

Fever and neutropenia

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Background

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Despite considerable progress in the management of the complications of HSCT, infections remains an important cause of post-transplant morbidity and mortality.



History of Empiric Therapy for Fever and Neutropenia 1970's

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Schimpff et al. 1971, starting antibiotics empirically at onset of fever in the neutropenic patient reduce morbidity and mortality



Axioms for Management of Patients with Fever and Neutropenia

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Fever is of infectious etiology until proven otherwise

- Characteristic signs and symptoms are often absent
- Organisms of low virulence can cause serious infections
- Untreated infections can rapidly disseminate and be fatal
- Multiple infections are common and empiric broad-spectrum antibiotics should be administered immediately

Common Bacterial Causes of Fever in Neutropenia Patients

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Gram-positive

S. aureus

Coagulase negative staphylococci

S. pneumoniae

S. pyogenes

Viridans group

Enterococcus sp.

Corynebacterium sp.

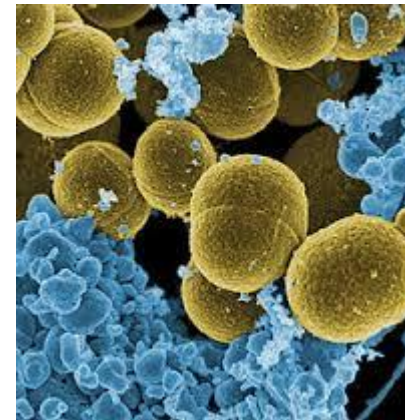


Gram-negative

E. coli

Klebsiella sp.

Pseudomonas aeruginosa



European Group for Blood and Marrow
Transplantation - Nurses Group



Definitions



Definitions

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Febrile neutropenia is a special situation where bacterial infections must be the main target of the empirical anti infective therapy.

The definitions of fever and neutropenia are general criteria that should be used to identify patients in whom empirical antibiotic therapy must be initiated.

Fever

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Fever is defined as a single oral temperature measurement of $>38.3\text{-C}$ (101-F) or a temperature of $>38.0\text{-C}$ (100.4-F) sustained over a 1-h period. Use of axillary temperatures is discouraged, because they may not accurately reflect core body temperature. Rectal temperature measurements (and rectal examinations) are avoided during neutropenia to prevent colonizing gut organisms from entering the surrounding mucosa and soft tissues.

Neutropenia

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- **Neutropenia** is defined as an ANC of < 500 cells/mm³ or an ANC that is expected to decrease to < 500 cells/mm³ during the next 48 h.
- **Profound neutropenia:** sometimes used to describe neutropenia in which the ANC is < 100 cells/mm³; a manual reading of the blood smear is required to confirm this degree of neutropenia.
- **Functional neutropenia:** patients whose hematologic malignancy results in qualitative defects. These patients should also be considered to be at increased risk for infection, despite a “normal” neutrophil count.

Aim

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To assist practitioners in making decisions about **appropriate care** for neutropenic patients who present with signs and symptoms of potentially serious infections . The **recommendations** are derived from well-tested patterns of clinical practice that have emerged from cancer therapy clinical trials; modifications of these recommendations are based upon careful review of data from recent scientific publications. For example, it is recommended neutropenic patients who are **not febrile** but who have new signs or symptoms that suggest infection have **empirical antibiotics initiated**.

Risk assessment- 1

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Assessment of risk for complications of severe infection should be undertaken at presentation of fever

- the type of empirical antibiotic therapy :
 - oral
 - intravenous [IV]

- venue of treatment
 - inpatient vs
 - outpatient

- and duration of antibiotic therapy



Risk assessment-2

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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.

Low-risk patients, including those with anticipated brief (<7 days duration) neutropenic periods or no or few co morbidities, are candidates for oral empirical therapy .

Initial Evaluation-2

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What cultures should be collected and what specific tests should be performed during the initial assessment?

