Approach to febrile neutropenia in pediatric cancer

Abolghasemi H
Professor of pediatrics
hematologist oncologist

Baqiyatallah university of medical sciences

definition

- Fever: a single oral temperature of > 38.3°C (101°F) or a temperature of 38°C (100.4°F) sustained over at least 1hr or that occures twice within 24 h period.
- Neutropenia: absolute neutrophil count (ANC) of less than 0.5x109 (<500 cells/µL); or a count of 1.0x109 (<1000 cells/ µL)with a predicted decrease below 0.5x109 in next 48 hours.
- Profound neutropenia: ANC less than 0.1x109 (<100 cells/µL)
- Prolonged neutropenia: Neutropenia lasting more than 7 days

Definition

- Central Venous Catheter (CVC) Infections:
  - Exit Site infection: redness, tenderness, induration or purulence within 2cm of CVC exit site.
  - CVC Tunnel/Portacath Pocket infection: infection of the subcutaneous tissue surrounding the CVC tunnel tract, or site of subcutaneous port.
- Hypotension: systolic blood pressure less than fifth percentile for age and sex, or need for vasopressor support
- Respiratory failure: an arterial oxygen pressure of less than 60mmHg in room air, or need for supplemental oxygen , or mechanical ventilation in a patient with no known respiratory compromise at baseline

Key points

- Fever is frequently the only clinical manifestation of serious infection in a neutropenic cancer patient,
- Infection is the major cause of treatment related mortality for children with cancer
- Prompt initiation of empiric, broad-spectrum, intravenous antibiotic therapy is the single most important life-saving intervention in these patients. Treat as an emergency.

FACTORS LEADING TO INFECTIOUS SUSEPTILITY

- Underlying disease
- Type of therapy
- Degree and duration of neutropenia
- Skin and mucosal barrier
- Malnutrition
- Defect in humoral and cellular immunity
- Colonizing microbial flora
- Forein bodies (shunt or CVCs)

Risk factors for fungal disease

- Recrudescence of fever after recovery of neutrophils
- Persistent fevers
- Active GVHD
- Prolonged recent corticosteroid usage
- Development of lower respiratory symptoms
- Development of new focal populonodular skin rash
- Upper respiratory symptoms
- Sinus tenderness
- Halo or cresents sign or cavitation on CT chest image
- Shoulder pain
- Focal neurologic finding with concomitant mastoiditis or empyema on CT head
- Galactomanan positivity or positive fungal culture in blood or urine

Fever: Temperature 38.3°C × 1 or 38.0°C × 2 at least 1 h apart
Neutropenia: ANC <0.5 × 10^9/l or <1.0 × 10^9/l and falling

↓

Initial evaluation

History: Chills, rigors, fever within 1 h of CVC flush

Recent immunosuppressive therapy

Symptoms of AGE, URI, pain

Physical examination: Vitals, CVC exit site(s), skin/mucosa, perineum

Laboratory assessment: CBC with differential

Blood culture from each CVC lumen (peripheral, see text)

Culture from all suspicious sites (throat, skin, stool, catheter site)

