamethoxazole-Trimethoprim	15-20 mg trimethoprim/kg/day IV divided q6h 8-12 mg/kg/day PO divided bid	Max PO dose: 320 mg TMP	Dose adjustments required for renal impairment (GFR <30 mL/min/1.73 m ²) Caution short stability of IV SMX-TMP and high fluid burden of IV doses
Linezolid	<12 yo: 30 mg/kg/day divided TID ≥12 yo: 20 mg/kg/day divided BID	600 mg per dose	Renal dose adjustment with dialysis
Amikacin	Dose per pharmacy protocol 22.5 mg/kg/day divided q8h		Therapeutic drug monitoring required Dose adjustments required for renal impairment (GFR <50 mL/min/1.73m ²); nephrotoxic and ototoxic agent
Azithromycin	Dose and regimen dependent on suspected infection. Usual dose 10 mg/kg x 1 day followed by 5 mg/kg x 4 days (IV or PO)	Usual max 500 mg per dose	Use with caution with GFR <10 mL/min/1.73 m ²
Antifungals			
Fluconazole	IV or PO:	800 mg per day on Day 1	Dose adjustments required for renal impairment (GFR

	12 mg/kg/day on day 1 followed by 12 mg/kg/day in 1-2 divided doses	600 mg per day on subsequent days	<30 mL/min/1.73 m ²)
Micafungin	Infants ≥ 4 mo and <15kg: 5-7 mg/kg/day IV once daily Children 2-8 yo and ≤40 kg: 3-4 mg/kg IV once daily >40 kg: 150 mg IV once daily	150 mg per dose	No renal dose adjustments
Amphotericin B liposomal (Ambisome)	3 mg/kg/day IV once daily (up to 5 mg/kg/day)		Infusion reactions; pre-med with acetaminophen and diphenhydramine or Hydrocortisone For rigors: consider meperidine No renal dose adjustments; monitor for nephrotoxicity
Voriconazole	<2 yo: 9 mg/kg/dose IV every 12 h PO: 9 mg/kg every 12h 2 to <12 yo: 9 mg/kg/dose IV every 12 h x 2 doses, then 8 mg/kg IV every 12 h PO: 9 mg/kg every 12h; max 350 mg per dose 12-14 yo <50 kg: 9 mg/kg/dose IV every 12 h x 2 doses, then 8 mg/kg IV every 12 h PO: 9 mg/kg every 12h, max 350 mg per dose ≥50 kg: 6 mg/kg/dose IV every 12 h x 2 doses, then 4 mg/kg IV every 12 h PO: 200 mg q12h ≥ 15 yo: 6 mg/kg/dose IV every 12 h x 2 doses, then 4 mg/kg IV every 12 h PO: 200 mg q12h		Therapeutic Drug monitoring required GFR <50 mL/min: consider using PO due to potential accumulation of cyclodextrin from IV formulation Monitor liver function Monitor for drug interactions: doses of voriconazole or interacting drugs may need modification.
<u>Anti-virals</u>			
Acyclovir	30 mg/kg/day IV divided q8h 1000 mg PO per day divided in 3-5 doses	80 mg/kg/day	For mucocutaneous herpes lesions suspected in immunocompromised host Dose adjustments required for renal impairment (GFR <25 mL/min/1.73 m ²) Consult dosing handbook (e.g, Lexicomp) for dosing for other indications