Infections in Immunocompromised Hosts

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Slides courtesy of David van Duin, MD, PhD
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Populations

- Solid organ transplant (SOT)
- Ventricular assist devices (VAD)
- Hematopoietic stem cell transplant (HSCT)
- Hematologic malignancies
- Burn injuries

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Some specific issues in immunocompromised hosts

- Donor issues
- Antimicrobial prophylaxis
  - What is in the protocol?
  - What is prescribed?
  - What is the patient actually taking?
- Immunosuppression
  - Current IS
  - Prior IS
    - Treatment for rejection
    - Induction
    - Pre-transplant IS
    - Graft vs. Host disease (GVHD) treatment

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Differential diagnosis in Transplant

- Broad: bacterial, fungal, viral, parasitic, non-infectious
- Delay in treatment often associated with worse outcomes
- Difficult to provide empiric treatment for all possible etiologies
- More than one infection may be present at the same time

I don't always attend on the Transplant ID service…
But when I do, I throw away Ockham's razor

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Solid Organ Transplantation

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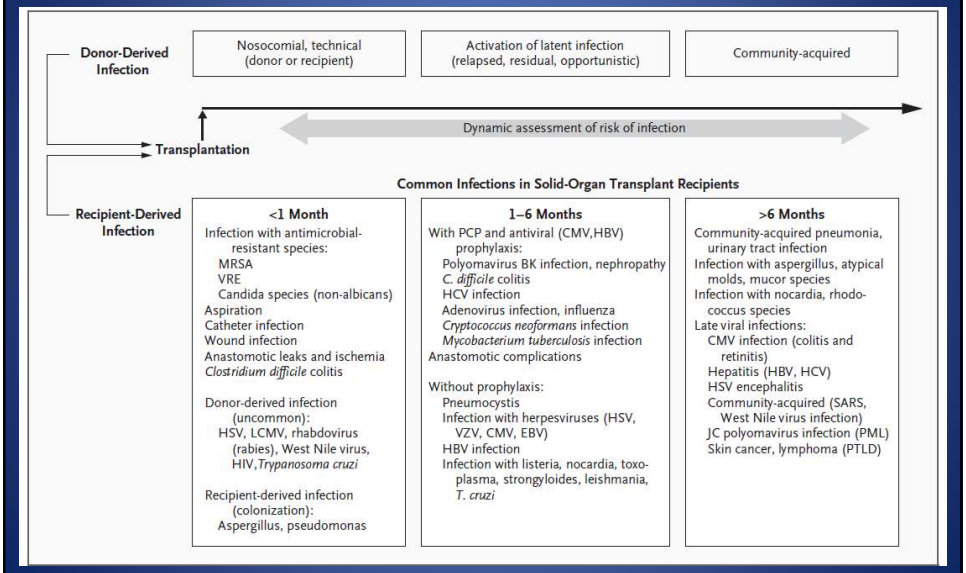
Timeline of Infectious Risk



Fishman. NEJM 2007;357:2601

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Risk for infection after SOT

- Exposures
  - Donor-derived
  - Recipient-derived
  - Nosocomial
  - Community
- "net state of immunosuppression"

Fishman. NEJM 2007;357:2601

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Donor-derived infections

Table 1
Potential donor-derived infectious diseases transmissions reported to the OPTN, 2005–2009

Disease	Number of Donor Reports	Number of Recipients with Confirmed Transmission	Number of DDD-Attributable Recipient Deaths
Virus	86	31	8
Bacteria	38	26	7
Fungus	30	26	8
Mycobacteria	26	10	2
Parasite	21	13	4
Total infections	201	106	29

Chong et al. Inf Dis Clin N Am 2013;27:253

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CMV: A common donor-derived infection

THE FOURTH INTERNATIONAL CONSENSUS GUIDELINES IN THE MANAGEMENT OF CYTOMEGALOVIRUS IN SOLID ORGAN TRANSPLANTATION

Background
Many exciting advances in CMV management have recently occurred, necessitating an update to guidelines.

Methods
In 2024, with support from The Transplantation Society, CMV experts from across the world reviewed current evidence in 6 working groups and updated CMV recommendations using GRADE.

Diagnostics: A greater emphasis on CMV-QNAT testing calibrated to the WHO standard.

Prevention: New data support the option of letermovir prophylaxis in D+/R- kidney and the use of PET in D+/R- liver transplant. Surveillance after prophylaxis increasing.

Immunology: New CMV-CMI testing recommendations in R+ kidney transplant to help personalize prophylaxis.

Treatment: Valganciclovir and ganciclovir remain mainstays of treatment; thresholds for discontinuation remain challenging in the era of highly sensitive testing.

Resistance: Maribavir is now recommended as a principal alternative in cases of resistance, unless clinically unwell with high viral loads when foscarnet is preferred.

Pediatrics: Prevention strategies include prophylaxis, PET, or surveillance after short-term prophylaxis. More data on new drugs needed.

Conclusion
This new edition of the guidelines provides a comprehensive look at best-practices related to CMV management after organ transplantation.

Future Directions
The future of CMV management looks very promising and we are well on our way to defeating the "Troll of Transplantation".