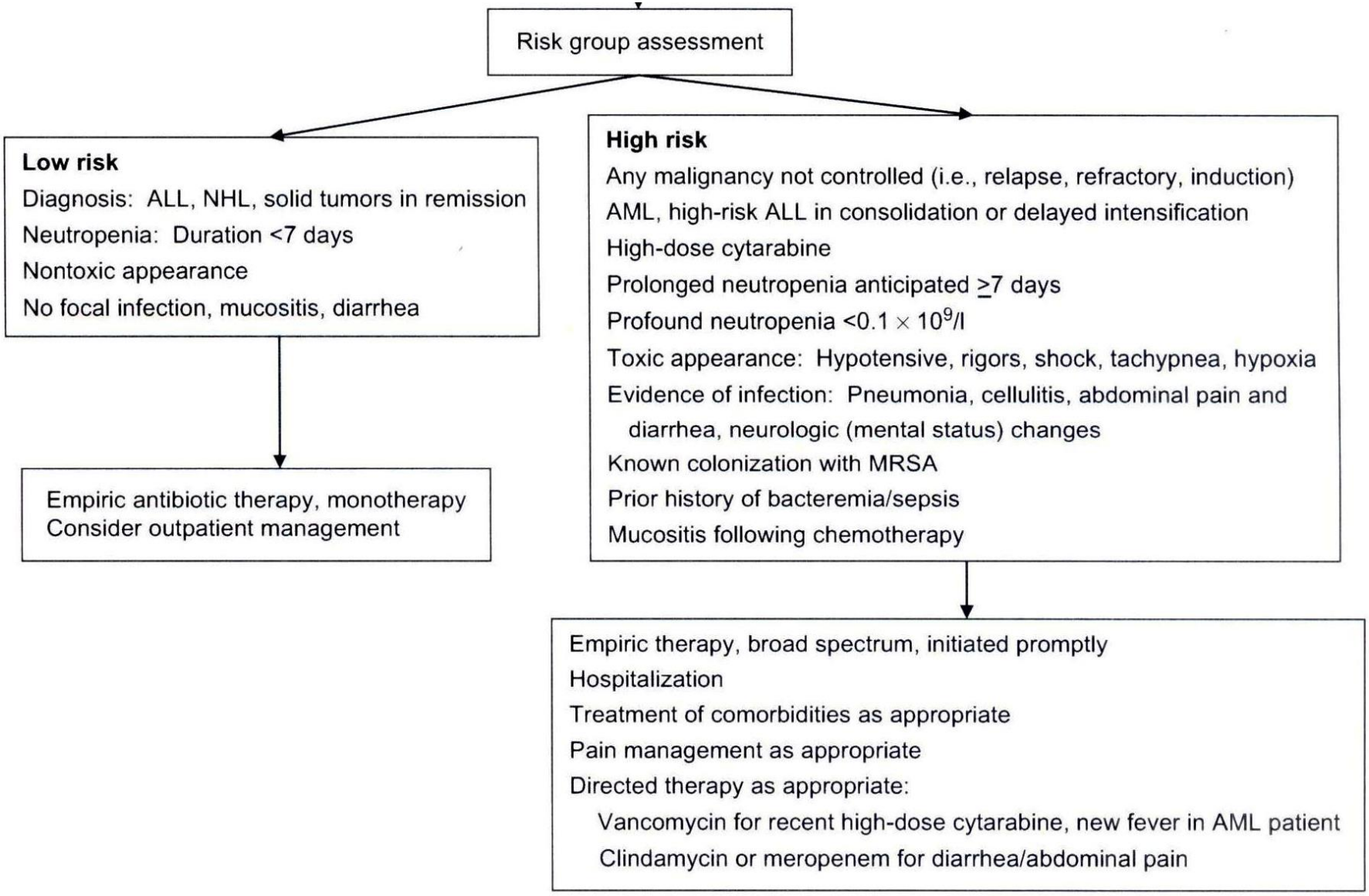
Urinalysis and urine culture

Stool culture, *C. difficile* toxin, rotavirus for diarrhea/abdominal pain

Electrolytes, BUN, creatinine, liver transaminases

Imaging: CXR if signs/symptoms of pulmonary process

CT as necessary per physical findings (sinuses, chest, abdomen, pelvis)


Risk group assessment
Low risk
Diagnosis: ALL, NHL, solid tumors in remission
Neutropenia: Duration <7 days
Nontoxic appearance
No focal infection, mucositis, diarrhea
Empiric antibiotic therapy, monotherapy
Consider outpatient management
High risk
Any malignancy not controlled (i.e., relapse, refractory, induction)
AML, high-risk ALL in consolidation or delayed intensification
High-dose cytarabine
Prolonged neutropenia anticipated ≥7 days
Profound neutropenia <0.1 × 10^9/l
Toxic appearance: Hypotensive, rigors, shock, tachypnea, hypoxia
Evidence of infection: Pneumonia, cellulitis, abdominal pain and diarrhea, neurologic (mental status) changes
Known colonization with MRSA
Prior history of bacteremia/sepsis
Mucositis following chemotherapy
Empiric therapy, broad spectrum, initiated promptly
Hospitalization
Treatment of comorbidities as appropriate
Pain management as appropriate
Directed therapy as appropriate:
Vancomycin for recent high-dose cytarabine, new fever in AML patient
Clindamycin or meropenem for diarrhea/abdominal pain

