Activated 2008

Renewal 2022

Children's Cancer Hospital Egypt

57357

Last update in July 2021

CCHE-ID#01/08/2022

Based on

(NCCN & IDSA guidelines)

Guidelines for management of febrile neutropenic patients

Initial assessment of febrile and neutropenic patients; do the following:

1. Vital signs

2. Draw CBC, chemistry STAT

3. Focus of infection

4. C & S (if CVL from all lumens)

Low Risk features

1. Vitally stable.
2. No evident focus of infection, no abdominal pain or appearance of illness, no history of previous sepsis.
3. ANC ≥ 100 and anticipated rise within 7 days.
4. ALL during maintenance after W 20, OS, HD, Intraocular Retinoblastoma, favorable, unfavorable histology WT, Low grade glioma, GCT, Intermediate risk neuroblastoma and soft tissue sarcoma.

Need Outpatient management

High Risk features

1. **Clinically unstable** (Hypotension, tachypnea, new or worsening tachycardia, mental status changes, decreased urine output and organ dysfunction. A de-escalation policy will be adopted)
2. **Presence of any comorbid medical problem** including:

a) *GIT manifestation* such as **significant** abdominal pain, nausea, vomiting or diarrhea (De-escalation therapy will be adopted in case of previous history of typhlitis)

b) ***Newly* developed** chest infiltrates or hypoxemia. (Refer to pneumonia guidelines)

c) CVL ***infection*.**

3. ANC ≤100 and/ or anticipated to extend ≥ 7 days ***(in conjunction with any comorbid condition).***
4. ***Diagnoses***: AML, MDS, ALL (during induction, re-induction, consolidation and maintenance till W19 in standard or high risk; till W9 in low risk), NHL and Burkitt's lymphoma, high risk Medulloblastoma, ATRT, Extraocular Retinoblastoma, high risk neuroblastoma, relapsing patients on intensive salvage chemotherapy (ICE, CCE, TCE) and post BMT (autologous/allogenic) for the first 6 months, patients with GVHD on immunosuppressive therapy).

Need Inpatient management

Outpatient management - for Low risk features

Febrile, non-neutropenic patients are not eligible for this scheme

Oral	IV
❖ **Amoxicillin/ Clavulanic acid** (20-40mg/kg/day dose q 8hrs) If patient is allergic, use **Clindamycin** (30-40mg/kg/day - max daily dose 1800 mg/day) **+ Ciprofloxacin** (10mg/kg/12hrs) **OR**	❖ **Ceftriaxone** (50mg/kg/day) **±** **Amikacin** (15mg/kg/day) **FOR 3 DAYS**
❖ **Cefdinir** (7mg/kg/12hrs - max dose 600 mg/ day) **ALL patients on maintenance therapy including MTX (in absence of any comorbid conditions)**	

Note: AML patients receive prophylactic levofloxacin throughout their treatment.

Criteria required for oral therapy:

(Proper patient education to be provided to the patient)

- If patient able to tolerate and absorb.
- Compliance of the care giver.
- Patient and physician decision.
- Age > 2 years.

Re-assess in 3 days

Admission ← → Discharge± Oral antibiotic

Follow UP:

I. **Daily assessment of clinical condition (Vital signs and/or evolving focus of infection) By telephone, or personal contact.**
II. **Check ordered baseline CBC, CRP & blood C&S in 48-72 hours**

Indications for admission:

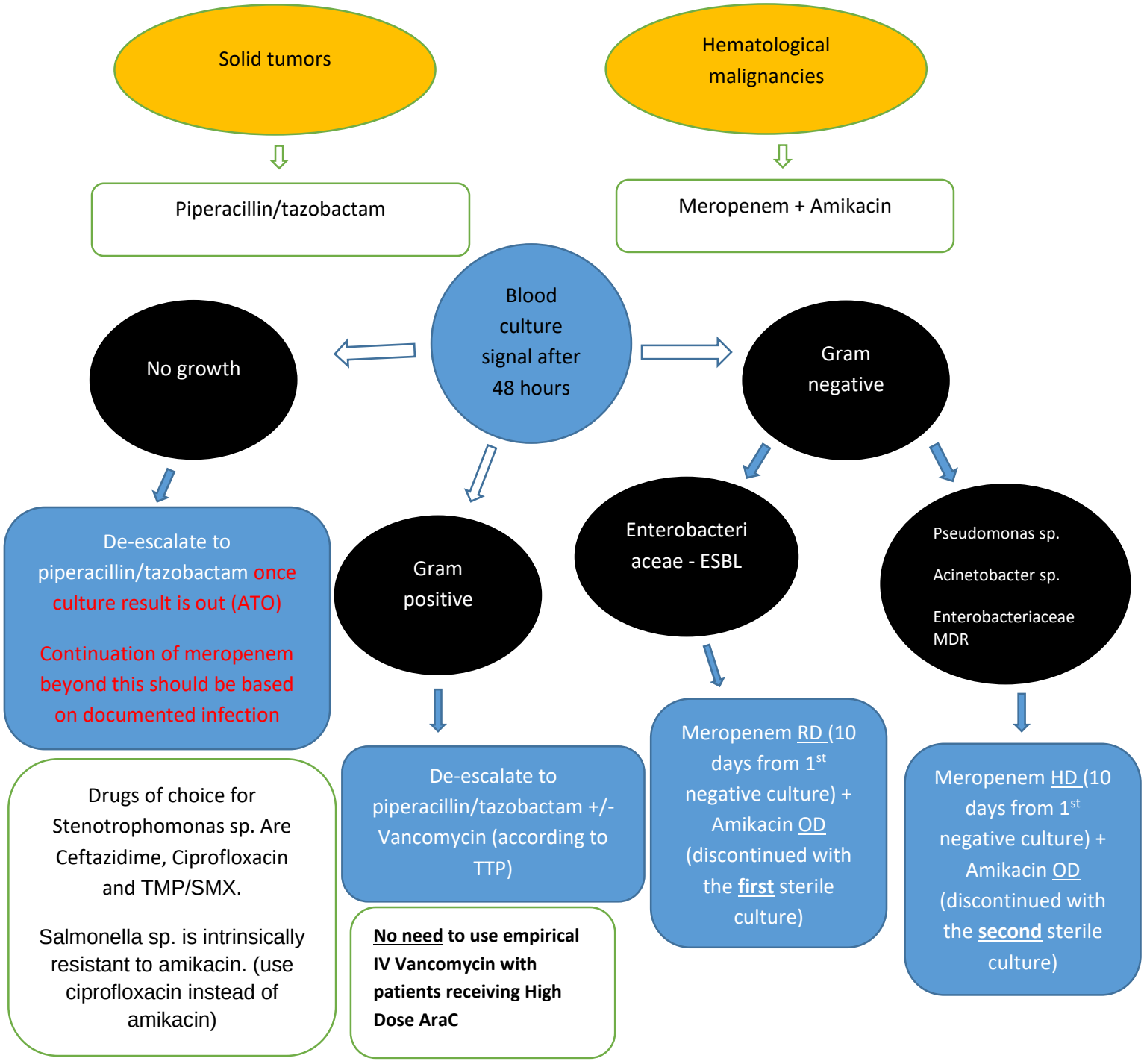
- **Vital instability**
- **Worsening symptoms & signs of infection.**
- **Positive culture.**

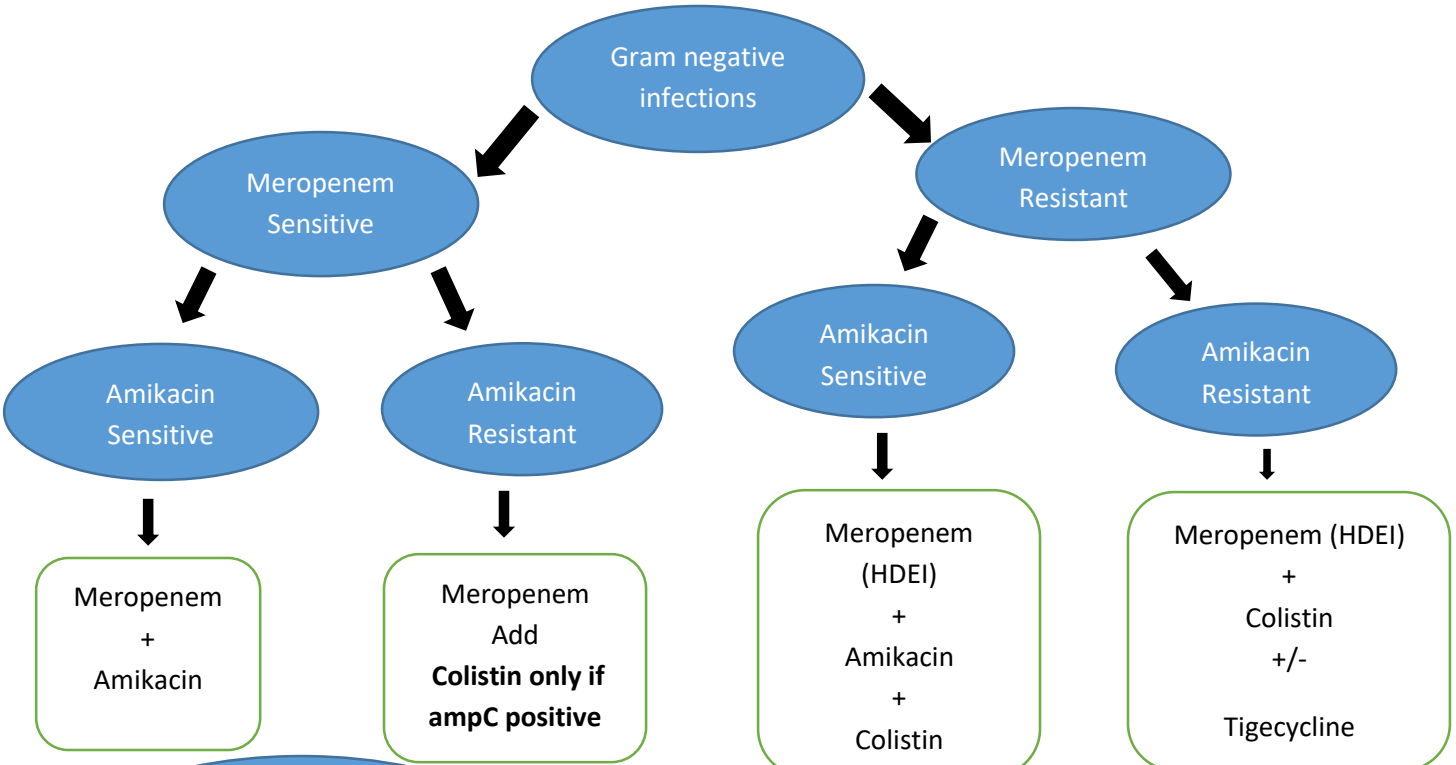
Stable/regressive patients *regardless of temperature*, DO NOT MANDATE ADMISSION

Specific reasons to return to clinic/ER:

- **New symptoms/signs reported by the patient**
- **Persistent or recurrent fever at days 3–5**
- **Inability to continue prescribed antibiotic regimen (i.e. oral intolerance)**

Inpatient management





Meropenem sensitive, MIC ≤2:
20 mg/kg over 30 minutes

Meropenem sensitive, MIC 4:
20 mg/kg over 3 hours

Discontinue 1 sensitive agent with the second sterile culture

Note: follow amikacin level (peak for efficacy and trough for safety) in all patients on amikacin *(except empirical)*

Note: Amikacin can be replaced with Gentamicin in case of better comparative MIC – same duration

Anti Gram positive coverage (Vancomycin / Teicoplanin)

- Blood culture (**consider TTP** for non-MRSA, duration 7 days)
- Serious catheter related infection (tunnel infection, or cellulitis around the exit site).
- Significant Skin and soft tissue infections (empirical Vancomycin is first line rather than Linezolid and Tigecycline).
- Vital instability or other evidence of severe sepsis, septic shock or pneumonia.

- **Linezolid to be added in case of current or previous infection with VRE/VRSA**

In case **of previous history of ESBL** bacteremia start on **Carbapenem.**

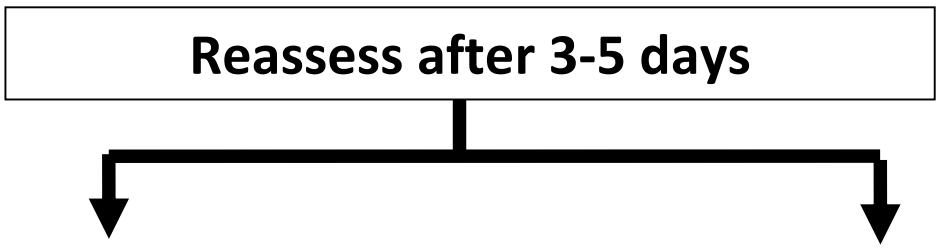
In case of **previous history of carbapenemase resistant enterobacteraecae (CRE) or clinical instability** ADD **Colistin and Inform IC/ID personnel**.

All patients with hematological malignancies will get a rectal swab on admission- and monthly thereafter. Patients with MDR-GN colonization (in routine rectal swab) will start empiric Meropenem (HD) + Amikacin + Colistin once febrile. The empiric regimen should be de-escalated once the blood culture result is out (**after 48 hours**).

For cases of septic shock

- Rapid interventions are needed.
- Fluid resuscitation.
- Oxygen.
- Hemodynamic monitoring.
- **ICU Consultation.**

- Patients presented with neutropenia **(regardless of fever pattern)** with clinical infection:
  - Refer to specific guidelines.
  - Consult for further management.



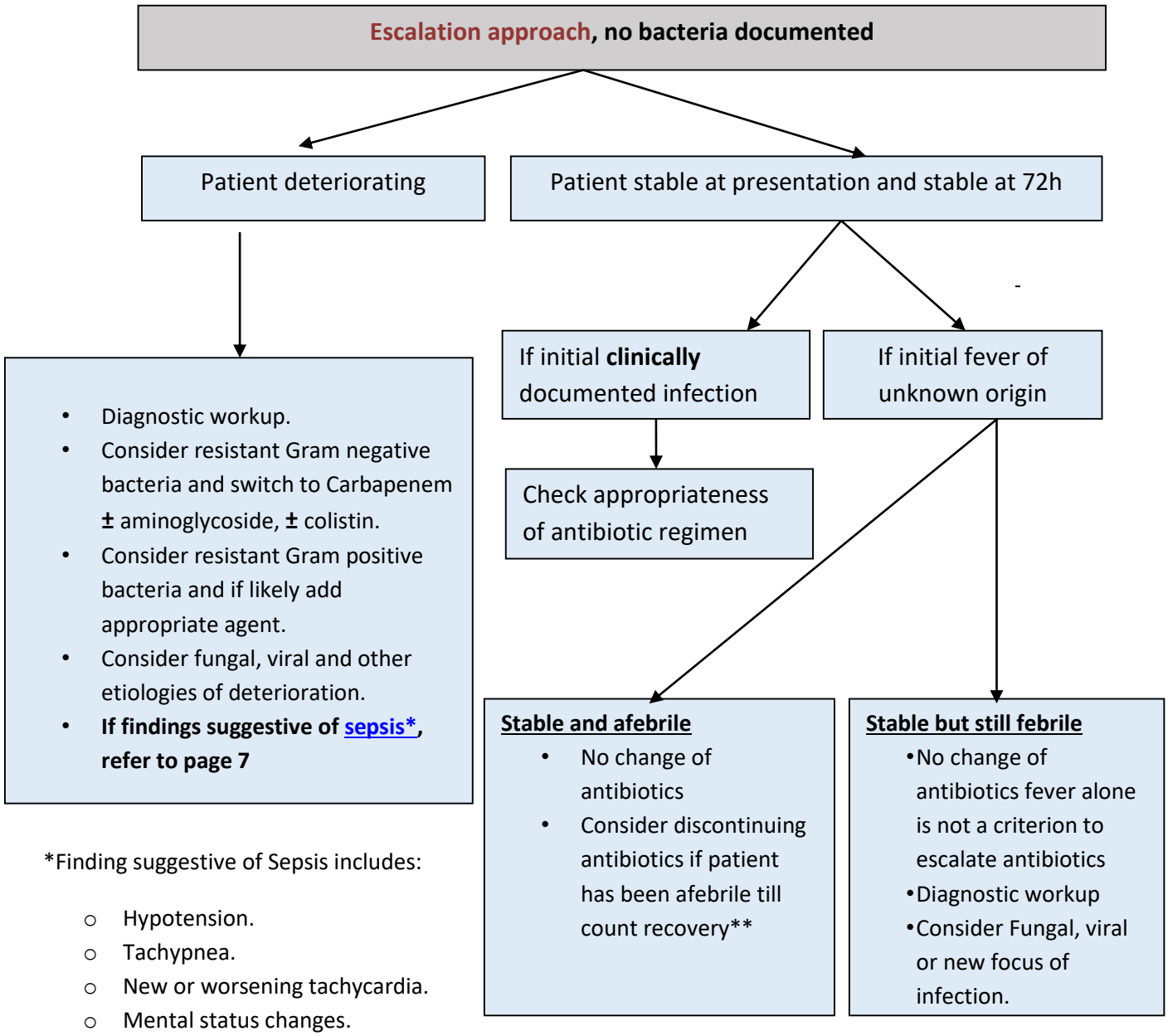
Patient controlled

Continue on the same regimen, de-escalate **(according to guidelines)**.

