ONCOLOGY MANAGEMENT OF FEBRILE NEUTROPENIA GUIDELINE
PRIMARY USE: HEMATOLOGY/ONCOLOGY & INFECTIOUS DISESASES

Definition: Febrile neutropenia (FN) is defined as a period in which a patient with cancer is at increased risk of infectious complications and antimicrobial therapy is necessary. Neutropenia is defined as an absolute neutrophil count (ANC) less than 500/mm^3 or expected decline to less than 500/mm^3 in 48 hours. Fever is defined as a single oral or axillary temperature greater than 38.3°C (101°F) or two oral or axillary temperatures greater than 38.0°C (100.4°F) in one hour.[1-4]

Incidence: FN remains a frequent cause of hospitalization in children treated for cancer. With good supportive care, mortality during FN is now of the order 1–3%. Less than 50% of children show a clinical or microbiological focus of infection during FN and the incidence of severe adverse outcomes such as intensive care admission and death is low. Thus the focus of care has shifted to management by risk stratification, potentially allowing a reduction in the intensity and/or duration of therapy in low risk patients.[5]

Etiology: The etiology of febrile neutropenia episodes may be noninfectious, bacterial, viral, or fungal. The most common gram positive bacterial pathogens include *staphylococci* spp., *viridans streptococci*, and *enterococci* spp.. The most common gram negative bacterial pathogens include *E. coli* and *P. aeruginosa*. Anaerobic bacteria are less commonly isolated. The most common fungal pathogens are *Candida* spp. and *Aspergillus* spp.. Mucormycosis group are other fungal pathogen isolated less frequently. The most common viral pathogens include respiratory pathogens and those causing gastroenteritis.[3,6]

Guideline Inclusion Criteria:

Patients with a cancer diagnosis presenting in an outpatient clinic, emergency department, or hospitalized with the following symptoms:

1) Fever is defined as a single oral or axillary temperature greater than 38.3°C (101°F) **OR** two oral or axillary temperatures greater than 38.0°C (100.4°F) in one hour.
2) Neutropenia defined as ANC < 500/mm^3 or expected decline to < 500/mm^3 in the next 48 hours as determined by the treating oncologist.
3) Actively receiving treatment or within 6 months of completing treatment for the cancer diagnosis

Guideline Exclusion Criteria:

- Patients with diagnosis of aplastic anemia due to no expected bone marrow recovery within a reasonable time period.
- Acquired or congenital bone marrow failure syndrome (e.g. Diamond-Blackfan anemia, congenital neutropenia including Kostmann syndrome, Fanconi anemia, Shwachman-Diamond syndrome).
- Lack of oncology diagnosis (i.e. viral suppression)

Diagnostic Evaluation:[1-4]

The evaluation of children with fever and neutropenia needs to be complete and completed as quickly as possible.

Blood cultures obtained during the evaluation of fever and neutropenia are important. Most pediatric patients undergoing chemotherapy treatment have indwelling intravenous catheters; it is essential to obtain a blood culture from every lumen of the central venous line (CVL). Consider obtaining a peripheral blood culture at the same time. Blood cultures should be obtained at the time of presentation and approximately every 24 hours with persistent fever and/or positive blood cultures.[7,8]

Urinalysis and urine culture should be considered if able to obtain a clean catch specimen (non-catheterized), before initiation of antibiotics. However, urine collection should not delay treatment.

Chest radiography should be considered for children with fever and neutropenia who have respiratory symptoms.

Viral swabs, stool tests and wound cultures should be guided by presenting symptoms.

Comprehensive metabolic panel (CMP) and complete blood count (CBC) should be obtained, at the time of presentation for every patient. Antibiotic therapy should not be delayed while awaiting results.

History: Assess for[1-4]

- Date of last chemotherapy treatment and details of therapy.
- Onset of fever and highest temperature, history of preceding low grade fever. Use of antipyretics.
- Other symptoms as diarrhea, nausea, vomiting, pain (oral, abdominal, rectal), rash, drainage, cough, rhinorrhea.
- Prior history of infections, organism cultured and site of infection.
- Previous history of infection methicillin-resistant staphylococcus aureus (MRSA) or multi-drug resistant organism (MDRO).

Physical Examination:[1-4]

- Assess for signs and symptoms of shock. Review vital signs.
- Detailed exam of entire body looking for signs and symptoms of local infection.
- Examine CVL site for evidence of redness or drainage.

Imaging Tests:

On admission:[1-4]

- Obtain chest radiography (CXR) in patient with respiratory symptoms.
- Obtain abdominal ultrasound (US) in patient with abdominal pain.

Persistent fever (fever duration ≥ 96 hours) or recurrent fever (new fever after 24-48 afebrile period) while recovering from neutropenia:[15-19]

- Consider chest computed tomographic scan (CT) after one week (7 days) of empiric antimicrobial therapy with persistent daily fevers.[5]
- Consider abdominal CT scan in patient with recurrent fever when recovering from neutropenia.[5]
- Do not recommend pelvic CT scan as it is not generally valuable diagnostically given the risks associated with additional radiation exposure.

Laboratory Tests:[1-4]

- If CVL in place, obtain blood culture at onset of fever from all lumens.
- Consider peripheral-blood cultures concurrent with obtaining CVL cultures.
- Obtain a CMP and CBC.
- Consider urinalysis and urine culture, if able to obtain clean catch (non-catheterized specimen).
- Consider respiratory studies in symptomatic patients: nasal wash for respiratory studies by rapid antigen, DFA, and/or PCR, throat swab.
- Consider stool studies in symptomatic patients: bacterial, viral studies or *clostridium difficile* testing.
- Do not use β-D Glucan assay (Fungitell®) for prospective monitoring of invasive fungal disease.[13,14]
- If completed, obtain galactomannan testing in bronchoalveolar lavage (BAL) and cerebrospinal fluid in patients at high risk for invasive fungal disease in symptomatic patients.

Critical Points of Evidence

Evidence Supports

Blood cultures obtained during the evaluation of fever and neutropenia. If an indwelling intravenous catheter is present it is essential to obtain a blood culture from every lumen of the CVL.[1-4]

Use of antipseudomonal B-lactam monotherapy as empiric therapy in febrile neutropenic patients.[1-4, 20]

No change to empiric antibiotics in patients who are clinically stable with persistent fever.[1-4,21,22]

Initiation of empiric antifungal therapy in patients at high risk of invasive fungal disease experiencing persistent or recurrent fever ≥ 96 hours despite broad spectrum antibiotic therapy with an unclear etiology.[1-4]

Management of patients experiencing low risk febrile neutropenia episodes in the outpatient setting without evidence of bone marrow recovery with oral antibiotics.[23-32]

Evidence Lacking/Inconclusive

Consider not using serum Galactomannan.[3]

Optimal timing of imaging of chest or abdomen in patients with persistent or recurrent fever with neutropenia.[1-4, 15-19]

Optimal timing to discontinue or de-escalate empiric antibiotics in high risk febrile neutropenia episode patients.[33-40]

When to initiate antifungal therapy and which antifungal agent to select in patients at low risk of invasive fungal disease.[1-4,41-42]

Optimal timing to discontinue empiric antifungal therapy.[1-4,41-42]