Risk Stratification

Validated Pediatric Risk Stratification Strategies for Low-Risk Patients

Strategy Factor	Rackoff et al (1996)	Alexander et al (2002)	Rondinelli et al (2008)	Santolaya et al (2001)	Ammann et al (2003)	Ammann et al (2010)
Patient & disease related factors	None	AML, Burkitt's lymphoma, ALL induction, progressive disease, relapsed with BM+	2 points for CVC; 1 point for age ≤ 5 years	Relapsed leukemia; chemotherapy within 7 days of episode	BM involvement, CVC, pre-B cell leukemia	4 points for chemotherapy more intensive than ALL maintenance
Episode-specific factors	Absolute monocyte count (AMC)	↓BP, ↑RR, O2 < 94%, new CXR changes, altered mental status, severe mucositis, Vomiting or abd pain, focal infect, other clinical reason for inpatient treatment.	4.5 pts. for clinical site of infection; 2.5 pts. for no URTI; 1 pt. each for fever > 38.5, and Hemoglobin ≤ 70	CRP ≥ 90 mg/L; hypotension; platelets ≤ 50,000	No clinical signs of viral infection, CRP > 50 mg/L, WBC ≤ 500/µL , Hemoglobin >100 g/L	5 points for Hemoglobin ≥90 g/L , 3 pts. each for WBC < 300/µL, and platelets less than 50,000
Rule formulation	AMC ≥100/µL: low risk of bacteremia, HSCT, high risk	Absence of any risk factors, low risk for serious medical complication; HSCT, high risk	Total score < 6 low risk of serious infectious complication; HSCT, high risk	Zero risk factors, only low platelets, or only < 7 days from chemo, low risk for invasive bacterial infection	3 or less risk factors, low risk of significant infection; HSCT, high risk	Total score < 9, low risk of adverse FN outcome; HSCT, high risk
Demonstrated to be valid	USA	UK	Brazil	Chile	Europe	Europe

Lehrnbecher T et al. J Clin Oncol 30: 4427-4438

We need guidline

- Fever with neutropenia is the most common complication of cancer chemotherapy
- High risk of serious complications, but only a minority of patients have invasive infections
- Treatment involves hospitalization of all patients
- Risk-adapted guidelines are well established for adults.
- For children there is lack of consensus on safe reduction of standard therapy in patients at low risk of complications

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

Risk Stratification Challenge

Predicting infectious complications in neutropenic children and young people with cancer (IPD protocol)

The PICNICC Collaboration Study (Predicting Infectious Complications of Neutropenic sepsis In Children with Cancer)

- Builds on the findings of the previous meta-analysis
- Aims to undertake a collaborative meta-analysis using individual participant data (IPD) from existing data sets for the studies with defined clinical decision rules (CDRs) for risk stratification in FN children.
- This data will be pooled and reanalyzed applying individual CDRs across studies with the primary aim of finding the most validated criteria that could be used to define a more accurate and unanimous predictive rule.
- Study currently ongoing.

Phillips *et al. Systematic Reviews* 2012, **1**:8
http://www.systematicreviewsjournal.com/content/1/1/8

Risk Stratification at St. Jude (Phase 1 of a 3-Phase ongoing study)

Risk Prediction in Pediatric Cancer Patients With Fever and Neutropenia

Hakim H., Flynn P.M., Srivastava D.K., et al. Pediatr Infect Dis J 2010; 29:53-59

Phase 1: Retrospective review. Initial predictive factors identified

- underlying diagnosis,
- severity of fever,
- patient's clinical appearance,
- Absolute neutrophil count

Phase 2: Prospective cohort study to validate these predictive factors, plus assess predictive role of inflammatory markers like CRP, procalcitonin

Phase 3: Will be a randomized clinical trial to evaluate risk stratified management of FN

Assessing severity of FN

Patient and disease related factors

- Type of malignancy: AML; Pre-B ALL; Burkitt's lymphoma; progressive malignancy; relapse with BM involvement.
- Type of chemotherapy: HSCT; ALL induction; chemotherapy any chemo more intensive than ALL maintenance therapy.
- Timing of chemotherapy: Given within 7 days prior to onset of FN episode
- Other factors: presence of central venous catheter (CVC); age ≤ 5 years

Episode specific factors

- Vital signs: Fever ≥ 38.5; hypotension; tachypnea; hypoxia < 94%
- Other Signs and Symptoms: altered mental status; severe mucositis; vomiting or abdominal pain; focal infection; upper respiratory tract infect; any other specific clinical reason for inpatient admission.
- Laboratory: Hemoglobin: ≤ 70 g/L; Platelets: < 50,000/μL; WBC: <300 / < 500; AMC: ≥ 100/μL (low risk);
- Imaging: New chest X-ray changes