- complete blood cell (CBC) count
 - leukocyte count
 - platelet count
- serum levels:
 - creatinine
 - urea nitrogen
- electrolytes
- hepatic transaminase enzymes
- total bilirubin



Initial Evaluation-1

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BLOB cultures

- If no catheter, **2 sets** from venipuncture
- If catheter, all lumens + peripheral
- Anaerobic cx if abdominal pathology
- Repeat only as indicated, or following a (+) cx



a “set”:

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a “set” consists of 1 venipuncture or catheter access draw of 20mL of blood divided into 1 aerobic and 1 anaerobic blood culture bottle

VOLUME: total sample limit would be 7 mL for a 10-kg patient and 28 mL for a 40-kg patient .

Paediatric patients: proportionately smaller volumes of blood culture samples are suggested. Some centers limit blood draws to no more than 1% of a patient’s total blood volume.

Do You Really Need a Peripheral Culture?

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- Useful in the determination of catheter-related bacteremia
- Guides use of antibiotic lock therapy and duration
 - of systemic therapy
- Comparison of 2 lumen data has 62% sensitivity,
- 93% specificity
- Improves sensitivity of blood cultures
- 5 – 9% of all pathogens missed if only line cultures done.
- Missed organisms include alpha strep, E coli, Klebsiella, Pseudomonas

Empirical antibiotic therapy

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- **High-risk** patients require **hospitalization** for IV empirical antibiotic therapy
- 2. **Monotherapy** with cefepime, (meropenem or imipenem-cilastatin), or piperacillin-tazobactam, is **recommended**
- 3. Other antimicrobials (amino glycosides) may be added to the initial regimen for management of complications (eg, hypotension and pneumonia) or if **antimicrobial resistance** is suspected or proven
- 4. Afebrile neutropenic patients who have **new signs or symptoms** suggestive of infection should be evaluated and treated as **high-risk** patients
- 5. Low-risk patients should receive initial oral or IV empirical antibiotic doses in a clinic or hospital setting; they may be transitioned to outpatient oral or IV treatment if they meet specific clinical criteria

Bacterial infections

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Preventive measures:

- isolation measures
- low bacterial diet
- management on central IV lines

As newer drugs and newer methods of delivery are developed, approaches to prophylaxis will evolve.

In evaluating the evidence regarding the management of patients with fever and neutropenia, a systematic weighting of the level and grade of the evidence for making a recommendation have used.(Table 2)

Category /grade		Definition
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Strength of Recommendation and Quality of evidence.

A	Good evidence to support a recommendation for or against use.
B	Moderate evidence to support a recommendation for or against use.
C	Poor evidence to support a recommendation.

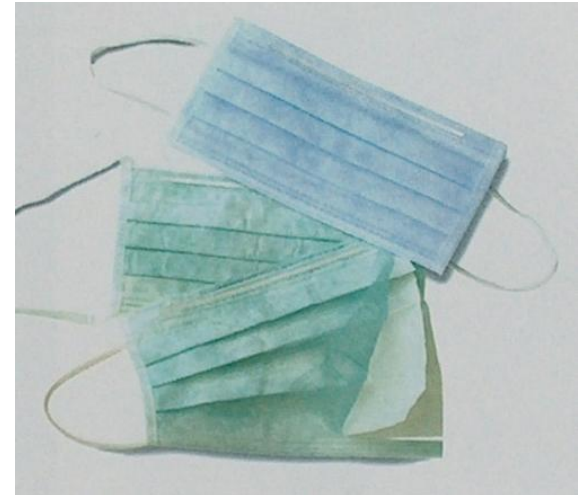
Quality of Evidence

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

Environmental Precautions -1

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- Hand hygiene
- Standard barrier precautions should be followed for all patients
- HSCT recipients should be placed in private (ie, singlepatient) 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



Environmental Precautions -2

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The need for environmental HEPA filtration for autologous HSCT patients has not been established

Ongoing hospital construction and renovation have been associated with an increased risk of nosocomial mold infection, especially aspergillosis, in severely immunocompromised patients .

Therefore, whenever possible, HSCT patients who remain immunocompromised should avoid areas of hospital construction or renovation the rooms of hospitalized neutropenic patients .



