« Infection among haematological patients».

Dr Georgala Aspasia.
Maladies Infectieuses
Institut Jules Bordet
20/04/2024

Individualized risk stratification is important-1

- Host defects caused by underlying disease, activity of malignancy
- Type, dose, duration and temporal sequence of immunosuppressive therapy
- Depth, rapidity and duration of neutropenia
- Multiple episodes of neutropenia
- Antibacterial and antifungal preexposure (e.g. prophylaxis)
- The presence of mucosal injury
- Metabolic factors/comorbidities
- The immunomodulating effects of viruses (e.g. CMV)

Dimitrios P Kontoyiannis. Division of Internal Medicine the University of Texas, MD Anderson Cancer Center. IDWeek 2023, Boston, MA(USA).

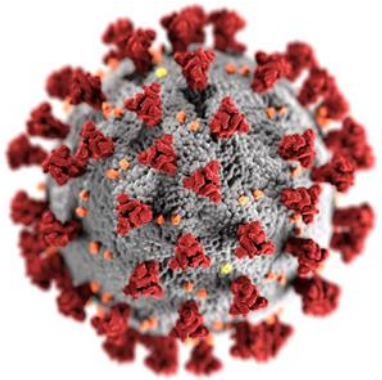
Individualized risk stratification is important-2

- Tempo of illness
- Daily assessment of localizing symptoms
- Recent unusual exposures
- Daily thorough physical exam, signs might be subtile
- History of bacterial of other infections
- Known bacterial colonization
- Assessment of PK/PD of current treatment
- SOFA score, optimal level of care (e.g., ICU)

Dimitrios P Kontoyiannis. Division of Internal Medicine the University of Texas, MD Anderson Cancer Center. IDWeek 2023, Boston, MA(USA).

Common Etiologic agents of Infection in Immunocompromised Patients (adapted from R.H. Rubin & L.S. Young, Clinical Approach to Infection in the Immunocompromised Host, 4th edition)

Type of immune defect

Class of organism	Cellular immunodeficiency	Humoral immunodeficiency	Neutropenia
Viruses	CMV, HSV, VZV, JC-BK virus	CMV	(-)
Bacteria	*Listeria monocytogenes*, *Mycobacterium avium-intracellulare*, *Mycobacterium tuberculosis*, *Nocardia* spp., *Salmonella* spp.	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, STA, other streptococci	*Escherischia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, Enterobacteriacae, STA → (r)ESCAPES
Fungi	*Aspergillus* spp., *Candida* spp., *Histoplasma capsulatum*, *Coccidioides immitis*, Mucoraceae family, *Pseudoallescheria boydii*		*Aspergillus* spp., *Candida* spp., Mucoraceae family, *Pseudoallescheria boydii*, *Fusarium* spp.
Protozoa	*Toxoplasma gondii*, *Strongyloides stercoralis*, *Leishmania*		

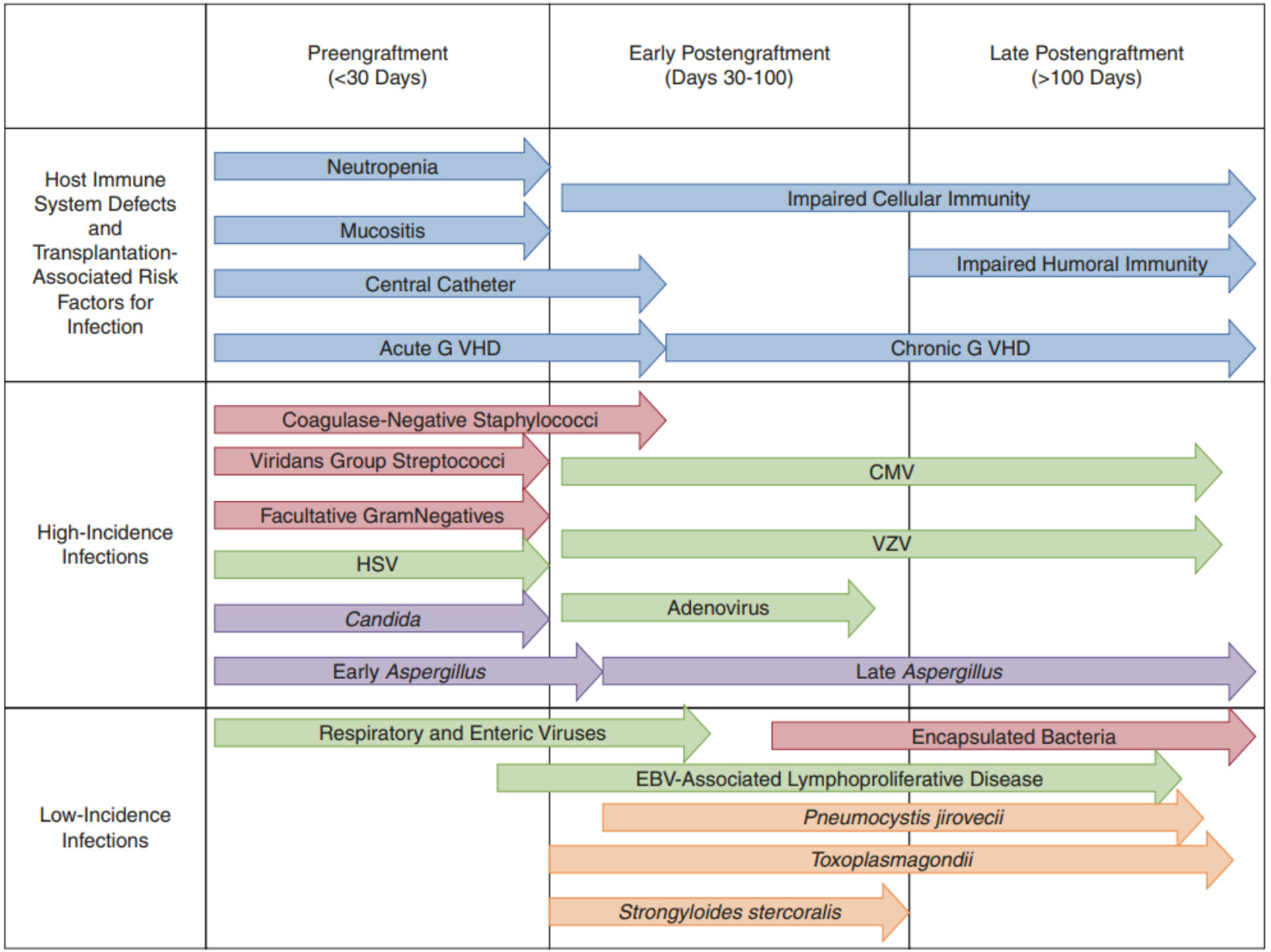


Fig. 11.1 Timeline of host immune defects and infections in Allo-HSCT recipients. Predictable opportunistic infections encountered following allo-HSCT. Immune defects and transplant-associated risk factors are shaded in blue, bacterial infections in pink, viral infections in green, fungal infections in purple, and parasitic infections in orange

Marcus R.Pereira et al. Department of Medicine – Infectious Diseases, Columbia University Medical Center, New York, NY, USA. Principles and Practice of Transplant Infectious Diseases. © Springer Science+Business Media, LLC, part of Springer Nature 2019 209 A. Safdar (ed.)

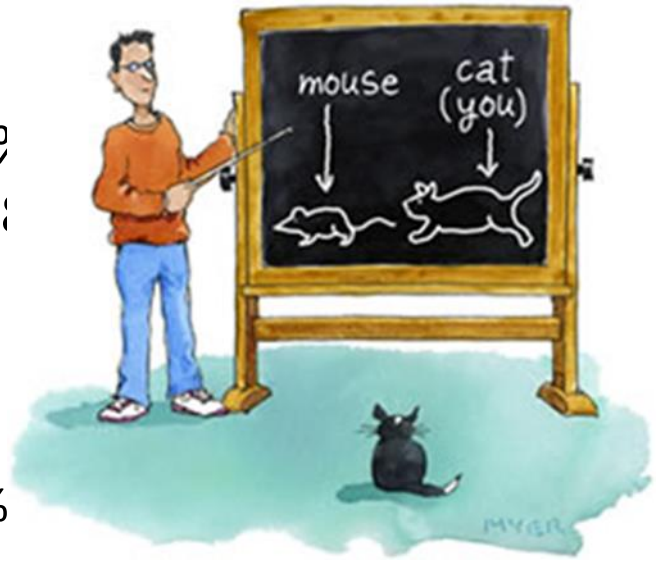
Febrile neutropenia

Fever in neutropenic patients is defined as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38°C (100.4°F) sustained over a one-hour period : IDSA / Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. A. Freifeld et al. Clin Infect Dis. 2011;52(4):e56

The definition of neutropenia may vary from institution to institution, but neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 or 1000 cells/µL, severe neutropenia as an ANC <500 cells/µL or an ANC that is expected to decrease to <500 cells/µL over the next 48 hours, and profound neutropenia as an ANC <100 cells/µL [2]. The risk of clinically important infection rises as the neutrophil count falls below 500 cells/microL and is higher in those with a prolonged duration of neutropenia (>7 days). Further, the risk for bacteremic infection increases as the ANC decreases below 100 cells/microL. For the purposes of this discussion, **we are defining severe neutropenia as an ANC <500 cells/microL (<0.5 x 10^9/L).**

Febrile neutropenia: some figures

- Incidence :
  - ✓Leukemia and HSCT : 80% - 90 %
  - ✓Solid tumor or lymphoma : 5 – 8
- Mortality :
  - ✓Overall :
    - Solid tumors : 9.5 %
    - Lymphoma and leukemia : 14 %
  - ✓Infection-related :
    - Solid tumors : 2.3 %
    - Lymphoma and leukemia : 5 %



Bucaneve et al, NEJM 2005;353:977-987
Cullen et al, NEJM 2005;353:988-998
Gafter-Gvili et al, Ann Intern Med 2005;142:979-995