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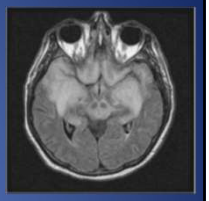
Unusual donor-derived infections



- Rabies
  - 1 donor, 4 recipients: 100% mortality
- West Nile Virus
  - 2 donors, 8 recipients: 1 death, 2 coma
- Lymphocytic choriomengitis virus
  - 2 donors, 8 recipients: 88% mortality
  - LCMV could not be detected in either donor
  - 1 donor had pet hamster with LCMV
- Balamuthia mandrillaris
  - 2 donors, 8 recipients: 2 deaths, 1 neuro sequellae

Srinivasan et al. NEJM 2005;352:1103
Chong et al. Inf Dis Clin N Am 2013;27:253

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Recipient-derived infections

- Active, uncontrolled infection
  - LVAD associated bacteremia
  - Infection limited to organ to be explanted
- Colonization
- Recurrence of infectious indication for transplant
  - HCV
- Asymptomatic infection
  - strongyloides
- Latent infection
  - TB
  - Herpes viruses (CMV, EBV, HSV, VZV)

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Nosocomial infections

- Device-related
  - Line-associated blood stream infection
  - Catheter or stent associated UTI
  - Ventilator associated pneumonia
- Surgery-related
  - Wound infection
  - Intra-abdominal abscess
- Outbreaks
- Multi-drug resistant organisms

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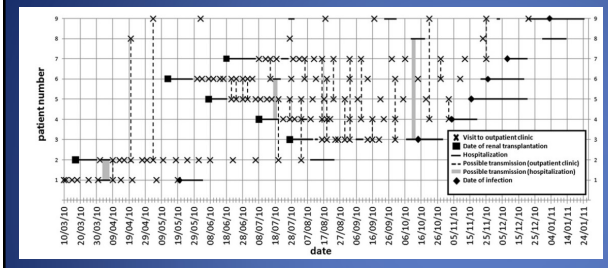
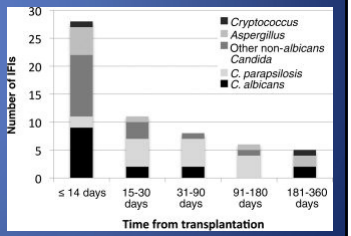
Outbreaks



Pneumocystis in pediatric renal transplant recipients



C. parapsilosis after liver transplantation

Raghuram et al. Liver Transplant 2012;18:1100
Brunot et al. Transplant Proc 2012;44:2818

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American Journal of Transplantation 25 (2025) 848–859

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

Carbapenem-resistant Enterobacterales in solid organ transplant recipients

Angelique E. Boutzoukas [1,2], Weixiao Dai [3], Eric Cober [4], Lilian M. Abbo [5], Lauren Komarow [3], Liang Chen [6], Carol Hill [2], Michael J. Satlin [7], Matthew Grant [8], Bettina C. Fries [9], Gopi Patel [10], Todd P. McCarty [11], Cesar A. Arias [12,13,14], Robert A. Bonomo [15,16,17,18,19,20,21], David van Duin [22,*], for the Antibacterial Resistance Leadership Group and the MDRO Network Investigators

- Cases from CRACKLE-1 and -2
- 343 hospitalized patients with CRE
  - 121 SOT recipients
  - 242 non-SOT controls
- SOT with CRE were younger, more likely to be on dialysis, and less likely to come from nursing home
- 30-day mortality: 14% SOT vs 25% control

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Community acquired infections

- Immunosuppression does not prevent common infections…
- Manifestations may be different
- Common pathogens include:
  - Respiratory viruses
  - Skin flora (*S. aureus*, streptococci)
  - Enteric flora (GNR, enterococci)

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H1N1 Influenza post-SOT

	Adults	Children	p value*
Fever >38°C	115/144 (80%)	78/82 (95%)	0·003
Cough	132/145 (91%)	67/73 (92%)	1·000
Sore throat	50/134 (37%)	30/51 (59%)	0·013
Rhinorrhoea	40/134 (30%)	42/59 (71%)	<0·001
Headache	33/136 (24%)	26/50 (52%)	0·001
Myalgias	70/135 (52%)	21/43 (49%)	0·866
Gastrointestinal symptoms	66/154 (43%)	39/83 (47%)	0·636
Pneumonia on chest radiograph or CT scan	60/149 (40%)	13/81 (16%)	<0·001
Admission to hospital	112/154 (73%)	55/83 (66%)	0·373
Admission to the intensive care unit	27/154 (17·5%)	10/83 (12·0%)	0·357
Mechanical ventilation	18/153 (12%)	3/83 (4%)	0·063
Antiviral treatment within 48 h	43/138 (31%)	47/77 (61%)	<0·001
Antiviral treatment after 48 h	95/138 (69%)	30/77 (39%)	<0·001
Death	10/154 (7%)	0/83 (0%)	0·016

*Statistical differences are by χ^2 test.