STANDARD:

- ***B2 CLINICAL UNIT***
- ***B2.1 There shall be a designated inpatient unit of adequate space, design, and location that minimizes airborne microbial contamination.***
- ***B2 CLINICAL UNIT***
- ***B2.2 There shall be a designated area for outpatient care that reasonably protects the patient from transmission of infectious agents and allows, as necessary, for appropriate patient isolation, administration of intravenous fluids, medications, and/or blood products, and confidential donor examination and evaluation***

PubMed



The influence of high-efficiency particulate air filtration on mortality and fungal infection among highly immunosuppressed patients: a systematic review.

[Eckmanns T](#), [Rüden H](#), [Gastmeier P](#).

Source

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Abstract

BACKGROUND:

Patients with hematological malignancies who are treated with intensive chemotherapy or who receive bone marrow transplants are exposed to an increased risk of developing nosocomial fungal infections. The aim of this systematic review was to compare the effectiveness of high-efficiency particulate air (HEPA) filtration with that of non-HEPA filtration in decreasing the rates of mortality and fungal infection among patients with diagnosed hematological malignancies and neutropenia or among patients with bone marrow transplants.

METHODS:

Articles identified in a Medline search, guidelines, and books, as well as the bibliographies of review articles, monographs, and the articles identified by Medline, were researched. Randomized trials and observational studies comparing HEPA filtration with conventional room ventilation were selected for inclusion in the present review.

RESULTS:

Sixteen trials (9 with death as an outcome and 10 with fungal infection as an outcome) that compared HEPA filtration with non-HEPA filtration were selected for meta-analyses. We discovered no significant advantages of HEPA filtration in the prevention of death among patients with hematological malignancies with severe neutropenia in randomized controlled trials (RCTs; relative risk [RR], 0.86 [95% confidence interval {CI}, 0.65-1.14]) and in studies of a lower standard (non-RCTs; RR, 0.87 [95% CI, 0.60-1.25]).

CONCLUSIONS:

The placement in protected areas of patients with hematological malignancies with severe neutropenia or patients with bone marrow transplants appears to be beneficial, but no definitive conclusion could be drawn from the data available.

Catheter- related infections-1

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✓ Differential time to positivity >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)

✓ **Catheter removal recommended :**

1. CLABSI caused by *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria
2. Tunnel infection or port pocket site infection
3. Septic thrombosis
4. Endocarditis
5. Sepsis with hemodynamic instability
6. Or bloodstream infection that persists despite >72 h of therapy with appropriate antibiotics

Catheter- related infections-2

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- **Catheter may be retained:**
If documented CLABSI caused by coagulase-negative staphylococci, 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.
- ***Hand hygiene, maximal sterile barrier precautions, and cutaneous antiseptics with chlorhexidine during CVC insertion are recommended for all CVC insertions***

Catheter- related infections-2

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Antifungal Prophylaxis ?