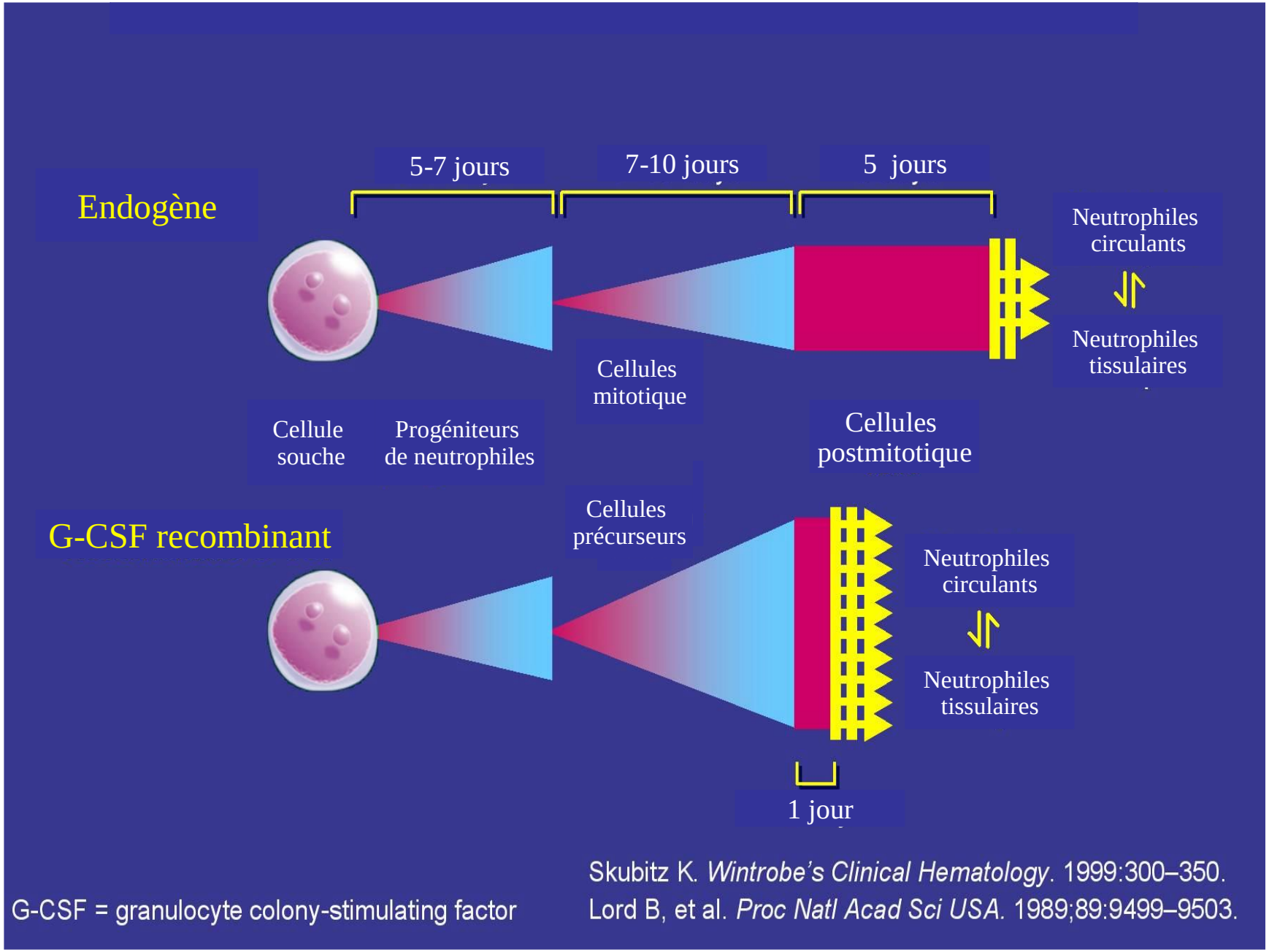
Preventing febrile neutropenia

Simple hygiene rules

- Cooked food
- Strict mouth hygiene
- Meticulous body hygiene
- Avoid crowdy areas
- Avoid gardening/do-it-yourself activities
- Sterile manipulation of implanted catheter
- HEPA filters

Room/hospital environment

- 2 bed room: solid organ neoplasia and lymphoma
- 1 bed room + HEPA filter + additional precautions (for neutropenic patients): AL, allo- & auto- recipients
- Additional precautions for multi-drug resistant bacteria, Clostridium difficile, respiratory viruses, MRSA(MSSA), BK ,…
- Air and water quality
- Dry laundry without humidity


Endogène
5-7 jours
7-10 jours
5 jours
Neutrophiles circulants
Neutrophiles tissulaires
Cellules mitotique
Cellule souche
Progéniteurs de neutrophiles
Cellules postmitotique
G-CSF recombinant
Cellules précurseurs
Neutrophiles circulants
Neutrophiles tissulaires
1 jour
G-CSF = granulocyte colony-stimulating factor
Skubitz K. *Wintrobe's Clinical Hematology*. 1999:300–350.
Lord B, et al. *Proc Natl Acad Sci USA*. 1989;89:9499–9503.

Colony stimulating factors

IDSA
Infectious Diseases Society of America

No

Freifeld AG et al. Clin Infect Dis. 2011;52(4):e56.

ASCO®
American Society of Clinical Oncology

Yes

Smith TJ et al. J Clin Oncol. 2015;33(28):3199.

Antibacterial Prevention

- Profound neutropenia (ANC<100/mm^3) for more than 7days, damaged mucous membranes or skin, presence of indwelling catheters, severe periodontal disease, a history of dental procedures, status of malignancy or organ engraftment and impairment of other immune functions
- Non-resorbable AB→TMP-STX & nalidixic acid→ fluoroquinolones(norfloxacin, ofloxacin, ciprofloxacin, levofloxacin, moxifloxacin) & others(roxithromycin, amoxicillin, amoxicillin-clavulnate)
- Blockbusters: TMP-STX and Quinolones
- Shift from GNB to GPC and infectious morbidity mainly due to GPC

Yoshida M and Ryuzo O, CID 2004 - Zinner SH, Schweiz Med Wochenschr Suppl. 1983
Bow EJ et al. CID 1995 - Imrie KR et al. Bone Marrow Transplant. 1995
Kern WV et al, Antimicrobial Agents Chemother 1994
Bucaneve G et al. NEJM 2005 - Bow EJ et al, Ann Intern Med 1996
Vehreschild Jj et al, Int J Antimicrob Agents 2012

Table 2. Characteristics of Bacterial Isolates and Number with Resistance to Levofloxacin.

Characteristic	Levofloxacin (N=339)	Placebo (N=336)
Microbiologically documented infection	74	131
No. with bacteremia	62	115
Single gram-positive isolate	37	54
S. aureus	0	10
Coagulase-negative staphylococcus	31	32
Streptococcus species	5	9
Other gram-positive organisms	1	3
Single gram-negative isolate	15	38
Pseudomonas species	6	8
E. coli	7	22
Other gram-negative organisms	2	8
Polymicrobial isolate	10	23
Gram-positive organisms only	5	5
Gram-positive and gram-negative organisms	5	18
No. without bacteremia	12	16
Single gram-positive isolate	5	7
Single gram-negative isolate	6	9
Polymicrobial isolate	1	0
Levofloxacin resistance in single-agent bacteremias — no. resistant/total no. available for analysis	41/47	32/68
Gram-positive isolate	31/34	28/44
S. aureus	0	1/7
Coagulase-negative staphylococcus	27/30	26/31
Streptococcus species	4/4	1/3
Other gram-positive organisms	0	0/3
Gram-negative isolate	10/13	4/24
Pseudomonas species	4/6	1/4
E. coli	5/5	2/16
Other gram-negative organisms	1/2	1/4

Bucaneve et al, N Engl J Med 2005

If fluoroquinolone prophylaxis is used, resistance has to be monitored carefully.
In fact, the benefit of fluoroquinolone prophylaxis may not last long and beyond 20 % R to fluoroquinolone in *E. coli*, you will loose any benefit.

Antimicrobial Prophylaxis for Adult Patients With Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update

Randy A. Taplitz, Erin B. Kennedy, Eric J. Bow, Jennie Crews, Charise Gleason, Douglas K. Hawley, Amelia A. Langston, Loretta J. Nastoupil, Michelle Rajotte, Kenneth V. Rolston, Lynne Strasfeld, and Christopher R. Flowers

Purpose
To provide an updated joint ASCO/Infectious Diseases Society of America (IDSA) guideline on antimicrobial prophylaxis for adult patients with immunosuppression associated with cancer and its treatment.

Methods
ASCO and IDSA convened an update Expert Panel and conducted a systematic review of relevant studies from May 2011 to November 2016. The guideline recommendations were based on the review of evidence by the Expert Panel.

Results
Six new or updated meta-analyses and six new primary studies were added to the updated systematic review.

Recommendations
Antibacterial and antifungal prophylaxis is recommended for patients who are at high risk of infection, including patients who are expected to have profound, protracted neutropenia, which is defined as $<$ 100 neutrophils/μL for $>$ 7 days or other risk factors. Herpes simplex virus–seropositive patients undergoing allogeneic hematopoietic stem-cell transplantation or leukemia induction therapy should receive nucleoside analog-based antiviral prophylaxis, such as acyclovir. *Pneumocystis jirovecii* prophylaxis is recommended for patients receiving chemotherapy regimens that are associated with a $>$ 3.5% risk for pneumonia as a result of this organism (eg, those with $\geq$ 20 mg prednisone equivalents daily for $\geq$ 1 month or on the basis of purine analog usage). Treatment with a nucleoside reverse transcription inhibitor (eg, entecavir or tenofovir) is recommended for patients at high risk of hepatitis B virus reactivation. Recommendations for vaccination and avoidance of prolonged contact with environments that have high concentrations of airborne fungal spores are also provided within the updated guideline. Additional information is available at *www.asco.org/supportive-care-guidelines*.

J. Clin Oncol 2018;38 (30) 3043-3054

Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines

Malgorzata Mikulska [a,*], Diana Averbuch [1,b], Frederic Tissot [1,c], Catherine Cordonnier [d], Murat Akova [e], Thierry Calandra [f], Marcello Ceppi [g], Paolo Bruzzi [g], Claudio Viscoli [a] on behalf of the European Conference on Infections in Leukemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN)

J Infect 2017 Oct 25. pii: S0163-4453(17)30322-5. doi: 10.1016/j.jinf.2017.10.009. [Epub ahead of print]

2 RCTs+12 observational studies; FQ prophylaxis:

- No effect on mortality (pooled OR 1.01, 95%CI 0.73-1.41
- Lower rate of BSI(pooled OR 0.57, 95%CI 0.43-0.74
- Lower episodes of fevere during neutropenia (pooled OR 0.32, 95% CI 0.20-0.50)
- In few studies, FQ prophylaxis resulted in an increased colonisation or infection with FQ- or multi-drug resistant strains

The possible benefits of FQ on BSI rate, **but not on overal mortality**, should be weighed against its impact in terms of toxicity and changes in local ecology in single centres.

Ann Hematol (2015) 94:1441–1450
DOI 10.1007/s00277-015-2447-3

ORIGINAL ARTICLE

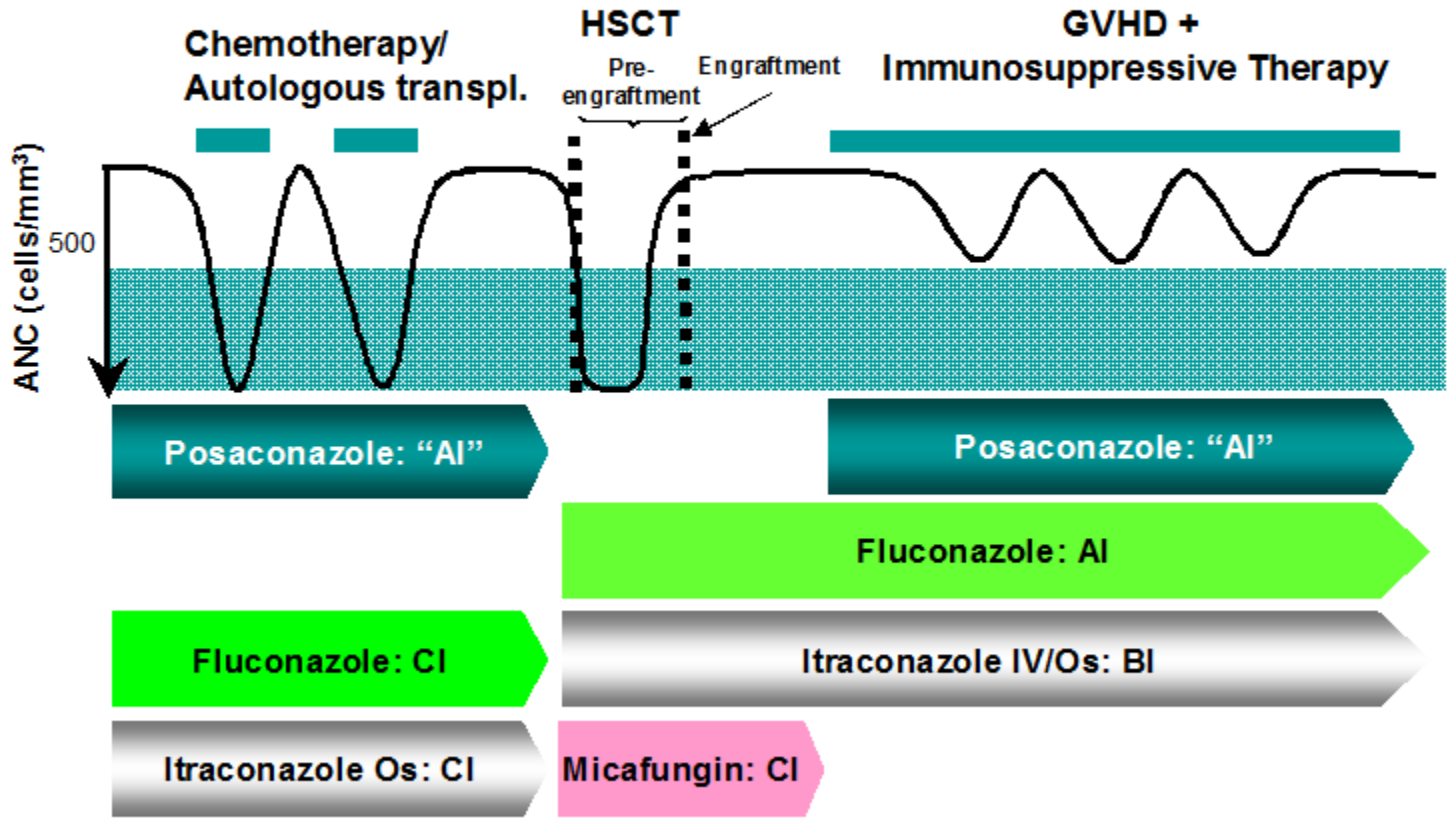
Antiviral prophylaxis in patients with solid tumours and haematological malignancies—update of the Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO)

