FEBRILE NEUTROPENIA IN CHILDREN AND ADOLESCENTS WITH CANCER

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SIOP Supportive Care WG, chair
The survival in childhood cancer has increased dramatically due to the advances in specific cancer treatment and also due to the advances in SUPPORTIVE CARE!

One of the complications of cancer/cancer treatment is FEBRILE NEUTROPENIA and needs URGENT TREATMENT!

- Diagnostic approach: clinical features, laboratory markers, imaging
- Risk stratification
- Initial treatment: Empiric Antibacterial Treatment
- Empiric antifungal treatment
  - when to start, how to modify
  - when to stop
- Modifications

GUIDELINES are very important
FEBRILE NEUTROPENIA-INTERNATIONAL GUIDELINES

- **INTERNATIONAL PEDIATRIC FEBRILE NEUTROPENIA GUIDELINE**.


- Infectious Disease Society of America (IDSA)
- ESMO, ASCO
- European Conference on Infections in Leukemia (ECIL) ECIL-4 was (Pediatric Group Considerations for Fungal Diseases and Antifungal Treatment in Children)

FEBRILE NEUTROPENIA

• Absolute neutrophil count (ANC) < 500 / mm$^3$ + Fever

• ANC may be 500 - 1000 / mm$^3$, but
  ANC expected to fall to < 500 / mm$^3$ within 24 - 48 hours

• Fever → Oral- once > 38.3°C or > 1 hour > 38°C

• Fever → Axillary once > 38.5°C or > 38°C at least twice, 4 hours apart.
  EORTC Br J Hem 1997
RISK FACTORS (LOW,HIGH)

- Duration of neutropenia (7-10 days)
- Depth of neutropenia (ANC<100)
- Cancer type (leukemia, Solid tm, early stage NHL)
- Status (remission, relapse/progressive dx)
- Treatment type (conventional, SCT)
- Sepsis or sign/symptoms of documented severe infection
- Additional organ/system disorder
- Age

- MASCC (Multinational Association for Supportive Care in Cancer) SCORE INDEX - B1-ADULTS-Scores ≥21, low risk of complications. Max.score 26, Klastersky et al JCO 2000:18:3038
# Pediatric FN Low risk Stratification Studies (Validated)

| Table 3: Validated Pediatric Risk Stratification Strategies for Low-Risk Patients |
|---|---|---|---|---|---|
| **Patient and disease related factors** | **Episode specific factors** | **Rule formulation** | **Successful validation** |
| None | AML, Burkitt lymphoma, induction ALL, progressive disease, relapsed with marrow involvement | Absolutely monocyte count > 100 / μL = low-risk of bacteremia | USA (Madsen 2002)[132] |
| 2 points for central venous catheter, 1 point for age ≤5 years | 4.5 points for clinical site of infection, 2.5 points for no URTI, 1 point each for fever >38.5°C, hemoglobin ≤7g/dL | Absence of any risk factor = low-risk of serious medical complication | UK (Dommett 2009)[133] |
| Relapsed leukemia, chemotherapy within 7 days of episode | CRP >90 mg/d, hypotension, platelets ≤50 G/L | Total score <6 = low-risk of serious infectious complication | Brazil (Rondinelli 2006)[23] |
| Bone marrow involvement, central venous catheter, pre-B-cell leukemia | Absence of clinical signs of viral infection, CRP >50 mg/dL, white blood cell count <0.5 G/L, hemoglobin >10g/dL | Zero risk factors or only low platelets or only <7 days from chemotherapy = low-risk of invasive bacterial infection | South America (Santolaya 2002)[24] |
| 4 points for chemotherapy more intensive than ALL maintenance | 5 points for hemoglobin > 90 g/L, 3 points each for white blood cell count <0.3 G/L, platelet < 50 G/L | Three or fewer risk factors = low-risk of significant infection | Europe (Amman 2010,13 Macher 2010)[20] |

**Rule formulation**

- Absolutely monocyte count > 100 / μL = low-risk of bacteremia
- Absence of any risk factor = low-risk of serious medical complication
- Total score <6 = low-risk of serious infectious complication
- Zero risk factors or only low platelets or only <7 days from chemotherapy = low-risk of invasive bacterial infection
- Three or fewer risk factors = low-risk of significant infection
- Total score <9 = low-risk of adverse FN outcome

**Successful validation**

- USA – United States of America; UK – United Kingdom; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; URTI – upper respiratory tract infection; CXR – chest radiograph; CRP – C-reactive protein; FN – fever and neutropenia