Evidence Against

Routine use of pelvic CT in patients with persistent and recurrent fever with neutropenia.[1-4,15-19]

Routine use β-D Glucan assay (Fungitell®) for prospective monitoring of invasive fungal disease in all patients.[1-4,13,14]

Practice Recommendations and Clinical Management

ADMISSION AND DISCHARGE CRITERIA FOR LOW AND HIGH RISK FEBRILE NEUTROPENIA EPISODES

1) Any cancer patient experiencing a febrile neutropenia episode will be admitted to the hospital for intravenous antibiotics for a minimum of 36 hours. If already admitted, intravenous antibiotics will be continued for a minimum of 36-48 hours.[5]

(Strong recommendation, moderate-quality evidence)

2) Utilize a risk stratification strategy to identify patients at low and high risk of infectious complications (i.e. bacteremia, significant bacterial infection) that includes patient-specific factors, treatment-specific factors, and episode-specific factors which can be assessed by providers at the time of presentation. Patients with one or more patient-specific factors, treatment-specific factors, and/or episode-specific factors are considered a high risk febrile neutropenia episode. Patients without any patient-specific factors, treatment-specific factors, and/or episode-specific factors are considered to be a low risk febrile neutropenia episode.[1-5]

(Strong recommendation, low-quality evidence)

- Patient-specific factors include age and diagnosis of Trisomy 21.
- Treatment-specific factors include cancer associated co-morbidities that put patients at a higher risk of prolonged neutropenia and risk of infection.
- Episode-specific factors include medical conditions at the time of presentation or signs/symptoms of a focal infection that put patients at a higher risk of infection.

3) All patients/families must meet the eligibility criteria prior to being discharged, demonstrate understanding of outpatient follow-up instructions, and have antibiotic prescriptions in-hand prior to discharge, if applicable.[1-4]

(Strong recommendation, low-quality evidence)

Low Risk Febrile Neutropenia Episode[1-5,23-40]

4) Patients meeting low risk criteria and without evidence of a focal infection can be considered for early discharge with or without oral antibiotics if well-appearing, resolution of fever for ≥ 24 hours, and blood culture is negative for minimum 36-48 hours.

- If patients have evidence of bone marrow recovery defined as an ANC > 500/mm^3 or at least two consecutive increasing ANC values with last ANC > 100/mm^3 then upon discharge no oral antibiotic is necessary. Studies have shown an acceptable low risk of fever reoccurrence and bacterial infection (less than 5%) when utilizing an ANC cutoff of 100/mm^3 and/or criteria to define a rise in ANC; however this relies heavily on careful selection of factors considered as low risk febrile neutropenia episodes
- If there is no evidence of bone marrow recovery then patients should receive an oral antibiotic upon discharge to be taken until there is evidence of bone marrow recovery.

(Strong recommendation, moderate-quality evidence)

5) Patients meeting low risk criteria that do not meet criteria for early discharge (i.e. clinically deteriorate/ill-appearing, remain febrile, and/or blood cultures become positive) and/or are found to have a focal infection no longer meet criteria for low risk and should be managed as a high risk patient.

(Weak recommendation, very low-quality evidence)

High Risk Febrile Neutropenia Episode

6) Patients meeting high risk criteria should be assessed at admission for signs and symptoms of focal infection or medical conditions that may require an additional or alternative antimicrobial therapy.

(Strong recommendation, moderate-quality evidence)

7) Patients meeting high risk criteria and experience resolution of fever in less than 96 hours should continue intravenous antibiotics until evidence of bone marrow recovery, negative blood cultures at 48 hours, afebrile for at least 24 hours, and/or completion of defined duration of therapy, if focal infection documented.

(Strong recommendation, low-quality evidence)

8) Patients meeting high risk criteria who do not experience resolution of fever in less than 96 hours should expand antimicrobial coverage to include fungal pathogens and antibiotic therapy be assessed for any necessary changes.

(Strong recommendation, moderate-quality evidence)

LABORATORY TESTING[1-5]

1) Obtain blood cultures at the onset of fever from all lumens of a CVL.

(Strong recommendation, low-quality evidence)

2) Consider obtaining peripheral blood cultures when obtaining cultures from a CVL.

(Weak recommendation, low-quality evidence)

3) Consider obtaining a urinalysis (UA) and urine culture in patients in which a clean-catch or midstream specimen is possible. No in/out catheter specimens should be obtained.

(Weak recommendation, low-quality evidence)

4) Do not use β-D Glucan (Fungitell®) testing for prospective monitoring of invasive fungal disease.[13,14]

(Strong recommendation, low-quality evidence)

5) If completed, obtain galactomannan testing in BAL and cerebrospinal fluid in patients at high risk for invasive fungal disease in symptomatic patients.

(Weak recommendation, low-quality evidence)

IMAGING[1-5]

1) Consider obtaining a CXR in symptomatic patients. It has been shown that a CXR in asymptomatic children will show pneumonia in less than 5% of the cases.

(Strong recommendation, moderate-quality evidence)

2) Consider CT of the lungs and/or targeted imaging (CT or US of abdomen) of other suspected areas in patients with persistent fever for ≥ 96 hours despite broad spectrum antibiotic therapy or new fever in the context of persistent neutropenia for evaluation of invasive fungal disease.[15-19]

(Strong recommendation, moderate-quality evidence)

3) Consider obtaining ENT consultation for nasal endoscopy in patients with persistent fever for ≥ 96 hours despite broad spectrum antibiotic therapy for evaluation of invasive fungal disease.[15-19]

(Weak recommendation, low-quality evidence)

ANTIBIOTIC MANAGEMENT[1-4, 20,45-54]

1) Cefepime monotherapy is the recommended first line agent for empiric antibiotic therapy in patients experiencing a febrile neutropenia episode because it provides the most optimal coverage of common and virulent pathogens such gram negative organisms (i.e. *Pseudomonas aeruginosa*) and viridans group streptococci based on local resistance data.

- A retrospective review of DCMCCT oncology patients with blood cultures positive for viridans group streptococci identified 8 patients and 5 of the 8 isolates were resistant to piperacillin-tazobactam whereas only 2 of the 8 isolates were resistant to cefepime. Viridans group streptococci shows more favorable susceptibility to cefepime.
- Overall based on 2013-2014 antibiogram data cefepime shows more favorable susceptibility than piperacillin-tazobactam for common gram negative pathogens.
  - *E. coli*: cefepime 100% susceptible and piperacillin-tazobactam 98%
  - *Klebsiella* spp.: cefepime 100% susceptible and piperacillin-tazobactam 93-95%
  - *Serratia marcescens*: cefepime 89% susceptible and piperacillin-tazobactam 70%
  - *Enterobacter* spp.: cefepime 99% susceptible and piperacillin-tazobactam 85%
  - *Pseudomonas aeruginosa*: cefepime 85% susceptible and piperacillin-tazobactam 91%. Cefepime is more favorable when comparing blood isolates, 22 patients identified and only 95% susceptible to piperacillin-tazobactam whereas 100% susceptible to cefepime.
- Vancomycin is not recommended as part of empiric therapy if patient is hemodynamically stable/well-appearing and gram positive bacteria is not documented or strongly suspected. No benefit (i.e. mortality, time to defervescence) has been identified if no microbiologically or clinically defined gram positive infection at time of vancomycin initiation. Additionally local data does not suggest a high prevalence of pathogens requiring vancomycin (e.g. MRSA, viridans group streptococci) to warrant inclusion in empiric regimens at this time. The risks of unnecessary vancomycin therapy include emergence of vancomycin resistant *enterococcus* and toxicity.