Patient uncontrolled
On D+5

Consider **(in hematology patients)** Anti-fungal addition & fungal screening AND **(in solid tumors)** GM & fungal screening in case of persistent fever OR breakthrough fever after 5 days of Antibiotic therapy.

1. Modification to initial antibiotic regimen should be guided by clinical and microbiological data.
2. Unexplained persistent fever in patient with stable conditions **rarely requires an empirical change of antibiotics.**
3. If Vancomycin or other anti-gram positive antibiotics was started initially, it may be stopped after 48 hrs if there is no evidence for gram positive infections.

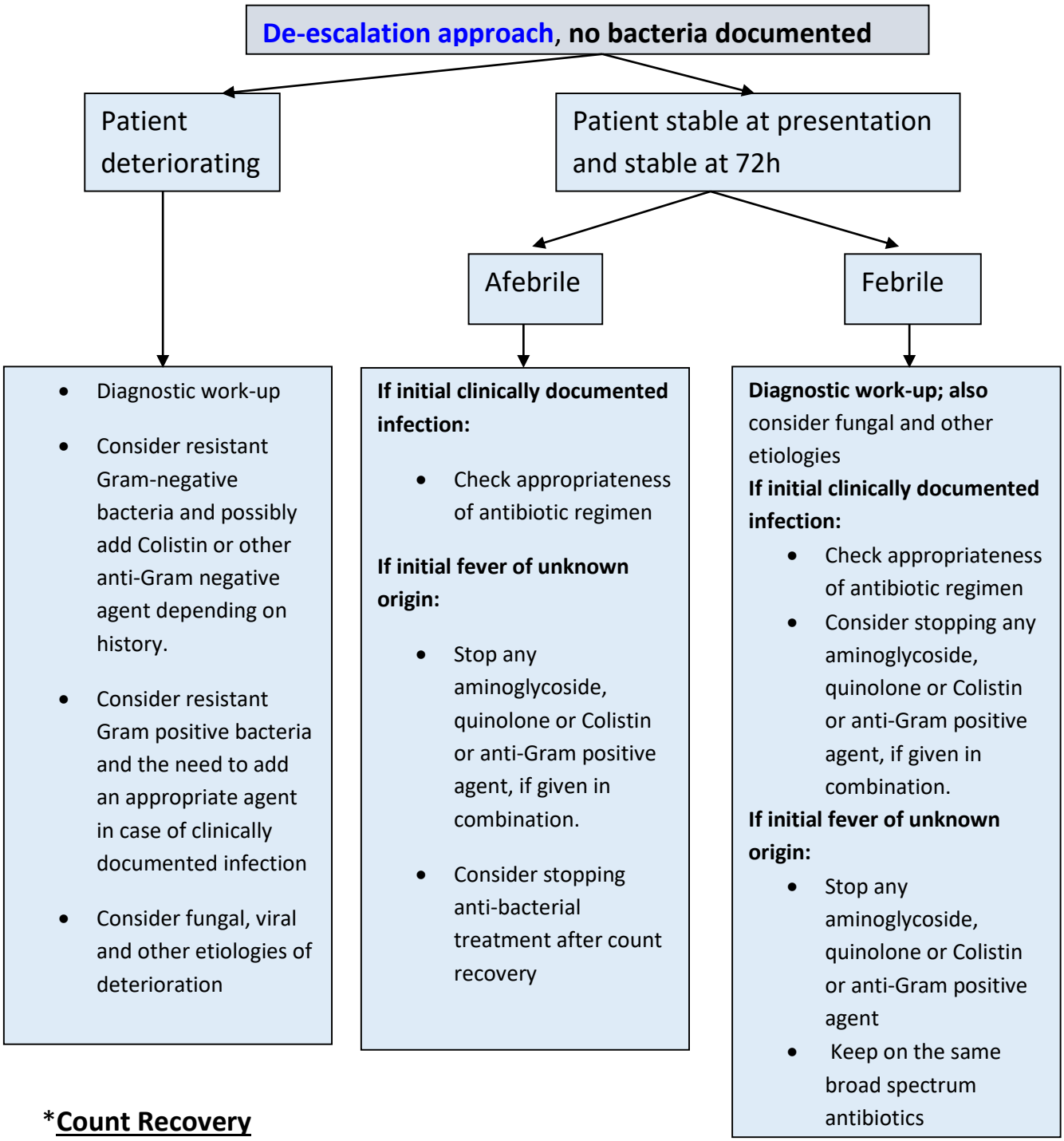


*Finding suggestive of Sepsis includes:

- Hypotension.
- Tachypnea.
- New or worsening tachycardia.
- Mental status changes.
- Decreased urine output and organ dysfunction.

**Count Recovery

- Rising ANC
- Rising Monocytes.
- In high risk patients ANC ≥200 for 2 successive days.



*__Count Recovery__

- Rising ANC & Monocytes (persistent APC count ≥300 FOR 2 SUCCESSIVE DAYS)
- In high risk patients ANC ≥300 for 2 successive days.

Development of Clinical Instability While Receiving Antibacterial Therapy

Findings suggestive of sepsis

Hypotension, tachycardia, mental status changes, organ dysfunction

- **Repeat physical examination to identify the source of infection.**
- **Repeat blood cultures.**
- **Re-consideration of radiologic studies.**

Empiric modification of antimicrobial therapy <u>pending culture results</u>

Consider patient history.

Empiric shifting of ABCS

- **Patients receiving Piperacillin/tazobactam**:
  Empiric shifting to a Carbapenem + Amikacin (or Colistin)
- **Patients receiving Carbapenem:**
  Empiric addition of Colistin.

+

Empiric addition of vancomycin

+

(For patients not receiving a systemic antifungal)

Empiric addition of Echinocandin

Empiric treatment for:

1. ALL during consolidation or maintenance.
2. T-Lymphoblastic lymphoma
3. NHL/BL, HD.
4. LCH.

Prophylactic treatment for:

1. ***AML*** *induction and intensification (whether on primary or salvage protocols)* → *PROPHYLACTIC VORICONAZOLE DURING ADMISSION all through periods of neutropenia.* ***NO NEED TO DISCHARGE PATIENTS ON VORICONAZOLE/LEVOFLOXACIN AFTER RECOVERY (WHETHER 1ry or 2ry PROPHYLAXIS)***
2. ***Newly diagnosed ALL*** *patients during induction (and Burkitt's leukemia) on D1,* ***Relapsing ALL*** *patients on D6 chemotherapy* → *PROPHYLACTIC ANIDULAFUNGIN DURING ADDMISSION*

Pre-emptive treatment for: All solid tumors

Liposomal Amphotericin B (1mg/kg/day)

On D+5 (if febrile) till recovery

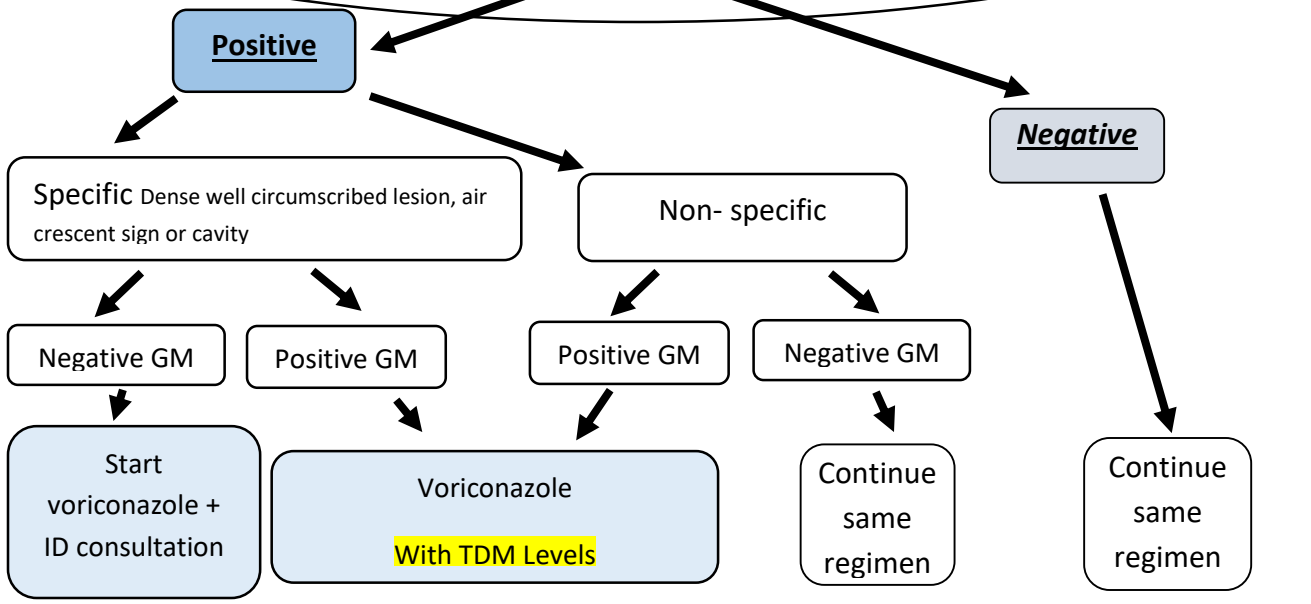
Anidulafungin
LD: 1.5mg/kg once
MD: 0.75mg/kg/day
Voriconazole
As per route and patient weight

Any admitted solid patient with Fever and Neutropenia will start GM screening twice weekly (starting day 3) & CT chest once weekly

D+5 febrile neutropenia (hematological malignancies) OR D+7 (solid tumors), patient is febrile →

Fungal screening:

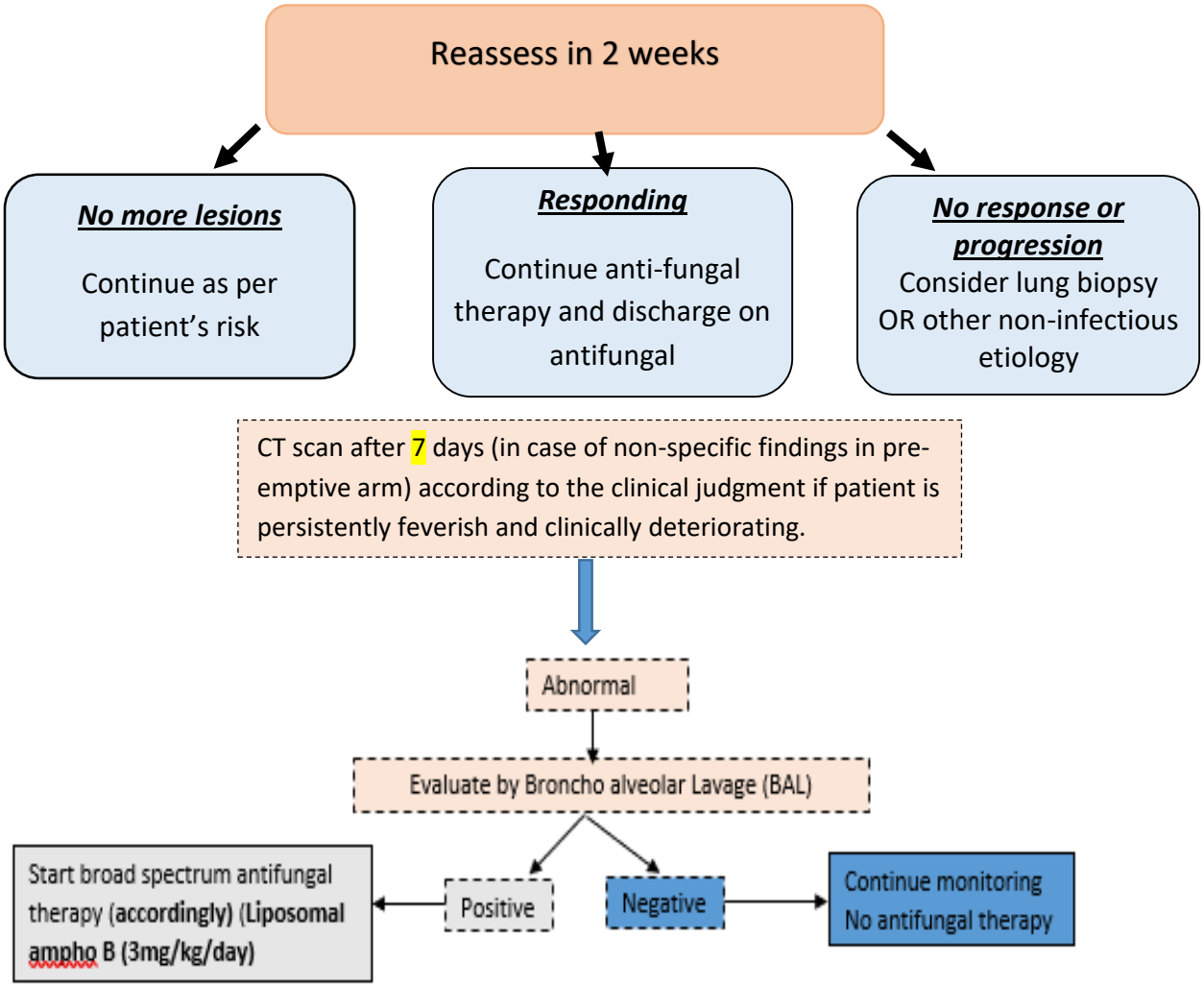
1. CT chest and sinuses, 2. Abdominal US
3. Other investigation if indicated
4. Galactomannan will be done in case of CT findings highly suspicious of fungal infection (non-solid patients)



Positive GM = Two positive consecutive GM ≥ 1.0 with rising pattern. Otherwise, negative.

Screening GM twice weekly:

- ***A negative test rules out IFI***
- ***A positive test indicates possible IFI***



Voriconazole should be:

- **Discontinued once the chest findings resolve in all patients with solid tumors.**
- **Discontinued after W19 total XV continuation in ALL (SR, HR) patients, and W9 in ALL (LR) patients.**
- **Discontinued after consolidation in patients on LMB protocol.**
- **Continued till end of intensive treatment in AML patients (before maintenance) and till end of treatment for patients on salvage chemotherapy.**

If otherwise, ID consultation is mandatory

For all patients on voriconazole:

TDM should be done **1 week** after therapy initiation **OR** dose modification, then on a **monthly** basis.

Patients on voriconazole should be re-assessed with CT-chest 2 weeks after starting therapy, then on monthly basis.

Documented fungal infection

- Histopathological documentation

OR

- Blood culture positivity + Galactomannan positive in two consecutive results.

(A) Aspergillosis, Fusariosis and trichosporonosis:

- Will shift to voriconazole (**with TDM levels**)

(B) Mucor, zygomycetes:

- **Induction: Liposomal ampho B (5mg/kg/day), daily for 2-3weeks for all patients, then**

Maintenance

>13 years start Posaconazole, with TDM levels.

<13 years continue on Liposomal Ampho B (5mg/kg/day) every other day.

(or posaconazole with TDM levels)

2ry prophylaxis (as per patient risk)

When patients are shifted from liposomal amho B to posaconazole, consider overlap period till Posaconazole reaches steady state.

Patient should be educated to take posaconazole with fatty/acidic meals.

❖ For any combination antifungal therapy, **ID team leader approval is mandatory**.

Candidemia in blood

Candida metastatic work up
- Echo
- Us liver spleen kidney
- Fundus examination *

*after neutrophil Recovery

Source control
- CVC removal

On Echinocandin prophylaxis ?

NO = Start Echinocandin

YES = Voriconazole

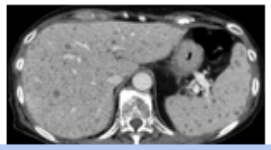
On Voriconazole prophylaxis ?