*Validation refers to clinically adequate discrimination of a group at low risk of complications*
INITIAL EVALUATION OF FN

- History
- PE (skin, perioral, perirectal areas!)
- Blood culture from all lumens of CVC-catheter 1C
- Peripheral blood culture 2C
- Urinalysis and culture 2C Pyuria may be absent in neutropenic children

Klaassen I, Ped Blood Ca 2011;56:868-70' NONINVASIVE

- Chest x-ray-if symptomatic 1B (abnormal chest x-ray in asymptomatic children is low (1-2.3%)
- In endemic areas for malaria -thick blood films
- Cultures of lesions and stool (if diarrhea)
- (Throat culture)
- CBC, biochemistry
- Imaging and other tests when necessary

Should we have peripheral-blood cultures in addition to CVC cultures? Pediatric studies

The utility of peripheral-blood cultures in addition to CVC cultures is controversial. Weak recommendation—balancing increased yield of bacteremia against pain/inconvenience and contaminants associated with peripheral cultures.

Adamkiewicz T, PIDJ 1999; Scheinemann K, Support Care Cancer 2010;

Table 5  Studies that describe the proportion of episodes of true bloodstream infection that are only positive on peripheral culture [modified from [5]]

<table>
<thead>
<tr>
<th>First author [reference]</th>
<th>Study type</th>
<th>Patient type</th>
<th>Number of patients</th>
<th>Number of episodes of true bloodstream infection</th>
<th>Adult or pediatric</th>
<th>Peripheral positive and CVC negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adamkiewicz [1]</td>
<td>Retrospective</td>
<td>Hem/Onc</td>
<td>89</td>
<td>35</td>
<td>Pediatric</td>
<td>2 (5.7%)</td>
</tr>
<tr>
<td>Scheinemann</td>
<td>Retrospective</td>
<td>Hem/Onc</td>
<td>224</td>
<td>228</td>
<td>Pediatric</td>
<td>28 (12.3%)</td>
</tr>
</tbody>
</table>
Strength of Recommendation and Quality of Evidence

- **Category/Grade Definition**
  - **A** Good evidence to support a recommendation for or against use.
  - **B** Moderate evidence to support a recommendation for or against use.
  - **C** Poor evidence to support a recommendation.

- **Quality of Evidence**
  - **I** Evidence from >1 properly randomized, controlled trial.
  - **II** Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
  - **III** Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

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Reproduced with the permission of the Minister of Public Works and Government Services Canada.
IDSA 2010-Culture of the sites listed below should be guided by clinical signs and symptoms (not routinely).

- **Stool**: If diarrhea → *Clostridium difficile toxin assay*. In US-limited value for bacterial pathogen cultures/ova and parasite examination, unless recent travel to/residence in areas of endemicity.

- **Urine**: Culture

- **CSF**: if meningitis is suspected. Platelet transfusion should be given prior to LP if low platelets

- **Skin**: Aspiration or biopsy of skin lesions suspected of being infected. Gram staining, and culture

- **Respiratory specimens**: Sputum samples for routine bacterial culture- if productive cough. LRT specimens obtained by BAL are recommended for patients with an infiltrate on chest imaging.

- **Nasal wash** or BAL specimens - for symptoms of *respiratory virus infection*, particularly during an outbreak or during winter. *adenovirus, influenza A and B virus, RSV, and parainfluenza virus*.

(KebudiR et al, SIOP2015-Samples of 74 respiratory tract infection episodes (51 children with cancer) were evaluated with simultaneous detection of 20 respiratory viruses. A respiratory viral pathogen was obtained in 43 (58%) of the analyzed samples. Rhinovirus (25%), Coronavirus (13.9%), RSV (13.9%), Metapneumovirus (4.6%), Bocavirus (2.3%), Parainfluenza (9.3%), influenza A (H3N2) (9.3%). Four (9.3%) had severe pneumonia (2 rhinovirus) and 11 (25.5%) mild lower respiratory tract infections.)
• Documented infection rate ~ % 30–60 (Clinical/microbiological)
• % 85 - 90 of documented infections in immunocompromised patients are due to BACTERIA. Recently Gram (+) > Gram (-)