(Strong recommendation, high-quality evidence)

2) Consider adding metronidazole for any patient (low or high risk) experiencing abdominal pain, mucositis, perirectal abscess, colitis, and/or signs and/or symptoms consistent with typhlitis for anaerobic activity is recommended; unless patient is already receiving an antibiotic with anaerobic activity such as meropenem or piperacillin-tazobactam. Recommend enteral route for suspected *C. difficile* infection.

(Strong recommendation, low-quality evidence)

3) If at any time a patient experiences hemodynamic instability the addition of vancomycin for gram positive organism coverage and tobramycin for gram negative organism coverage is recommended. Tobramycin is preferred over gentamicin based on local resistance data among gram negative organisms (e.g. *Pseudomonas aeruginosa*, *E. coli*, *Serratia* spp.).

(Strong recommendation, low-quality evidence)

4) If at any time a patient's blood cultures becomes positive for a gram positive organism the addition of vancomycin is recommended.

(Strong recommendation, low-quality evidence)

5) If at any time a patient's blood cultures becomes positive for a gram negative organism the addition of tobramycin is recommended. Tobramycin is preferred over gentamicin based on local resistance data among gram negative organisms (e.g. *Pseudomonas aeruginosa*, *E. coli*, *Serratia* spp.).

(Strong recommendation, low-quality evidence)

6) In patients whose coverage was expanded to include vancomycin and/or tobramycin for double coverage and the patient is hemodynamically stable/well-appearing with no microbiologic resistance documented to justify continuation and/or blood

cultures negative at least 36-48 hours, may consider discontinuing vancomycin and/or tobramycin. Continuation of double gram negative coverage or vancomycin has not demonstrated improved clinical outcomes, whereas increased adverse effects have been documented.

(Strong recommendation, moderate-quality evidence)

7) Empiric antibiotics should not be modified in clinically stable patients (i.e. no respiratory distress, hemodynamically stable, no focal findings on physical exam, normal neurologic status) based solely on persistent fever.

(Strong recommendation, low-quality evidence)

8) If a patient has a serious allergy to cephalosporins AND anaphylaxis to penicillin

- If a patient has a serious allergy to cephalosporins AND anaphylaxis to penicillin
  - If a patient is hemodynamically stable/well-appearing then aztreonam and vancomycin are recommended for adequate coverage of gram negative and gram positive pathogens. The addition of vancomycin is necessary because aztreonam only provides coverage for gram negative pathogens.
  - If a patient is hemodynamically unstable/ill-appearing then meropenem and vancomycin are recommended.
- If a patient has a Cephalosporin allergy only, then (Zosyn) piperacillin/tazobactam. Add vancomycin if hemodynamically unstable
- If a patient has anaphylaxis to penicillin only then Cefepime. Add vancomycin if hemodynamically unstable

(Strong recommendation, moderate-quality evidence)

9) Low risk febrile neutropenia episode patients that meet criteria for early discharge with no evidence of bone marrow recovery may be discharged on oral ciprofloxacin to be taken until evidence of bone marrow recovery.

(Strong recommendation, moderate-quality evidence)

10) High risk febrile neutropenia episode patients should continue antibiotic therapy until evidence of bone marrow recovery (ANC > 500/mm^3 or at least 2 consecutive increasing ANC values and last ANC > 100/mm^3). Antibiotics may be adjusted for focal infection.

(Strong recommendation, moderate-quality evidence)

ANTIFUNGAL MANAGEMENT[1-4,41,42]

1) Patients experiencing persistent or recurrent fever for ≥ 96 hours despite broad spectrum antibiotic therapy with an unclear etiology should receive empiric antifungal therapy based on their antifungal risk category.

- High risk of invasive fungal disease: AML, relapsed AML/ALL, receiving intensive chemotherapy regimens likely to cause prolonged neutropenia (i.e. >7-10 days), or allogenic HSCT
- Low risk of invasive fungal disease: all other patients not meeting the high risk criteria (i.e. standard risk ALL, lymphoma, solid tumors)

(Strong recommendation, moderate-quality evidence)

2) High risk of invasive fungal disease patients experiencing persistent or recurrent fever ≥ 96 hours despite broad spectrum antibiotic therapy with an unclear etiology should initiate liposomal amphotericin B.

(Strong recommendation, low-quality evidence)

3) Low risk of invasive fungal disease patients experiencing persistent or recurrent fever ≥ 96 hours despite broad spectrum antibiotic therapy with an unclear etiology should consider initiation of micafungin.

(Weak recommendation, low-quality evidence)

4) Empiric antifungal therapy should be continued in the absence of documented or suspected invasive fungal diseases until patient experiences bone marrow recovery.

(Weak recommendation, low-quality evidence)

Consults/Referrals:

- Consider Infectious Disease consultation in high risk febrile neutropenic patients with persistent symptoms/fever and patients with MDRO organisms.
- Consider ENT consultation in high risk febrile neutropenic patients with signs or symptoms of sinusitis.
- Consider surgical consultation if nodular lesions amendable to biopsy are present.

Patient Disposition

Discharge Criteria for Low Risk Patients:[23-40]

- Patient and family must meet eligibility criteria:
  - Current admission is not a readmission after previous discharge as a "Low Risk" patient.
  - Family must live within 1 hour radius of Dell Children's Medical Center of Central Texas.
  - Family is reliable and will call for recurrent fever, worsening condition, or with any concerns.
  - Family has telephone access.
  - Family has adequate transportation to return to clinic for appointments and for any new fever.
  - Age ≥ 1 year.
  - Afebrile ≥ 24 hours.
  - Blood cultures negative for at least 36-48 hours.[7,8,43,44]
  - Patient is well appearing (i.e. normal vital signs for at least 12 hour prior to discharge).
  - No high risk cancer-associated co-morbidity, medical condition, or focal infection. Exclusion criteria as follows:
    - Diagnosis of Trisomy 21
    - AML, Infant ALL, ALL at diagnosis/relapse < 28 days, ALL not in remission > 28 days, Intensive B-NHL/relapse Leukemia protocol, and Intensive chemotherapy regimens likely to cause prolonged neutropenia, > 7-10 days.
    - Hypotension, shock, hemorrhage, dehydration, or organ failure.
    - Changes in respiratory status (e.g. hypoxia, distress, compromise, pneumonitis).
    - New onset abdominal pain, mucositis (requiring IV narcotics, unable to tolerate PO), or perirectal/other soft tissue abscess.
    - Altered mental status, neurological changes, or irritability/meningism.
    - Current or history of ICU admission with FN episode.
- Outpatient antibiotic therapy, ciprofloxacin, is recommended if patient does not have evidence of bone marrow recovery at time of discharge. Bone marrow recovery defined as an ANC > 500/mm^3 or at least two consecutive increasing ANC values AND last ANC > 100/mm^3.
  - If antibiotic therapy is necessary patient must be able to tolerate oral antibiotic(s).
  - If antibiotic therapy is necessary then family/caregiver must have the home antibiotics in hand prior to discharge. It is preferred to have the antibiotics filled at Seton Central Outpatient Pharmacy (SCOP).
  - Oral antibiotic is recommended to be taken until patient demonstrates evidence of bone marrow recovery.
- Parent information sheet must be given to family and reviewed with them.
- Documentation by provider in the medical record that the parent information sheet was given and reviewed, that patient meets eligibility criteria, and the antibiotics have been given to family.
- First follow-up appointment must be scheduled and entered in patient's depart plan.
- Email must be sent to hemeonc.signout informing nursing and clinic staffs of patient's discharge and plan for close outpatient follow up.