YES = start Echinocandin
*Check voriconazole level if low = +dose
(alternative option if pt is stable and vori sensitive)

Follow candida identifications & sensitivity results

C. albicans	C. Parapsilosis	C. Tropicalis	C. Glabrata	C. Krusei
Echinocandin → Step down → Fluconazole	Liposomal – amphoB → Step down → Fluconazole if sensitive	Echinocandin → Step down → Fluconazole if sensitive	Echinocandin → Step down → Voriconazole	Echinocandin → Step down → Voriconazole

- If Candida is azole-susceptible, step-down to fluconazole in stable patients after 5days of intravenous (iv) therapy
- Culture every 48h to establish time point clearance of candida
- Duration of therapy for candidemia if no metastatic complications is 14 days after documented clearance of Candida



Small, target-like abscesses in liver or spleen (bull's-eye lesions) or in the brain, or, meningeal enhancement

Chronic Disseminated Candidiasis (CDC) Or Hepatosplenic Candidiasis (HSC)

Possible → Radiological only

Probable → Blood culture or B-d-glucan or candida PCR → Radiological + mycology

Proven → Tissue biopsy

TTT guidelines

Hepatosplenic Candidiasis HSC

-Echinocandin or Voriconazole(VRC)
- Step to oral voriconazole or fluconazole according to resistant
- Duration until resolution of lesion on Imaging (several months)
- If persistent systemic manifestation (fever) = short term course of steroid (1mg/kg/d for 1w then tapper)

Candida Chorioretinitis*

-Voriconazole(VRC)
- If azole resistant = liposomal –amphoB (LAM)
- If macula affected = intravitreal (LAM) or (VRC) injection .
- If vitritis = vitrectomy is considered
- Duration = 4-6w

- Echinocandins achieve therapeutic concentrations in all infection sites with the exception of the eye, CNS, and urine
- Fundus ex should be done after neutrophil recovery to visualize lesion if present
- Growth of *Candida* from respiratory secretions usually indicates colonization and rarely requires treatment with antifungal therapy

Antibiotics		
Penicillins and penicillin+βLactamase inhibitor combinations		
Amoxicillin/Clavulanate	4:1 formulation	20-40 mg/kg/day, q8hrs, maximum 1500 mg/day
	2:1 formulation (>40 kg), >12yrs	1 tablet/8hrs , double potency tab/12hrs
Penicillin G	Mild-moderate infections	100,000 to 150,000 units/kg/day in divided doses every 6 hours; maximum daily dose: 8 million units/**day**
	Severe infections	200,000 to 300,000 units/kg/day in divided doses every 4 to 6 hours; maximum daily dose: 24 million units/**day**
	CNS infections	300,000 units/kg/day divided every 4 to 6 hours; maximum daily dose: 24 million units/**day**
Piperacillin/Tazobactam	general dosing, FN, Pneumonia	100 mg/kg/6hrs over 30 min, max 4000 mg/dose
Cephalosporins and cephalosporin+βLactamase inhibitor combinations		
Cefoperazone/Sulbactam	general dosing, FN	50 mg/kg/8hrs over 30 min, max 4000 mg/dose
	Critically ill patients	80 mg/kg/8hrs over 30 min, max 4000 mg/dose
	Post operative prophylaxis	10 mg/kg/8hrs over 30 min, max 2000 mg/dose
Cefepime	general dosing, FN, pneumonia, meningitis	50 mg/kg/8hrs over 30 min, max 2000 mg/dose
Ceftriaxone	general dosing	50mg/kg/24hrs over 30 min (max 1000 mg)
	severe infections	100 mg/kg/24 over 30 min (max 4000 mg)
	CNS	50mg/kg/12hrs over 30 min (max 4000 mg/day)
	Pneumonia	50 mg/kg/12hrs over 30 min (max 2000 mg/day) - or 100 mg/kg/24hrs
Ceftazidime	general dosing	50mg/kg/8hrs over 30 min, max 2000 mg/dose
Cefdinir	general dosing	7 mg/kg/12hrs, max 600 mg/day
Cefazolin	Surgical prophylaxis	30 mg/kg within 60 minutes prior to procedure, max 1000 mg/dose
Ceftazidime/Avibactam	general dosing 4:1 ratio	50 (ceftazidime) mg/kg/8hrs over 30 min, max 2000 mg (ceftazidime) /dose

Carbapenems		
Ertapenem	<12 yrs	15 mg/kg/12hrs over 30 min, max 500 mg/dose
	>=12 yrs	1000 mg q 24hrs over 30 min
Meropenem	FN (empirical), blood stream infections, severe skin infections, IAI	20 mg/kg/8hrs over 30 min, max 1000 mg/dose
	blood stream infections - CR	40 mg/kg/8hrs over 180 min, max 2000 mg/dose
	meningitis	40 mg/kg/8hrs over 30 min, max 2000 mg/dose
	skin infections (non severe, nor necrotizing)	10 mg/kg/8hrs over 30 min, max 500 mg/dose
Imipenem/Cilastatin	blood stream infections	15 mg/kg/6hrs over 30 min, max 1000 mg/dose
	blood stream infections - CR	25 mg/kg/6hrs over 60 min, max 1000 mg/dose
Fluroquinolones		
Ciprofloxacin	oral	10-20mg/kg/12hrs, max 750 mg/dose
	IV	10 mg/kg/8hrs, max 400 mg/dose
Levofloxacin	<5yrs	10 mg/kg/12hrs, max 750 mg/day (doses up to 500 mg over 60 min, over 90 min for higher doses)
	>=5yrs	10 mg/kg/24hrs, max 750 mg (doses up to 500 mg over 60 min, over 90 min for higher doses)
Aminoglycosides		
Gentamicin	general dosing	7.5mg/kg/day over 30-60 min
Amikacin	CNS	7.5 mg/kg/8hrs over 30min (max 1500 mg/day)
	general, severe infections	15mg/kg/**day** over 60min (max 1500 mg/day)
	severe infections	20 mg/kg/24hrs over 60 min (max 1500 mg/day)

Polymixins		
Colistin	general dosing, MD	2.5 mg/kg/12hrs over 30 min, max 180 mg/dose CBA
	general dosing, LD	5 mg/kg/once over 30-60 min, max 300 mg/dose CBA
	inhalation	75-150 mg/12hrs CBA
	intraventricular/ITH	1-4.2 mg/24hrs CBA (1 mg D1 - 2 mg D2 then 4.2 mg)
Tetracyclines		
Tigecycline	<8yrs	1.2 mg/kg/12hrs over 30 min, max 50 mg
	>=12yrs	50 mg/12hrs over 30 min
	BSIs sensitive to Tigecycline ONLY	2 mg/kg/12hrs over 30 min, max 100 mg
Glycopeptides and derivatives		
Teicoplanin	sepsis, bone, severe skin infections	10 mg/kg/12hrs over 30 min for 3 doses (max 800 mg/dose) then once daily (max 1000 mg/day)
Vancomycin	IV	15mg/kg/6hrs over 90 min, max 900 mg/dose
	oral (C. diff.)	10mg/kg/6hrs, max 500 mg/dose
	intraventricular/ITH	10-20 mg/day
Oxazolidinones		
Linezolid	<12 yrs	10 mg/kg/8hrs over 30 min, max 600 mg/dose
	>=12yrs	600 mg/12hrs over 30-60 min
Sulfonamides		
lfamethoxazole/Trimethopri	prophylaxis PCP	5mgTMP/kg/day (1 or 2 divided doses), 3 days/week, max 320mgTMP/day
	therapeutic PCP	20mgTMP/kg/day (3 or 4 divided doses), daily, max 320mgTMP/dose
	UTI	5mgTMP/kg/12hrs, max 160mgTMP/dose

Others		
Metronidazole	oral	30-50 mg/kg/day (3 divided doses), max 2250 mg/day
	IV, general dosing	10 mg/kg/8hrs over 60 min, max 500 mg/dose
	severe infections	10 mg/kg/6hrs, max 1000 mg/dose
	non severe C.diff. - oral	10 mg/kg/6hrs, max 500 mg/dose
Clindamycin	oral - mild to moderate infections	10-25 mg/kg/day, max 1800 mg/day
	oral - severe infections (osteomyelitis/SSTI)	30-40 mg/kg/day, max 1800 mg/day
Azithromycin	CAP, otitis media	10 mg/kg day1, 5 mg/kg days 2-5, max 500 mg/dose
	URTI	10 mg/kg/24hrs for 3 days, max 500 mg/dose
Rifampicin	General dosing	10 mg/kg/24hrs, max 600 mg

Antifungals		
Azoles		
Voriconazole	<2yrs	9mg/kg/12hrs
	2-<12yrs (LD)	9mg/kg/12hrs for 2 doses
	2-<12yrs (MD)	8mg/kg/12hrs (IV) - 9mg/kg/12hrs (PO), max 350 mg/dose
	12-14yrs - <50kg PO	9mg/kg/12hrs, max 350 mg/dose
	12-14yrs - >50kg PO	200 mg/12hrs
	12-14yrs - <50kg IV (LD)	9mg/kg/12hrs
	12-14yrs - <50kg IV (MD)	8mg/kg/12hrs
	12-14yrs - >50kg IV (LD)	6mg/kg/12hrs
	12-14yrs - >50kg IV (MD)	4mg/kg/12hrs
	>=15yrs IV (LD)	6mg/kg/12hrs
	>=15yrs IV (MD)	4mg/kg/12hrs
	>=15yrs <40kg PO	100 mg/12hrs
	>=15yrs >=40kg PO	200 mg/12hrs
Fluconazole	Systemic and CNS candidiasis/cryptococcal	12 mg/kg/24hrs, max 800 mg/dose
	Oropharyngeal candidiasis	6 mg/kg/24hrs, max 400 mg/dose
	BMT and surgical prophylaxis	6 mg/kg/24hrs, max 400 mg/dose
Posaconazole (susp)	Prophylaxis 6mo-6yrs	200 mg/8hrs
	Prophylaxis >6yrs	300 mg/8hrs
	treatment 6mo-6yrs	200 mg/6hrs
	treatment >6yrs	300 mg/6hrs

Echinocandins		
Caspofungin	LD	70 mg/m2 once (max 70 mg)
	MD (candidiasis, aspergillosis)	50 mg/m2/24hrs (max 50 mg), may increase dose to 70 mg/m2 (max 70 mg) in case of inadequate clinical response on D5
Micafungin	Prophylactic	1 mg/kg/24hrs, max 50 mg/dose
	Therapeutic	3 mg/kg/24hrs, max 150 mg/dose
Anidulafungin	LD	3 mg/kg/24hrs, max 200 mg/dose
	MD -candidiasis	1.5 mg/kg/24hrs, max 100 mg/dose
	Prophylactic	LD: 1.5 mg/kg/24hrs max 100 mg/dose, MD: 0.75 mg/kg/24hrs max 50 mg/dose
Polyenes		
Liposomal amphotericin B	Empirical therapy	1 mg/kg/24hrs
	Pre-emptive therapy	3 mg/kg/24hrs
	Invasive fungal infection	3 mg/kg/24hrs
	Mucormycosis	5 mg/kg/24hrs
	CNS infection	5 mg/kg/24hrs

Febrile Neutropenia-Risk stratification checklist criteria excluding patients from Low Risk Protocol

	Tick all relevant exclusion criteria	
	On Admission	At 48 hours
Age		
Age < 2 year		
Associated medical conditions requiring hospitalization		
Shock or compensated shock		
Hemorrhage		
Dehydration (moderate to severe)		
Altered mental status		
Chest infection (lower resp tract inf)		
Mucositis grade3-4		
Respiratory distress (gr 3, 4)		
Perirectal or other soft tissue abscess		
Rigors		
Organ failure		
GIT infection		
Cancer associated co morbidities		
ALL at diagnosis/relapse <28 days		
ALL not in remission <28 days		
AML		
Infantile ALL		
Intensive B-NHL protocol (1st 2 cycles)		
Allogenic BMT or Autologous PBSC transplant		
Sequential high dose chemotherapy with PBSC rescue		
History		
PICU admission (during last 3m)		
Non adherence - social concern		
-Patient concern		
Inability to tolerate oral antibiotics		
Downs syndrome		

Risk stratification and discharge criteria

Low risk

- Solid tumors patients, receiving intermittent chemotherapy, do mostly outpatient treatment.

Management:

- Oral Augmentin / Ciprofloxacin
- In case of Augmentin allergy: Clindamycin
- Phone follow up twice weekly
- Once weekly FU in OPC till count recovers

Discharge Criteria:

- **48 hours of negative cultures in conjunction with either being afebrile for 48 hours OR rising count**.

Intermediate risk

- Leukemia in remission
- relapsing solid tumors
- HR NBL

Management:

Evaluate patients on individual basis
If looks good and has no obvious source, give one dose of IV Ceftriaxone 3 days and send home on oral Augmentin/ Ciprofloxacin

Discharge on:

- Oral Augmentin / Ciprofloxacin
- In case of Augmentin allergy: Clindamycin
- Phone follow up twice weekly
- Once weekly FU in OPC till count recovers

High risk

- Infants < 1 year
- Leukemia induction or in relapse, Burkitt's lymphoma induction, constitute the highest risk group and are always admitted for IV antibiotics

Management:

- ***Any patient, regardless of risk stratification (all admitted cases) can be discharged on either off antibiotics OR oral antibiotics as long as:***
  - No source of infection
  - Afebrile ≥ 48 hours
  - Looks well
  - Negative cultures
  - APC > 100 and ANC is rising (~ 150-200)

NB:

All AML patients are kept in-house, past their Nadir after chemotherapy, until their WBC count recovers, (**APC > 250 on 2 consequetive days**) ***even if afebrile***

1.0 BACKGROUND AND RATIONALE

Infectious diseases are important causes of morbidity and mortality in patients with cancer. In certain instances, the malignancy itself can predispose patients to severe or recurrent infections.

Neutropenia has been recognized for many decades as a major risk factor for the development of infections in cancer patients undergoing chemotherapy. Effective strategies to anticipate, prevent, and manage infectious complications in neutropenic cancer patients have led to improved outcomes. Due to advances in antimicrobial therapy, it is now uncommon for patients with acute leukemia or that undergoing stem cell transplantation to die from infections during the neutropenic period. Although neutropenia remains a key factor for infections, other immunocompromised states pose at least equal risk.

These Guidelines are for **empirical treatment of fever and neutropenia** in pediatric cancer patients and should be applied in conjunction with careful, individual patient evaluation and with an understanding of host factors that predispose patients to specific infectious diseases and with an understanding of antimicrobial susceptibility patterns.

1.1 Host Factors That Predispose Patients to Infectious Complications

Immunodeficiency Associated With Primary Malignancy

Certain malignancies are inherently associated with immune deficits. Patients with hematologic malignancies and myelodysplastic syndrome (MDS) may be leukopenic due to infiltration of the marrow with malignant cells or due to a dysfunctional marrow.

Patients with advanced or refractory malignancy have a greater risk of infectious complications than those who respond to therapy. Refractory hematologic malignancies can be associated with marrow failure from the underlying disease itself and from multiple lines of prior immunosuppressive therapy.

Solid tumors may predispose patients to infection because of anatomic factors. Tumors that overgrow their blood supply become necrotic, thus forming a nidus for infection. Endobronchial tumors may cause recurrent post obstructive pneumonias. Abdominal tumors may obstruct the genitourinary or hepatobiliary tracts, predisposing patients to pyelonephritis and cholangitis, respectively.

Direct invasion through the colonic mucosa is associated with local abscess formation and sepsis by enteric flora. Patients undergoing surgery for malignancies may be at high risk for infectious complications as a result of the type of surgery, extent of tumor burden, preoperative performance status, and previous surgery, chemotherapy, and radiation therapy. Patients with advanced malignancy are also commonly malnourished, which further increases the risk of infection.

1.2 Neutropenia

The absence of granulocytes; the disruption of the integumentary, mucosal, and mucociliary barriers; and the inherent microbial flora shifts that accompany severe illness and antimicrobial usage predispose the neutropenic patient to infection. The signs and symptoms of infection are often absent or muted in the absence of neutrophils, but fever remains an early, although nonspecific, sign.

Approximately 48% to 60% or more of the patients who become febrile have an established or occult infection. Roughly 10% to 20% or more of patients with neutrophil counts less than 100/mcL will develop a bloodstream infection. Primary sites of infection are the alimentary tract (i.e., mouth, pharynx, esophagus, large and small bowel, and rectum), sinuses, lungs, and skin.

The pathogens responsible for initial infections early in the course of fever and neutropenia (F&N) are primarily bacteria, whereas antibiotic- resistant bacteria, yeast, other fungi, and viruses are common causes of subsequent infections. *Coagulase-negative staphylococci, S.aureus, viridans* group *streptococci,* and *enterococci* are the major Gram-positive pathogens. Coliforms (e.g*., Escherichia coli, Klebsiella, Enterobacter species*) and *Pseudomonas aeruginosa* are the most common Gram-negative infections complicating neutropenia. Herpes simplex virus (HSV), respiratory syncytial virus (RSV), parainfluenza, and influenza A and B are also occasionally initial pathogens.

Infections due to *Candida* species may occur later in the course of neutropenia, particularly as a consequence of gastrointestinal (GI) mucositis. *Aspergillus* species and other filamentous fungi are an important cause of morbidity and mortality in patients with severe and prolonged neutropenia. Deaths resulting from infections identified at the onset of fever during neutropenia remain uncommon, and most infection-associated deaths result from subsequent infections during the course of neutropenia.

2.0 MANAGEMENT OF NEUTROPENIC PATIENTS WITH FEVER AND NEUTROPENIA

2.1 F&N definition

Fever is defined as a single temperature 38.3°C or more orally or 38.0°C over 1 hour in the absence of an obvious cause. Although uncommon, a patient with neutropenia and signs or symptoms of infection (that is, abdominal pain, severe mucositis, perirectal pain) without fever should be considered to have an active infection. The concomitant administration of corticosteroids may also blunt the fever response as well as any localizing signs of infection. The NCCN guidelines define neutropenia as either:

1) An absolute neutrophil count (ANC) less than 500/mcL, or

2) An ANC less than 1000/mcL and a predicted decline to 500/mcL or less over the next 48 hours.