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

Low risk

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

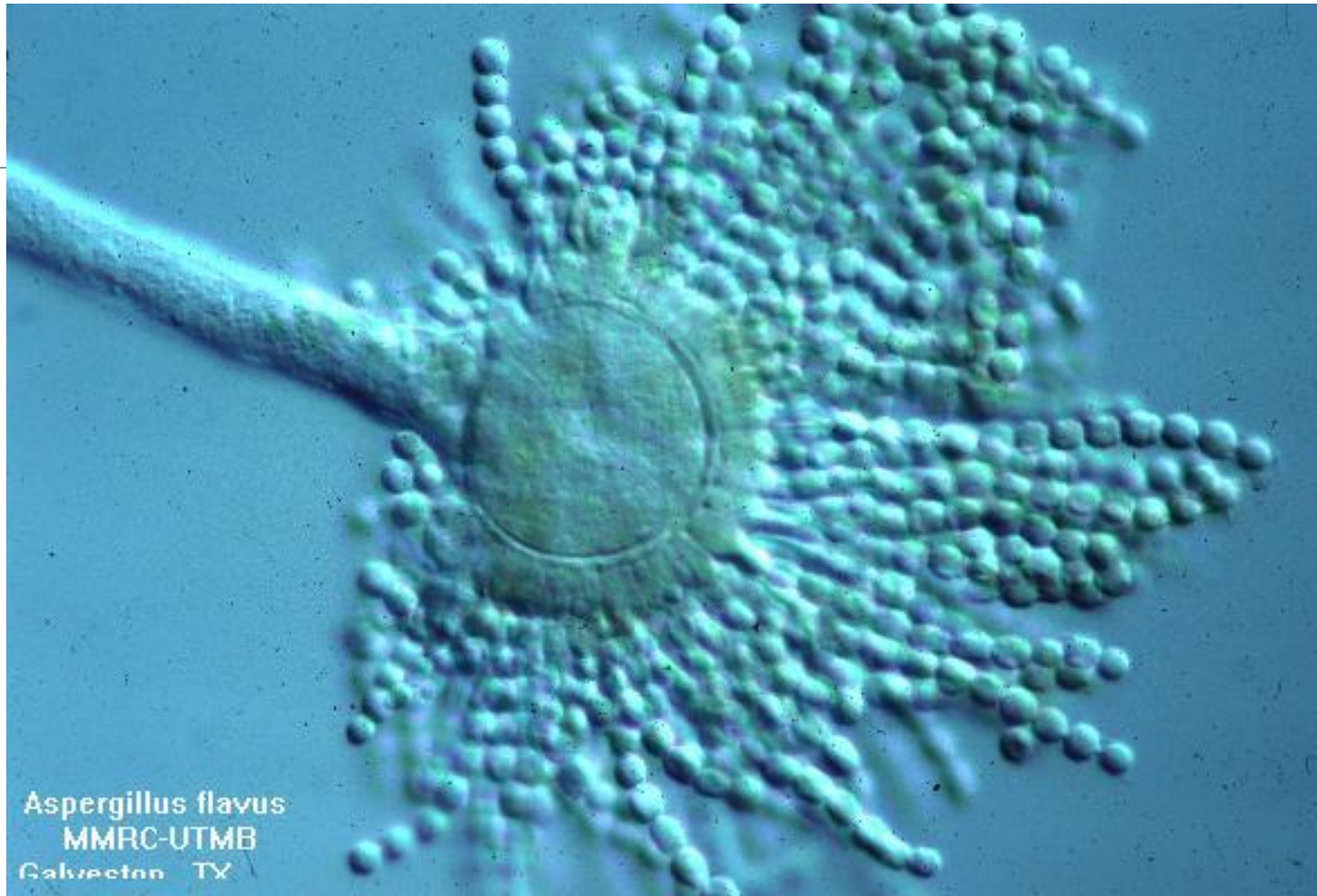


An International Comparison of Current Strategies to Prevent Herpesvirus and Fungal Infections in Hematopoietic Cell Transplant Recipients

[Margaret Pollack](#),^{1,*} [Judson Heugel](#),^{1,6,*} [Hu Xie](#),¹ [Wendy Leisenring](#),¹ [Jan Storek](#),^{2,3} [Jo-Anne Young](#),^{3,4} [Manisha Kukreja](#),³ [Ronald Gress](#),^{3,5} [Marcie Tomblyn](#),^{3,7} and [Michael Boeckh](#)^{1,3}

Abstract

Herpes virus (CMV, HSV, VZV) and invasive fungal infections continue to cause significant morbidity and mortality in allogeneic hematopoietic cell transplant (HCT) recipients despite the availability of effective therapies. In this study, we developed an internet-based survey, which was distributed to all HCT centers participating in the CIBMTR program, to gather information on strategies utilized for the prevention of disease due to herpes virus and fungal infections between 1999 and 2003. The survey response rate was 72%, representing 175 programs from 32 countries. Generally, reported center strategies were in accord with the CDC guidelines published in 2000, with 81% of programs using low-dose acyclovir prophylaxis for HSV seropositive patients, 99% of programs reporting use of a CMV prevention strategy during the first 100 days post-transplant for all patients at risk of CMV disease, and 90% of programs using antifungal prophylaxis. Seventy percent of programs reported routine use of a CMV prevention strategy in high-risk patients after day 100. The greatest departure from published guidelines was the use of acyclovir prophylaxis for VZV seropositive recipients in 75% of programs. There were very few reported changes within centers in practices over the study time period. Significant regional variations were found with regard to surveillance procedures and treatment durations. There were no significant differences in treatment practices by center size and very few differences found between those centers that reported treating primarily pediatric patients versus primarily adult patients. In summary, our survey demonstrates overall agreement with published guidelines for the prevention of disease due to herpesviruses and fungal infections with significant regional differences found in duration of antiviral prophylaxis, duration of preemptive therapy, and duration and dosing of antifungal prophylaxis. Center size and age of primary patient population were not associated with many reported differences in strategies.