Follow-Up Care for Low Risk Patients Meeting Early Discharge Criteria:

- The patient should have daily telephone or clinic follow-up. Twice per week follow up should be planned in the Children's Blood and Cancer Center (CBCC) clinic (with labs/exam). Remaining 5 days should include telephone follow-up.
- Telephone follow up on weekdays will include call by clinic nurse during the weekday. Weekend telephone follow up with be from the on-call NP. All calls should be made prior to 2pm.

Discharge Criteria for High Risk Patients:

- Must have evidence of bone marrow recovery.
- Parent information sheet must be given to family and reviewed with them.
- Family has telephone access.
- Family has adequate transportation to return to clinic for appointments and for any new fever.
- Afebrile ≥ 24 hours.
- Blood cultures negative for at least 36-48 hours.[7,8,43,44]
- Patient is well appearing (i.e. normal vital signs for at least 12 hour prior to discharge).
- If patient to be discharged on oral or intravenous antibiotics then family/caregiver(s) must receive the appropriate education and training.
    - If oral antibiotic therapy then patient must be able to tolerate oral antibiotic(s).
    - If oral antibiotic therapy is necessary then family/caregiver must have the home antibiotics in hand prior to discharge. It is preferred to have the antibiotics filled at Seton Central Outpatient Pharmacy (SCOP).
- First follow-up appointment must be scheduled and entered in patient's depart plan.
- Email must be sent to hemeonc.signout informing nursing and clinic staffs of patient's discharge.

Guidelines for Readmission:

- Recurrent fever (Fever is defined as a single oral or axillary temperature greater than 38.3°C (101°F) or two oral or axillary temperatures greater than 38.0°C (100.4°F) in one hour).
- New exam findings for focal infection.
- Not tolerating or not adherent to oral antibiotics.
- Respiratory distress.
- Non-adherence to phone or clinic follow-up.
- Blood culture turns positive.
- Physician concern.

Prevention:

- Parent information sheet to be provided at discharge which includes guidelines for when they should call, antibiotic administration guidelines, required outpatient follow up, and instructions for home temperature checks.
- Family to be given thermometer at discharge.
- Family to check temperature 2-3 times per day at home and any time they suspect a temperature.
- If patient has a fever they will return immediately to CBCC outpatient clinic or ER for DCMCCT readmission.

Outcome Measures:

- Readmission rate and reason for readmission (i.e. fever, documented infection)
- Antimicrobial utilization (inpatient, outpatient)
- Hospital duration and cost
- Antibiotic-related adverse effects (i.e. superinfection, therapy limiting side effects, resistance)

Addendums:

1. Antimicrobial Dosing Guide for Febrile Neutropenia
2. Outpatient Management for Low Risk Febrile Neutropenia

Febrile Neutropenia Pathway
Hematology & Oncology Patients
Evidence Based Outcome Center

PEDIATRIC EBOC
EVIDENCE BASED OUTCOMES CENTER

Criteria for High Risk Febrile Neutropenia Episode

- Age < 1 year
- Diagnosis of Trisomy 21

Cancer associated co-morbidities

- AML
- Infant ALL
- ALL at diagnosis/relapse < 28 days or not yet in remission
- ALL not yet in remission
- Intensive B-NHL/relapse Leukemia protocol

Medical conditions

- Evidence of Focal Infection
- Hypotension, shock, hemorrhage, dehydration, or organ failure
- Changes in respiratory status (i.e. hypoxia, distress, compromise, pneumonitis)
- New onset abdominal pain, mucositis (requiring IV narcotics, unable to tolerate PO), or perirectal/other soft tissue abscess
- Altered mental status, neurological changes, or irritability/ meningism

Other

- Readmission after discharge as "Low Risk" patient

1

High Risk of Invasive Fungal Disease

- AML
- High Risk ALL
- High Dose Steroids
- Relapsed ALL/AML
- Allogenic HSCT

2

Inclusion Criteria (Clinic, Emergency Department, or Hospitalized patients)

- Fever defined as oral or axillary temperature > 101°F (38.3ºC) once **OR** two temperatures > 100.4°F (38.0ºC) in a 1 hour period
- Neutropenia defined as ANC < 500/mm3 or expected decline to < 500/mm3 in the next 48 hours
- Actively receiving treatment or within 6 months of completing treatment for the cancer diagnosis

EXCLUSION CRITERIA

- Aplastic Anemia (due to no expected bone marrow recovery)
- Bone Marrow Failure Syndrome (acquired/congenital)
- Lack of oncology diagnosis (i.e. viral supression)

- **Always admit patient and begin intravenous antibiotics for minimum 36-48 hours, initiate Cefepime**
  Consider additional or alternative antibiotic if known history of resistant pathogen or allergy
  (Refer to Addendum 1 for additional antibiotic guidance)
- **Obtain blood culture from all lumens of central venous catheter (CVC)**
- Consider peripheral blood culture when obtaining culture from CVC

ALERT!
Refer to addendum 1 for antibiotic guidance if patient experiences clinical deterioration, hemodynamic instability, new fever, diagnosed with focal infection, or blood culture becomes positive.
Febrile Neutropenia Antibiotic Management Guidelines

Sepsis Pathway

Meets Criteria for High Risk? 1
- No → Develops evidence of focal Infection? 1
  - YES → **Febrile Neutropenia Antibiotic Management Guidelines**
    If clinically stable, empiric therapy should not be changed based on persistent fever alone
  - NO → **Meets Criteria for Early Discharge?**
    Criteria:
    - Well appearing
    - Afebrile ≥ 24 hours
    - Blood culture negative ≥ 36-48 hours
    - NO → **Febrile Neutropenia Antibiotic Management Guidelines**
    - Yes → **Evidence of Bone Marrow Recovery:** ANC > 500/mm3 **OR** At least 2 consecutive increasing ANC values AND last ANC > 100/mm3
      - Yes → **No Outpatient Antibiotic Therapy** → **Discharge** (Refer to Addendum 2 for Outpatient Follow-up Instructions)
      - No → **Outpatient Oral Antibiotic Therapy**
        First Line Antibiotic: Ciprofloxacin
        To be taken until evidence of bone marrow recovery → **Discharge** (Refer to Addendum 2 for Outpatient Follow-up Instructions)
- Yes → Fever Resolves in < 96 hours?
  - No → Clinically unstable or new findings:
    Assess current Antibiotics
    Febrile Neutropenia Antibiotic Management Guidelines
    → High Risk of Invasive Fungal Disease? 2
    - YES → **ADD** liposomal amphotericin B Or micafungin
    - No → Antifungals not routinely recommended
    → Fever Resolves in < 96 hours?
    - No → **Manage Off Pathway Consider ID Consult**
    - Yes → **Evidence of Bone Marrow Recovery:** ANC > 500/mm3 **OR** At least 2 consecutive increasing ANC values AND last ANC > 100/mm3
      - Yes → Discontinue anti-infectives **and/or** De-escalate for focal infection → **Discharge** (Refer to Addendum 2 for Outpatient Follow-up Instructions)
      - No → Continue until evidence of bone marrow recovery
  - Yes → **Evidence of Bone Marrow Recovery:** ANC > 500/mm3 **OR** At least 2 consecutive increasing ANC values AND last ANC > 100/mm3
    - Yes → Discontinue anti-infectives **and/or** De-escalate for focal infection → **Discharge** (Refer to Addendum 2 for Outpatient Follow-up Instructions)
    - No → Continue until evidence of bone marrow recovery