Michael Sandherr[1] · Marcus Hentrich[2] · Marie von Lilienfeld-Toal[3] · Gero Massenkeil[4] · Silke Neumann[5] · Olaf Penack[6] · Lena Biehl[7,8] · Oliver A. Cornely[7,9]

Anti-CMV

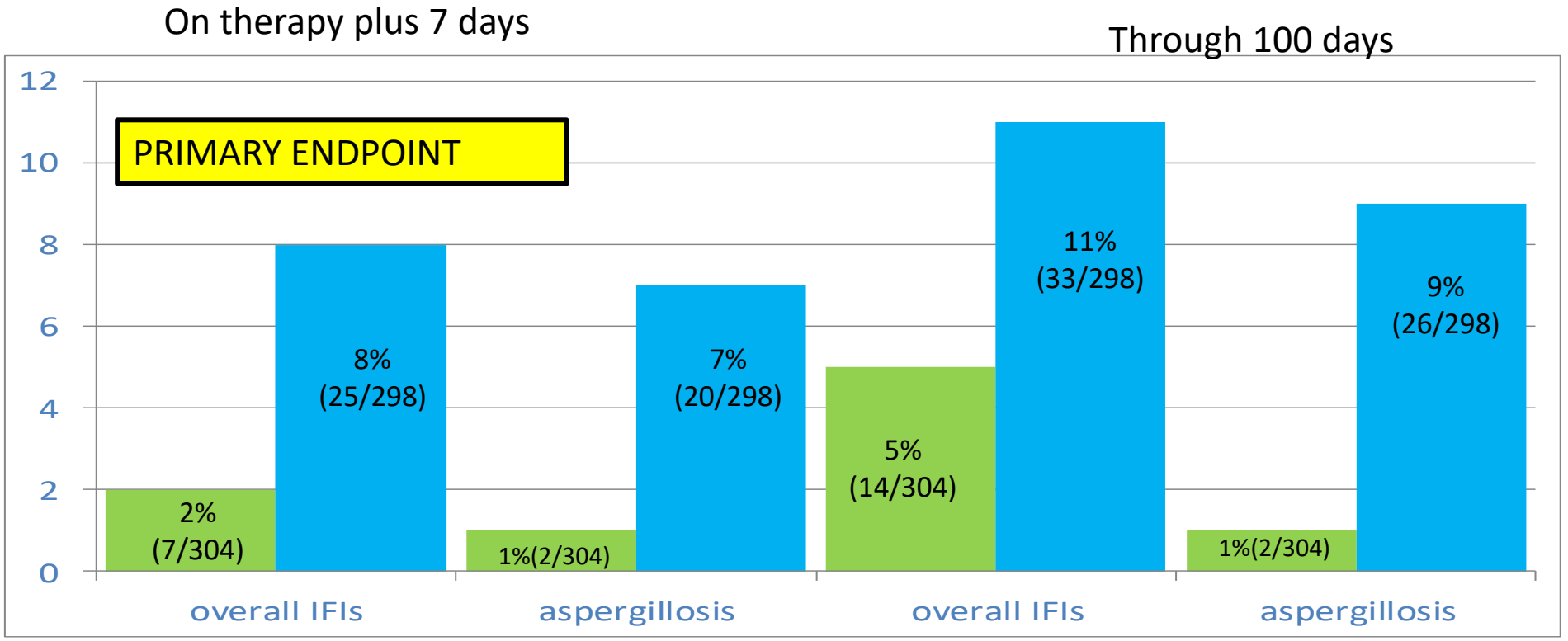
Yes for antiviral prophylaxis with aciclovir.

Antifungal prophylaxis in leukemia patients: ECIL recommendations



From Aoun M, Buvé K, Maertens J, Klastersky J, In "Cancer Supportive Care : Advances in Therapeutic strategies". GH Lyman and J. Crawford (eds). Informa Healthcare USA, New York 2008 : 89-114.

Posaconazole in neutropenic patients: results – proven/probable



- Posaconazole oral suspension (200mg TID) (cumulative exposure : median 23 days, mean 29 days)
- Flucoconazole (400mg QD) or itraconazole (200 mg BID) (cumulative exposure : median 20 days, mean 25 days)

Cornely OA, NEJM 2007;356:348-359

Score derived from logistic equation of the MASCC predictive model (1386 Patients with Febrile Neutropenia)

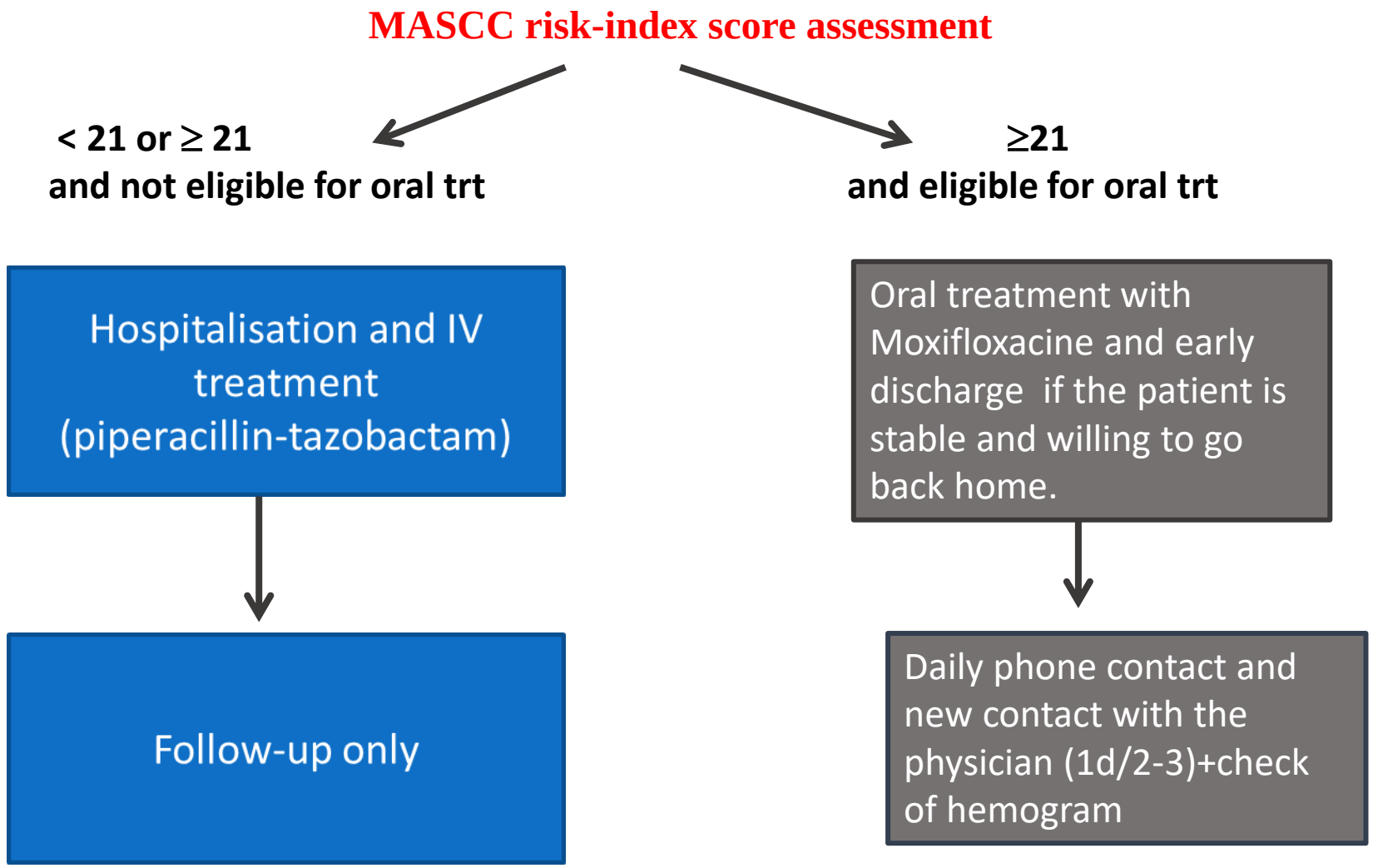
Characteristic	Points
Burden of illness	
▪ No or mild symptoms	5
▪ Moderate symptom	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection in hematological ca	4
Outpatient status	3
No dehydration	3
Age < 60 years	2

MASCC
WWW.MASCC.ORG

Threshold: score ≥ 21(maximum 26) predicting less than 5% of severe complications

J. Klastersky et al. JCO 2001

Flow-chart of study design (unicentric study – Institut Jules Bordet)



Loizidou A., ICCAC 2012 – San Francisco 2012

Pseudomonas aeruginosa bacteraemia among haematological patients

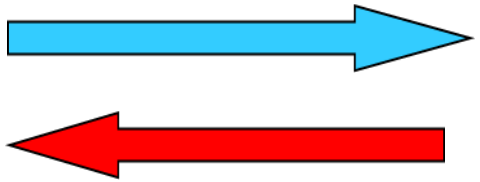
- 441 cases (2004-2010)
- 66 due to *P. aeruginosa*
- 22 (33%) due to MDR strains
- Mortality
  - Higher in MDR strains (37% vs 23%, P=0.26)
  - Higher if inadequate empiric therapy (83% vs 18.8%,P=0.01)

Cattaneo C et al, Ann Hematolo 2012:91:1299-1304.

Single drug therapy

First line

- Ceftazidime
- Cefepime
- Piperacillin/tazobactam



Second line

- Carbapenems :
- Imipenem
- Meropenem

Other options:
Ceftazidime-avibactam
Ceftolozane-tazobactam
Aminoglycosides
Colistine
Vancomycine, Tigecyclin
Associations

Retrospective 11-yr study (1998-2008):428 neutropenic patients admitted in the ICU with severe sepsis or septic shock.