Aspergillus.

Viral infections

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- **Herpes simplex virus (HSV) reactivation can occur during pre-engraftment phase. After engraftment, the herpesviruses, particularly cytomegalovirus (CMV), are major pathogens.**
- Herpes simplex virus (HSV)–seropositive patients undergoing allogeneic HSCT 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 .

Special points: sepsis

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Sepsis : “The clinical suspicion of infection and evidence of a systemic response”

Systemic response is usually defined by a combination of two or more of the following: hypothermia ($<36^{\circ}\text{C}$), hyperthermia ($>38^{\circ}\text{C}$), tachycardia, tachypnea, leukocytosis, or neutropenia.

Kline, Nursing Care of Children and Adolescents with Cancer, 2002).



Special points: septic shock.

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Septic Shock:

- Septic shock is a more progressive stage of sepsis, defined by persistent hypotension that does not respond to fluid resuscitation
- Septic SHOCK is oftentimes caused by gram-negative bacteria, but CAN be caused by gram-positive bacteria, fungi, or viruses

Kline, Nursing Care of Children and Adolescents with Cancer, 2002).

Clinical manifestación- sepsis

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Typically, patients with sepsis arrive with the following signs and symptoms:

- May or may not be ill appearing
- Tachycardia
- Tachypnea
- **Warm, flushed skin**
- **Normal blood pressure**
- **Normal urine output**
- **Bounding pulses**



Remember: Patients presenting with neutropenic sepsis may or may NOT have fever.

Do NOT rely on fever as an indicator of sepsis

Clinical manifestación- septic shock

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The patient in septic shock will typically arrive with the following:

While typically ill -appearing, these patients may be well appearing upon arrival so do NOT base on looks alone

- **Tachycardia**
- **Tachypnea**
- **Cool, dry skin**
- **Hypotension that is persistent and is not resolved with fluid resuscitation**
- **Weak or absent peripheral pulses**
- **Decreased Capillary Refill**
- **Decreased (or even absolutely NO) urine output**

Comments

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- ❑ Severe sepsis and septic shock are common causes of morbidity and mortality.
- ❑ Interventions directed at specific endpoints, when initiated early in the "golden hours" of patient arrival at the hospital, seem to be promising.



Comments

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- Early hemodynamic optimization, administration of appropriate antimicrobial therapy, and effective source control of infection are the cornerstones of successful management.



....to take home

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- ❑ All patients with fever and neutropenia should be evaluated for level of risk (high or low), have history and physical examination performed, have cultures and radiological tests performed

...to take home

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- ❑ All patients with fever and neutropenia should be evaluated for level of risk (high or low), have history and physical examination performed, have cultures and radiological tests performed
 - To initiate treatment with broad-spectrum empirical antibiotics promptly (ie, within 2 h of presentation) is vital.
 - ❑ In the absence of effector cells, primarily neutrophils, signs and symptoms of inflammation may be lacking and rapid progression of invasive bacterial infections may occur, so antibiotics are a life-saving measure in this situation

....to take home

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Pediatric patients who receive antibiotics for fever and neutropenia in less than 60 min have decreased intensive care needs 2015-02-07

By Jennifer L. Salstrom MD, PhD, Rebecca L. Coughlin MEd, Kathleen Pool MSN,CPNP, Melissa Bojan BSN, Camille Mediavilla BSN, William Schwent MBA, Michael Rannie MS, Dawn Law MBA, Michelle Finnerty BS, Joanne Hilden MD



https://www.cure4kids.org/ums/home
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...to take home

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- Regardless of venue, clinical vigilance and immediate treatment are the universal keys to managing neutropenic patients with fever and/or infection.
- Whatever new approaches may be developed, the central issue of prophylaxis remains unchanged: a balance must be struck between effective infection prevention and the risk of antimicrobial-resistant infections caused by overuse of antibiotics.



Thank you
Merci
Gracias