Table 2: Clinical presentation and complications of influenza A in adult and paediatric recipients of solid-organ transplants

Kumar et al. Lancet ID 2010;10:521

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S. aureus bacteremia post-SOT

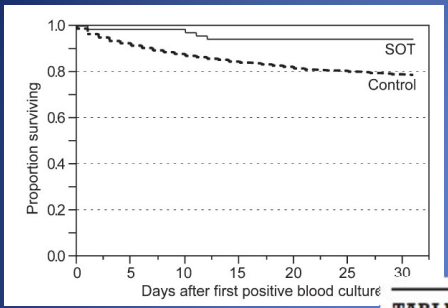

TABLE 3. Cox proportional hazards analysis 30-day mortality in entire SAB cohort (n = 2959)

Variable	RR (95% CI)	*P*
Age	1.03 (1.02–1.03)	<0.001
Methicillin resistance	1.21 (1.03–1.41)	0.02
SOT recipient	0.37 (0.11–0.88)	0.02

SAB: S. aureus bacteremia. SOT: solid organ transplant recipient.

Malinis et al. Transplantation 2012;93:1045

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Net State of Immunosuppression

- Type, dose, and timing of immunosuppressive agents administered
- Nutritional, metabolic factors; renal dysfunction; age; comorbidities
- Breach of mucosal barriers (skin, gut); foreign bodies
- Hypogammaglobulinemia
- Neutropenia

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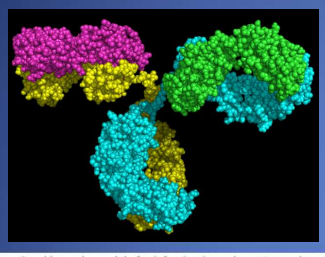
Hypogammaglobulinemia



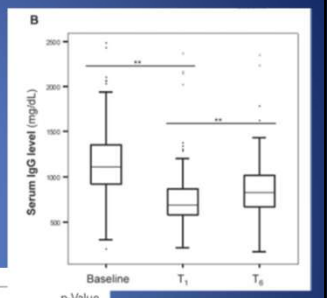


Table 6: Cox proportional hazards models for infection in each posttransplant period

Overall infection between T_1 and T_6	Adjusted HR[1]	95% CI	p-Value
Recipient age, years*	1.02	1.00–1.04	0.024
Reoperation during month 1	1.82	1.00–3.32	0.049
AR during month 1	1.83	1.04–3.21	0.035
Bacterial infection between T_1 and T_6	Adjusted HR[2]	95% CI	p-Value
Recipient age, years*	1.03	1.01–1.05	0.006
AR during month 1	2.13	1.15–3.93	0.016
HGG of any class at T_1	1.81	1.03–3.17	0.038
Overall infection after T_6	Adjusted HR[3]	95% CI	p-Value
Previous SOT	2.98	1.49–5.94	0.002
AR between T_1 and T_6	5.28	2.27–12.27	0.000
HGG of any class at T_6	2.31	1.18–4.55	0.015
Bacterial infection after T_6	Adjusted HR[4]	95% CI	p-Value
Recipient age, years*	1.03	1.00–1.06	0.028
Previous SOT	4.93	2.02–12.06	0.000
AR between T_1 and T_6	8.57	3.36–21.85	0.000
HGG of any class at T_6	4.66	1.89–11.48	0.001

Fernandez-Ruiz
AJT 2012;12:2763

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Hematopoietic Stem Cell Transplantation

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HSCT principles: maximizing graft vs tumor while minimizing graft vs host effects

graft

host

tumor

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Stem cell types

- Allogeneic vs. autologous
- Sources
  - Bone marrow
  - Mobilized peripheral blood stem cells
  - umbilical cord blood

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Transplant Conditioning

- Goals:
  - Eradicate disease, or decrease number of malignant cells
  - Suppress host immunity and prevent rejection of donor cells
- Modalities:
  - Irradiation
  - Chemotherapy
  - Biologics

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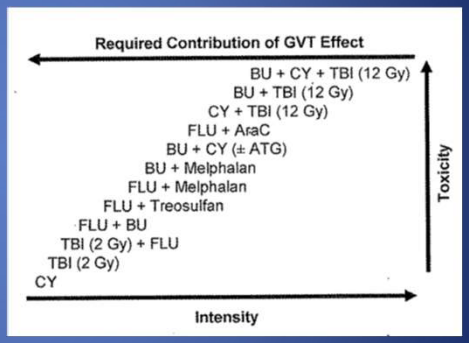
Reduced Intensity Conditioning

- AKA “mini”-transplant, “non-myeloablative”
- Aimed at decreasing early mortality and enhancing donor anti-host (anti-disease) reactivity



Rezvani et al. in Transplant Infections 2009 Ed. Bowden et al.