Table 5. Multivariate analysis of factors associated with in-hospital mortality

Variable, N (%) or Median (25th–75th)	Alive (n = 215)	Dead (n = 213)	Odds Ratio (95% Confidence Interval)	*p*
Age, yrs	47 (35–57)	54 (43–65)	1.036 (1.02–1.05)	<.0001
Intensive care unit admission during the second period (between 2004 and 2008)	139 (64.6)	105 (49.3)	0.56 (0.36–0.89)	.01
Shock	123 (57.2)	181 (85.0)	2.69 (1.65–4.38)	<.0001
Acute respiratory failure	61 (28.4)	171 (80.3)	1.98 (1.14–3.44)	.015
Neurologic failure	7 (3.2)	37 (17.4)	4.03 (1.03–15.8)	.04
Hepatic failure	7 (3.2)	20 (9.4)	1.49 (1.16–1.91)	.002
Early acute noninfectious conditions	77 (35.8)	98 (46.0)	1.69 (1.06–2.68)	.02
Initial combination antibiotic therapy	210 (97.7)	181 (85.0)	0.164 (0.05–0.51)	.002
Indwelling catheter removal	68 (31.6)	39 (18.3)	0.50 (0.30–0.85)	.01

Goodness of fit (Hosmer-Lemeshow) chi-square *p* value = .64. Area under the receiver operating characteristic curve = .74.

β-lactam+ aminoglycoside

↓mortality

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Legrand M, Crit Care Med 2012

Febrile neutropenic episodes were not created the same….

Underlying disease.
- High risk
- Intermediate risk
- Low risk

Diagnosis:
- FUO
- Clinical infection
- Bacteraemia
- Microbiologically defined infection(other than bacteraemia)

Episode course:
- Afebrile
- Febrile

Risk:
- Mortality
- Septic choc/ICU
- Bacteraemia
- Recurrent fever

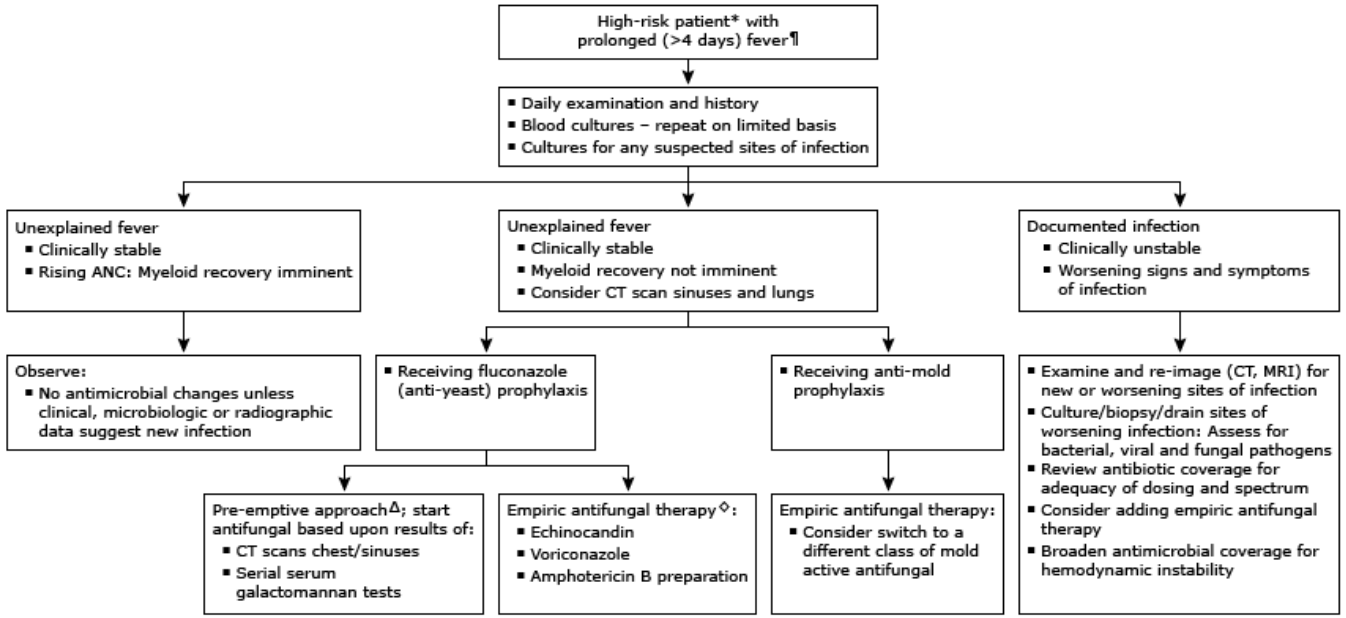
Benefits:
- Antibiotic duration
- Clostridium difficile infection
- Resistance
- IFI
- Hospitalisation length

Dina Averbuch (Secretary Infectious Disease Working Party EBMT), Hadassah Medical Center, Jerusalem, Israel – IDWeek 2023, Boston, MA(USA).

Causes of Persistent or New Neutropenic Fever

- Resistant occult new bacterial infection (e.g. VRE, ESBL)
- Failure of antibiotics/antifungals given for prior infection
- Chemo-induced mucosal injury (endotoxemia)
- Non-bacterial infection (virus, AFB, toxoplasmosis)
- Malignancy-related fevers, Sweet syndrome
- Superinfection with MDR fungi
- Drug fever
- {Cytokine release syndrome (CARTT)}
- Engraftment syndromes, acute GVHD
- HLH
- Transfusion fever
- Other uncommon, including combinations of the above

Reassessment of the high-risk patient with persistent neutropenic fever after four days of empiric therapy



ANC: absolute neutrophil count; CT: computed tomography; MRI: magnetic resonance imaging.

* We consider patients to be high-risk if they have either of the following characteristics: neutropenia (ANC <500 cells/microL following cytotoxic chemotherapy) anticipated to last >7 days OR significant comorbid conditions. It should be noted that in the Infectious Diseases Society of America guidelines, an ANC ≤100 cells/microL is used as the cutoff for high-risk neutropenia.

¶ Fever in a neutropenic patient is defined as a single temperature >38.3°C (101°F) or a sustained temperature >38.0°C (100.4°F) for >1 hour.

Δ Limited data to support recommendation.

◇ Spectrum activity and adverse effect profiles vary among antifungals. An echinocandin is often selected for patients without specific concern for infection with mold due to its favorable adverse effect profile. Refer to UpToDate text for detail.

Adapted with permission from: Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52(4):e56-93. Copyright © 2011 Oxford University Press. https://www.idsociety.org/practice-guideline/neutropenic-patients-with-cancer/ (Accessed on March 29, 2023).

Special considerations:

- Antibiotic resistance
- Addition of an antifungal agent
- Catheter removal
- Myeloid reconstitution syndrome

Antibiotic resistance

MRSA
VRE
Penicillin- & ceftriaxone-(R)St pneumoniae
GP bugs-(R)vancomycine(Leuconstoc, Lactobacillus, Pediococcus spp)
GNB-MDR: E.coli, Pseudomonas aeruginosa, Citrobacter spp, Acinetobacter baumanii, Stenotrophomonas spp
GNB – ESBL+/ GNB-CPE+

(R)ESCAPES

Germs Develop Antibiotic Resistance

Select Germs Showing Resistance Over Time

Since the discovery of penicillin more than 90 years ago, germs have continued to develop new types of resistance against even our most powerful drugs. While antibiotic development has slowed, antibiotic resistance has not. This table demonstrates how rapidly important types of resistance developed after approval and release of new antibiotics, including antifungals.

Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus*[20, 21]	1942
		Penicillin-resistant *Streptococcus pneumoniae*[9,10]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[11]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[12,13]	1988
		Vancomycin-resistant *Staphylococcus aureus*[14]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[15]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[16]	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[17]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[18]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[19]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[20]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[21]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[22]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[23]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[24]	2015

Revised Dec. 2019

CDC U.S. Department of Health and Human Services Centers for Disease Control and Prevention

- The new pandemic is here: multi-drug resistant organisms=MDRO and this is our new major preoccupation.

↳ old AB (colistine, fosfomycine), new AB(tigecycline, ceftazidime-avibactam, meropenem-vaborbactam, cefiderocol,….), new combinations (ceftazidime-avibactam+aztreonam), new anti-CGP(daptomycin, linezolid, tigecycline)

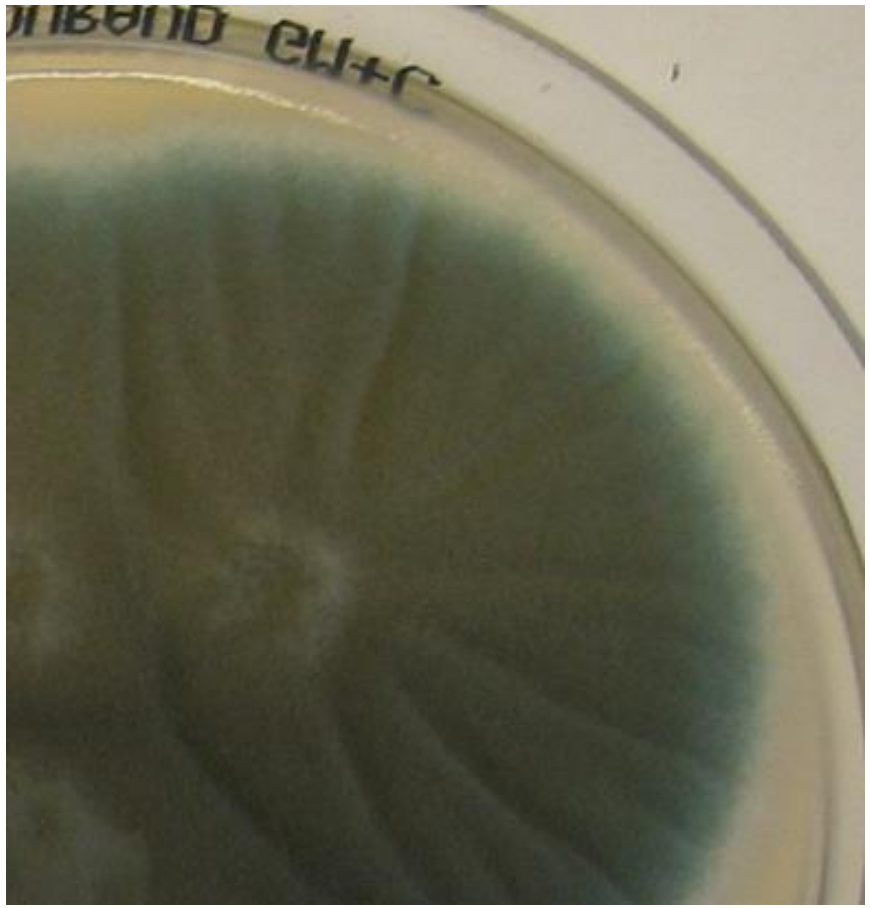
- Risk factors:
  - Previous infection or colonisation by MDRO
  - Recent use of antibacetrial drugs (therapeutic/prophylactic)
  - Treatment in hospital with high rates of resistance

→ Get familiar with your patient's past-, present- and future-bacterial history

- **How to reduce MDRO**: stop prophylaxis, target therapy, discontinue unneeded empiric treatments, initiate antibiotic stewardship programs