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AML=Acute myeloid leukemia; Pre-B ALL= Precursor B-cell acute lymphoblastic leukemia; BM= Bone marrow; HCST=hemotopoietic stem cell transplantation; WBC= White blood count; CRP= C-reactive protein; AMC= Absolute monocyte count

Working Group(WG)-1: Initial Presentation

Specific clinical questions were put together for guidelines development:

- What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low or high risk for poor outcomes?
- What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?
- What empiric antibiotics are appropriate for children with high-risk FN?
- In children with low-risk FN:
  - is initial or step-down outpatient management as effective and safe as inpatient management?
  - is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?

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WG-1Recommendation: Risk Stratification

Qs.1:

What clinical features and laboratory markers can be used to classify pediatric patients with FN as being at low or high risk for poor outcomes?

- Adopt a validated risk stratification strategy and incorporate it into routine clinical management (1C)

Key message

Each treating center must choose a strategy and incorporate it into routine clinical practice

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WG-1Recommendation: Evaluation

Qs.2:

What clinical, laboratory, and imaging studies are useful at the initial presentation of FN to assess the etiology of the episode and guide future treatment?

- Obtain blood cultures at onset of FN from all lumens of central venous catheter (CVC) (1C)
- Consider peripheral blood cultures concurrent with obtaining CVC cultures (controversial) (2C)
- Consider urinalysis and urine culture in patients where clean catch midstream specimen is readily available (2C)
- Obtain chest X-ray only in symptomatic patients (1B)

Key messages

- Upfront blood cultures essential in all patients with FN
- Other evaluations are recommended in the clinical context but should not delay initiation of antibiotics.

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WG-1Recommendation: Treatment

Qs.3:

What empiric antibiotics are appropriate for children with high-risk FN?

High-risk FN

- Use monotherapy with antipseudomonal B- lactam (penicillins/cephalosporins), or carbapenem as empiric therapy (1A)
- Reserve the addition of second gram negative agent (aminoglycoside), or glycopeptide for clinically unstable patients; patients with suspicion of resistant infection; or in centers with high rate of resistant pathogens (1B)
- Need for synergism like enterococcus, mycobacterium, endocarditis, cryptococcal meningitis

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WG-1Recommendation: Treatment

Key Messages

(Evidence-based)

High-risk FN

- Specific choice of antibiotics should be based on institutional resistance patterns, and should be reviewed periodically.
- Antipsuedomonal penicillin monotherapy is *non-inferior* to aminoglycoside containing regimens for initial management, and has less toxicity.
- No significant difference in efficacy, toxicity, or mortality found between antipseudomonal penicillins(piperacillin-tazobactam; ticarcillin-clavulanic acid) vs cefipime vs carbapenems
- Ceftazidime monotherapy should not be used if there are concerns of Gram-positive or resistant Gram-negative infections.

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Vancomycin should be consider

- AML receiving high dose cytarabine risk of strep viridians
- Presentation with hypotension and shock
- Prior history of alpha –hemolytic streptococcus infection
- Catheter site infection or skin breakdown
- Colonization with resistant organism
- Vegetation on Echo
- Severe pneumonia

WG-1Recommendation: Treatment

Qs.4 (a):

In children with low-risk FN: Is initial or step-down outpatient management as effective and safe as inpatient management?

Low-risk FN

- Consider initial or step down outpatient management if infrastructure is in place to ensure careful monitoring and follow-up (2B)

Key Message:

The infrastructure for close monitoring and reliable evaluation with ready access to appropriate medical care must be in place.

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WG-1Recommendation: Treatment

Qs.4 (b):

In children with low-risk FN: Is initial or step-down oral antibiotic management as effective and safe as management with parenteral antibiotics?

Low-risk FN

- Consider this route of administration if child is able to reliably tolerate oral antibiotics (2B)

Key Message:

- Oral route presents the challenges of palatability of formulations for children, and reliable achievement of therapeutic drug levels especially in the presence of mucositis and/or impaired gastrointestinal absorption
- Oral antibiotics used successfully in children with low risk FN are fluoroquinolones alone; or in combination with amoxicillin- clavulanate

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Working Group 2: Ongoing Management

TIMING:

24-72 hours after initiation of empiric antibacterial treatment

Specific clinical questions put together for guidelines development:

- Modification of treatment: when and how should the initial antibiotic therapy be modified during the pediatric FN episode?
- Cessation of treatment: when can empiric antibiotics be discontinued in patients with low- and high-risk FN?