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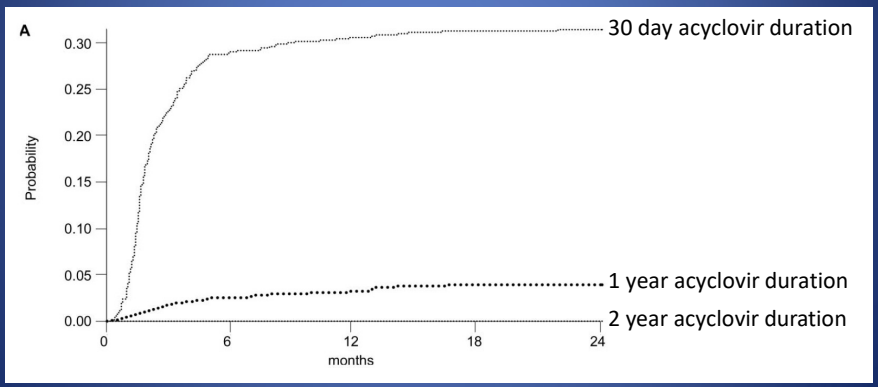
Early viral infections: HSV Acyclovir prophylaxis



Erard et al. JID 2007;196:266

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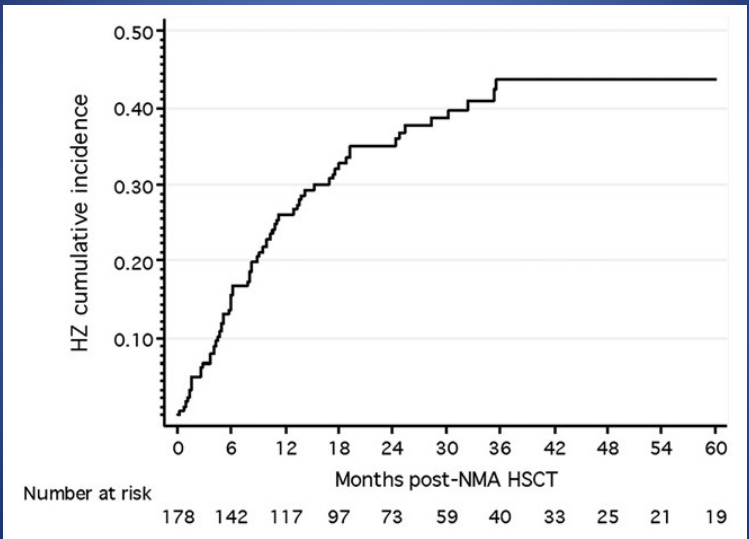
Late viral complications: herpes zoster



Su et al. Biol Blood Marrow Transplant 2011;17:1012

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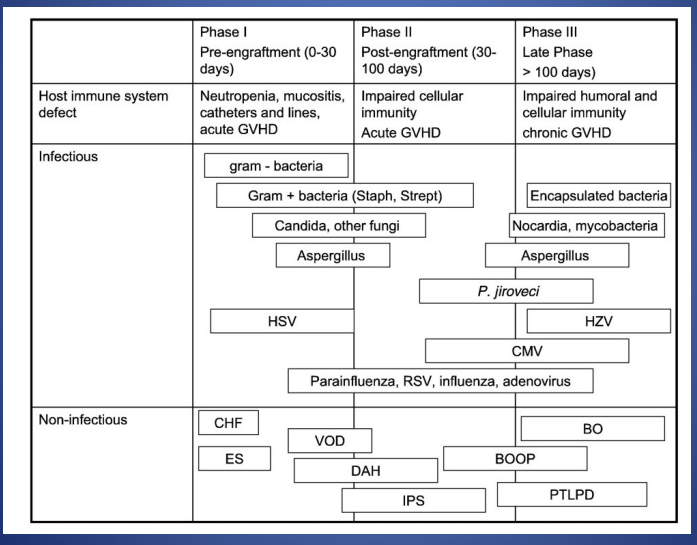
Pulmonary complications after HSCT



Rahman Safadi et al. Eur J Int Med 2009;20:268

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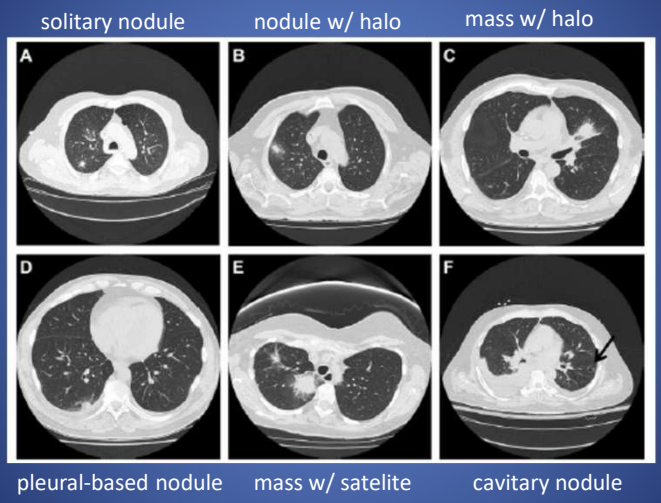
DPN: "dreaded pulmonary nodulosis"



Wingard et al. Blood 2012;120:1791

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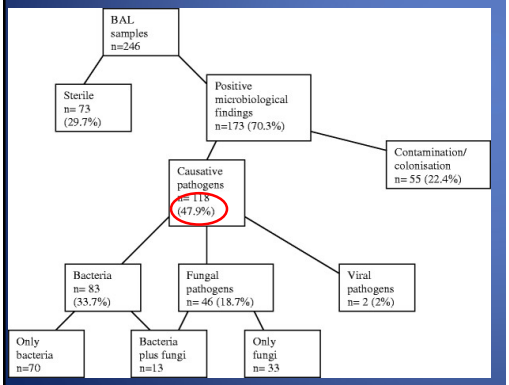
Diagnostic options for DPN