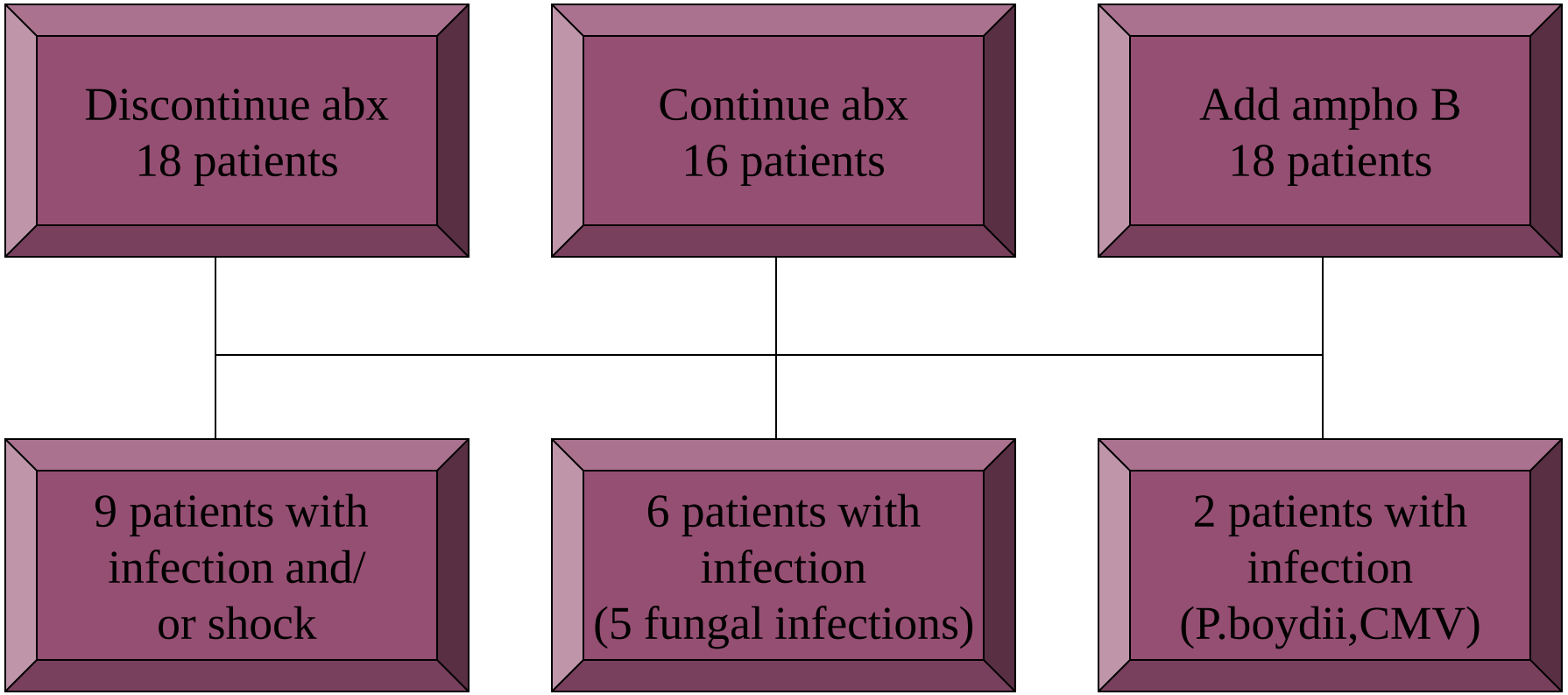
Wingard JR et al. Curr Opin Hematol. 2012;19(1):21.
Bow EJ. Curr Opin Infect Dis. 2011;24(6):545.
Averbuch D et al./ECIL-4,2011. Haematologica. 2013;98(12):1836.
Freifeld AG et al. Clin Infect Dis. 2011;52(4):e56.
Rolston KV. Clin Infect Dis. 2005;40 Suppl 4:S246.

Addition of an antifungal agent



The beginning

Patients persistent febrile neutropenia for 7 days



Abx : antibiotics

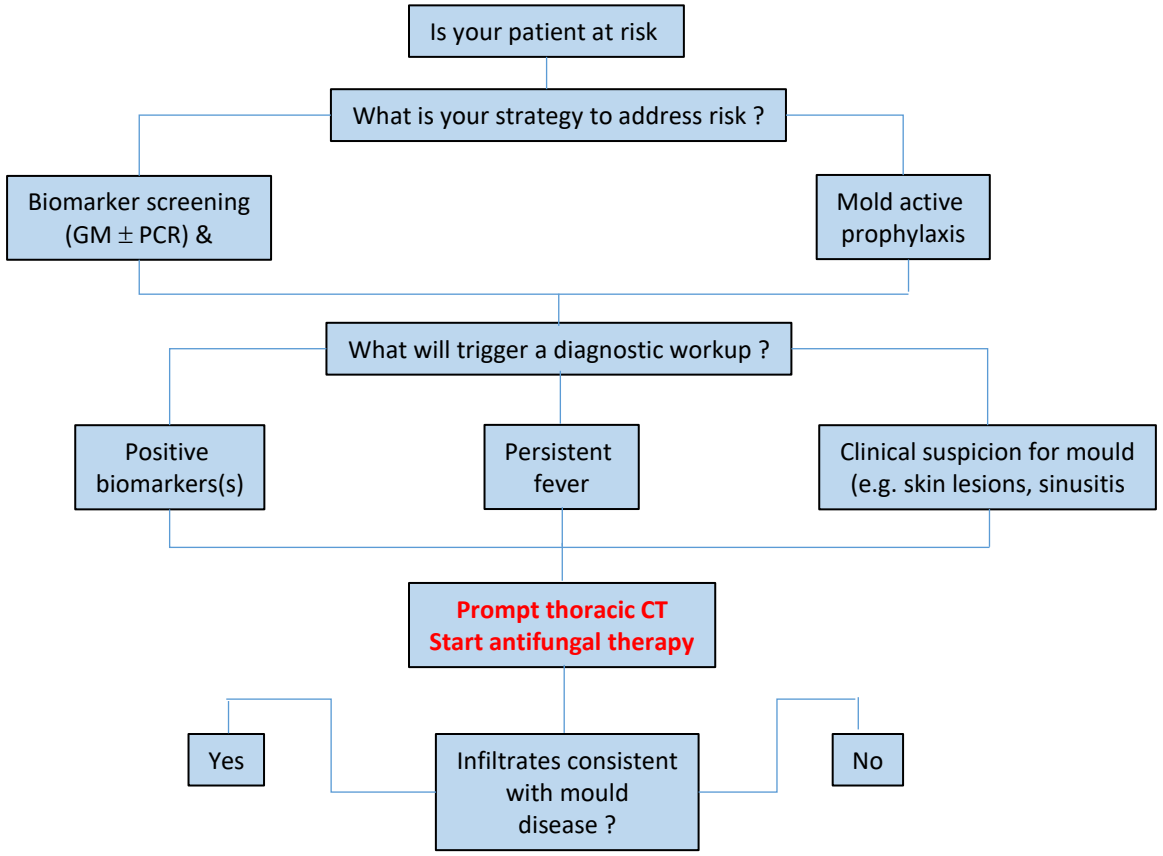
Pizzo et al, Am J Med 1982;72:101-111

Measures of the success (%) of empiric antifungal therapy with conventional or liposomal amphotericin B, voriconazole or caspofungin

	Ampho B	Liposomal ampho B vs Ampho B	Liposomal ampho B vs Vorico	Liposomal ampho B vs Caspo	Vorico	Caspo
No patients	344	343	422	539	415	556
Overall success	49.4	50.1	30.6	33.7	26.0	33.9
Resolution of fever	58.1	58.0	36.5	41.4	32.5	41.2
No breakthrough fungal infections	89.2	90.1	95.0	95.5	98.1	94.8
Resolution of baseline infections	72.7	81.8	66.7	25.9	46.2	51.9
Survival for 7 days	89.5	92.7	94.1	89.2	92.0	92.6
No discontinuation for toxic effects or lack of efficacy	81.4	85.7	93.4	85.5	90.1	89.7

Aoun et al, Cancer Supportive Care; ed GH Lyman, J Crawford, Informa Healthcare USA 2008:89-114

General diagnostic algorithm for persistent fever* in hematology patients



* After 72-96 hours of appropriate empiric antibacterials with negative BCs
** Modified antibacterials based on local epidemiology/bacterial colonization (e.g. VRE, ESBL), prior hx of MDR bacterial infection
& ß-D-Glucan lacks specificity, PCR still not fully standardized

Dimitrios P Kontoyiannis. Division of Internal Medicine the University of Texas, MD Anderson Cancer Center.
IDWeek 2023, Boston, MA(USA).

Clinical Infectious Diseases

MAJOR ARTICLE

Empiric vs Preemptive Antifungal Strategy in High-Risk Neutropenic Patients on Fluconazole Prophylaxis: A Randomized Trial of the European Organization for Research and Treatment of Cancer

Johan Maertens,[1] Tom Lodewyck,[2] J. Peter Donnelly,[3] Sylvain Chantepie,[4] Christine Robin,[5] Nicole Blijlevens,[3] Pascal Turlure,[6] Dominik Selleslag,[2] Frédéric Baron,[7] Mickael Aoun,[8] Werner J. Heinz,[9] Hartmut Bertz,[10] ZdeněkRáčil,[11] Bernard Vandercam,[12] Lubos Drgona,[13] Valerie Coiteux,[14] Cristina Castilla Llorente,[15] Cornelia Schaefer-Prokop,[3] Marianne Paesmans,[8] Lieveke Ameye,[8] Liv Meert,[16] Kin Jip Cheung,[16] Deborah A. Hepler,[17] Jürgen Loeffler,[18] Rosemary Barnes,[19] Oscar Marchetti,[20,21] Paul Verweij,[3] Frederic Lamoth,[20] Pierre-Yves Bochud,[20] Michael Schwarzinger,[22] and Catherine Cordonnier,[5] for the Infectious Diseases Group and the Acute Leukemia Group of the European Organization for Research and Treatment of Cancer

[1]Department of Hematology, University Hospitals Leuven, Leuven, Belgium; [2]Department of Hematology, Algemeen Ziekenhuis St Jan, Brugge, Belgium; [3]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands; [4]Department of Hematology, Caen University Hospital, Caen, France; [5]Department of Hematology, Centre Hospitalier Universitaire Henri Mondor, Créteil, France; [6]Department of Hematology, Centre Hospitalier Universitaire Limoges, Limoges, France; [7]Department of Hematology, University of Liège and University Hospital of Liège, Liège, Belgium; [8]Department of Internal Medicine, Institut Jules Bordet, Brussels, Belgium; [9]Department of Hematology/Oncology, Caritas Hospital, Bad Mergentheim, Germany; [10]Department of Hematology/Oncology, Faculty of Medicine and Medical Centre, University of Freiburg, Freiburg, Germany; [11]Department of Hematology, Masaryk University Brno and Institute of Hematology and Blood Transfusion, Prague, Czech Republic; [12]Department of Internal Medicine/Infectious Diseases, Cliniques Universitaires St. Luc, Brussels, Belgium; [13]Department of Oncohematology, Comenius University and National Cancer Institute, Bratislava, Slovakia; [14]Service des maladies du sang, Centre Hospitalier Régional Universitaire Lille, Lille, France; [15]Department of Hematology, Gustave Roussy Cancer Campus, Villejuif, France; [16]European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium; [17]Merck & Co, Inc, Kenilworth, New Jersey, USA; [18]Department of Internal Medicine II, Universitaetsklinikum, Würzburg, Germany; [19]Department of Infection, Immunity and Biochemistry, Cardiff University, Cardiff, United Kingdom; [20]Department of Medicine, Lausanne University Hospital, Lausanne, Switzerland; [21]Department of Infectious Diseases, Ensemble Hospitalier de la Côte, Morges, Switzerland; and [22]Translational Health Economics Network, Bordeaux University Hospital, Bordeaux, France

Background. Empiric antifungal therapy is considered the standard of care for high-risk neutropenic patients with persistent fever. The impact of a preemptive, diagnostic-driven approach based on galactomannan screening and chest computed tomography scan on demand on survival and on the risk of invasive fungal disease (IFD) during the first weeks of high-risk neutropenia is unknown.

Methods. Patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and allogeneic hematopoietic cell transplant recipients were randomly assigned to receive caspofungin empirically (arm A) or preemptively (arm B), while receiving fluconazole 400 mg daily prophylactically. The primary end point of this noninferiority study was overall survival (OS) 42 days after randomization.