Early Discharge Criteria for Low Risk Patients

- Caregivers demonstrate understanding of outpatient follow-up instructions
- Antibiotic prescription is filled and delivered prior to discharge or easily accessible by caregivers immediately after discharge
- Lives within 1 hour and no social concerns

dell children's medical center of central texas
A member of the Seton Family of Hospitals

For questions concerning this pathway,
Click Here
Last Updated August 1st, 2019

Febrile Neutropenia Antibiotic Management Guidelines
Hematology & Oncology Patients

ALERT!

Assess antibiotics if patient experiences clinical deterioration, hemodynamic instability, diagnosed with focal infection, or blood culture becomes positive.

High Risk Febrile Neutropenia Episode
OR
Low Risk Febrile Neutropenia Episode Not Meeting Criteria for Early Discharge

Clinically Stable
- No respiratory distress
- Hemodynamicaly stable
- No focal findings on physical exam
- Normal neurologic status

Cephalosporin Allergy?
- NO → Continue Cefepime*
- YES → Anaphylactic Penicillin Allergy?
  - NO → Piperacillin/ Tazobactam
  - YES → Is the Patient Hemodynamically Stable?
    - NO → Start Meropenem **And** Vancomycin
    - YES → Start Aztreonam **And** Vancomycin

Is the Patient Hemodynamically Stable?
- NO → **ADD** Vancomycin **And** **ADD** Tobramycin
- YES

Is abdominal pain, mucositis, perirectal abscess, colitis, and/or typhlitis present?
- YES → **ADD** Metronidazole *Not needed if on piperacillin/tazobactam*
- NO → Continue Current Therapy

Blood Culture Positive?
- NO → If clinically stable, empiric therapy should not be changed based on persistent fever alone [1]
- YES → Culture Positive for Gram Negative?
  - YES → **ADD** Tobramycin (if not already receiving)
  - NO → Culture Positive for Gram Positive?
    - YES → **ADD** Vancomycin (if not already receiving)

De-escalate Therapy Based on Susceptibilities
And
Complete Appropriate Duration of Therapy Based on Site/Source of Infection

→ **Febrile Neutropenia Pathway**

** if patient has penicillin allergy cefepime can be used**

dell children's medical center of central texas
A member of the Seton Family of Hospitals

For questions concerning this pathway,
Click Here
Last Updated August 1st, 2019

ADDENDUM 1
Antimicrobial Dosing Guide for Febrile Neutropenia

Antimicrobial	Dose	Dosing Interval	
Cefepime	50 mg/kg/dose	Every 8 hours	• Max dose = 2000 mg
Vancomycin	15 mg/kg/dose	Every 6 hours	• Max dose = 1000 mg • Default infusion time = 1 hour, if history of Red Man syndrome consider change to 2 hour infusion • Consider consultation with pharmacy to determine previous dosing regimen that provided therapeutic serum drug concentrations
Tobramycin	7.5 mg/kg/dose	Every 24 hours	• No max dose • Dose based on Ideal Body Weight or Adjusted Body Weight (if Actual Body Weight 30% greater than Ideal Body Weight) • Consider consultation with pharmacy to determine previous dosing regimen that provided therapeutic serum drug concentrations
Metronidazole	10 mg/kg/dose	Every 8 hours	• Max dose = 500 mg
Aztreonam	50 mg/kg/dose	Every 6 hours	• Max dose = 2000 mg
Meropenem	20-40 mg/kg/dose	Every 8 hours	• Max dose = 2000 mg
Micafungin	Weight < 25 kg: 4.5 mg/kg/dose Weight ≥ 25 kg: 3 mg/kg/dose	Every 24 hours	• Max dose = 100 mg

Liposomal Amphotericin B	5 mg/kg/dose	Every 24 hours	• No max dose
			• Round dose to nearest 50 mg
			• To decrease the incidence of infusion reaction consider pre-medications, must be given exactly 30 minutes prior to infusion
			  ○ Tylenol per protocol (PO)
			  ○ Diphenhydramine 1 mg/kg (max 50 mg/dose, IV/PO)
			  ○ Hydrocortisone 1 mg/kg (max 100 mg/dose, IV) (optional)
			• To decrease the risk of nephrotoxicity consider sodium loading with normal saline bolus or continuous infusion

ADDENDUM 2

Oncology Outpatient Management for Low Risk Febrile Neutropenia
Policy for Early Discharge Home on Oral Antibiotic Therapy
Dell Children's Medical Center of Central Texas
Children's Blood and Cancer Center

The following are guidelines for outpatient management of patients with low risk fever and neutropenia. They are intended to provide consistency within our practice, and not to replace good clinical judgment.

Children admitted to Dell Children's Medical Center with febrile neutropenia can be risk stratified into low and high risk of developing bacteremia and/or adverse events based on published literature and clinical experience. Patients meeting criteria for Low Risk may be considered for early discharge on oral antibiotics to continue empiric treatment for febrile neutropenia.

Definitions:

- *Neutropenia:* absolute neutrophil count (ANC) less than 500/mm3 or expected decline to less than 500/mm3 in 48 hours as determined by the treating oncologist.
- *Fever:* single oral or axillary temperature greater than 38.3°C (101°F) or two temperatures greater than 38.0°C (100.4°F) in a one hour period.
- *Early discharge:* For qualifying Low-Risk patients, discharge can occur as early as 36 hours after admission.
- *Recurrent fever:* single oral or axillary temperature ≥ 38.0°C (100.4°F).
- *Bone marrow recovery:* at least two consecutive increasing ANC values and last ANC > 100/mm^3.

Eligibility:

Inclusion:

1. Family must live within 1 hour radius of DCMC.
2. Family is reliable and will call for recurrent fever, worsening condition, or with any concerns.
3. Family has telephone access.
4. Family has adequate transportation to return to clinic for appointments and for any new fever.
5. Age ≥ 1 year.
6. Afebrile ≥ 24 hours.
7. Negative blood cultures for at least 36-48 hours.
8. Able to take oral antibiotics.
9. Well-appearing (i.e. normal vital signs for at least 12 hour prior to discharge).

Exclusion:

1. Age < 1 year.
2. Diagnosis of Trisomy 21.
3. AML.
4. Infant ALL.
5. ALL in Induction or not yet in remission.
6. ALL relapse (any time prior to maintenance therapy).
7. Intensive B-NHL/relapse Leukemia protocol.
8. BMT.
9. Intensive chemotherapy regimens likely to cause prolonged neutropenia (i.e. neutropenia >7-10 days).