2.2 Initial evaluation

The initial evaluation should focus on determining the potential sites and causative organisms of infection and on assessing the patient's risk of developing an infection-related complication (see FEV-1) [See page A in appendix]. A site-specific history and physical examination should be performed promptly, cultures should be obtained, and empiric antibiotics started soon after the time of presentation. The common sites of infection for patients with fever and neutropenia: such as the alimentary tract, groin, skin, lungs, sinus, ears, peri-vagina, peri-rectum, and intravascular access device sites) should be thoroughly assessed. Other important historical features to

consider include:

- Major co morbid illness.
- Medications.
- Time since last chemotherapy administration.
- Recent antibiotic therapy.
- Exposure to infections from household members.

Initial laboratory/radiology evaluation should include:

- A complete blood count with differential analysis.
- Platelets.
- Blood urea nitrogen.
- Creatinine.
- Electrolytes.
- Total serum bilirubin.
- Liver-associated enzymes.
- Renal function tests.

Oxygen saturation and urinalysis should be considered, depending on symptoms.

Chest radiographs should be done for all patients with respiratory signs or symptoms; however, radiographic findings may be absent in neutropenic patients with pulmonary infection.

2.3 Cultures:

Culture specimens should be collected during or immediately after completing the examination. Two blood samples should be cultured.

When obtaining blood cultures, there are 3 options:

1) One set can be obtained peripherally and one can be obtained from a central venous catheter (if present).

2) Both sets can be obtained peripherally.

3) Both sets can be obtained through the catheter (see FEV-1) [see page A in appendix].

The positive predictive value of a catheter culture is less than a peripheral culture. The approach of obtaining blood for culture from both the central catheter and peripherally may help determine whether the venous access device (VAD) is the source of bloodstream infection based on the differential time to positivity. However, some experts recommend that only blood from the VAD needs to be obtained for culture, without the requirement for a peripheral vein blood culture.

In the absence of lesions or clinical signs and symptoms, routine cultures of the anterior nares, oropharynx, urine, stool, and rectum are rarely helpful.

Diarrheal stools felt to be infectious should be tested for the presence of *Clostridium difficile*. In patients with diarrhea, consider testing for Rotavirus and Norovirus in winter months and during outbreaks.

Symptoms of urinary tract infection should be evaluated with a urinalysis and culture. Vascular access site inflammation or drainage should be cultured.

Biopsy with microbiologic and pathologic evaluation should be considered for new or undiagnosed skin lesions.

Viral cultures of mucosal or cutaneous lesions may identify HSV infections.

In patients with symptoms of respiratory viral infection, viral cultures and rapid viral antigen testing of the nasopharyngeal secretions can be useful in winter months and during local outbreaks of such infections.

2.4 Initial Empiric Antibiotic Therapy

All neutropenic patients should be treated empirically with broad spectrum antibiotics promptly at the first sign of infection (that is, fever). This is done to avoid the mortality associated with a delay in treatment in those patients who have a serious infection.

The selection of initial therapy should take into consideration the following factors (see FEV-2) [see page B in appendix]:

- The patient's infection risk assessment (FEV-3) [see page C in appendix].
- The antimicrobial susceptibilities of pathogens isolated locally
- The most common potentially infecting organisms, including antibiotic-resistant pathogens, such as extended spectrum beta-lactamase– producing Gram-negative rods, vancomycin-resistant enterococcus (VRE), and colonization with or previous infection with methicillin-resistant S.aureus (MRSA)
- The potential sites of infection
- The importance of a broad spectrum bactericidal antibiotic regimen that includes antipseudomonal coverage
- Clinical instability (for example, hypotension, organ dysfunction)
- Drug allergy

- Recent antibiotic use (including prophylaxis)

Recommended Approaches:

The panel considers each of the following three approaches to initial empiric management of febrile neutropenia to be appropriate based on the results of large, randomized controlled clinical trials.

The first approach is intravenous (IV) antibiotic monotherapy (all category 1 except where noted) with either imipenem/cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime (category 2B)[See page D in appendix]. Local institutional bacterial susceptibilities should be considered when selecting empiric antibiotic therapy. At hospitals where infections by antibiotic resistant bacteria (e.g., MRSA or drug- resistant Gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly.(MS-8) [see page O in appendix].

The second approach to initial empirical therapy is intravenous antibiotic, combination therapy using 3 options:

1. An aminoglycoside plus an antipseudomonal penicillin (with or without a beta-lactamase inhibitor) (category 1) [see page D in appendix].
2. Ciprofloxacin plus an antipseudomonal penicillin (category 1) [see page D in appendix]; or
3. An aminoglycoside plus an extended-spectrum antipseudomonal cephalosporin (ceftazidime or cefepime).

For patients at high risk for Pseudomonas infections (such as, history of previous Pseudomonas aeruginosa infections or presence of ecthyma

gangrenosum), initial combination therapy with the most active antipseudomonal agents available in the local setting should be considered. The third approach is the addition of intravenous vancomycin for specific indications either to intravenous monotherapy or to combination therapy.

Vancomycin should be reserved for specific indications and should not be considered as a routine component of initial therapy for fever and neutropenia.

2.5 Empiric Addition of Vancomycin

Reports of vancomycin-resistant and vancomycin- intermediate sensitive S.aureus are currently rare but are of key concern.

Empiric vancomycin use should be considered only in patients at high risk for serious Gram-positive infection, and should not be considered as a routine component of initial therapy for fever and neutropenia.

Vancomycin should be considered in the following clinical situations (see FEV-D) [see page F in appendix]:

- Clinically apparent, serious, intravenous catheter-related infections. Many of these infections are caused by *coagulase-negative staphylococcal* isolates, which are usually beta-lactam antibiotic resistant.
- The patient's blood cultures are positive for Gram-positive bacteria before final identification and susceptibility testing.
- Known colonization with penicillin/cephalosporin–resistant pneumococci or MRSA
- Hypotension or septic shock develops in the patient without an

identified pathogen (that is, clinically unstable).

- Soft tissue infection

Risk factors for viridans group streptococcal bacteremia (category 2B) [see page D in appendix]: severe mucositis (for example, associated with cytarabine) and prophylaxis with ciprofloxacin or TMP/SMX.

Although bloodstream infections by viridans group streptococci resistant to all beta-lactams are observed in patients with cancer, cefepime, imipenem/cilastatin, meropenem, and piperacillin-tazobactam have more reliable activity than ceftazidime against viridans group streptococci.

Addition of vancomycin produced no benefit compared to placebo with regard to defervescence, episodes of Gram-positive bacteremia, or use of empiric antifungal therapy in patients with hematologic malignancies and in HSCT recipients with neutropenic fever of unknown etiology that persisted for 48 to 60 hours after initial empiric piperacillin-tazobactam. A smaller randomized, placebo-controlled study did not show any advantage after adding teicoplanin (a glycopeptide antibiotic similar to vancomycin) in patients with neutropenic fever that persisted after 3 to 4 days of empiric imipenem.

In patients with neutropenic fever and severe mucositis who are receiving imipenem, meropenem, or piperacillin-tazobactam (that is, antibiotics with activity against oral flora), it does not appear that the addition of vancomycin is advantageous.

2.6 Agents with Broad Spectrum Activity Against Gram-Positive Pathogens

Linezolid, daptomycin, quinupristin/dalfopristin, and tigecycline are active against many Gram-positive organisms, including beta-lactam vancomycin-resistant pathogens. The ID team recommends that the use of these drugs be limited to specific situations involving infections caused by antibiotic–resistant organisms.

Resistance of Gram-positive organisms to linezolid is infrequent, but this agent needs to be used cautiously in patients with compromised bone marrow function because of the marrow toxicity associated with long-term use of linezolid. Thrombocytopenia is most common (0.3% to 10%) and increases with the duration of use. Linezolid should be considered for treatment of MRSA pneumonia in ventilated patients.

It can only be administered after the restriction form is approved by the ID team.

Recently, the FDA issued an alert about linezolid indicating that it is not approved for treatment of catheter-related infections, catheter-site infections, or Gram-negative infections.

Optimal therapy for VRE infections is not well defined. Linezolid, quinupristin-dalfopristin (active against E. faecium, but not E. faecalis), and daptomycin have been used in VRE bloodstream infections in patients with cancer with variable success rates. Removal of an infected catheter should always be strongly considered. In the absence of more definitive data, therapy with one of these agents is advised for VRE bacteremia.

2.7 Initial Empiric Therapy for Patients Who Are Clinically Unstable:-

Sepsis is suggested by signs of clinical instability including hypotension, tachypnea, new or worsening tachycardia, mental status changes, decreased urine output, and organ dysfunction. Initial therapy for sepsis should broadly cover pathogens that are likely to cause sepsis while minimizing the potential for inadequate treatment. The antibiotic regimen should be modified, if necessary, after culture results and susceptibility are known.

The initial empiric regimen for the neutropenic patient with clinical instability may include a broad spectrum beta-lactam (for example, imipenem, meropenem, or piperacillin-tazobactam) plus an aminoglycoside and vancomycin. Addition of fluconazole or an echinocandin should be strongly considered in patients not receiving antifungal prophylaxis.

Some experts also suggest that patients who have a history of *P.aeruginosa* colonization or of invasive disease should receive combination therapy with an antipseudomonal beta-lactam plus an aminoglycoside or ciprofloxacin.

In septic shock, rapid interventions need to be made. Fluid resuscitation, oxygen, invasive hemodynamic monitoring, and vasopressor agents may be required. Stress doses of hydrocortisone (intravenous 50 mg every 6 hours with or without fludrocortisone oral 50 mcg daily) have been associated with decreased mortality in patients with septic shock and with insufficient adrenal reserve. Stress-dose steroids are recommended for patients with septic shock who require vasopressor support.

2.8 Prognostic Factors in Patients With Bacteremia

The classification system for bacteremias in febrile neutropenic patients is based on size and presence of associated tissue involvement. Complex bacteremias are associated with the lung, liver and spleen, kidney, colon, bone and joints, veins and heart, meninges, soft tissues with necrosis, or skin/soft

tissue/wound/cellulitis greater than 5 cm. Simple bacteremias are associated with less tissue involvement (bacteruria, otitis, pharyngitis, soft tissue <5 cm). Profoundly neutropenic patients with simple bacteremias had a much higher response rate to antibiotics.

2.9 Empiric Antifungal Therapy in Persistent Neutropenic Fever

Empiric antifungal therapy for persistent febrile neutropenia unresponsive to broad spectrum antibacterial agents is used, because neutropenic patients are known to be at risk for invasive fungal infections, and because clinical examination and collection of cultures are not sufficiently sensitive for early detection of those infections.

Traditionally, empiric antifungal therapy is initiated after 4-7 days of empiric antibiotic therapy for fever and neutropenia, in patients who have remained febrile or have recrudescent fever. Empiric antifungal therapy for neutropenic fever principally involved switching from fluconazole to amphotericin B to broaden the antifungal spectrum to include molds such as *Aspergillus*. Subsequently, liposomal amphotericin B (L-AMB) proved to be safer than and as effective as conventional amphotericin B for empiric antifungal therapy.

Fluconazole has been used successfully as empiric therapy for neutropenic

fever in patients not receiving prophylaxis but is limited by lack of activity against molds. Intravenous followed by oral Itraconazole solution was as effective as, but less toxic than, conventional Amphotericin B when used as empiric therapy in an open, randomized study; these results led to FDA approval of Itraconazole solution for this indication. Itraconazole in the capsule formulation has erratic oral bioavailability and is therefore not suitable as empiric antifungal therapy. Itraconazole has negative inotropic effects and is contraindicated in patients with compromised cardiac function.

Echinocandins are active against *Candida* and *Aspergillus* species but have unreliable activity against most other opportunistic fungi.

This study strongly supports caspofungin as an option for empiric antifungal therapy. The other echinocandins, anidulafungin and micafungin, have not been studied specifically for empiric antifungal therapy

Newer azoles, such as voriconazole and posaconazole, and echinocandins are increasingly being used as prophylaxis against molds and Candida in high-risk patients. It is unclear whether patients who are already receiving mold-active Laboratory markers (such as serum galactomannan and beta-glucan) have important limitations, including falsely negative results in some patients already receiving prophylactic or empiric antifungals.

In patients receiving only yeast-active prophylaxis with fluconazole or no antifungal prophylaxis, empiric antifungal trials have shown that approximately 5% have baseline invasive fungal infections at the time of enrollment. Empiric antifungal therapy with anti-mold activity would be expected to benefit these few patients without incurring greater risk of

toxicity.

Pre-emptive antifungal therapy is a newly introduced concept that involves using characteristic changes in chest or sinus CT scans, laboratory markers, or both to trigger modification of the antifungal regimen, rather than provide empiric antifungals to all persistently febrile neutropenic patients.

Follow-up of Patients with Neutropenic Fever

Daily evaluation by a health care professional who is experienced in treating patients with fever and neutropenia is essential (see FEV-8) [see page G in appendix]. The daily examination should focus on a site-specific assessment, and **an infectious disease consultation should be considered for all complicated cases or progressive infections.** Time to defervescence ranges from 2 to 7 days (median, 5 days) for febrile cancer patients with neutropenia who receive appropriate initial antibiotic therapy.

Random additions or changes in antibiotics for persistent fever are discouraged in the absence of additional clinical or microbiologic evidence.

Current bacterial blood culture systems (such as the BACTEC™ continuous-monitoring culture system) can detect 90% to 100% of bacterial bloodstream pathogens within 48 hours of culture. For this reason, ordering additional cultures routinely before obtaining the results from the initial series is discouraged. Daily review of previously obtained cultures is critical, and the panel recommends documenting clearance of bloodstream bacterial or fungal infections with repeat blood cultures

Evaluation of Response and Duration of Therapy

It is generally recommended that antibiotics be continued until the ANC is 500 or more cells/mcL in cases of fever of unknown etiology.

Patients with Documented Infection Sites or Pathogens

Most experts recommend continuing antimicrobial therapy for documented infections at least until a patient's ANC recovers to 500/mcL or more (see FEV-10) but also recommend using a defined course of therapy appropriate for the specific infection. Thus, the duration of antimicrobial therapy may be longer than the duration of neutropenia in these patients. For example, most uncomplicated skin and alimentary tract mucosal infections can be treated with 7 to 14 days of therapy. For most bacterial bloodstream infections, 7 to 14 days of therapy is usually adequate, with longer durations (10-14 days) recommended for Gram-negative bacteremias. A longer duration (10-21 days) of treatment is also usually indicated for infections of the lungs or sinuses and for bacteremias. Complex intra-abdominal infections, such as typhlitis, should be treated until all evidence of infection has resolved, and there has been recovery from neutropenia.

The duration of treatment for HSV (uncomplicated, localized disease to the skin) and varicella zoster virus (VZV; uncomplicated, localized disease to a single dermatome) infections is 7 to 10 days (category 1) [see page D in appendix]. Life-threatening infections, such as invasive fungi or CMV, require individualized courses of therapy that are often prolonged. The duration of anti-infective therapy may need to be extended if further chemotherapy is required while treating a significant infection. This may occur with infections

that complicate leukemia or lymphoma treatments in which multiple cycles of intensive chemotherapy are required.

Patients with documented infections who become afebrile after the initiation of the empiric antibiotic regimen and who are at low risk for complications associated with infection may be candidates for outpatient antibiotic therapy. The regimen, whether oral or intravenous, should be appropriate for neutropenic fever and have activity against the specific infection.

Severe or Refractory Infections

Patients with documented infection sites or pathogens who do not respond to initial antimicrobial therapy pose a difficult management challenge and are at increased risk of infection-associated morbidity and mortality**. The panel strongly recommends that an infectious disease expert be consulted for all such patients.**

The lack of response may suggest:

- Inadequate serum or tissue levels of the antibiotic(s)
- Infection at a vascular site (that is, catheter or "closed space" infection)
- Emergence of a second infection.
- An infection with a pathogen resistant to the antimicrobial therapy being used.

Some documented infections fail to respond to appropriate therapy because of associated profound neutropenia. If possible, treatment should be optimized using broad spectrum antibiotic combinations that minimize other organ toxicity.

Patients With Persistent Neutropenia and Fever of Unknown Etiology

A critical component of treating patients with fever of unknown etiology is daily clinical evaluation. Careful, daily, site-specific examinations should be performed by a health care professional who has experience and expertise in managing neutropenia and fever. Reassessment should include a review of all previous cultures and radiographs.

If patients receive vancomycin as part of their initial empiric therapy, but they do not have a pathogen recovered or a site of infection identified justifying such treatment, then vancomycin should be discontinued.

Patients with fever of unknown origin who become afebrile soon after starting empiric therapy may have empiric antibiotics discontinued with ANC recovery (500 or more neutrophils/mcL) as long as the neutrophil count is likely to continue to increase (patients are often receiving a growth factor). This recommendation assumes that the patient is clinically well and afebrile for at least 24 hours before antibiotic discontinuation.