BAL: 48% diagnosis



Hummel et al. Ann Hematol 2008;87:291

CT guided biopsy: 61% diagnosis

Table 3. Diagnoses for lung biopsies that yielded a specific result

Diagnosis	No. of biopsies (%) ($n = 130$)
Malignancy	83 (63.8)
Lymphoma	43 (33.1)
Adenocarcinoma of lung	15 (11.5)
Squamous cell carcinoma	14 (10.8)
Non-small cell carcinoma	7 (5.4)
Malignant fibrous histiocytoma	2 (1.5)
Atypical squamous metaplasia	1 (0.8)
Metastatic adenocarcinoma	1 (0.8)
Infectious	45 (34.6)
Aspergillus species	16 (12.3)
Mycobacterium species	5 (3.8)
Other fungal infections	11 (8.4)
Pneumocystis carini	2 (1.5)
Mixed fungal infection	3 (2.3)
Bacterial infection	5 (3.8)
Abscess	3 (2.3)
BOOP	2 (1.5)

BOOP, bronchiolitis obliterans organizing pneumonia.

Gupta et al. Hematol Onc 2010;28:75

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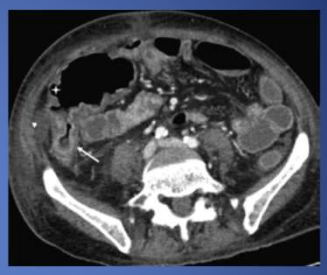
GI Infections

- Mucositis, dysphagia
  - CMV, HSV, VZV
  - Candida
  - bacteria
- Diarrhea
  - C. difficile
  - CMV, HSV
  - Adeno-, rota-, noro-, astrovirus
  - Cryptosporidium, microsporidium, giardia
  - MTB, NTM
  - Fungal: histoplasma, GI mucor



CMV colitis

Tuncer et al. W J Gastroenterol 2012;18:1851
Hordonneau et al. Clin Radiol 2013;68:620

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Clinical Microbiology and Infection 31 (2025) 1667–1676

Contents lists available at ScienceDirect

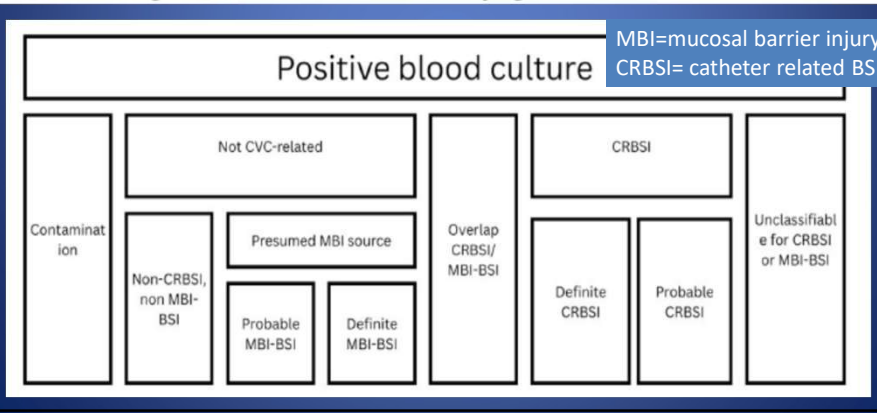
Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Position paper

Defining bloodstream and central venous catheter-related infections in patients following haematopoietic cell transplantation: position paper of the European Blood and Marrow Transplantation Society Infectious Diseases Working Party and Practice Harmonization and Guidelines Committee

Dina Averbuch [1,2,*], Malgorzata Mikulska [3,4], Jan Styczynski [5], Anne Bergeron [6], Simone Cesaro [7], Raffaella Greco [8], Dionysios Neofytos [9], Francesco Onida [10], José Luis Piñana [11,12], Isabel Sanchez-Ortega [13], Paul E. Verweij [14], Ibrahim Yakoub-Agha [15], Rafael de la Camara [16,†], Per Ljungman [17,18,†]



MBI=mucosal barrier injury
CRBSI= catheter related BSI

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Table 2
EBMT IDWP and Practice Harmonization Committee proposed definitions of primary definite and probable bloodstream infection