**CLINICAL AND MICROBIOLOGICAL DOCUMENTED INFECTIONS IN PEDIATRIC FEBRILE NEUTROPENIA IN TURKEY** Kebudi R et al.

2004-24 centers-6 mo.-472 pts.- 829 episodes,
• 32 % of all episodes were documented microbiologically.
• 21% had bacteremia/fungemia
• 93 % of the documented microorganisms were bacteria,
  Gram+ bacteria were seen more frequently than Gram- bacteria.
• 6.4 % were fungi and
• 0.4 % were viruses (RSV).
• In some episodes, multiple microorganisms were found.
EMPIRICAL ANTIBIOTHERAPY

• In general,

• The standard of care in febrile neutropenic children → THEY SHOULD BE HOSPITALIZED AND TREATED URGENTLY WITH i.v. WIDE SPECTRUM EMPIRIC ANTIBIOTICS

• Empiric therapy should be modified according to culture results, clinical situation.
EMPIRICAL ANTIBIOTHERAPY

- wide spectrum*
- high bactericidal drug levels in serum
- Low toxicity
- Easy to administer

*Effective for (Gram -, P aeruginosa, S viridans )

** Each center, should evaluate their microbiological results.

IDSA Guidelines:
- Monotherapy
- Duotherapy
- Vancomisin / teicoplanin + mono/duotherapy
HIGH RISK FN- EMPIRICAL ANTIBIOTHERAPY
MONOTHERAPY RECOMMENDED 1A

- Ceftazidime
- Cefepime
- Imipenem
- Meropenem

Kebudi R et al, Cefepime vs ceftazidime-Med Pediatr Oncol 2001
Vural S...Kebudi R. Imipenem vs piperacilin tazobactam .Pediatr Int. 2010

- Cefoperazon / sulbactam
- Piperacilin tazobactam

Ayan İ et al, Med Pediatr Oncol 1998,
Görgün Ö et al Turkish Hematology Oncology J 1999

Antipseudomonal beta-laktam
Antipseudomonal penicilin (piperacilin-tazobactam**, ticarcilin + clavulanic a.)
Antipseudomonal cephalosporin (cefepime*) (ceftazidime should not be used if resistant Gram + / Gram – microorganism is suspected)
Carbapenem (pseudomembranous colitis)
HIGH RISK FN- EMPIRICAL ANTIBIOTHERAPY

• Monotherapy is recommended.1A.
• Aminoglicoside or glicopeptides should not be used for initial empirical therapy; should be added according to culture results or if :1B
  • If patient is clinically unstable, (hypotension, oliguria, septic shock!)
  • Suspicion of resistant infection
  • Centers with high incidence of resistant strains
Glicopeptides (vancomycin/teicoplanin)
• (IDSA 2010→Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site), skin-soft tissue infection, pneumonia, hemodynamic instability, colonisation with MRSA or Pneumococci resistant to penicilin/cefalosporins, modification if severe mucositis)
  • Strong recommendation, moderate evidence.
LOW RISK FEBRILE NEUTROPENIA IN CHILDREN – EMPIRICAL TREATMENT

- Start i.v. Antibiotics in the hospital (evaluate fever, clinical conditions, culture) and continue in the hospital
- Cultures(-) at 48 hr, good clinical condition, no fever for 24 hr
  a) p.o./i.v. treatment at home
  b) p.o. treatment in hospital
  c) if ANC, PLT improving stop treatment, discharge
- 1 dose of i.v. Antibiotic in hospital, continue i.v./p.o. treatment at home
- Only oral treatment at home or hospital
- Outpatient treatment: quality of life, reduced cost
LOW RISK FEBRILE NEUTROPENIA

In children with low-risk FN, inpatient or step-down outpatient management may be implemented if infrastructure is in place to ensure careful monitoring and follow-up 2B.

For children with low-risk FN, oral antibiotic administration is appropriate assuming that the child is able to tolerate oral administration reliably.

Fluorokinolons (7 studies, n 581); Fluorokinolons + amoxicillin + clavulonic asid (3 studies, n159); cefixime (1s, n 45); 676 patients, n.s. difference in treatment failure/modification/infection/ mortality)


OUTPATIENT TREATMENT ONLY IF

• Reliable caregiver, who can detect signs/symptoms
• Can be able to come to the hospital (<1 hr) asap
• Compliance
**CEFTRIAXONE FOR LOW RISK FEBRILE NEUTROPENIA**
Not recommended in centers with *P. Aeroginosa* is more than 1% of the pathogens