Patients who become afebrile but remain persistently neutropenic (500 neutrophils or less/mcL) should receive a more prolonged course of antibiotic therapy until the neutropenia resolves (see FEV-11) [see page I in appendix].. Lower risk patients can also be switched to oral antibiotics until their neutropenia resolves (that is, 500 mg ciprofloxacin every 8 hours plus 500 mg of amoxicillin/potassium clavulanate every 8 hours). **Patients with recurrent fever should be reassessed promptly to determine the need for a change in their antibiotic regimen or for addition of antifungal therapy.** In stable patients who fail to have neutrophil count recovery, have no documented

focus of infection, and have been afebrile for more than 7 to 14 days, some panel members support discontinuing empiric antimicrobial therapy (category 2B) [see page D in appendix].

Patients with a fever persisting beyond 4 days of initial antimicrobial therapy and with an unidentified source of infection should undergo reassessment of their antimicrobial therapy (see FEV-12) [see page J in appendix]. **The need for a change in therapy should be based on the patient's clinical status and likelihood of imminent bone marrow recovery.**

The clinically stable patient with persistent fever of unknown etiology may be safely watched without altering the initial antimicrobial therapy. Modifications of initial empiric antibiotic therapy should be based on specific new clinical findings and/or new microbiologic results; fever alone should not prompt changes in antimicrobial therapy. The major exception is the initiation of empiric antifungal therapy in patients who have persistent or recurrent fever after 4 to 7 days of empiric antibacterial therapy and who are not receiving mold-active prophylaxis (see "Empiric Antifungal Therapy"). Most experts advise continuing empiric antibiotic therapy until the absolute neutrophil count recovers.

Although fever resolution may be slow during neutropenia, persistent fever may result from a noninfectious etiology, such as drug fever. Persistent fever may also represent an inadequately treated infectious process, such as:

- A nonbacterial infection (fungal or viral)
- A bacterial infection that is resistant to empiric antibiotics
- A venous access or closed space infection

- Inadequate antimicrobial serum levels.

It is important to recognize that documented deep tissue infections may take longer than fever of unknown etiology to respond to antimicrobial therapy. In these cases, daily assessment of clinical improvement or failure depends on radiographic, culture and clinical examination data, as well as on the fever trends. Unusual infections (for example, toxoplasmosis) may complicate neutropenia, particularly if immunosuppressive agents (for example, high-dose corticosteroids) are also used. The panel strongly **recommends an infectious disease consultation for these patients.**

Development of Clinical Instability While Receiving Antibacterial Therapy

Although persistent neutropenic fever alone is not an indication to modify the antibacterial regimen, signs of breakthrough infection should prompt additional evaluation and consideration to modify therapy.

New findings suggestive of sepsis (for example, hypotension, tachycardia, mental status changes, and organ dysfunction) require the following:

1) Repeat physical examination to identify a source of infection 2) Repeat blood cultures

3) Consideration of radiological studies

4) Empiric modification of antimicrobial therapy pending on culture results

Information about the previous use of antibiotics and local sensitivity patterns of Gram-negative pathogens should guide empiric changes.

Empiric addition of vancomycin is warranted in the unstable patient (see FEV-

A, FEV-D) [see page K,L,M,N &F in appendix]. In patients receiving ceftazidime, the possibility of breakthrough infections (either from extended spectrum beta-lactamase–producing or from cephalosporinase- producing Gram-negative rods) should be considered and switching to imipenem or meropenem is appropriate pending culture results.

Addition of fluconazole or an echinocandin should be strongly considered for possible candidemia.

The antibiotic regimen should then be tailored based on culture and radiologic results.

Outpatient Management of Patients With Neutropenic Fever Initial Evaluation of Risk

Risk assessment attempts to predict the probability that a neutropenic patient will experience serious complications during a febrile episode; risk assessment also helps determine whether the patient who is at low risk for serious complications could safely receive treatment outside of the hospital and receive initial empiric therapy with oral antibiotics. Prospective trials have indicated that febrile neutropenic patients can be initially evaluated in the hospital, ambulatory clinic, or home and then treated effectively with broad spectrum intravenous, sequential intravenous/oral, or oral therapy.

Risk assessment should be performed as part of the initial evaluation.

Duration of Neutropenia and Risk

For decades clinicians have regarded depth and duration of neutropenia as critical determinants of a patient's risk for infection. Once the relationship

between the ANC and incidence of infections was demonstrated, the importance of increased neutrophil counts on outcomes was evident. In Bodey's original work, the fatality rate was highest (80%) in patients who initially started with neutrophil counts less than 100/mcL that did not change during the first week of infection compared to the lower rate (27%) in those patients who started out with neutrophil counts less than 1000/mcL, which then rose to greater than 1000/mcL.

Evaluation of Patients for Outpatient Therapy for Neutropenic Fever

Outpatient therapy should be considered only for low-risk patients who consent to home care, have a telephone, have access to emergency facilities, have an adequate and supportive home environment, and are within 1 hours travel time of a medical center or physician's office. Outpatient therapy requires a period of early monitored assessment and an observation period of 2 to 12 hours (category 2B) [see page D in appendix].

The assessment requires:

- A careful examination
- Review of laboratory results
- Review of social criteria for home therapy (as previously described)
- Assessment of whether oral antibiotics are feasible.

The observation period is used to confirm the patient is low risk, to observe and administer the first dose of antibiotics as well as monitor for reaction, to ensure the stability of the patient, to organize discharge plans to home and follow-up, to educate the patient, and to perform telephone follow-up within 12 to 24 hours.

Outpatient antimicrobial treatment may consist of broad spectrum antibiotics given at home or in the clinic or an oral regimen for carefully selected patients. For low-risk patients who are considered appropriate for oral therapy, the combination of ciprofloxacin with amoxicillin/clavulanate (both at 500 mg every 8 hours) is considered the regimen of choice based on multiple, well-designed randomized trials (category 1) [see page D in appendix]. Ciprofloxacin plus clindamycin is an acceptable alternative for penicillin-allergic patients. However, ciprofloxacin monotherapy is not considered by the panel to be an adequate broad spectrum agent because of the potential for serious breakthrough infections caused by viridans group streptococci.

Intravenous therapy may also be used for outpatient treatment of low-risk patients with fever and neutropenia with treatment given either in the home or day clinic setting.

Once-daily ceftriaxone has been used for empiric antibiotic therapy in a few noncomparative studies in centers where *Pseudomonas* is not a common pathogen.

Although ceftriaxone combined with a once- daily aminoglycoside is a convenient regimen for outpatient intravenous administration, therefore, the panel cannot recommend ceftriaxone with or without an aminoglycoside as empiric therapy for neutropenic fever. If this regimen is used, it should be restricted to low-risk patients at centers where *P.aeruginosa* infection is uncommonly observed.

Follow-Up of Outpatients with Fever and Neutropenia:

The panel recommends that patients be assessed daily while febrile, although some experts feel that less frequent follow-up may be appropriate after fever defervescence (see FEV-14).

A return to the clinic is recommended for:

- Any positive culture
- For persistent or recurrent fever at 3-5 days
- If serious subsequent infections or adverse events develop, or
- If the patient is unable to continue the prescribed antibiotic regimen (for example, because of oralintolerance).

3.0 DRUG INFORMATION AND DOSE MODIFICATION

GRAM-POSITIVE AGENTS	DOSE	SPECTRUM	COMMENTS/PRECAUTIONS
Vancomycin	15 mg/kg IV every 6 hr Adults dose 500mg Q6 maximum dose 4 grams per day	Gram-positive organisms with exception of VRE and a number of rare Gram-positive organisms. Not recommended as monotherapy	• Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present, Restricted antibiotic form required, , as well as TDM Dose adjustment in renal impairment.
Linezolid	IV and PO: 10	Gram-positive	• Hematologic toxicity may occur,

	mg/kg Q8H IV and PO: Children > 12 years: 600 mg Q12H IV and PO maximum dose per day: 1.2 grams	organisms including VRE -not recommended as monotherapy	thrombocytopenia most common (0.3% to 10%) • Serotonin syndrome rare, use cautiously with SSRI's1 • Not for routine use in fever and neutropenia although does not impair neutrophil recovery • Treatment option for VRE and MRSA • Peripheral/optic neuropathy with long-term use • Not recommended for line infections • Restricted antibiotic
Teicoplanin	10 mg/kg I.V. every 12 hours for 3 doses, followed by 10 mg/kg I.V. or I.M. once daily Adults:6 mg/kg (~400 mg) given every 12 hours for 3 doses, followed by 6 mg/kg/day;	Gram-positive organisms including VRE -not recommended as monotherapy	• Restricted antibiotic form is required.

	doses up to 12 mg/kg/day may be used		

Other antimicrobial Agents (category 1)	**DOSE**	**SPECTRUM**	**COMMENTS/PRECAUTIONS**
Imipenem/cilastatin sodium	Children:15mg /kg Q6 Adults: 500 mg IV every 6 h	• Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms • Preferred against extended spectrum beta-lactamase (ESBL) and serious	• Use for suspected intra-abdominal source • Meropenem is preferred over imipenem for suspected /proven CNS infection • Imipenem may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency • Empiric therapy for neutropenic fever
Meropenem	Children:20mg /kg Q8 Adults: 1000 mg IV every 6 h max 6 gram per day in case of CNS infection		

Piperacillin/tazobacta m	Children:100mg/kgQ8 Adults:4.5 grams IV every 6 h	• Enterobacter infections. • Carbape nem-resistant Gram-negative rod infections are an increasing problem at a number of centers Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organism • Requires dose adjustment in patients with renal insufficiency	• Effective in nonsocomial pneumonia and intra-abdominal infections • Lack of clinical trial experience in neutropenic patients • Use for suspected intra-abdominal source • Not recommended for meningitis • Use for suspected intra-abdominal source • Not recommended for meningitis May result in false positive galactomannan3 • Empiric therapy for neutropenic fever
Cefepime	Children:50mg /kgQ8 Adults: 2 grams IV every 8 h	• Broad spectrum activity against most Gram-positive and Gram-negative organisms	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for

			neutropenic fever - Requires dose adjustment in patients with renal insufficiency.
Ceftazidime	Children:50mg /kgQ8 Adults: 2 grams IV every 8 h max 6gram/day	• Relatively poor Gram-positive activity • Breakthrough streptococcal infections reported • Not active against most anaerobes and Enterococcus spp.	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for neutropenic fever based on resistance among certain Gram-negative rods requires Dose adjustment in patients with renal insufficiency.
cefoperazone and Sulbactam	Children:80mg /kgQ8 Adults: 1.2 g (cefoperazone) every 8 hours; maximum daily	Upper and lower respiratory and urinary tract infections; skin, soft tissue, bone and joint infections; septicemia, meningitis,	requires Dose adjustment in patients with renal insufficiency.

	dose: 4 g (sulbactam)	peritonitis, cholecystitis, cholangitis, pelvic inflammatory disease, endometritis, gonorrhea, and other abdominal and genital tract infections	
Aminoglycosides :	**DOSE**	**SPECTRUM**	**COMMENTS/PRECAUTIONS**
Gentamicin	2.5 mg/kg/dose every 8 hours Once daily dosing:7.5 mg/kg/dose every 24 hours (maximum: 120 mg)	• Activity primarily against Gram-negative organisms • Gentamicin is synergistic with beta-lactams against susceptible S. aureus and Enterococcus infections	• Nephrotoxicity and ototoxicity limit use •Combination therapy with anti-pseudomonal penicillin +/- beta-lactamase inhibitor or extended spectrum cephalosporin Dosing individualized with monitoring of levels requires Dose adjustment in patients with renal insufficiency.
Amikacin	7.5 mg/kg/dose every 12 hours Once daily		
OTHER ANTIBACTERIAL AGENTS	**DOSE**	**SPECTRUM**	**COMMENTS/PRECAUTIONS**
Ciprofloxacin	IV: 10 mg/kg Q12H	• Good activity against Gram-	Avoid for empiric therapy if patient recently treated

	I IV maximum dose per day: 1.2 grams Po: 10 - 20 mg/kg Q12H PO maximum dose per day: 1.5 grams	negative and prophylaxis atypical (e.g., Legionella spp.) organisms • Less active than "respiratory" fluoroquinolones against Gram-positive organisms • No activity against anaerobic organisms	with fluoroquinolone • Increasing Gram-negative resistance in many centers • Oral antibiotic combination therapy in low-risk patients (with amoxicillin/clavulanate or clindamycin) In combination with antipseudomonal penicillin in higher risk patients
Levofloxacin	Infants ≥6 months and Children <5 years: 10 mg/kg/dose every 12 hours Children ≥5 years: 10 mg/kg/dose every 24 hours; maximum dose: 500 mg	• Good activity against Gram-negative and atypical (e.g., Legionella spp.) organisms • Improved Gram-positive activity compared to ciprofloxacin • Limited activity against anaerobes • Prophylaxis in neutropenic patients5,6	Prophylaxis may increase bacterial resistance and superinfection7 • Limited studies as empirical therapy in patients with fever and neutropenia
Ceftraiaxon	Children:80	widely distributed	

	mg/kg/day24 hours Meningitis:100 mg/kg/day	throughout the body including gallbladder, lungs, bone, bile, CSF (diffuses into the CSF at higher concentrations when the meninges are inflamed)	
Amoxacillin-Clavuolonic	20-40 mg (amoxicillin component)/kg/ day in divided doses every 8 hours		
Clindamycin	IV: Infants: 10 mg/kg Q6H IV maximum dose per day: 4.8 grams PO: 20-40 mg/kg/day PO maximum dose per day: 1.8 grams		
Trimethoprim/sulfam ethoxazole (TMP/SMX);	Prophylaxis: Oral: 5 mg/kg/dose for 3 days of every week every 12 hours for 3		Highly effective as prophylaxis against P. jirovecii in high risk patients

	consecutive days, (maximum dose: Trimethoprim 320 mg and sulfamethoxaz ole 1600 mg daily) (CDC, 2009) Treatment: 15-20 mg TMP/kg/day in divided doses every 6-8 hours		
ANTIFUNGAL AGENTS - Azoles	**DOSE**	**SPECTRUM**	**COMMENTS/PRECAUTIONS**
Fluconazole	Prophylaxis: PO: 6 mg/kg Q24H Treatment: IV :10mg/kg Q24 maximum dose per day: 600 mg Adults:400mg/ kg/day	Active against Candida fungi	Candida glabrata is associated with variable resistance in vitro and Candida krusei is always resistant
Itraconazole	Children: PO: 5 BID mg/kg daily Adult: 200 mgBID maximum dose per day: 600 mg	Active against dimorphic histoplasmosis , coccidioidomyc osis and C. neoformans • Active against Candida,	• Inactive against molds (eg, Aspergillus species, Zygomycetes) • Itraconazole has negative inotropic properties and is contraindicated in patients

		Aspergillus species and some of the rarer molds	with significant cardiac systolic dysfunction
Voriconazole	7 mg/kg/dose every 12 hours maximum: 400 mg (with TDM Levels)	• Active against dimorphic fungi and C. neoformans • Active against Candida, Aspergillus species and some of the rarer molds • Active against dimorphic fungi and C. neoformans • Standard of care as primary therapy for invasive aspergillosis (category 1)1,3 • Effective in candidemia in non-neutropenic patients2	• Poor activity against Zygomycetes • IV formulation should be used with caution in patients with significant pre-existing renal dysfunction based on potential to worsen azotemia
NB. Azoles inhibit fungal cell membrane synthesis and inhibit cytochrome P450 isoenzymes that may lead to impaired clearance of other drugs metabolized by this pathway. Fluconazole is a less potent inhibitor of cytochrome P450 isoenzymes than the mold-active azoles. Drug-drug interactions are common and need to be closely monitored (consult package inserts for details). Reversible liver enzyme abnormalities are observed.			
ANTIFUNGAL AGENTS - AMPHOTERICIN	**DOSE**	**SPECTRUM**	**COMMENTS/PRECAUTIONS**

B			
Amphotericin B	Varies on indication, generally 1mg/kg/day or 1.5 mg/kg/every other day	Broad spectrum of antifungal activity including Candida, Aspergillus sp(excluding Aspergillus terreus) Zygomycetes rarer molds Cryptococcus neoformans, and dimorphic fungi	• Substantial infusional and renal toxicity including electrolyte wasting • Saline loading may reduce nephrotoxicity• Infusional toxicity may be managed with anti-pyretics, an anti-histamine, and meperidine (for rigors
Liposomal amphotercin B	3 mg/kg/d IV		Reduced infusional and renal toxicity compared to AmB-D-Restricted form is required
NB. According to CCHE policy a saline loading guidelines as premedication before adminstration of AmB (attached)			
ANTIVIRAL AGENTs	**DOSE**	**SPECTRUM**	**COMMENTS/PRECAUTIONS**
Acyclovir	Prophylaxis: (750 mg/m2 IV or 10 mg/kg IV every 8 H) Treatment: significant HSV or VZV (1500 mg/m2 IV every 8H for 7-10 days)	HSV , VZV	Hydration to avoid crystal nephropathy with high dose adjustment in patients with renal insufficiency.