Level of certainty	Criteria
Definite BSI	One positive blood culture or NCT with non-commensal[a] Two separate positive blood cultures with commensal pathogen [5] (same genus and species) with the same susceptibility profile if tested[b] in the presence of any sign of deterioration in patient' clinical condition that can be compatible with infection, or increase in inflammation markers (per local protocol)
Probable BSI	One positive blood culture with VGS in the presence of any sign of clinical or laboratory deterioration compatible with infection
Definite BSI of presumed MBI source	One positive culture or NCT with an intestinal pathogen in a patient with appropriate clinical context[c,d] 2 or more positive blood cultures with VGS and/or *Rothia* spp in the presence of any clinical or laboratory sign compatible with infection in patients with an appropriate clinical context[c]
Probable BSI of presumed MBI source	One positive blood culture with VGS in the presence of any sign of clinical or laboratory deterioration compatible with infection in patients with an appropriate clinical context[c]
Definite CRBSI	Pathogen grows from a culture of the catheter tip AND same pathogen (genus and species) from at least one percutaneous blood culture + *in vitro* susceptibility testing results in the same resistance pattern (if done in both isolates)[b] If semiquantitative or quantitative cultures were performed—they shall meet criteria: semiquantitative (>15 CFU per catheter segment) or quantitative (>10^2 CFU per catheter segment) 2 blood cultures (from a catheter hub and percutaneous) with the same pathogen If quantitative criteria with a ratio of >3:1 CFU/mL of blood (catheter vs. percutaneous) OR if meet DTTP[e] criteria
Probable CRBSI (i.e. definite BSI with CVC as probable source)	2 blood cultures (from a catheter hub and percutaneous) with the same pathogen: CoNS, *S. aureus*,[f] *Candida parapsilosis*,[f] *Bacillus* spp, *Micrococcus* spp, or *Propionibacterium* spp AND do not meet quantitative/DTTP[e] criteria (or not performed) AND other sources excluded Pathogen detected in blood cultures (CVC only or percutaneous only if drawing blood cultures from CVC is impossible) that typically causes CRBSI: • At least two positive blood cultures for the same genus and species CoNS, *Bacillus* spp, *Micrococcus* spp, or *Propionibacterium* spp cultures (same genus and species) with the same susceptibility profile if identified in both[b]; • Single-positive blood culture with *S. aureus*[f] and *Candida parapsilosis*[f] with the absence of another plausible source

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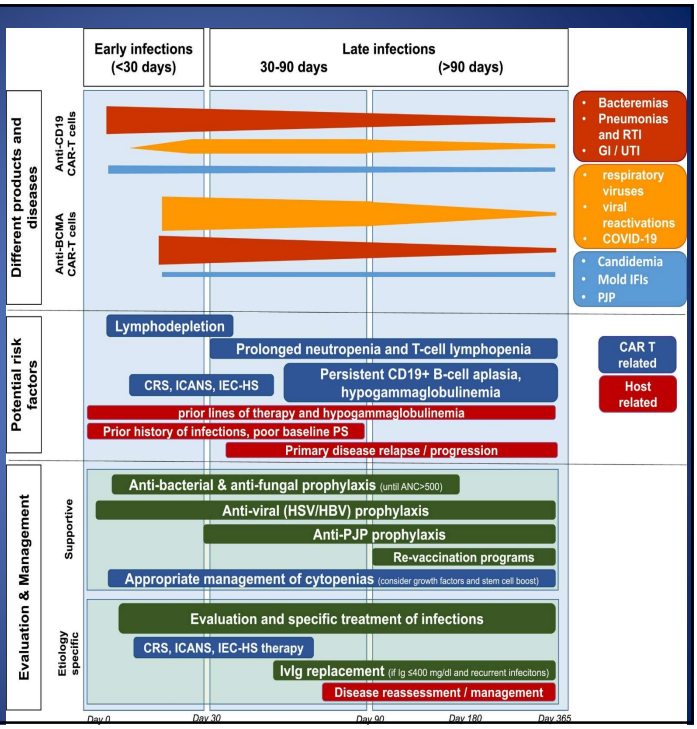
Chimeric Antigen Receptor T-cell therapy (CAR-T)



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Screening pre-CAR-T

Routine:

- HIV antibody (reflex nucleic acid testing if positive)
- HBsAg, anti-HBc and anti-HBs*
- HCV IgG (reflex nucleic acid testing if positive)
- *Treponema pallidum*
- CMV IgG
- HTLV-1 IgG

If respiratory symptoms present:

- Multiplex nasal swab PCR for respiratory viruses

If antiviral prophylaxis not universally practiced:

- HSV-1 and 2 IgG
- VZV IgG

Based on risk factors:

- Toxoplasma gondii IgG
- Mycobacterium tuberculosis blood test
- Strongyloides stercolaris† IgG
- Endemic mycosis serologies‡

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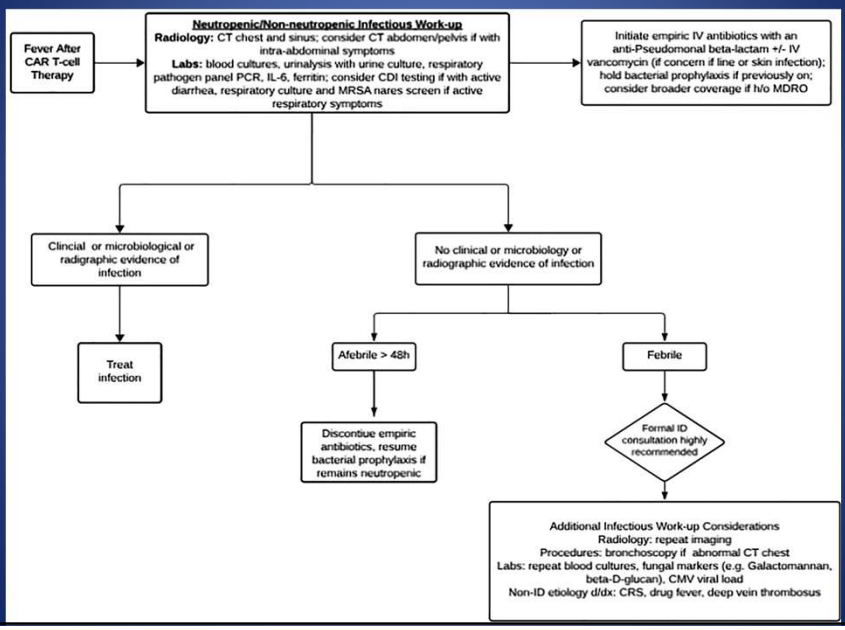
Fever workup after CAR-T