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Success</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preis, 1993</td>
<td>64</td>
<td>%81</td>
<td>i.v. ceftriaxone ± teikoplanin</td>
</tr>
<tr>
<td>Korthaus, 98</td>
<td>126</td>
<td>%78</td>
<td>i.v. ceftriaxone ± teikoplanin</td>
</tr>
<tr>
<td>Kaplinsky, 94</td>
<td>41</td>
<td>%79</td>
<td>i.v. ceftriaxone</td>
</tr>
<tr>
<td>Mustafa, 96</td>
<td>19</td>
<td></td>
<td>i.v. ceftriaxone</td>
</tr>
<tr>
<td>Petrilli, 2000</td>
<td>116</td>
<td>%75, %83</td>
<td>i.v. ceftriaxone</td>
</tr>
</tbody>
</table>
## Follow up of FN Patient

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B1. Ongoing Management</strong></td>
<td></td>
</tr>
<tr>
<td>Re-evaluation of clinical features of sepsis or resolution of infection is recommended daily in each episode of FN.</td>
<td>1C Strong recommendation Low-quality evidence</td>
</tr>
<tr>
<td>Re-assignment of risk stratification may be undertaken at 24, 48 and 72 hours following presentation.</td>
<td>2C Weak recommendation Low-quality evidence</td>
</tr>
</tbody>
</table>

If fever continues: blood culture every 48 hours (and other suspected sites)  
(3C) Semeraro M, Pediatr Blood Cancer 2010; 54: 284-90

**Biomarkers: IL-8, CRP and procalcitonin**
- No proven evidence for efficacy in routine use
MODIFICATIONS TO INITIAL EMPIRICAL THERAPY
WHEN, HOW?

Modification may be considered

- if persistent fever and patient not stable (hypotension/shock), ESCALATION with agents for recommended Gram -, Gram +, anaerobic bacteria (glicopeptide/aminoglicoside) 1C

- if positive blood culture results suspicious for resistant bacteria 1A.
  - MRSA: Consider early addition of glicopeptide (vancomycin, teicoplanin), linezolid, or daptomycin (B-III).
  - VRE: Consider early addition of linezolid or daptomycin (B-III).
  - ESBLs: Consider early use of a carbapenem (B-III).
  - KPCs: Consider early use of polymyxin-colistin/tigecycline(C-III).

- If clinical response at 24-72 hrs, no microbiological documentation, aminoglycoside/glicopeptide may be discontinued 1B- DEESCALATION

- If clinically stable, no modification recommended due fever 1C
- Think of fungal/viral microorganisms!
When to stop treatment: IDSA-ANC > 500 mm³
IPFNG- Stop when No fever, ANC > 100-500/mm³

- **All patients**: No fever for 24 hours, blood culture (-) at 48 hours, if marrow is recovering, treatment may be stopped (1C)

- **Low risk FN**: 
  
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>B3. When to Discontinue</td>
<td>1B Strong recommendation Moderate-quality evidence</td>
</tr>
<tr>
<td>Intravenous antibiotics can be discontinued in low risk patients who have negative blood cultures, who are afebrile and who have evidence of marrow recovery prior to resolution of neutropenia.</td>
<td></td>
</tr>
</tbody>
</table>

- if patient may be closely followed, outpatient treatment is suggested to be as effective and safe as inpatient treatment (2B).
When to stop treatment?

- Low risk Pediatric FN- Recurrence of fever after cessation of treatment
  - Marrow recovery 1%
  - Regardless of Marrow recovery 5%
  - No marrow recovery 14%
  - ANC \( \geq 100 \)? (no evidence for threshold)
- Treatment may be stopped only if the patient may be closely followed 24 hours/7 days.
- High Risk FN- If there is no marrow recovery, the duration of treatment is not known.
- 1979 Pizzo HRFN 7. day no fever, tx stopped, (7/17) morbidity, 2 ex *E. coli* bacteriemi
- New data needed
EMPIRICAL ANTIFUNGAL TREATMENT

Risk stratification
Evaluation
Treatment:
when to start,
when to stop,
which agent,
which dose?
Empiric Antifungal Treatment- Risk Stratification

• HIGH RISK of IFD : 1B
  • AML , relapsed acute leukemia,
  • highly myelosuppressive chemotherapy for other cancer
  • undergoing allogeneic HSCT
  • persistent fever (96 hours) despite prolonged broadspectrum antibiotic therapy and expected prolonged neutropenia(10 days);
  • (high dose steroids, mucositis, high CRP at day 4, CVC)

• All others (standard risk ALL, lymphoma, solid tm) should be categorized as IFD LOW RISK (1B)