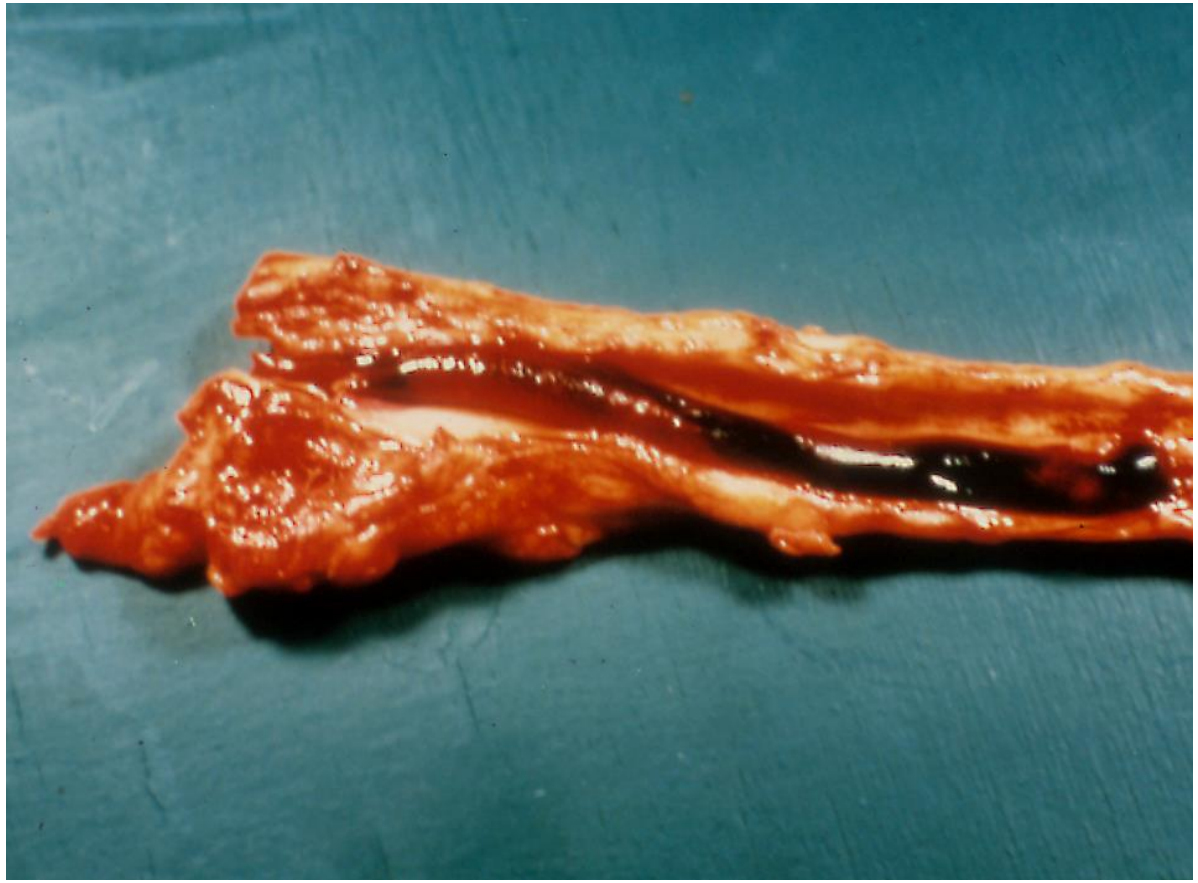
Results. Of 556 patients recruited, 549 were eligible: 275 in arm A and 274 in arm B. Eighty percent of the patients had AML or MDS requiring high-dose chemotherapy, and 93% of them were in the first induction phase. At day 42, the OS was not inferior in arm B (96.7%; 95% confidence interval [CI], 93.8%–98.3%) when compared with arm A (93.1%; 95% CI, 89.3%–95.5%). The rates of IFDs at day 84 were not significantly different, 7.7% (95% CI, 4.5%–10.8%) in arm B vs 6.6% (95% CI, 3.6%–9.5%) in arm A. The rate of patients who received caspofungin was significantly lower in arm B (27%) than in arm A (63%; $P < .001$).

Conclusions. The preemptive antifungal strategy was safe for high-risk neutropenic patients given fluconazole as prophylaxis, halving the number of patients receiving antifungals without excess mortality or IFDs.

Clinical Trials Registration. NCT01288378; EudraCT 2010-020814-27.

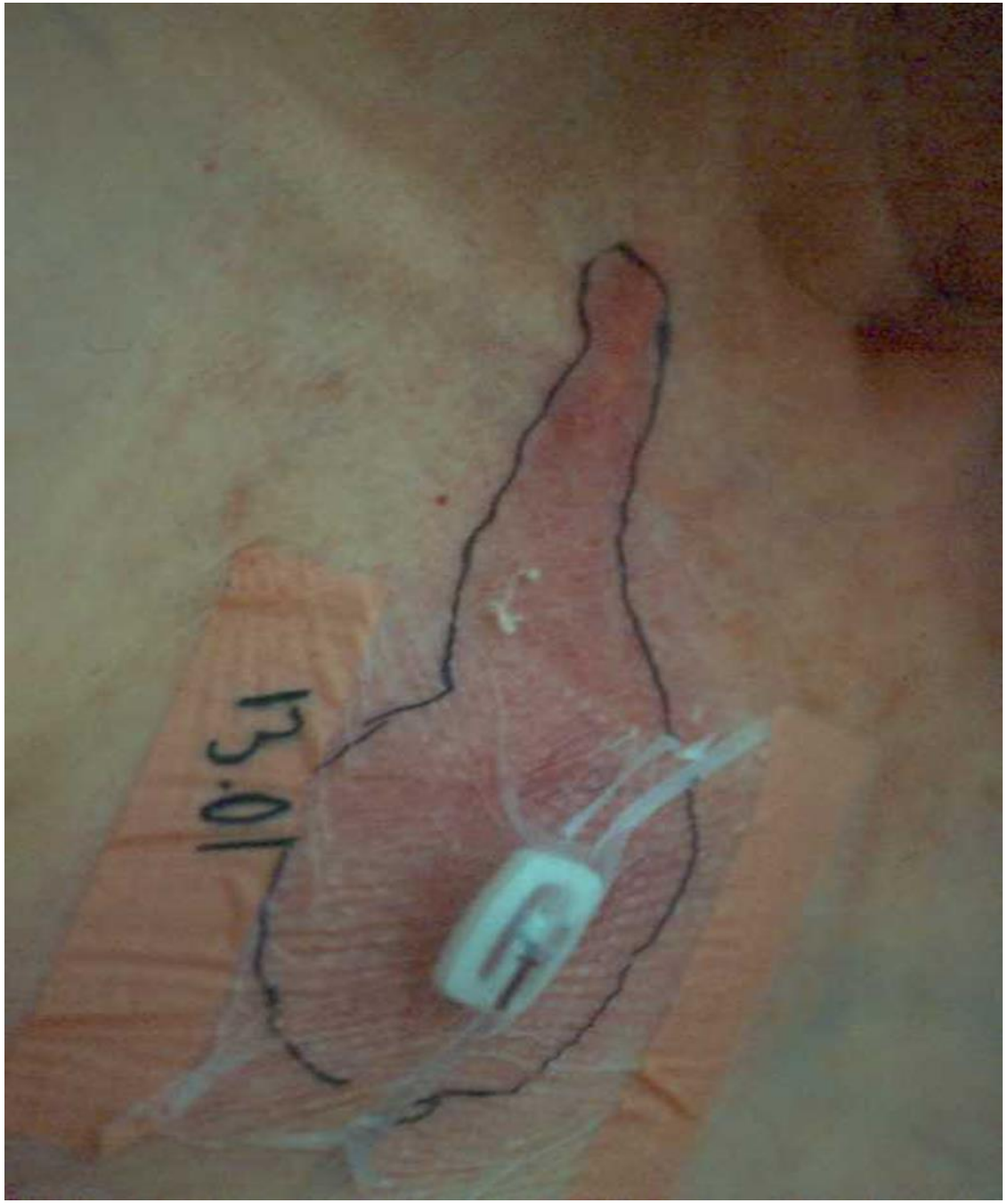
Keywords. neutropenia; empiric; preemptive; antifungal; galactomannan.

Catheter removal



- CVC-related infections are frequent in patients with neutropenic fever
- CVC must be removed when the bacteraemia is associated to:
  - MSSA/MRSA
  - *Pseudomonas aeruginosa*
  - *Candida* species
  - Other fungi (*Fusarium* spp, *Exophiala* spp, *Magnusiomyces capitatum*)
  - Rapidly growing nontuberculous mycobacteria
- If CVC removed: improved clearance of the infection, ↓mortality (observational studies), ↓relapse
- Duration of ABtherapy=14days
- CGN-Staphylococci & Enterococci: the catheter may be retained

Fowler VG Jr et al. Clin Infect Dis. 1998;27(3):478
Dugdale DC et al. Am J Med. 1990;89(2):137
Hanna H et al. Arch Intern Med. 1995;155(22):2429
Raad I et al. Clin Infect Dis. 2004
Legrand M et al. Crit Care Med. 2012;40(1):43



- Tunnel infection
- Port pocket infection
- Septic thrombosis
- Endocarditis
- Sepsis with hemodynamic instability
- Bloodstream infection that persists≥72h of therapy with appropriate antibiotics
- Deep tissue infection

CVC to be removed
Extend ABtherapy: 4-6weeks

Myeloid reconstitution syndrome

Neutropenic fever syndromes in patients undergoing cytotoxic therapy for acute leukemia and myelodysplastic syndromes

E J Bow [1]

Affiliations + expand

PMID: 19549578 DOI: 10.1053/j.seminhematol.2009.03.002

Abstract

Fever represents the major surrogate of infection in neutropenic cancer patients. A number of neutropenic fever syndromes have been recognized, the causes and significance of which will vary depending upon the clinical context. First neutropenic fever syndromes are typically of bacterial origin, the character of which may be influenced by whether antibacterial chemoprophylaxis has been administered. Persistent neutropenic fevers are documented during the empirical systemic antibacterial therapy for the first neutropenic fever, the cause of which is likely outside the spectrum of activity of the initial therapy. Recrudescent neutropenic fevers, defined by the appearance of a new fever after defervescence of the first fever, are often a function of invasive fungal infection or gram-positive infections outside the spectrum of the initial empirical antibacterial regimen. The myeloid reconstitution syndrome occurs in parallel with neutrophil recovery from aplasia and may not necessarily represent new infection. Recognition of these patterns can help the clinician make better clinical judgments and management plans.

Conclusion

- 30 to 40% of febrile neutropenic patients do not respond to empiric initial AB.
- Close monitoring and rapid adjustment to clinical and microbiological results.
- Any clinical deterioration should prompt coverage of resistant GNB, GPC and fungi $\rightarrow$ **follow your epidemiology(patient, institution, country)**
- Fever alone in stable condition is not an indication to change.
- Persisting fever beyond day 5 is a trigger for extensive investigations (and early antifungal therapy).