NB. High-dose acyclovir and valacyclovir have been used as prophylaxis for CMV. Because these agents have weak activity against CMV, a strategy of CMV surveillance
and pre-emptive therapy with ganciclovir, valganciclovir, or foscarnet is required among patients at high risk for CMV disease Antiviral prophylaxis should be targeted to specific high-risk patients .In non-transplant high-risk patients, prophylaxis should be administered to patients
seropostive for HSV or VZV (or with a history of chicken pox). In HSCT recipients, prophylaxis is only indicated if either the donor or recipient is seropositive for the virus in question. The indicated doses for antiviral agents are for adults with normal renal function; consult package insert for dose modification in pediatrics and in patients with renal impairment.
Prophylactic antiviral doses may be higher than those routinely used in immunocompetent persons (for example, for recurrent cold sores); there is substantial variability in the prophylactic doses of acyclovir used in different clinical trials in patients with hematologic malignancies and HSCT recipients.

Adopted from the IDSA Guidelines:

GUIDELINE RECOMMENDATIONS FOR THE EVALUATION AND TREATMENT OF PATIENTS WITH FEVER AND NEUTROPENIA

I. *What Is the Role of Risk Assessment and What Distinguishes High-risk and Low-risk Patients with Fever and Neutropenia?*

Recommendations

Assessment of risk for complications of severe infection should be undertaken at presentation of fever (A-II) [see page D in appendix]. Risk assessment may determine the type of empirical antibiotic therapy (oral vs intravenous [IV]), venue of treatment (inpatient vs outpatient), and duration of antibiotic therapy (A-II) [see page D in appendix].

Most experts consider high-risk patients to be those with anticipated

prolonged (>7 days duration) and profound neutropenia (absolute neutrophil count [ANC] <100 cells/ mm3 following cytotoxic chemotherapy) and/or significant medical co-morbid conditions, including hypotension, pneumonia, new-onset abdominal pain, or neurologic changes. Such patients should be initially admitted to the hospital for empirical therapy (A-II) [see page D in appendix].

Low-risk patients, including those with anticipated brief (<7 days duration) neutropenic periods or no or few comorbidities, are candidates for oral empirical therapy (A-II) [see page D in appendix].

Formal risk classification may be performed using the Multinational Association for Supportive Care in Cancer (MASCC) scoring system (B-I) [see page D in appendix].

I. High-risk patients have a MASCC score , 21 (B-I) [see page D in appendix]. All patients at high risk by MASCC or by clinical criteria should be initially admitted to the hospital for empirical antibiotic therapy if they are not already inpatients (B-I) [see page D in appendix].
II. Low-risk patients have a MASCC score>21 (B-I) [see page D in appendix].
III. Carefully selected low-risk patients may be candidates for oral and/or outpatient empirical antibiotic therapy (B-I) [see page D in appendix].

II. *In Febrile Patients With Neutropenia, What Empiric Antibiotic Therapy Is Appropriate and in What Venue?*

I. Modifications to initial empirical therapy may be considered for patients at risk for infection with the following antibiotic-resistant organisms,

particularly if the patient's condition is unstable or if the patient has positive blood culture results suspicious for resistant bacteria (B-III) [see page D in appendix].

These include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococcus (VRE), extended-spectrum b-lactamase (ESBL) – producing gram-negative bacteria, and carbapenemase-producing organisms, including *Klebsiella pneumoniae* carbapenemase (KPC). Risk factors include previous infection or colonization with the organism and treatment in a hospital with high rates of endemicity.

I. MRSA: Consider early addition of vancomycin, linezolid, or daptomycin (B-III) [see page D in appendix].
II. VRE: Consider early addition of linezolid or daptomycin (B-III) [see page D in appendix].
III. ESBL: Consider using a carbapenem
IV. KPCs: Consider early use of polymyxin-Colistin or tigecycline

III. *When and How Should Antimicrobials be Modified During the Course of Fever and Neutropenia?*

Recommendations

Modifications to the initial antibiotic regimen should be guided by clinical and microbiologic data (A-II) [see page D in appendix].

Unexplained persistent fever in a patient whose condition is otherwise stable rarely requires an empirical change to the initial antibiotic regimen. If an infection is identified, antibiotics should be adjusted accordingly (A-I) [see page D in appendix].

Documented clinical and/or microbiological infections should be treated with

antibiotics appropriate for the site and for the susceptibilities of any isolated organisms (A-I) [see page D in appendix].

Patients who remain hemodynamically unstable after initial doses with standard agents for neutropenic fever should have their antimicrobial regimen broadened to include coverage for resistant gram-negative, gram-positive, and anaerobic bacteria and fungi (A-III) [see page D in appendix].

Low-risk patients who have initiated IV or oral antibiotics in the hospital may have their treatment approach simplified if they are clinically stable (A-I) [see page D in appendix].

I. An IV-to-oral switch in antibiotic regimen may be made if patients are clinically stable and gastrointestinal absorption is felt to be adequate (A-I) [see page D in appendix].
II. Selected hospitalized patients who meet criteria for being at low risk may be transitioned to the outpatient setting to receive either IV or oral antibiotics, as long as adequate daily follow-up is ensured (B-III) [see page D in appendix].If fever persists or recurs within 48 h in outpatients, hospital re-admission is recommended, with management as for high-risk patients (A-III) [see page D in appendix].

IV. *How Long Should Empirical Antibiotic Therapy is given?*

Recommendations

In patients with clinically or microbiologically documented infections, the duration of therapy is dictated by the particular organism and site; appropriate antibiotics should continue for at least the duration of neutropenia (until ANC is > 500 cells/mm3) or longer if clinically necessary (B-III) [see page D in appendix].

In patients with unexplained fever, it is recommended that the initial regimen be continued until there are clear signs of marrow recovery; the traditional endpoint is an increasing ANC that exceeds 500 cells/mm3.

V. *When Should Antibiotic Prophylaxis be given, and With What Agents?*

Recommendations

Fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC <100 cells/mm3 for .7 days) (B-I) [see page D in appendix]. Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered to be roughly equivalent, although levofloxacin is preferred in situations with increased risk for oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among Gram-negative bacilli is recommended.

VI. *What Is the Role of Empirical or Pre-emptive Antifungal Therapy and Which Antifungal should be used?*

Recommendations

High risk

Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after 4–7 days of antibiotics and whose overall duration of neutropenia is expected to be >7 days. Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving antimold prophylaxis, but switching to a different class of antimold antifungal that is given intravenously should be considered.

Low Risk

In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended.

VII. *When Should Antifungal Prophylaxis be given and With What Agents?*

Recommendations

High risk

Prophylaxis against Candida infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant (HSCT) recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute

leukemia. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives.

Prophylaxis against invasive Aspergillus infections with posaconazole should be considered for selected patients >13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) in whom the risk of invasive aspergillosis without prophylaxis is substantial.

Prophylaxis against Aspergillus infection in pre-engraftment allogeneic or autologous transplant recipients has not been shown to be efficacious. However, a mold-active agent is recommended in patients with prior invasive aspergillosis, anticipated prolonged neutropenic periods of at least 2, or a prolonged period of neutropenia immediately prior to HSCT.

Low Risk

Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is <7 days

VIII. *What Is the Role of Antiviral Prophylaxis and What Virus Infections Require Antiviral Treatment?*

Recommendations

Herpes simplex virus (HSV)–seropositive patients undergoing allogeneic HSCT or leukemia induction therapy should receive acyclovir antiviral prophylaxis.

Antiviral treatment for HSV or varicella-zoster virus (VZV) infection is only indicated if there is clinical or laboratory evidence of active viral disease.

Respiratory virus testing (including testing for influenza, parainfluenza, adenovirus, respiratory syncytial virus [RSV], and human metapneumovirus) and chest radiography are indicated for patients with upper respiratory symptoms (eg, coryza) and/or cough.

Yearly influenza vaccination with inactivated vaccine is recommended for all patients being treated for cancer. Optimal timing of vaccination is not established, but serologic responses may be best between chemotherapy cycles (>7 days after the last treatment) or >2 weeks before chemotherapy starts.

IX. *How are Catheter-Related Infections Diagnosed and Managed in Neutropenic Patients?*

Recommendation

Differential time to positivity (DTP) >120 min of qualitative blood cultures performed on specimens simultaneously drawn from the CVC and a vein suggests a central line–associated blood stream infection (CLABSI).

For CLABSI caused by *S. aureus, P. aeruginosa*, fungi (Candida non-albicans,

any filamentous fungi after ID consultation), or mycobacteria, catheter removal is recommended in addition to systemic antimicrobial therapy for at least 14 days.

Catheter removal is also recommended for:

- Tunnel infection or
- Port pocket site infection,
- Septic thrombosis,
- Endocarditis,
- Sepsis with hemodynamic instability, or
- Bloodstream infection that persists despite >72 h of therapy with appropriate antibiotics.

For documented CLABSI caused by coagulase-negative staphylococci, the catheter may be retained using systemic therapy with or without antibiotic lock therapy.

Prolonged treatment (4–6 weeks) is recommended for complicated CLABSI, defined as the presence of deep tissue infection, endocarditis, septic thrombosis or persistent bacteremia or fungemia occurring >72 h after catheter removal in a patient who has received appropriate antimicrobials (A-II for S. aureus, C-III for other pathogens).

X. *What Environmental Precautions should be Taken When Managing Febrile Neutropenic Patients?*

Recommendations

Hand hygiene is the most effective means of preventing transmission of infection in the hospital.

Standard barrier precautions should be followed for all patients, and infection-specific isolation should be used for patients with certain signs or symptoms.

HSCT recipients should be placed in private (ie, single-patient) rooms. Allogeneic HSCT recipients should be placed in rooms with >12 air exchanges/h and high-efficiency particulate air (HEPA) filtration.

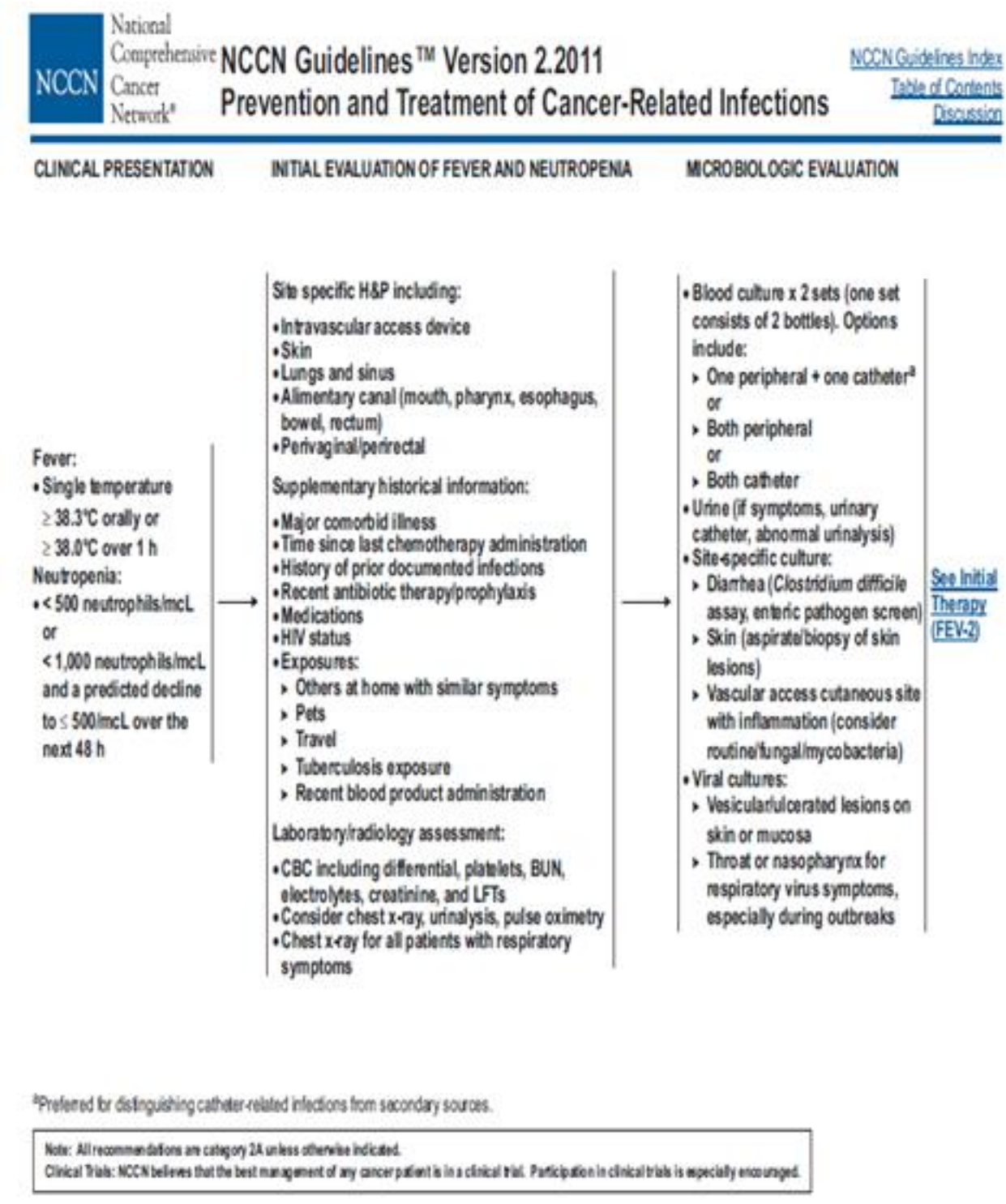
Plants and dried or fresh flowers should not be allowed in the rooms of hospitalized neutropenic patients.

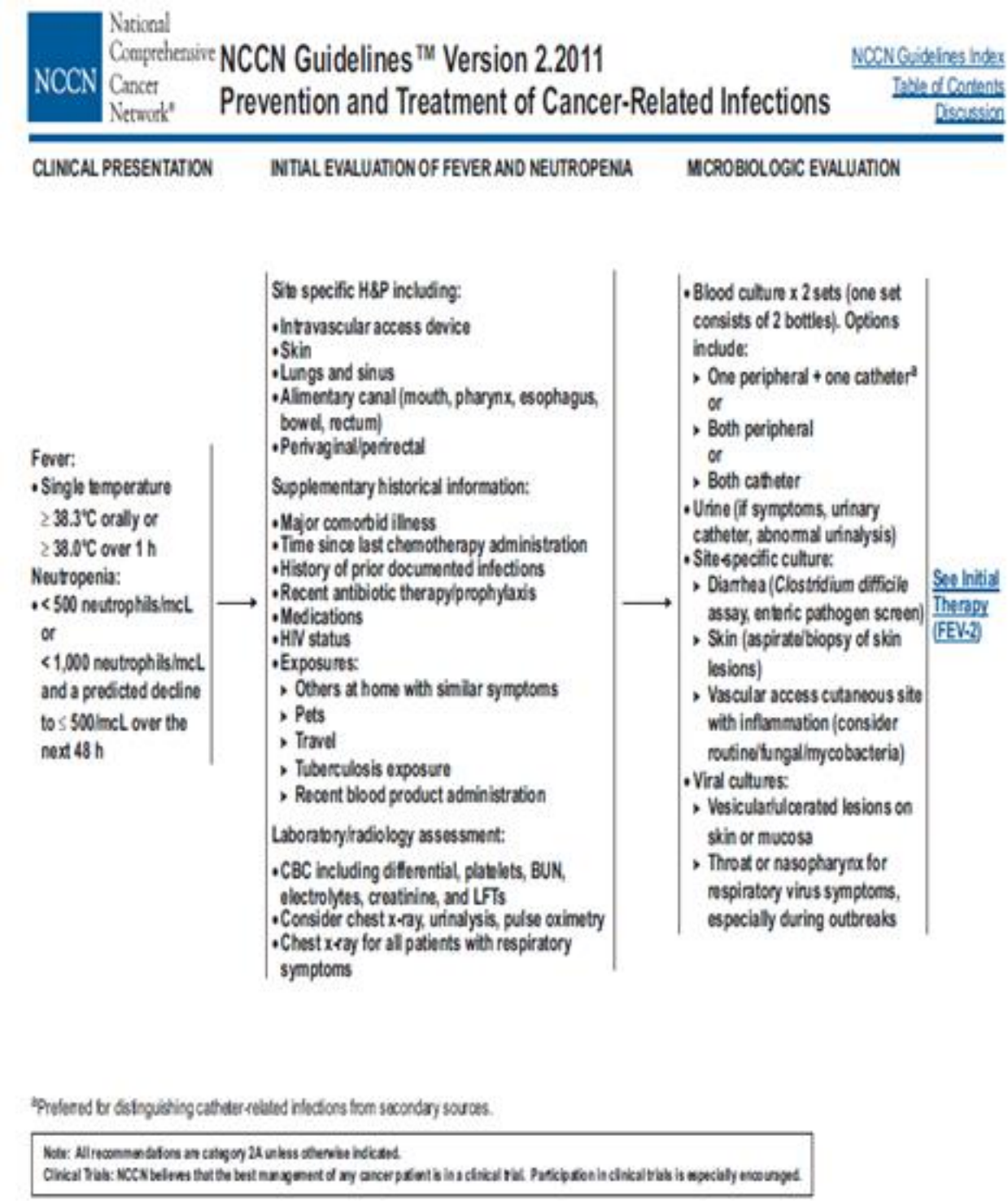
Hospital work exclusion policies should be designed to encourage health care workers (HCWs) to report their illnesses or exposures

4.0 REFERENCES

- NCCN
- IDSA

5.0APPENDICES


National Comprehensive Cancer Network
NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections
NCCN Guidelines Index
Table of Contents
Discussion
CLINICAL PRESENTATION
INITIAL EVALUATION OF FEVER AND NEUTROPENIA
MICROBIOLOGIC EVALUATION
Fever:
• Single temperature
≥ 38.3°C orally or
≥ 38.0°C over 1 h
Neutropenia:
• < 500 neutrophils/mcL
or
< 1,000 neutrophils/mcL and a predicted decline to ≤ 500/mcL over the next 48 h
Site specific H&P including:
• Intravascular access device
• Skin
• Lungs and sinus
• Alimentary canal (mouth, pharynx, esophagus, bowel, rectum)
• Perivaginal/perirectal
Supplementary historical information:
• Major comorbid illness
• Time since last chemotherapy administration
• History of prior documented infections
• Recent antibiotic therapy/prophylaxis
• Medications
• HIV status
• Exposures:
▸ Others at home with similar symptoms
▸ Pets
▸ Travel
▸ Tuberculosis exposure
▸ Recent blood product administration
Laboratory/radiology assessment:
• CBC including differential, platelets, BUN, electrolytes, creatinine, and LFTs
• Consider chest x-ray, urinalysis, pulse oximetry
• Chest x-ray for all patients with respiratory symptoms
• Blood culture x 2 sets (one set consists of 2 bottles). Options include:
▸ One peripheral + one catheter[a]
or
▸ Both peripheral
or
▸ Both catheter
• Urine (if symptoms, urinary catheter, abnormal urinalysis)
• Site-specific culture:
▸ Diarrhea (Clostridium difficile assay, enteric pathogen screen)
▸ Skin (aspirate/biopsy of skin lesions)
▸ Vascular access cutaneous site with inflammation (consider routine/fungal/mycobacteria)
• Viral cultures:
▸ Vesicular/ulcerated lesions on skin or mucosa
▸ Throat or nasopharynx for respiratory virus symptoms, especially during outbreaks
See Initial Therapy (FEV-2)
[a]Preferred for distinguishing catheter-related infections from secondary sources.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.