• Environmental factors such as proximity to construction work also influence the risk for invasive aspergillosis
  • Panackal CID 2010, Halduven D Med Mycol 2009
• CLINICAL AND MICROBIOLOGICAL DOCUMENTED INFECTIONS IN PEDIATRIC FEBRILE NEUTROPENIA IN TURKEY
  ABANT 2004-24 centers
  6 mo.-472 pts.- 829 episodes, median 6 yrs, leukemia %50

• INVASIVE FUNGAL INFECTIONS IN CHILDREN WITH CANCER -ABANT 2006-25 centers
  1 yr-124 pts- 127 episodes, median 8.4 yr, leukemia% 72
  (14 proven- 7 Aspergillosis, 4 mucor, 1 fusarium, 2 candida)

  Ünüvar A, Keser M. On behalf of 25 centers

• VIRAL INFECTIONS-ABANT 2008
IMAGING STUDIES JCO 2012

• thorax CT detects pneumonia (IFI) earlier than X-ray

• Radiographic findings children with proven pulmonary IFD are often nonspecific. In particular, in children < 5 years of age, typical signs of pulmonary IFD (halo sign, air crescent sign, and cavities) are not seen in the majority of patients. Multiple nodules, infiltrates may be seen.

• The role of routine sinus imaging (such as by CT) during prolonged FN is uncertain, (sinonasal IFD). Notably, children <2 years of age have not had sufficient pneumatization of the sinus cavities, and thus, sinus imaging is rarely informative in this age range.

• abdominal imaging, US is recommended.

• Celkan T....KebudiR. Hepatosplenic Fungal Infections in Children With Leukemia-Risk Factors and Outcome: A Multicentric Study. J Pediatr Hematol Oncol. 2019 → 40 children with leukemia and HSFI from 12 centers. All cases were radiologically diagnosed with abdominal ultrasound, which was performed at a median of 7 days. ( Mucor 1-pathology; Candida -8-blood cultures. 22 had fungal infection in additional sites, mostly lungs. 9 died.

• KebudiR, ..KaramanS et al. CNS fungal infections in Children With Leukemia-Risk Factors and Outcome: A Multicentric Study. 39 patients,15 centers(18 surgery)'(10 aspergillus,4 candida, 1 mucor, 1 Trichoderma,) 9 granulocyte susp’1 ecmo, 46 % died.
### Antifungal evaluation-Summary of Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C2. Evaluation</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Recommendations on Imaging Studies in Children</strong></td>
<td></td>
</tr>
<tr>
<td>In high-risk children with persistent febrile neutropenia beyond 96 hours or</td>
<td>2B</td>
</tr>
<tr>
<td>in patients with focal clinical findings, imaging studies (e.g., CT-scan of</td>
<td>Weak recommendation</td>
</tr>
<tr>
<td>the lung or adequate imaging of the symptomatic region) should be performed.</td>
<td>Moderate-quality evidence</td>
</tr>
<tr>
<td>Pre-emptive antifungal treatment with a mold active agent should be initiated</td>
<td>2B</td>
</tr>
<tr>
<td>and further diagnostic work-up (e.g., BAL, biopsy) should be considered.</td>
<td>Weak recommendation</td>
</tr>
<tr>
<td>Notably, typical signs of invasive pulmonary fungal disease are often</td>
<td>Moderate-quality evidence</td>
</tr>
<tr>
<td>missing, in particular in the younger age group.</td>
<td></td>
</tr>
</tbody>
</table>
Empiric Antifungal Treatment- Evaluation

- **IFD high risk**: Consider prospective monitoring of serum galactomannan twice per week in IFD high-risk hospitalized children for early diagnosis of invasive aspergillosis (2B)
- **IFD low risk**: In IFD low-risk patients, do not implement routine galactomannan screening (1C)
- **All patients**: Consider galactomannan in BAL and CSF to support diagnosis of pulmonary or CNS aspergillosis (2C)
- In children, do not use -D-glucan testing for clinical decisions until further pediatric evidence has accumulated (1C)

*It is important to note that some antibacterial compounds (such as piperacillin-tazobactam) may cause false-positive GM results in pediatric and adult patients.*
EMPIRICAL ANTIFUNGAL TREATMENT

- High risk for IFD, persistent or recurrent fever of unclear etiology that is unresponsive to prolonged (96 hours) broad-spectrum antibacterial agents, initiate empiric antifungals (1C)
- Low risk for IFD, consider empiric antifungal therapy in setting of persistent FN (2C)
- All patients
- Use caspofungin (50 mg/m²/d-first day 70) or liposomal amphotericin (1-3 mg/kg/d)(1A) for empiric antifungal therapy (1A)
- In limited resource settings, amphotericin B deoxycholate (AmB-D), may be used.
- Continue until resolution of neutropenia (ANC >500/uL) in the absence of documented or suspected IFD.
- Preemptive antifungal treatment not recommended
ANTIFUNGAL THERAPY