10. Any hemodynamic instability at presentation requiring interventions (i.e. fluid resuscitation, inotropes).

11. New onset abdominal pain, mucositis (requiring IV narcotics), or perirectal/other soft tissue abscess.
12. Evidence of respiratory changes at presentation (i.e. hypoxia, distress, compromise, pneumonitis).
13. Altered mental status, neurological changes, or irritability/meningism.
14. Not tolerating oral (including oral medications).
15. Evidence of focal infection (bacteremia, pneumonia, cellulitis, typhlitis, etc.).
16. History of ICU admission with prior febrile neutropenia episode.
17. Readmission after discharge as "Low Risk" patient.
18. Non-adherence and/or social concerns.

Antibiotic Guidelines:
If a child meets eligibility for early discharge, they may be discharged on one of the following antibiotics. The selection of home antibiotics may depend on insurance coverage. Recommend initiation of oral antibiotics prior to discharge so that patient takes at least one dose prior to discharge to demonstrate tolerability.

Antibiotics should be continued until evidence of bone marrow recovery.

1. Preferred: ciprofloxacin,
   - 10mg/kg/dose (max dose 750mg) PO BID.
   - Oral suspension cannot be given via feeding tubes because the suspension is oil-based and adheres to the feeding tube; however the tablets can be crushed and safely given via feeding tubes.
   - Available dosage forms
     - Tablets: 100mg, 250mg, 500mg. 750mg.
     - Oral suspension: 250 mg/5 mL (100 mL), 500 mg/5 mL (100 mL)
2. Alternative: levofloxacin,
   - <5 years old: 10mg/kg/dose (max dose 750mg) PO BID.
   - ≥5 years old: 10mg/kg/dose (max dose 750mg) PO Qday.
   - Both oral solution and tablets can be safely given via feeding tubes.
   - Available dosage forms
     - Tablets: 250mg, 500mg. 750mg.
     - Oral solution: 25 mg/mL (10 mL, 20 mL, 100 mL, 200 mL, 480 mL)

Follow-up Instructions:
Close follow up is required for any child discharged home early on oral antibiotics. Remember, these are patients who did not have evidence of bone marrow recovery at discharge. This close follow up will be discontinued once there is evidence of bone marrow recovery.

1. The patient should have daily telephone or clinic follow-up.
   a. Twice per week follow up should be planned in the oncology clinic (with labs/exam)
   b. Remaining 5 days should include phone follow-up
   c. Phone follow up on weekdays will include call by clinic nurse during the weekday. Weekend phone follow up with be from the on-call NP. Calls should be made prior to 2pm these days.

Home Instructions for Parents:
1. Parent information sheet including guidelines for when they should call, antibiotic administration guidelines, and required outpatient follow up, and instructions for home temperature checks.

a. Family to be given thermometer at discharge
b. Family to check temperature 2-3 times per day at home and any time they suspect a temperature.

c. If patient has a fever they will return immediately to CBCC outpatient clinic or ER for DCMC readmission.

Discharge checklist:

All of the following must occur prior to discharge:

- Patient and family must meet eligibility criteria.
- Family has home antibiotics in hand prior to discharge. It is preferred to have the antibiotics filled at Seton Central Outpatient Pharmacy (SCOP).
- Parent information sheet must be given to family and reviewed with them.
- Documentation by the provider in the medical record that the parent information sheet was given and reviewed, that patient meets eligibility criteria, and antibiotics have been given to family.
- First follow-up appointment must be scheduled and entered in patient's depart plan.
- Email must be sent to hemeonc.signout informing nursing and clinic staff of patient's discharge and plan for close outpatient follow up.

Guidelines for readmission:

1. Recurrent fever
2. New exam findings for focal infection
3. Not tolerating or not adherent to oral antibiotics
4. Respiratory distress
5. Non-adherence to phone or clinic follow-up
6. Blood culture turns positive
7. Physician concern

References:

1. Gea-Banacloche J. Evidence-based approach to treatment of febrile neutropenia in hematologic malignancies. *Hematology Am Soc Hematol Educ Program*. 2013;2013(1):414–422.
2. Lehrnbecher T, Phillips R, Alexander S, et al. Guideline for the Management of Fever and Neutropenia in Children With Cancer and/or Undergoing Hematopoietic Stem-Cell Transplantation. *Journal of Clinical Oncology*. 2012;30(35):4427–4438.
3. Freifeld AG, Sepkowitz KA. No place like home? Outpatient management of patients with febrile neutropenia and low risk. *J. Clin. Oncol.* 2011;29(30):3952–3954.
4. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clin. Infect. Dis.* 2011;52(4):427–431.
5. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin. Infect. Dis.* 2011;52(4):e56–93.

ADDENDUM 3

Low Risk Fever Neutropenia Oncology Patient Discharge Information

dell children's medical center of central texas
A member of the Seton Family of Hospitals

IMPORTANT PHONE NUMBERS OF YOUR HEALTH CARE TEAM:
Children's Blood and Cancer Center: 512-628-1900
(Monday – Friday 7am-5:30pm)
Medlink answering service: 512-323-5465 (ask for on-call pediatric oncologist)
(Nights/Weekends/Holidays)

Prior to discharge: you are required to have:

- A thermometer for home use
- Antibiotic prescription in hand
- Adequate transportation to return to CBCC for follow up or DCMC for admission
- Working phone number to receive daily calls from the CBCC nurse or nurse practitioner
- Follow up appointment scheduled with CBCC

Instructions for home

- Check temperature 2-3 times a day AND any time you suspect a fever
  Notify your oncology team if temperature is 100.4 or higher
- Follow up with your oncology team at the CBCC at least twice a week until lab counts recover
  Next follow up appointment: _____
- Plan to stay within a one hour driving distance from DCMC
- You will return immediately to CBCC outpatient clinic or DCMC ER for readmission if fever returns before counts have improved

Antibiotic Instructions

- ☐ Give Ciprofloxacin _____mg_____times a day
- ☐ Give Levofloxacin _____mg_____times a day
- ☐ Give _____
- ☐ Do NOT stop taking your antibiotics until instructed by your oncology team
- ☐ Take antibiotics on an empty stomach
- ☐ Oral magnesium and antacids should not be given within two hours of oral antibiotics

CALL YOUR HEALTH CARE TEAM RIGHT AWAY IF YOUR CHILD HAS:

- **Fever of 100.4 or higher**-do not give Tylenol until doctor instructs you to. Do NOT give Motrin.
- Other signs of infection such as pain, redness or swelling anywhere in the body (sore throat, ear ache, stiff neck, pain when urinating or having bowel movements, pain or redness at broviac or port-a-cath site), or chills.
- Bleeding, including a nose bleed, bleeding from the gums that does not stop with 5-10 minutes of gentle pressure, blood in urine or stool, vomit or stool that looks black, easy bruising, or tiny red, freckles on the skin.
- Difficulty breathing
- A change in behavior or level of consciousness. Being very sleepy and being very irritable, or not making sense while talking.
- Sudden change in vision or severe headache
- Vomiting or diarrhea three times in 24 hours, or not being able to eat or drink.
- Problems with central line
- Severe mucositis (mouth sores), or is unable to eat or drink.