National Comprehensive Cancer Network
NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections
NCCN Guidelines Index
Table of Contents
Discussion
CLINICAL PRESENTATION
INITIAL EVALUATION OF FEVER AND NEUTROPENIA
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• Time since last chemotherapy administration
• History of prior documented infections
• Recent antibiotic therapy/prophylaxis
• Medications
• HIV status
• Exposures:
▸ Others at home with similar symptoms
▸ Pets
▸ Travel
▸ Tuberculosis exposure
▸ Recent blood product administration
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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

INITIAL THERAPY FOR FEVER AND NEUTROPENIA[b,c]

Initial antibiotic therapy should be based on:
- Infection risk assessment (See FEV-3)
- Potential infecting organisms include vancomycin-resistant enterococcus (VRE) and extended spectrum beta-lactamase (ESBL)
- Colonization with or prior infection with methicillin-resistant *Staphylococcus aureus* (MRSA)
- Site of infection
- Local antibiotic susceptibility patterns
- Organ dysfunction/drug allergy
- Broad spectrum of activity
- Previous antibiotic therapy
- Antipseudomonal coverage
- Bactericidal

→

- Intravenous antibiotic monotherapy (choose one):
  - Imipenem/cilastatin (category 1)
  - Meropenem (category 1)
  - Piperacillin/tazobactam[d] (category 1)
  - Cefepime (category 1)[e]
  - Ceftazidime[f] (category 2B)
- Intravenous antibiotic combination therapy:
  - Aminoglycoside[g] + antipseudomonal penicillin (category 1) ± beta-lactamase inhibitor (category 1)
  - Aminoglycoside + extended-spectrum cephalosporin (cefepime, ceftazidime)
  - Ciprofloxacin + antipseudomonal penicillin (category 1)
  - Use of vancomycin, linezolid, daptomycin or quinupristin/dalfopristin is not routinely recommended[h,i]
- Oral antibiotic combination therapy for low risk patients:
  - Ciprofloxacin + amoxicillin/clavulanate (category 1) (for penicillin-allergic patients, may use ciprofloxacin + clindamycin)
  - Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used

→

Site-Specific Evaluation and Therapy:
Mouth, Esophagus and Sinus/Nasal (FEV-4)

Abdominal Pain, Perirectal Pain, Diarrhea, Vascular Access Devices (FEV-5)

Lung Infiltrates (FEV-6)

Cellulitis, Wound, Vesicular Lesions, Disseminated Papules or other lesions, Urinary Tract Symptoms, Central Nervous System Symptoms (FEV-7)

OR

Follow-up (FEV-8)

[b] Consider local antibiotic susceptibility patterns when choosing empirical therapy. At hospitals where infections by antibiotic resistant bacteria (eg, MRSA or drug-resistant gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly.

[c] See Antibacterial Agents (FEV-A) for dosing, spectrum, and specific comments/cautions.

[d] May interfere with galactomannan measurement.

[e] Meta-analysis reported increased mortality associated with cefepime in randomized trials of neutropenic fever. Based on the results of the FDA's meta-analyses, the FDA has determined that cefepime remains an appropriate therapy for its approved indications.

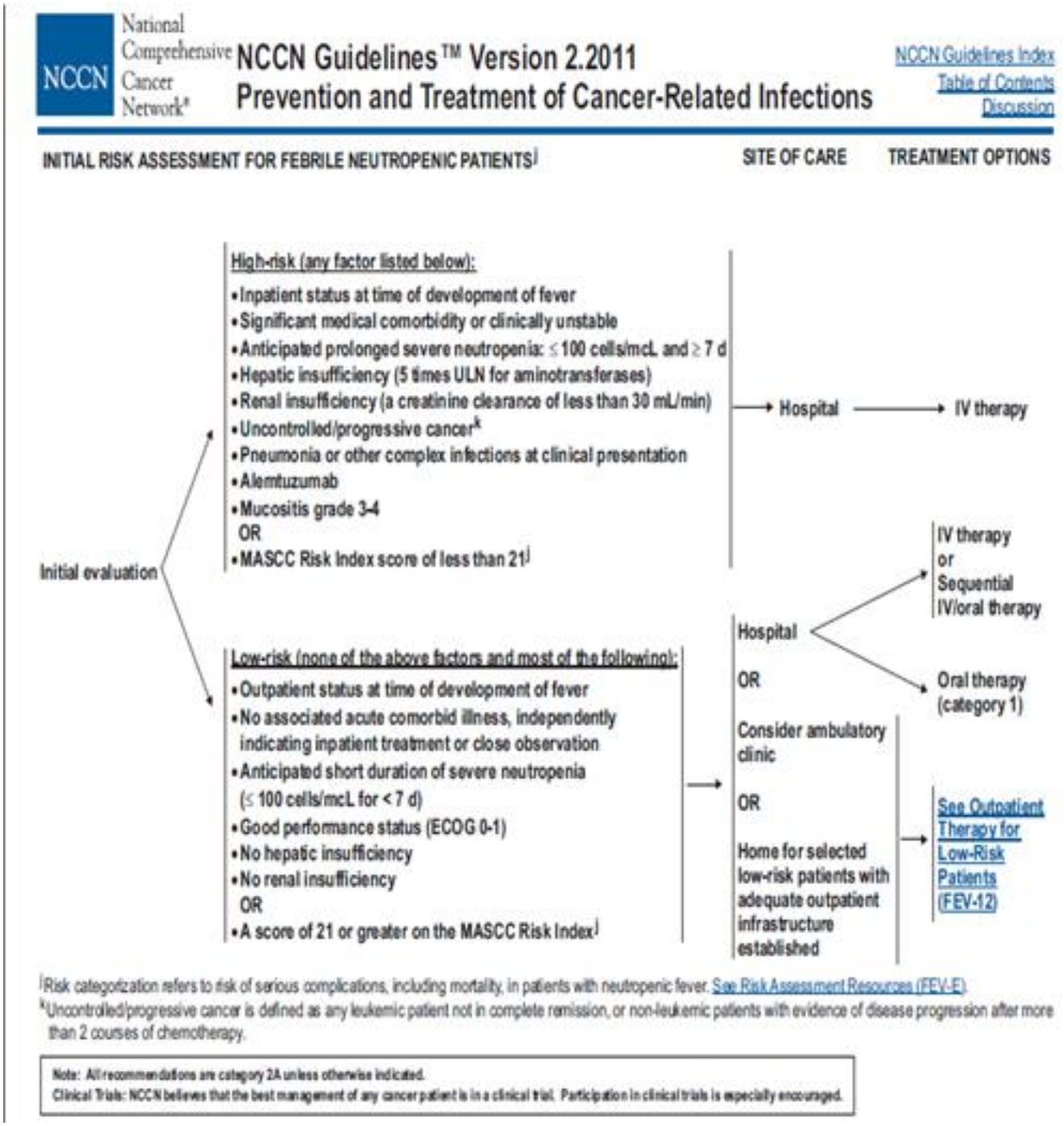
[f] Weak Gram-positive coverage and increased breakthrough infections limit utility.

[g] Some authorities recommend avoidance of aminoglycosides because of potential nephrotoxicity, which may be diminished by once-daily administration. Once-a-day aminoglycoside therapy should be avoided for treatment of meningitis or endocarditis.

[h] Although there are published studies regarding the use of some of these agents in neutropenic patients, the NCCN panel strongly recommends that these agents should not be routinely used as initial empirical therapy for neutropenic fever because of concerns about resistance and breakthrough infections.

[i] See Appropriate Use of Vancomycin and Other Agents for Gram-positive Resistant Infections (FEV-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.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National Comprehensive Cancer Network
NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections
NCCN Guidelines Index
Table of Contents
Discussion
INITIAL RISK ASSESSMENT FOR FEBRILE NEUTROPENIC PATIENTS[j]
SITE OF CARE
TREATMENT OPTIONS
Initial evaluation
High-risk (any factor listed below):
•Inpatient status at time of development of fever
•Significant medical comorbidity or clinically unstable
•Anticipated prolonged severe neutropenia: ≤ 100 cells/mcL and ≥ 7 d
•Hepatic insufficiency (5 times ULN for aminotransferases)
•Renal insufficiency (a creatinine clearance of less than 30 mL/min)
•Uncontrolled/progressive cancer[k]
•Pneumonia or other complex infections at clinical presentation
•Alemtuzumab
•Mucositis grade 3-4
OR
•MASCC Risk Index score of less than 21[j]
Hospital
IV therapy
Low-risk (none of the above factors and most of the following):
•Outpatient status at time of development of fever
•No associated acute comorbid illness, independently indicating inpatient treatment or close observation
•Anticipated short duration of severe neutropenia (≤ 100 cells/mcL for < 7 d)
•Good performance status (ECOG 0-1)
•No hepatic insufficiency
•No renal insufficiency
OR
•A score of 21 or greater on the MASCC Risk Index[j]
Hospital
OR
IV therapy or Sequential IV/oral therapy
Oral therapy (category 1)
Consider ambulatory clinic
OR
Home for selected low-risk patients with adequate outpatient infrastructure established
See Outpatient Therapy for Low-Risk Patients (FEV-12)
[j]Risk categorization refers to risk of serious complications, including mortality, in patients with neutropenic fever. See Risk Assessment Resources (FEV-E)
[k]Uncontrolled/progressive cancer is defined as any leukemic patient not in complete remission, or non-leukemic patients with evidence of disease progression after more than 2 courses of chemotherapy.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

APPROPRIATE USE OF VANCOMYCIN AND OTHER AGENTS FOR GRAM-POSITIVE RESISTANT INFECTIONS

- Vancomycin should not be considered as a routine component of initial therapy for fever and neutropenia. Because of the emergence of vancomycin-resistant organisms, empiric vancomycin should be avoided except for serious infections associated with the following clinical situations:
  - Clinically apparent, serious, catheter-related infection
  - Blood culture positive for Gram-positive bacterium prior to final identification and susceptibility testing
  - Known colonization with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*
  - Hypotension or septic shock without an identified pathogen (ie, clinically unstable)
  - Soft tissue infection
  - Risk factors for viridans group streptococcal, bacteremia (category 2B): severe mucositis (eg, associated with high-dose cytarabine) and prophylaxis with quinolones or TMP-SMX (see manuscript)[a]
- Vancomycin should be discontinued in 2-3 days if a resistant Gram-positive infection (eg, MRSA) is not identified.
- Linezolid, quinupristin/dalfopristin, and daptomycin may be used specifically for infections caused by documented vancomycin-resistant organisms (eg, VRE) or in patients for whom vancomycin is not an option. Vancomyocin or linezolid should be considered for ventilator associated MRSA pneumonia.

(See FEV-A 1 of 4)

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF DAILY FOLLOW-UP

- Daily site-specific H&P
- Daily review of laboratory tests and cultures: document clearance of bacteremia, fungemia with repeat blood cultures
- Evaluate for response to therapy and drug toxicity:
  - Fever trends
  - Signs and symptoms of infection
- Evaluation of drug toxicity including end-organ toxicity (LFTs and renal function tests at least 2x/wk)

→ Evaluate overall response to empiric therapy in 3-5 d[v] (72-120 h)

RESPONDING
- Decreasing fever trend
- Signs and symptoms of infection are stable or improving
- Patient is hemodynamically stable

→ See Follow-up Therapy (FEV-9)

NONRESPONDING
- Persistently or intermittently febrile
- Signs and symptoms of infection are not improving
- Patient may be hemodynamically unstable
- Persistent positive blood cultures

→ See Follow-up Therapy (FEV-11)

[v] See Adjunctive Therapies (FEV-F).

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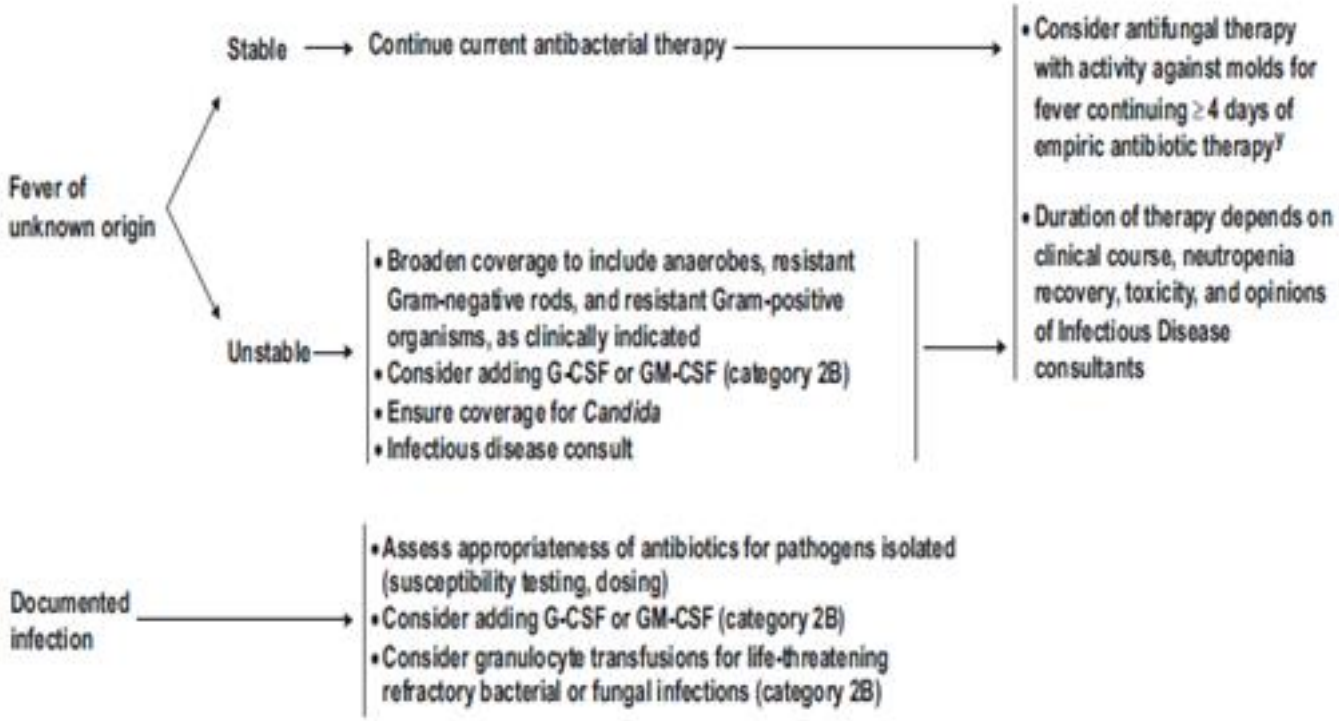
National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

FOLLOW-UP THERAPY FOR NONRESPONDING PATIENTS | **SUGGESTED DURATION OF THERAPY**



[γ]The timing to add empirical antifungal therapy varies with the risk of invasive mold infection but generally ranges between 4-7 d of neutropenic fever. In patients at high risk for mold infection (neutropenia > 10 d, allogeneic stem cell transplant recipients, high-dose corticosteroids), the panel recommends adding empirical antifungal therapy after 4 d unless patient is receiving prophylaxis directed against molds. See Discussion of antifungal prophylaxis versus empirical antifungal therapy.