- Conventional amphotericin B, Liposomal amphotericin B

- AZOLES: Fluconazole, Voriconazole, Posaconazol:

<table>
<thead>
<tr>
<th></th>
<th>Vori</th>
<th>Ravu</th>
<th>Posa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Aspergillus</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Fusarium</td>
<td>++</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>Scedosporium</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>-</td>
<td>?</td>
<td>++</td>
</tr>
</tbody>
</table>

- ECHINOCANDINS: Caspofungin, Micafungin, Anidulafungin:

<table>
<thead>
<tr>
<th>Highly active</th>
<th>Very active</th>
<th>Some activity</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>Candida parapsilosis</td>
<td>Coccidioides immitis</td>
<td>Zygomycetes</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>Candida guilliermondii</td>
<td>Blastomyces dermatididis</td>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>Aspergillus fumigatus</td>
<td>Scedosporium spp</td>
<td>Fusarium spp</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>Aspergillus flavus</td>
<td>Paecilomyces variotii</td>
<td>Trichosporon spp</td>
</tr>
<tr>
<td>Candida kefyr</td>
<td>Aspergillus terreus</td>
<td>Histoplasma capsulatum</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis carinii*</td>
<td>Candida lusitaniae</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HEMATOPOIETIC GROWTH FACTORS (G-CSF / GM-CSF)

- Prophlaxis (primary/secondary) →
- Therapy of neutropenia → Not recommended.

Exceptions:
Hypotension
Severe soft tissue infection
Sepsis and multiorgan failure
Systemic fungal infection
Severe neutropenia of long duration+ documented infection that does not respond to antibiotics

Febrile Neutropenia-SIOP-SIOP PODC Supportive Care WG projects

- **PICNICC** (Predicting Infectious Complications of Neutropenic sepsis In Children with Cancer) Collaboration by Bob Philips (Planned and discussed in the Supportive Care Working Group)

- **SIOP PODC**: Clinical Supportive Care Guidelines for the Treatment of Children with Cancer in a Low Income Setting.

  Trijn Israels MD PhD ¹, Lorna Renner MD FRCPCH ², Marc Hendricks MD FCPaeds ³, Peter Hesseling MD PhD ⁴, Scott Howard MD ⁵, Liz Molyneux FRCPCH FCEM ⁶

- Reviewer: Kebudi R, deWetterng M, Sung L
Febrile neutropenia

• Approach To Pediatric Febrile Neutropenia And Cost Of Febrile Neutropenia Treatment in Developing Countries : A Global Survey

(presented in SIOP London 2012)
Summary of the aim and questions of the survey on Febrile neutropenia

• AIM
  "Increasing awareness that "neutropenic fever" needs urgent treatment, and guiding the practitioner to treatment options according to availability of resources/medicine"

• Participants - 24 LIC/MIC + 5HI Countries
  East Asia & Pacific 1
  Europe & Central Asia 2
  Latin America & the Caribbean 11
  Middle East & North Africa 4
  South Asia 3
  Sub Saharan Africa 3
Conclusions of the febrile neutropenia survey

• There is significant correlation between income of the countries and the approximate time duration of the patient to reach the hospital from home after fever, as income decreased, the time duration to reach the hospital increased (rs= -0.469 (p=0.002).

• There is significant correlation between lower middle and high income and upper middle and high income respectively; rs=-0.576 (p=0.01 and rs=-0.411 (p=0.037) in this respect. There is no correlation between lower middle income countries and upper middle income countries (rs= -0.253 (p>0.05).

• In some countries, appropriate antibiotics for febrile neutropenia are not easily available.

• The mortality rate from febrile neutropenia is more than 10% in some countries.

• In about 25% of the countries, the family has to pay for the expenses.
Febrile Neutropenic Child

Urgent empirical antibiotic treatment

Fever (-) / clinically well * → Evaluate at 48-72 h. → Fever (+) / clinically poor *

Continue treatment

If Monotherapy + Aminoglicoside-glicopeptide

96 h. fever (+) + Evaluate for antifungal

ANC > 500 / mm³ ← Fever (-) clinically well → 5-7. day ANC < 500

Stop treatment

fever (-) fever (+)

complete treatment to 14 days?

* Pathogen (+) -> appropriate treatment