The doctor may instruct you to go to the emergency room at Dell Children's Medical Center or to the CBCC. If you go to the ER, wear a mask and tell the ER nurse and doctor the above information. Make sure they know your child cannot have a urinary catheter, rectal temperatures, enemas or suppositories, If your child has a fever, the team should begin your child on antibiotics as soon as possible.

Parent signature_____ Nurse Signature _____

EBOC Project Owner: Marisol Fernandez, MD

Approved by the Oncology Management of Febrile Neutropenia Evidence-Based Outcomes Center Team

Revision History

Date Approved: 2/1/2016
Revision Dates: 2/1/2018, 8/01/2019
Next Revision Date: 8/01/2022

EBOC Team:
Marisol Fernandez, MD
Amy Fowler, MD
Kim Cuellar, PharmD
Kathryn Merkel, PharmD
Becky Gregory
Patrick Boswell
Frank James, MBA

EBOC Committee:
Sarmistha Hauger, MD
Dana Danaher RN, MSN, CPHQ
Mark Shen, MD
Deb Brown, RN
Robert Schlechter, MD
Levy Moise, MD
Sujit Iyer, MD
Tory Meyer, MD
Nilda Garcia, MD
Meena Iyer, MD
Michael Auth, DO

References:

1) Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):427-31.
2) Lehrnbecher T, Phillips R, Alexander S, 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(35):4427-38.
3) Lehrnbecher T, Phillips R, Alexander S, et al. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation Recipients: 2017 update. J Clin Oncol. 2017 (35:2082-2094)
4) Haeusler GM, Phillips RS, Lehrnbecher T, et al. Core outcomes and definitions for pediatric fever and neutropenia research: a consensus statement from an international panel. Pediatr Blood Cancer. 2015 Mar;62(3):483-9.
5) Alexander SW, Pizzo PA. Current considerations in the management of fever and neutropenia. Curr Clin Top Infect Dis. 1999;19:160-80.
6) Dommett R, Geary J, Freeman S, et al. Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutopaenia in a UK, multicentre, shared care setting. Eur J Cancer. 2009 Nov;45(16):2843-9.
7) Viscoli C and Castagnola E. Prophylaxis and Empirical Therapy of Infection in Cancer Patients. In: Mandell GL, Bennett JC, Dolin R, eds. Mandell, Douglas, and Bennett's: Principles and Practice of Infectious Disease. Vol 2. 7th ed. Philadelphia, PA: Elsevier; 2010:3793-3807.
8) Rosenblum J, Lin J, Kim M, Levy AS. Repeating blood cultures in neutropenic children with persistent fevers when the initial blood culture is negative. Pediatr Blood Cancer. 2013;60(6):923-7.
9) Wattier RL, Dvorak CC, Auerbach AD, Weintrub PS. Repeat blood cultures in children with persistent fever and neutropenia: Diagnostic and clinical implications. Pediatr Blood Cancer. 2015;62(8):1421-6.
10) Taccone A, Occhi M, Garaventa A, Manfredini L, Viscoli C. CT of invasive pulmonary aspergillosis in children with cancer. Pediatr Radiol. 1993;23(3):177-80.
11) Burgos A, Zaoutis TE, Dvorak CC, et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics. 2008;121(5):e1286-94.
12) Hovi L, Saxen H, Saarinen-pihkala UM, Vettenranta K, Meri T, Richardson M. Prevention and monitoring of invasive fungal infections in pediatric patients with cancer and hematologic disorders. Pediatr Blood Cancer. 2007;48(1):28-34.
13) Castagnola E, Furfaro E, Caviglia I, et al. Performance of the galactomannan antigen detection test in the diagnosis of invasive aspergillosis in children with cancer or undergoing haemopoietic stem cell transplantation. Clin Microbiol Infect. 2010;16(8):1197-203.
14) Mokaddas E, Burhamah MH, Khan ZU, Ahmad S. Levels of (1→3)-β-D-glucan, Candida mannan and Candida DNA in serum samples of pediatric cancer patients colonized with Candida species. BMC Infect Dis. 2010;10:292.
15) Badiee P, Alborzi A, Karimi M, et al. Diagnostic potential of nested PCR, galactomannan EIA, and beta-D-glucan for invasive aspergillosis in pediatric patients. J Infect Dev Ctries. 2012;6(4):352-7.
16) Agrawal AK, Saini N, Gildengorin G, et al. Is routine computed tomographic scanning justified in the first week of persistent febrile neutropenia in children with malignancies? Pediatr Blood Cancer 2011;57:620–624.
17) Flynn PM, Shenep JL, Crawford R, et al. Use of Abdominal Computed Tomography for Identifying Disseminated Fungal Infection in Pediatric Cancer Patients. Clin Infect Dis. 1995 Apr;20(4):964-970.
18) Rao AD, Sugar EA, Barrett N, Mahesh M, Arceci RJ. The utility of computed tomography in the management of fever and neutropenia in pediatric oncology. Pediatr Blood Cancer. 2015.
19) Ho DY, Lin M, Schaenman J, et al. Yield of diagnostic procedures for invasive fungal infections in neutropenic febrile patients with chest computed tomography abnormalities. Mycoses. 2011;54(1):59-70.
20) Kropshofer G, Kneer A, Edlinger M, et al. Computed tomography guided percutaneous lung biopsies and suspected fungal infections in pediatric cancer patients. Pediatr Blood Cancer 2014;61:1620-1624.
21) Uygun V, Karasu GT, Ogunc D, Yesilipek A, Hazar V. Piperacillin/tazobactam versus cefepime for the empirical treatment of pediatric cancer patients with neutropenia and fever: a randomized and open-label study. Pediatr Blood Cancer. 2009;53(4):610-4.
22) Lee JW, Pizzo PA. Management of the cancer patient with fever and prolonged neutropenia. Hematol Oncol Clin North Am. 1993;7(5):937-60.
23) De pauw BE, Raemaekers JM, Schattenberg T, Donnelly JP. Empirical and subsequent use of antibacterial agents in the febrile neutropenic patient. J Intern Med Suppl. 1997;740:69-77.
24) Innes HE, Smith DB, O'reilly SM, Clark PI, Kelly V, Marshall E. Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. Br J Cancer. 2003;89(1):43-9.
25) Manji A, Beyene J, Dupuis LL, Phillips R, Lehrnbecher T, Sung L. Outpatient and oral antibiotic management of low-risk febrile neutropenia are effective in children--a systematic review of prospective trials. Support Care Cancer. 2012;20(6):1135-45.
26) Teuffel O, Ethier MC, Alibhai SM, Beyene J, Sung L. Outpatient management of cancer patients with febrile neutropenia: a systematic review and meta-analysis. Ann Oncol. 2011;22(11):2358-65.
27) Vidal L, Ben dor I, Paul M, et al. Oral versus intravenous antibiotic treatment for febrile neutropenia in cancer patients. Cochrane Database Syst Rev. 2013;10:CD003992.
28) Ahmed N, El-mahallawy HA, Ahmed IA, Nassif S, El-beshlawy A, El-haddad A. Early hospital discharge versus continued hospitalization in febrile pediatric cancer patients with prolonged neutropenia: A randomized, prospective study. Pediatr Blood Cancer. 2007;49(6):786-92.
29) Santolaya ME, Alvarez AM, Avilés CL, et al. Early hospital discharge followed by outpatient management versus continued hospitalization of children with cancer, fever, and neutropenia at low risk for invasive bacterial infection. J Clin Oncol. 2004;22(18):3784-9.