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WG-2 Recommendations Treatment Modification

(24-72 hours after start of empiric treatment)

If responding to empiric therapy

- Do not modify initial coverage based solely on persistence of fever, if child is otherwise clinically stable (1C)
- Discontinue double gram-negative, or empiric glycopeptides coverage (if initiated) after 24-72 hours UNLESS this combination is justified by specific microbiologic indication (1B)

If NOT responding to empiric therapy

- If persistent fever and clinically unstable:
  - escalate initial empiric antibacterial regimen to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria (1C)

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WG-2 Recommendations: Treatment Cessation

(24-72 hours after start of empiric treatment)

For all patients

- Discontinue empiric antibiotics if:
  - blood culture negative at 48 hours,
  - afebrile for at least 24 hours, and
  - there is evidence of bone marrow recovery

(1C)

For low-risk FN

- Consider discontinuation of empiric antibiotics in low-risk patients at 72 hours irrespective of marrow recovery status, if:
  - blood culture negative,
  - afebrile for at least 24 hours, as long as
  - careful follow-up is ensured

(2B)

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WG-3 Recommendation: IFD Risk Stratification

Qs.1:

What clinical parameters can classify pediatric patients with persistent FN as high risk or low risk for invasive fungal disease (IFD)?

Patients with persistent fever despite 96 hours or more of broad-spectrum antibiotics can be stratified into:

- High-risk of IFD, if:
  - Have AML, or relapsed leukemia
  - Receiving HSCT, or on other highly immunosuppressive chemotherapy for any malignancy
  - Expected prolonged neutropenia (>10 days).
- Low-risk of IFD, if do not fulfil the above three criteria

(1B)

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WG-3 Recommendation: IFD Evaluation

Qs. 2:

What clinical features, lab tests, imaging studies, and procedures are useful to identify a fungal etiology for persistent/ recurrent FN despite broad spectrum antibiotics?

- IFD high risk:
  - Perform imaging to evaluate IFD. Should include CT of lungs and targeted imaging of other clinically suspected areas of infection (1B)
  - Consider CT imaging of sinuses in children > 2 years of age. (2C)
  - Consider prospective monitoring of serum galactomannan (GM) twice per week in hospitalized children for early diagnosis of invasive aspergillosis. (2B)
  - Consider galactomannan in BAL and CSF to support diagnosis of pulmonary of CNS aspergillosis (2C)
- IFD low risk: Do not implement routine GN screening. (1C)

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WG-3 Recommendation: IFD Empiric Treatment

Qs.3:

When should empiric antifungal therapy be initiated, what antifungal agents are appropriate, and when is it appropriate to discontinue empiric therapy?

- Start of therapy:
  - For IFD high risk: start empiric antifungal therapy if persistent or recurrent fever of unclear etiology at or beyond 96 hours of broad-spectrum antibacterial treatment. (1C)
  - For IFD low risk: consider empiric antifungal therapy if persistent or recurrent fever of unclear etiology at or beyond 96 hours of broad-spectrum antibacterial treatment. (2C)
- Choice of antifungal:
  - Caspofungin, or liposomal amphotericin b recommended for empiric treatment, where resources allow (1A).
  - Amphotericin-B in places with limited resources
- Prophylactic antifungal therapy in children with IFD high risk
  - No studies evaluating the safety of this approach in pediatric patients found.

Research needed to evaluate its safety and effectiveness in children.

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WG-3 Recommendation: IFD Empiric Treatment

OTHER ISSUES

Cessation of antifungal therapy, and

anti-fungal prophylaxis

- Cessation of antifungal therapy:
  - No data exists to guide this decision
  - International pediatric FN guideline panel agrees that empiric
  - therapy should be continued until absolute neutrophil count rises
  - to 100-500/μL, and no documented or suspected IFD.
- Prophylactic antifungal therapy in children with IFD high risk
  - No studies evaluating the safety of this approach in pediatric patients
  - found.
  - Research needed to evaluate its safety and effectiveness in children.

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