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Febrile Neutropenia

Multinational Association for Supportive Care in Cancer study

- Prospective observational study
- N=1,139
- Bacteremia documented in 26%
- Outcomes:
  - Resolution: 84%
  - Alive with at least one serious complication: 11%
  - Death: 5%

Klastersky et al. J Clin Oncol 2000;18:3038

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IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[9] Kent A. Sepkowitz,[2] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

Table 2. Strength of Recommendation and Quality of Evidence

Category/Grade	Definition
Strength of Recommendation	
A	Good evidence to support a recommendation for *or against* use.
B	Moderate evidence to support a recommendation for *or against* use.
C	Poor evidence to support a recommendation.
Quality of Evidence	
I	Evidence from ⩾1 properly randomized, controlled trial.
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Freifeld et al. CID 2011;52:e56

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Guideline recommendations

- High risk
  - Prolonged (anticipated >7 days) and profound neutropenia (≤100 cells/mm^3)
  - "comorbid medical problems"
    - Hypotension
    - Pneumonia
    - New abdominal pain or new GI symptoms
    - Neurologic changes
    - Line infection
    - Severe mucositis
  - Hepatic or renal insufficiency

Freifeld et al. CID 2011;52:e56

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MASCC score: less is worse

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms[a]	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease[b]	4
Solid tumor or hematologic malignancy with no previous fungal infection[c]	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms[a]	3
Outpatient status	3
Age <60 years	2

- 26 maximum score -> lowest risk
- <21 considered high risk

Freifeld et al. CID 2011;52:e56

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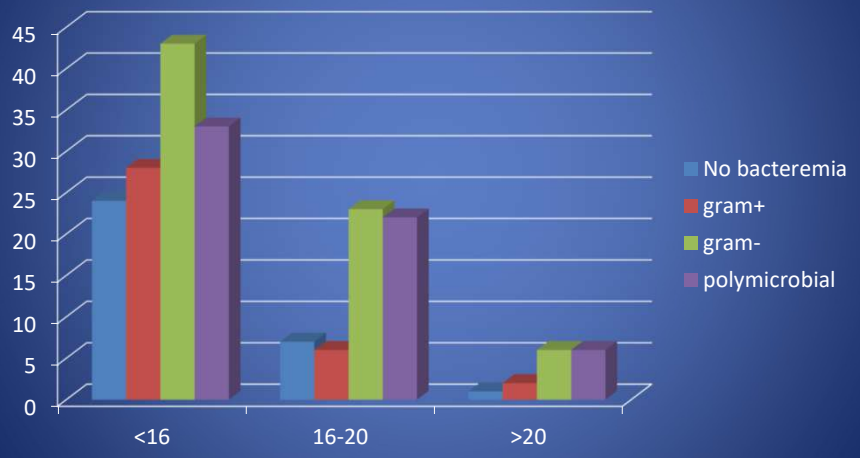
Mortality risk by MASCC score



Paesmans et al. Support Care Cancer 2011;19:1001

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Risk determines initial treatment

High risk patients…

- Require hospitalization
- Require initial IV antibiotics
- Most commonly HSCT preparation or acute leukemia induction chemotherapy

Low risk patients…

- May be treated as outpatients
- May be considered for oral antibiotics
- Most commonly solid tumors

Freifeld et al. CID 2011;52:e56

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High risk: Antibiotic regimens

- Monotherapy (A-I):
  - Cefepime
  - Piperacillin/tazobactam
  - Imipenem or meropenem
  - (Ceftazidime, dependent on local antibiogram)
- Potential additions for complications, or suspected resistance (B-III):
  - Fluoroquinolones
  - Aminoglycosides

Freifeld et al. CID 2011;52:e56

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Addition of vancomycin

- Hemodynamic instability or other evidence of severe sepsis
- Pneumonia
- Positive blood culture for gram-positive bacteria
- Clinically suspected serious catheter-related infection
- Skin or soft-tissue infection at any site
- Colonization with MRSA, PCN-R pneumococcus
- Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

Freifeld et al. CID 2011;52:e56

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Other initial modifications

- PCN allergy that preclude cephalosporins and carbapenems:
  - Aztreonam + vancomycin (A-II)
  - Ciprofloxacin + clindamycin (A-II)
- Colonization with:
  - VRE -> daptomycin or linezolid (B-III)
  - ESBL -> carbapenem (B-III)
  - Carbapenem-R GNR -> colistin or tigecycline (C-III)

Freifeld et al. CID 2011;52:e56

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Changes in therapy during fever course

- Guided by clinical and micro data (A-II)
- Stop gram+ coverage after 2 days if no gram+ pathogen is isolated (A-II)
- Consider empiric antifungal coverage after 4-7 days of fevers without identified source (A-II)
  ("the true utility of requiring empirical antifungal therapy for every neutropenic patient on the basis of persistent fever alone must be questioned.")
  - If already on an anti-mold agent for prophylaxis, consider switching to another class (B-III)

Freifeld et al. CID 2011;52:e56

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How long to continue?