Viral opportunistic infections

- CMV (preemptive treatment, prophylaxis)
- Non-CMV (e.g. Adenovirus, BKV, HHV-6, EBV)

Mycobacterial infections

↓

Diagnostic challenge

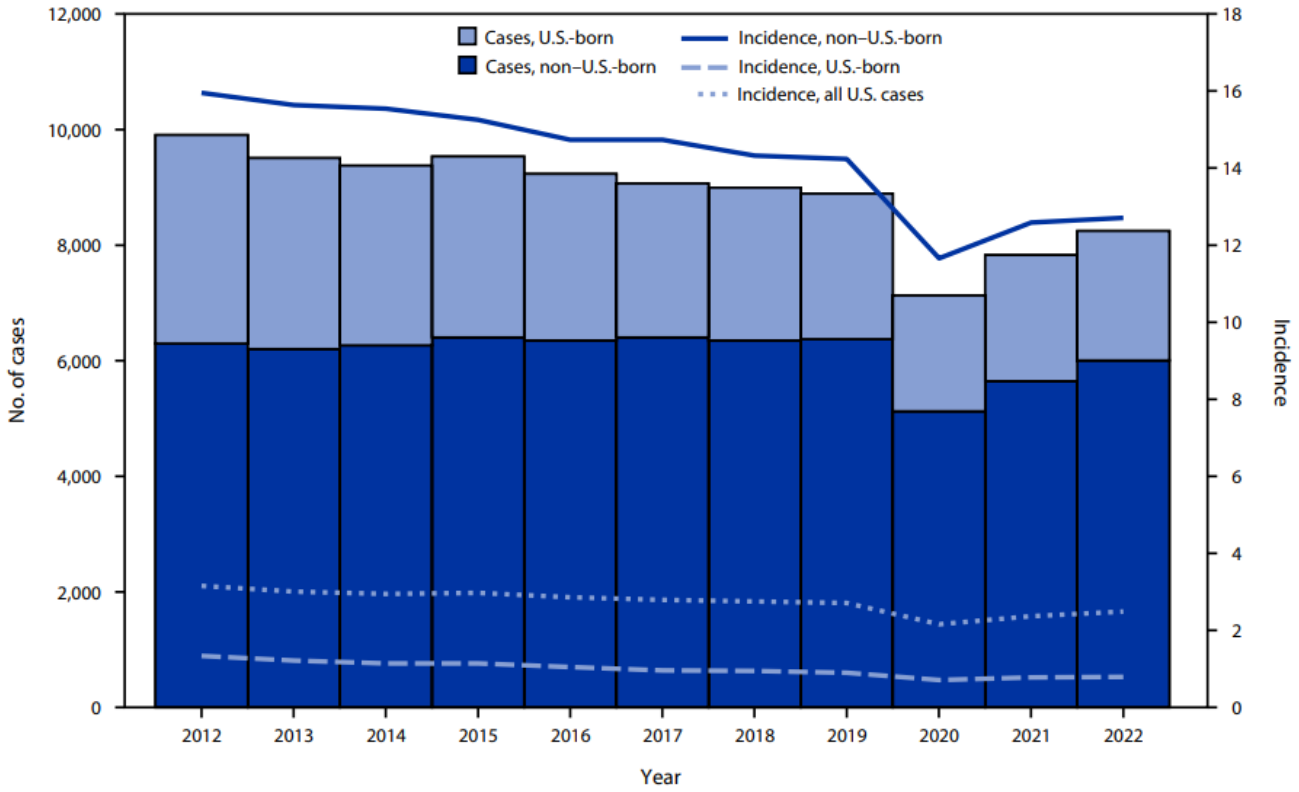
JOANNA NELSON MD Clinical Assistant Profesor – stanford University. IDWeek 2023, Boston, MA(USA).

Boston(MA) – Public Library

Mycobacterium tuberculosis in USA

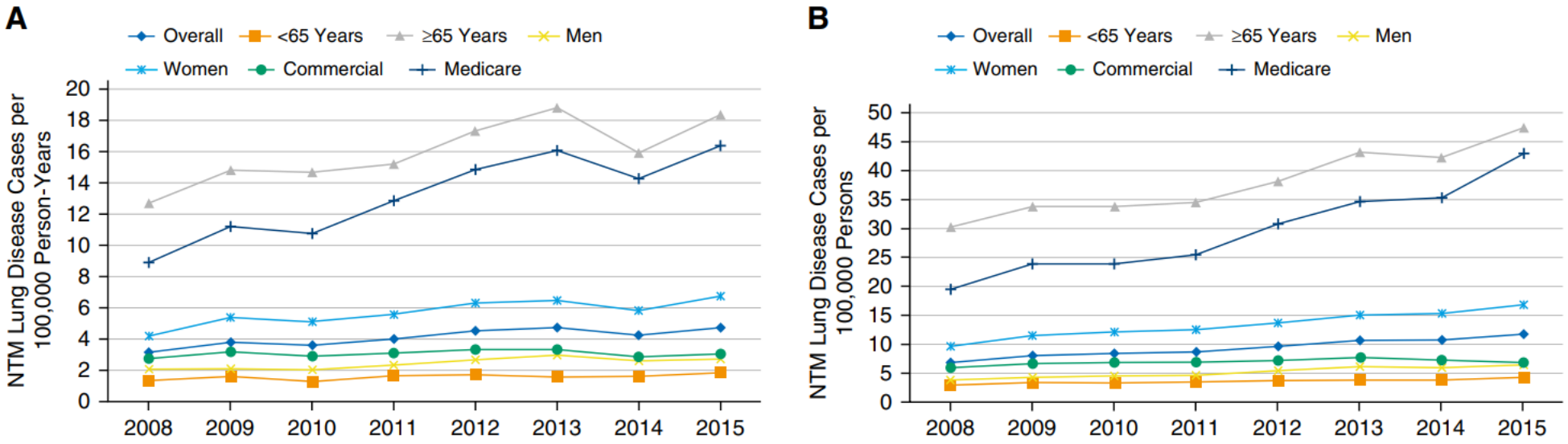
- Incidence in last 3 years increasing towards pre-pandemic levels
- Estimated 13 million living with latent tuberculosis infection

FIGURE. Tuberculosis disease cases* and incidence,† by patient U.S. birth origin status§,¶ — National Tuberculosis Surveillance System, United States, 2012–2022



Schildknecht KR, Pratt RH, et al. MMWR Morb Mortal Wkly Rep 2023;72:297-303

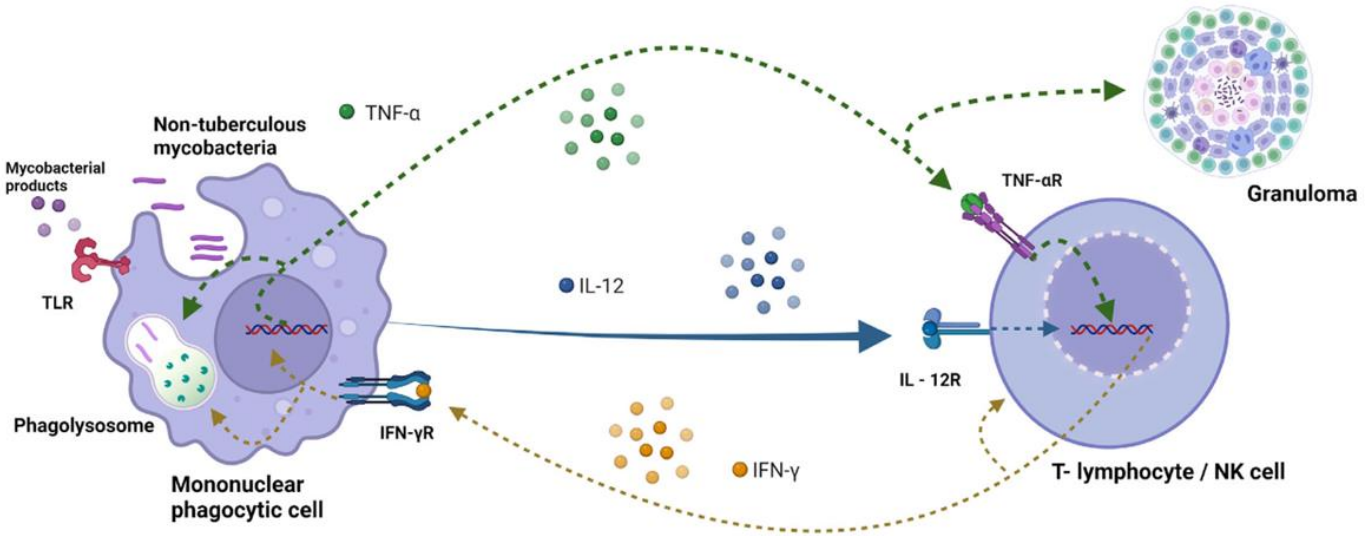
Increasing Prevalence of NTM



Annual prevalence increased from 6.78/100,000 in 2008 to 11.7/100,000 in 2015

Winthrop KL, Marras TK et al. Ann Am Thorax Soc 2020;17(2):178-185

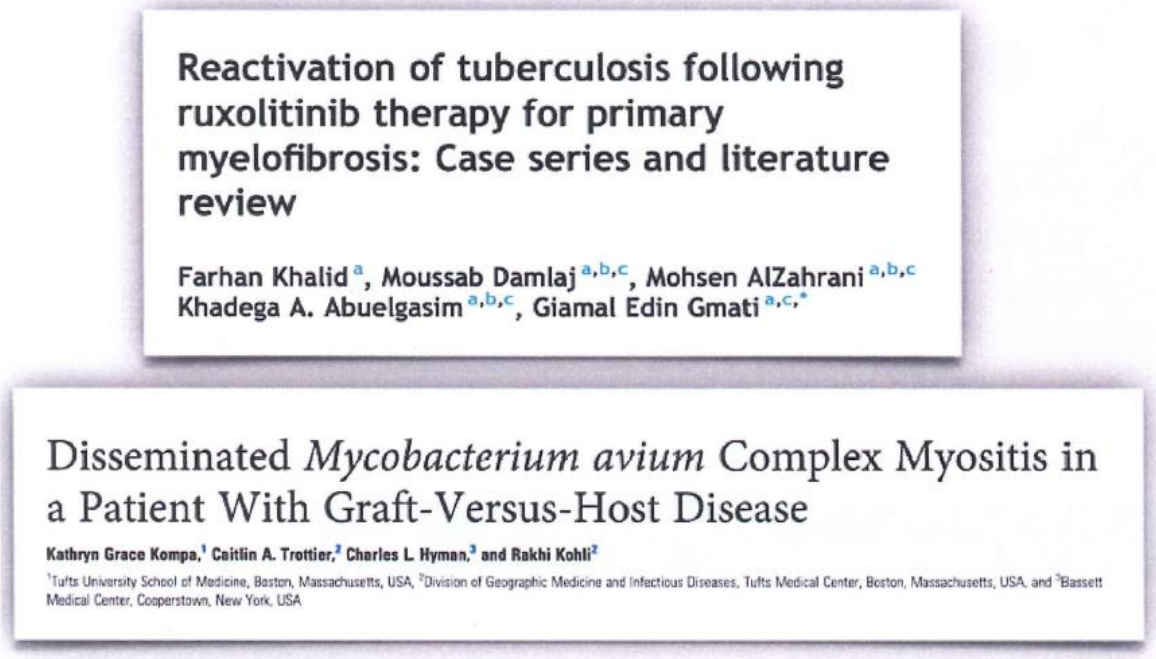
HSCT and Risk of Mycobacteria



- Impaired cellular immunity
  - Pre transplant conditioning regimen
  - Immunosuppression to prevent or treat GVHD
  - GVHD itself

El Zein S, et al. Transpla Infect Dis 2023 Aug 18: e14127

Ruxolitinib and Mycobacterial Disease



Reactivation of tuberculosis following ruxolitinib therapy for primary myelofibrosis: Case series and literature review

Farhan Khalid [a], Moussab Damlaj [a,b,c], Mohsen AlZahrani [a,b,c] Khadega A. Abuelgasim [a,b,c], Giamal Edin Gmati [a,c,*]

Disseminated *Mycobacterium avium* Complex Myositis in a Patient With Graft-Versus-Host Disease

Kathryn Grace Kompa,[1] Caitlin A. Trottier,[2] Charles L. Hyman,[3] and Rakhi Kohli[2]

[1]Tufts University School of Medicine, Boston, Massachusetts, USA, [2]Division of Geographic Medicine and Infectious Diseases, Tufts Medical Center, Boston, Massachusetts, USA, and [3]Bassett Medical Center, Cooperstown, New York, USA

- FDA Adverse Events Reporting system
  - Reporting Odds Ratio 9.2 (95% CI 7.5-11.4) for MTB
  - Reporting Odds Radio 8.3 (95% CI 5.5-12.6) for NTM

Khalid F, et al. Hematol Once Stem Cell There 2021;14(3):252-256
Kompa KG, et al. Open Forum Infect Dis 2022;9(8):ofac385
Anand K, et al. Clin Lymphoma Myeloma Leuk 2020;20(1):18-23

Parasitic infections

Please don’t forget… the others

Make sure that the WBC/neutrophils are back and the immunosuppression is minimal!!!