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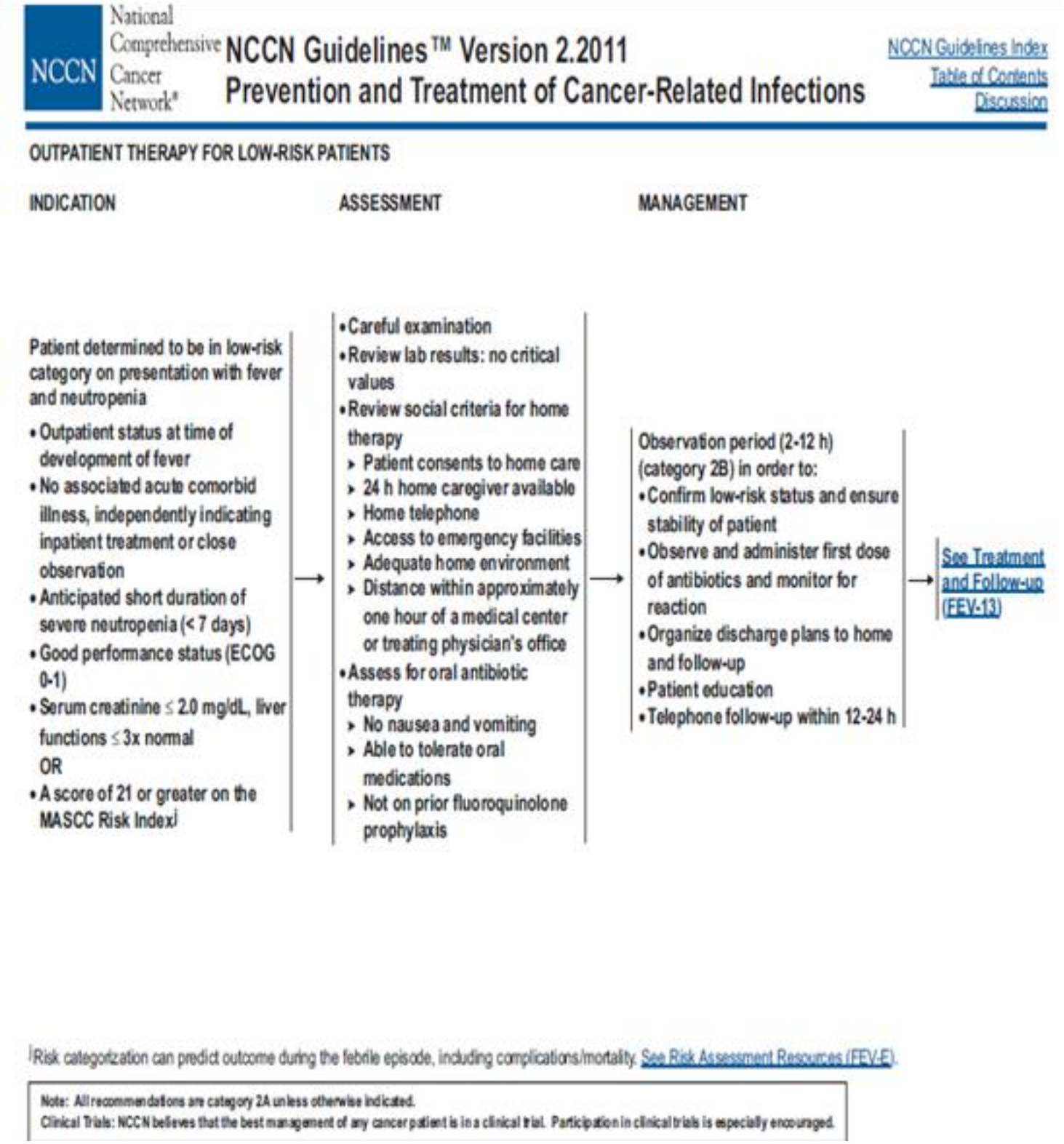
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National Comprehensive Cancer Network®
NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections
NCCN Guidelines Index
Table of Contents
Discussion
OUTPATIENT THERAPY FOR LOW-RISK PATIENTS
INDICATION
ASSESSMENT
MANAGEMENT
Patient determined to be in low-risk category on presentation with fever and neutropenia
• Outpatient status at time of development of fever
• No associated acute comorbid illness, independently indicating inpatient treatment or close observation
• Anticipated short duration of severe neutropenia (< 7 days)
• Good performance status (ECOG 0-1)
• Serum creatinine ≤ 2.0 mg/dL, liver functions ≤ 3x normal
OR
• A score of 21 or greater on the MASCC Risk Index[l]
• Careful examination
• Review lab results: no critical values
• Review social criteria for home therapy
▸ Patient consents to home care
▸ 24 h home caregiver available
▸ Home telephone
▸ Access to emergency facilities
▸ Adequate home environment
▸ Distance within approximately one hour of a medical center or treating physician's office
• Assess for oral antibiotic therapy
▸ No nausea and vomiting
▸ Able to tolerate oral medications
▸ Not on prior fluoroquinolone prophylaxis
Observation period (2-12 h) (category 2B) in order to:
• Confirm low-risk status and ensure stability of patient
• Observe and administer first dose of antibiotics and monitor for reaction
• Organize discharge plans to home and follow-up
• Patient education
• Telephone follow-up within 12-24 h
See Treatment and Follow-up (FEV-13)
[l]Risk categorization can predict outcome during the febrile episode, including complications/mortality. See Risk Assessment Resources (FEV-E).
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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

ANTIBACTERIAL AGENTS (References are on page 4)

GRAM-POSITIVE AGENTS[a]	DOSE	SPECTRUM	COMMENTS/PRECAUTIONS
Vancomycin	15 mg/kg IV every 12 h[b]	Gram-positive organisms with exception of VRE and a number of rare Gram-positive organisms	• Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present (See FEV-D)
Linezolid	600 mg PO/IV every 12 h	Gram-positive organisms including VRE	• Hematologic toxicity may occur, thrombocytopenia most common (0.3% to 10%) • Serotonin syndrome rare, use cautiously with SSRI's[1] • Not for routine use in fever and neutropenia although does not impair neutrophil recovery • Treatment option for VRE and MRSA • Peripheral/optic neuropathy with long-term use • Not recommended for line infections
Daptomycin	4-6 mg/kg IV d[b,c]	• Gram-positive organisms • Has in vitro activity against VRE but is not FDA-approved for this indication	• Equivalent to standard antistaphylococcal agents for *Staphylococcus aureus* bacteremia at 6 mg/kg dose in non-neutropenic patients[2] • Weekly CPK to monitor for rhabdomyolysis • Not indicated for pneumonia due to inactivation by pulmonary surfactant • Not studied in patients with fever and neutropenia • Myositis is a potential toxicity
Dalfopristin/ Quinupristin	7.5 mg/kg IV every 8 h	Gram-positive organisms including most VRE (does not have activity against *Enterococcus faecalis*) or intolerance to vancomycin	• Use limited by myalgias/arthralgias (up to 47%) • Requires central venous access delivery • Avoid use due to toxicity although coverage is good • Musculoskeletal pain syndrome is a potential toxicity

[a] These drugs are not recommended as monotherapy for fever in the setting of neutropenia and should only be added for documented infection with resistant Gram-positive organisms or if certain risk factors are present. (See FEV-D)

Continued on next page

[b] Requires dose adjustment in patients with renal insufficiency.

[c] Limited published data suggest utilizing higher doses up to 10 mg/kg.

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FEV-A

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

ANTIBACTERIAL AGENTS (References are on page 4)

ANTI-PSEUDOMONAL AGENTS[e]	DOSE	SPECTRUM	COMMENTS/PRECAUTIONS
Imipenem/cilastatin sodium	500 mg IV every 6 h[b]	• Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms • Preferred against extended spectrum beta-lactamase (ESBL) and serious *Enterobacter* infections. • Carbapenem-resistant Gram-negative rod infections are an increasing problem at a number of centers	• Use for suspected intra-abdominal source • Meropenem is preferred over imipenem for suspected /proven CNS infection • Imipenem may lower seizure threshold in patients with CNS malignancies or infection or with renal insufficiency • Empiric therapy for neutropenic fever (category 1)
Meropenem	1 gram IV every 8 h[b] (2 g IV every 8 h for meningitis)		• Effective in nonsocomial pneumonia and intra-abdominal infections • Lack of clinical trial experience in neutropenic patients
Piperacillin/tazobactam	4.5 grams IV every 6 h[b]	• Broad spectrum activity against most Gram-positive, Gram-negative and anaerobic organisms	• Use for suspected intra-abdominal source • Not recommended for meningitis • May result in false positive galactomannan[3] • Empiric therapy for neutropenic fever (category 1)
Cefepime	2 grams IV every 8 h[b]	• Broad spectrum activity against most Gram-positive and Gram-negative organisms	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for neutropenic fever (category 1)
Ceftazidime	2 grams IV every 8 h[b]	• Relatively poor Gram-positive activity • Breakthrough streptococcal infections reported • Not active against most anaerobes and *Enterococcus spp.*	• Use for suspected/proven CNS infection with susceptible organism • Increased frequency of resistance among Gram-negative rod isolates at some centers • Empiric therapy for neutropenic fever based on resistance among certain Gram-negative rods (category 2B)

[b] Requires dose adjustment in patients with renal insufficiency.
[d] Local antibiograms should be considered.
[e] None of these agents are active against MRSA or VRE.

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FEV-A

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

ANTIBACTERIAL AGENTS (References are on page 4)

OTHER ANTIBACTERIAL AGENTS	DOSE	SPECTRUM	COMMENTS/CAUTIONS
Ciprofloxacin	500-750 mg PO every 12 hours or 400 mg IV every 8-12 h[b]	• Good activity against Gram-negative and atypical (e.g., *Legionella spp.*) organisms • Less active than "respiratory" fluoroquinolones against Gram-positive organisms • No activity against anaerobic organisms	• Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis • Increasing Gram-negative resistance in many centers • Oral antibiotic combination therapy in low-risk patients (with amoxicillin/clavulanate or clindamycin) • In combination with antipseudomonal penicillin in higher risk patients
Levofloxacin	500-750 mg oral or IV daily[b]	• Good activity against Gram-negative and atypical (e.g., *Legionella spp.*) organisms • Improved Gram-positive activity compared to ciprofloxacin • Limited activity against anaerobes • Prophylaxis in neutropenic patients[5,6]	• Prophylaxis may increase bacterial resistance and superinfection[7] • Limited studies as empirical therapy in patients with fever and neutropenia
Aminoglycosides • Gentamicin • Tobramycin • Amikacin	Dosing individualized with monitoring of levels[b]	• Activity primarily against Gram-negative organisms • Gentamicin is synergistic with beta-lactams against susceptible *S. aureus* and *Enterococcus* infections	• Nephrotoxicity and ototoxicity limit use • Combination therapy with anti-pseudomonal penicillin +/- beta-lactamase inhibitor or extended spectrum cephalosporin (see FEV-2)
Trimethoprim/sulfamethoxazole (TMP/SMX)	Single or double strength daily or Double strength 3 times per wk as prophylaxis for *P. jirovecii*		• Highly effective as prophylaxis against *P. jirovecii* in high risk patients (see INF-5)

[b] Requires dose adjustment in patients with renal insufficiency.

Continued on next page

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ANTIBACTERIAL AGENTS REFERENCES

[1] Boyer EW, Shannon M. Serotonin syndrome. N Engl J Med 2005;352:1112-1120.
[2] Fowler VG, Boucher HW, Corey GR, et. al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus* aureus. N Engl J Med 2006;355:653-665.
[3] Aubry A, Porcher R, Bottero J, et al. Occurence and kinetics of false positive Aspergillus galactomannan test results following treatment with beta-lactam antibiotics in patients with hematological disorders. J Clin Microbio 2006;44(2):389-394.
[4] Stein GE, Craig WA. Tigecycline: A critical analysis. Clin Infect Dis 2006;43:518-524.
[5] Bucaneve G, Micozzi A, Menichetti F, et. al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 2005;353:977-987.
[6] Cullen M, Billingham SN, Gaunt C, et. al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005;353:988-998.
[7] Baden LR. Prophylactic antimicrobial agents and the importance of fitness. N Engl J Med 2005;353:1052-1054.

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National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
Table of Contents
Discussion

APPROPRIATE USE OF VANCOMYCIN AND OTHER AGENTS FOR GRAM-POSITIVE RESISTANT INFECTIONS

- Vancomycin should not be considered as a routine component of initial therapy for fever and neutropenia. Because of the emergence of vancomycin-resistant organisms, empiric vancomycin should be avoided except for serious infections associated with the following clinical situations:
  - Clinically apparent, serious, catheter-related infection
  - Blood culture positive for Gram-positive bacterium prior to final identification and susceptibility testing
  - Known colonization with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*
  - Hypotension or septic shock without an identified pathogen (ie, clinically unstable)
  - Soft tissue infection
  - Risk factors for viridans group streptococcal, bacteremia (category 2B): severe mucositis (eg, associated with high-dose cytarabine) and prophylaxis with quinolones or TMP-SMX (see manuscript)[a]
- Vancomycin should be discontinued in 2-3 days if a resistant Gram-positive infection (eg, MRSA) is not identified.
- Linezolid, quinupristin/dalfopristin, and daptomycin may be used specifically for infections caused by documented vancomycin-resistant organisms (eg, VRE) or in patients for whom vancomycin is not an option. Vancomyocin or linezolid should be considered for ventilator associated MRSA pneumonia.

(See FEV-A 1 of 4)

[a]Recent studies have shown that addition of vancomycin is likely to be unnecessary solely on the basis of neutropenic fever and mucositis when broad spectrum beta-lactam agents with activity against oral flora (eg, piperacillin/tazobactam or imipenem/cilastatin) are used.

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FEV-D

screening for enteric pathogen including rotavirus and norovirus in winter months and during outbreaks. Symptoms of urinary tract infection should be evaluated with a urinalysis and culture. Vascular access site inflammation or drainage should be cultured. Biopsy with microbiologic and pathologic evaluation should be considered for new or undiagnosed skin lesions (see Guidelines section on Microbiologic Evaluation). Viral cultures of vesicular or ulcerated mucosal or cutaneous lesions may identify HSV infections. In patients with symptoms of respiratory viral infection, viral cultures and rapid viral antigen testing of the nasopharyngeal secretions can be useful during local outbreaks of such infections.[77,78] However, note that rapid immunofluorescent viral antigen tests may be negative for H1N1 (swine flu).

Initial Empiric Antibiotic Therapy

The foundation of infection management is to administer empiric antibiotics in patients with F&N. This approach is necessary because currently available diagnostic tests are not sufficiently rapid, sensitive, or specific to identify or exclude microbial causes of fever from other noninfectious causes. All neutropenic patients should be treated empirically with broad spectrum antibiotics promptly at the first sign of infection (i.e., fever). This is done to avoid the mortality associated with a delay in treatment in those patients who have a serious infection.[4,79] Many highly effective antibiotic regimens are available, and those that are recommended are supported by randomized clinical trials.

Selection of initial therapy should consider the following:

- The patient's infection risk assessment;
- The antimicrobial susceptibilities of pathogens isolated locally;
- The most common potentially infecting organisms, including antibiotic-resistant pathogens, such as extended spectrum beta-lactamase–producing Gram-negative rods, vancomycin-resistant enterococcus (VRE), and colonization with or previous infection with methicillin-resistant *S.aureus* (MRSA);
- The potential sites of infection;
- The importance of a broad spectrum bactericidal antibiotic regimen that includes antipseudomonal coverage;
- Clinical instability (e.g., hypotension, organ dysfunction);
- Drug allergy;
- Recent antibiotic use (including prophylaxis).

Recommended Approaches

The panel considers each of the following three approaches to initial empiric management of febrile neutropenia to be appropriate based on the results of large, randomized controlled clinical trials (see Guidelines section on Initial Therapy for Fever and Neutropenia).[4,7,79]

The first approach is intravenous (IV) antibiotic monotherapy (all category 1 except where noted) with either imipenem/cilastatin, meropenem, piperacillin/tazobactam, or an extended-spectrum antipseudomonal cephalosporin (cefepime or ceftazidime [category 2B]).[2,80-83] Local institutional bacterial susceptibilities should be considered when selecting empiric antibiotic therapy. At hospitals where infections by antibiotic resistant bacteria (e.g., MRSA or drug-resistant Gram-negative rods) are commonly observed, policies on initial empirical therapy of neutropenic fever may need to be tailored accordingly.

A meta-analysis of randomized trials involving cefepime reported that cefepime was associated with increased all-cause mortality when used for empiric therapy for neutropenic fever, although no increase in infection-related mortality was noted.[84,85] A subsequent meta-analysis by the FDA, using additional data beyond what was used in the Yahav