30) Brack E, Bodmer N, Simon A, et al. First-day step-down to oral outpatient treatment versus continued standard treatment in children with cancer and low-risk fever in neutropenia. A randomized controlled trial within the multicenter SPOG 2003 FN study. Pediatr Blood Cancer. 2012;59(3):423-30.
31) Vedi A, Cohn R. Oral versus intravenous antibiotics in treatment of paediatric febrile neutropenia. J Paediatr Child Health. 2013;49(3):170-8.
32) Klaassen RJ, Allen U, Doyle JJ. Randomized placebo-controlled trial of oral antibiotics in pediatric oncology patients at low-risk with fever and neutropenia. J Pediatr Hematol Oncol. 2000;22(5):405-11.
33) Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. N Engl J Med. 1999;341(5):305-11.
34) Alexander SW, Wade KC, Hibberd PL, et al. Evaluation of risk prediction criteria for episodes of febrile neutropenia in children with cancer. J Pediatr Hematol Oncol. 2002 Jan;24(1):38-42.
35) Bash RO, Katz JA, Cash JV, Buchanan GR. Safety and cost effectiveness of early hospital discharge of lower risk children with cancer admitted for fever and neutropenia. Cancer. 1994;74(1):189-96.
36) Santolaya ME, Villarroel M, Avendaño LF, Cofré J. Discontinuation of antimicrobial therapy for febrile, neutropenic children with cancer: a prospective study. Clin Infect Dis. 1997;25(1):92-7.
37) Pizzo PA, Robichaud KJ, Gill FA, et al. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am J Med. 1979;67(2):194-200.
38) Hodgson-viden H, Grundy PE, Robinson JL. Early discontinuation of intravenous antimicrobial therapy in pediatric oncology patients with febrile neutropenia. BMC Pediatr. 2005;5(1):10.
39) Aquino VM, Tkaczewski I, Buchanan GR. Early discharge of low-risk febrile neutropenic children and adolescents with cancer. Clin Infect Dis. 1997;25(1):74-8.
40) Jones GR, Konsler GK, Dunaway RP, Gold SH, Cooper HA, Wells RJ. Risk factors for recurrent fever after the discontinuation of empiric antibiotic therapy for fever and neutropenia in pediatric patients with a malignancy or hematologic condition. J Pediatr. 1994;124(5 Pt 1):703-8.
41) Orudjev E, Lange BJ. Evolving concepts of management of febrile neutropenia in children with cancer. Med Pediatr Oncol. 2002;39(2):77-85.
42) Maertens JA, Madero L, Reilly AF, et al. A randomized, double-blind, multicenter study of caspofungin versus liposomal amphotericin B for empiric antifungal therapy in pediatric patients with persistent fever and neutropenia. Pediatr Infect Dis J. 2010;29(5):415-20.
43) Sekine L, Humbwavali J, Wolff FH, Barcellos NT. Caspofungin versus liposomal amphotericin B: are they really comparable?. Pediatr Infect Dis J. 2010;29(10):985-6.
44) Hakim H, Flynn PM, Knapp KM, Srivastava DK, Gaur AH. Etiology and clinical course of febrile neutropenia in children with cancer. J Pediatr Hematol Oncol. 2009;31(9):623-9.
45) Agyeman P, Kontny U, Nadal D, et al. A prospective multicenter study of microbiologically defined infections in pediatric cancer patients with fever and neutropenia: Swiss Pediatric Oncology Group 2003 fever and neutropenia study. Pediatr Infect Dis J. 2014;33(9):e219-25.
46) Cometta A, Kern WV, De bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. Clin Infect Dis. 2003;37(3):382-9.
47) Berger C, Kindli K, Niggli FK, Nadal D. Withholding initial vancomycin in febrile neutropenia despite implanted catheters. Eur J Pediatr. 2004;163(7):422-3.
48) Adcock KG, Akins RL, Farrington EA. Evaluation of empiric vancomycin therapy in children with fever and neutropenia. Pharmacotherapy. 1999;19(11):1315-20.
49) Feld R. Vancomycin as part of initial empirical antibiotic therapy for febrile neutropenia in patients with cancer: pros and cons. Clin Infect Dis. 1999;29(3):503-7.
50) Dompeling EC, Donnelly JP, Deresinski SC, Feld R, Lane-allman EF, De pauw BE. Early identification of neutropenic patients at risk of gram-positive bacteraemia and the impact of empirical administration of vancomycin. Eur J Cancer. 1996;32A(8):1332-9
51) Oude nijhuis C, Kamps WA, Daenen SM, et al. Feasibility of withholding antibiotics in selected febrile neutropenic cancer patients. J Clin Oncol. 2005;23(30):7437-44.
52) Johannsen KH, Handrup MM, Lausen B, Schrøder H, Hasle H. High frequency of streptococcal bacteraemia during childhood AML therapy irrespective of dose of cytarabine. Pediatr Blood Cancer. 2013;60(7):1154-60.
53) Gamis AS, Howells WB, Deswarte-wallace J, Feusner JH, Buckley JD, Woods WG. Alpha hemolytic streptococcal infection during intensive treatment for acute myeloid leukemia: a report from the Children's cancer group study CCG-2891. J Clin Oncol. 2000;18(9):1845-55.
54) Reilly AF, Lange BJ. Infections with viridans group streptococci in children with cancer. Pediatr Blood Cancer. 2007;49(6):774-80.
55) Paganini H, Staffolani V, Zubizarreta P, Casimir L, Lopardo H, Luppino V. Viridans streptococci bacteraemia in children with fever and neutropenia: a case-control study of predisposing factors. Eur J Cancer. 2003;39(9):1284-9.
56) Teuffel O, Amir E, Alibhai S, Beyene J, Sung L. Cost-effectiveness of Outpatient Management for Febrile Neutropenia in Children with Cancer. 2011; 127;e279
57) Robinson P, Lehrnbecher T, Phillips R, Dupuis L, Sung L; Strategies for Empriric Management of Pediatric Fever and Neutropenia in Patients with Cancer and Hematompoietic Stem-Cell Transplantation Recipients: A Systematic Review of Randomized Trials 2016 DOI: 10.1200/JCO.2015.65.8591

58) Lehrnbecher T, Robinson P, Fisher B Castagnolo E, Groll A, Steinbach W, Zaoutis T, Negeri Z, Beyene J, Phillips B, Sung L; Galactomannan, β-D-Glucan, and Polymerase Chain Reaction–Based Assays for the Diagnosis of Invasive Fungal Disease in Pediatric Cancer and Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis; CID 2016:63 (15 November)

59) Wagner S, Brack EK, Stutz-Grunder E, Agyeman P, Leibundgut K, Teuffel O, et al. (2018) The influence of different fever definitions on diagnostics and treatment after diagnosis of fever in chemotherapy-induced neutropenia in children with cancer. PLoS ONE 13(2): e0193227. https://doi.org/10.1371/journal.pone.0193227