Post engraftment syndrome

- Can complicate both auto and alloSCT, endothelial dysfunction is the driver
- Occurs around the time of engraftment
- Variable incidence (5% post autoSCT, 10-80% post alloSCT)
- Pre-engraftment syndrome can be seen in alloSCT recipients or umbilical cords
- Can be associated with rash and pulmonary infiltrates
- Spectrum of pulmonary manifestations (hypoxia/infiltrates, DAH, organizing pneumonia-with negative ID w/p, including BAL, skin biopsies to rule out infection)
- Corticosteroids are effective

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Drug-fever

- Relatively common, can start at any time during the drug administration
- Many culprits : B-lactams, sulfa, tetracyclines, AMB, vincristine, Ara-C, G-CSF, γ-INF
- With or without (in cytopenia) rash
- No eosinophilia in cytopenic patients
- Patient looks very stable, with or without chills
- Sometimes with associated syndrome (e.g. serotonine syndrome-linezolid, red man syndrome-vancomycin, DRESS)
- Fever (and rash) subsides in couple of days following the cessation of the drug
- Look at temporal associations

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Transfusion reactions

- Relatively common, start typically within 1-2 days from the administration of RBCs, WBCs or PLTs
- With or without rash (in cytopenia)
- Patients looks very stable, with or without chills.
- Sometimes associated syndromes (acute lung injury, acute hemolytic reactions)
- Fever subsides in couple of days following the completion of transfusion
- Look at temporal associations.

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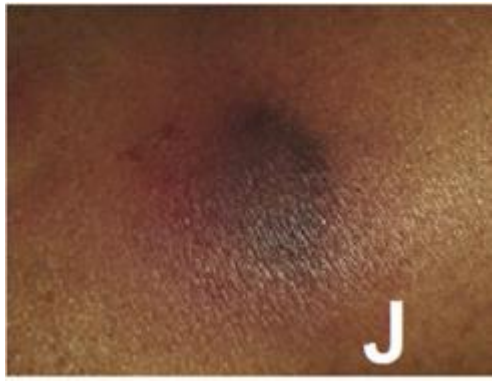
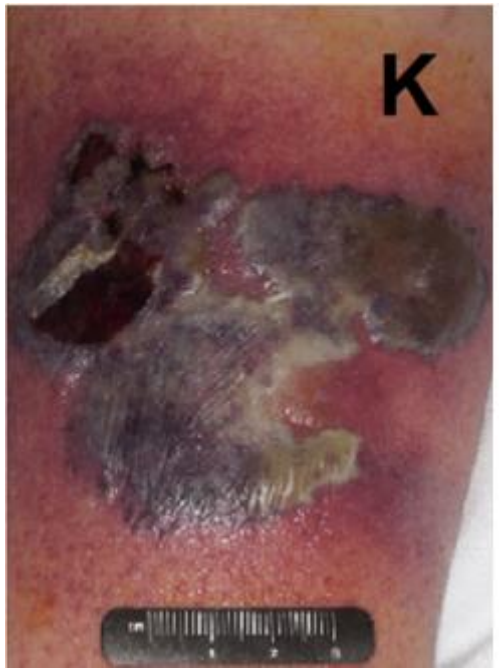
Non-infectious causes are common in febrile patients with leukemia with skin lesions

- 195 patients (pts) with leukemia and new skin lesions who had a skin Bx at MDACC
-
- **119 (61%)** of patients with non-infectious causes of skin lesions, the most common diagnoses were Leukemia Cutis (LC, 23%), drug reactions (12%) and Sweet's syndrome (SS, 7%)
- 48% of the pts with LC were febrile and 67 % had peripheral blasts
- LC most commonly presented as multiple maculopapular (48%) or nodular (37%) lesions
- Most of the pts with SS had AML (63%) with ANC<500 and were febrile (75%) but very stable
- SS LC presented as multiple nodular (50%), maculopapular (25%) or combination of the two (25%) skin lesions, very stable pts
- No differences in neutropenia duration of frequency of relapsed leukemia between pts with infectious vs. non-infectious causes

Sweet's Syndrome





Clinical clue : very stable patients despite multiple lesions

Often with B symptoms, can have chills

PETCT can be helpful (highlight BM disease only)

Corticosteroids are rapidly effective in SS/drug rash

Farmakiotis D et al. J Infect 2013Oct;67(4):265-72

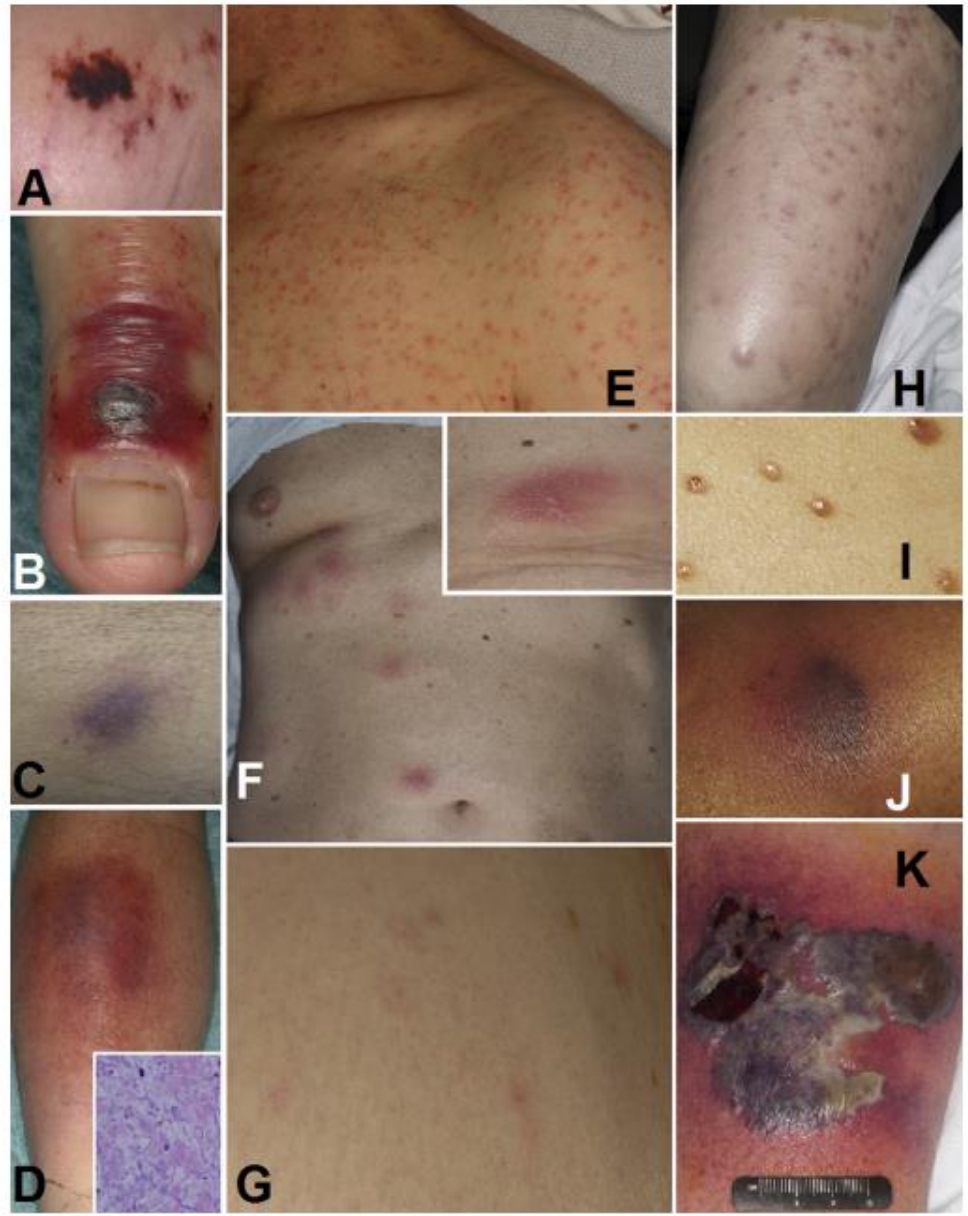


Figure 1 Infectious (*A-G*) versus noninfectious (*H-K*) causes of skin lesions in patients with leukemia. (*A*) Ecthyma gangrenosum. (*B*) Group B streptococcal cellulitis. (*C*) *Alternaria* skin infection. (*D*) Cutaneous aspergillosis. (*E*) Disseminated candidiasis (*C. parapsilosis*). (*F*) Disseminated fusariosis. (*G*) Disseminated *Mycobacterium abscessus*. (*H* and *I*) LC. (*J* and *K*) Sweet's syndrome.

Tumor fever in patients with non-leukemic malignancies

- Common in lymphomas (including Hodgkin's, intravascular lymphomas)
- Widespread metastatic carcinomas
- Tumors with liver metastases
- Colon, hepatocellular, and renal-cell carcinomas
- Brain tumors with thermoregulatory disorders
- Patients are very stable, B symptoms common
- Extreme leukocytosis without evidence of infection can be seen in patients with high tumor burden and carries poor prognosis (Granger J et al, Cancer 2009)
- ? Value of Naprosyn test (Chang JC and Gross HN, AJM 1984)

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Hemophagocytic lymphocytosis (HLH)

- CRS-like condition
- High ferritin, high IL-2R, high triglycerides, low fibrinogen, cytopenias, splenomegaly, low NK activity, hemophagocytosis in bone marrow)
- Definition is not standardized → incidence varies
- Challenging as infection, malignancy, its treatment can be the triggers
- Very ill patients, hard to differentiate from sepsis
- Treatment is immunosuppressive chemotherapy
- Poor prognosis and high rate of opportunistic superinfections

Otrock ZK.. Eby S, Clin Myel Lymphoma 2017

Other uncommon causes of fevers

- Opportunistic non-CMV viruses
  - Respiratory viruses
  - Parvovirus19
- Hematomas
- Venous thromboembolism
- Septic thrombophlebitis
- Intracranial hemorrhage/stroke
- Thrombotic Thrombocytopenic Purpura (Post alloSCT, GVHD)
- Adrenal insufficiency
- Thyroid disorders
- Vasculitis/automimmune causes
- Factitious fever

Conclusions

- The differential diagnosis had expanded nowadays, infection is not the only cause of persistent fevers
- There is no standardized work up, and bundles of interventions are applied in these patients simultaneously or sequentially
- Approaches are highly individualized, careful daily assessment is needed
- Sometimes cause of fever is multifactorial (e.g., {CARTT}, mucositis, infusion of blood products/antibiotics)
- Still these non-ID entities are the diagnosis of exclusion.

ID physicians
Microbiology

Teams managing
Control &
Prevention of
Infections

PET Scan

Who is helping you?

Vaccination

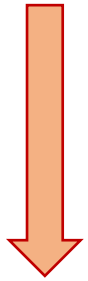
Cocooning

New concepts: liquid biopsies for infectious diseases.

These patients are not in the literature !
« evidence-based medicine » (randomized clinical trials) vs real life !

Clinical trial of empiric or targeted therapies

(inclusion/exclusion criteria)



Goal : homogeneous population, strict definitions, that gives drug(s) best chance to work

Slide : Russel E Lewis

Merci pour votre attention!