1. unexplained fever

Continue until ANC exceeds 500 cells/mm3 (B-II)

1. Documented infection:

- Guided by the organism and site.
- Treatment at least for duration of neutropenia (B-III)

OR

if all signs and symptoms have resolved and antibiotic course is completed: resume oral fluoroquinolone prophylaxis until marrow recovery (C-III).

Freifeld et al. CID 2011;52:e56

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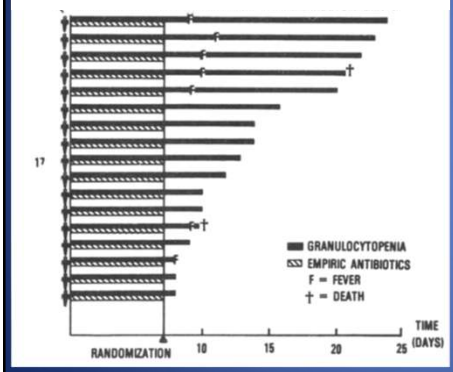
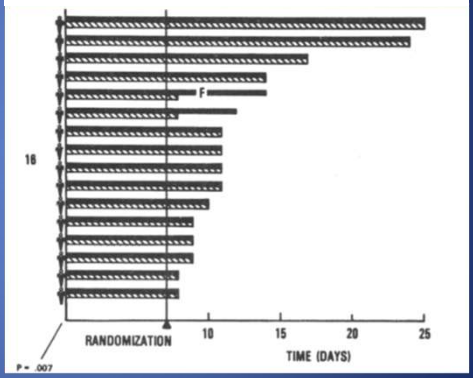
Duration of antibiotics

Randomized to stop on day 7 of antibiotics



Randomized to continue until ANC>500



Pizzo et al. Am J Med 1979;67:194

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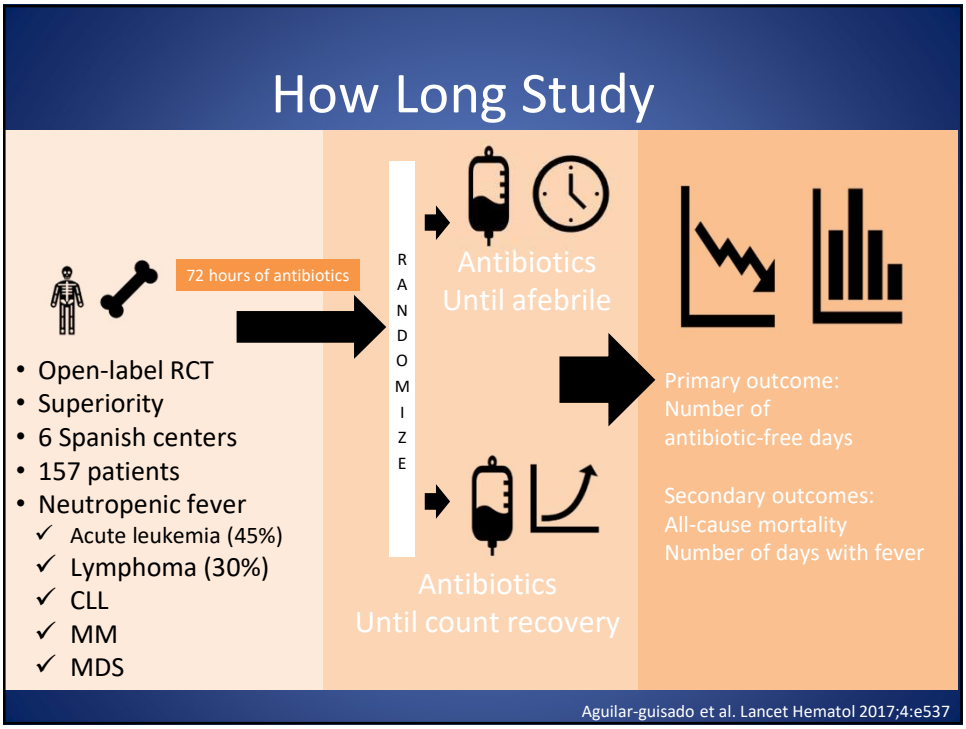
How Long Study



- Open-label RCT
- Superiority
- 6 Spanish centers
- 157 patients
- Neutropenic fever
  - ✓ Acute leukemia (45%)
  - ✓ Lymphoma (30%)
  - ✓ CLL
  - ✓ MM
  - ✓ MDS

Aguilar-guisado et al. Lancet Hematol 2017;4:e537

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How Long

	Experimental group (n=78)	Control group (n=79)	Between-group absolute difference (95% CI)	p value
Intention-to-treat population				
Number of patients (%)	78 (100%)	79 (100%)	..	..
Efficacy variable				
EAT-free days	16·1 (6·3)	13·6 (7·2)	−2·4 (−4·6 to −0·3)	0·026
Safety variables				
Crude mortality	1 (1·3)	3 (3·8)	NA	0·62
Days of fever	5·7 (5·0)	6·3 (5·9)	0·5 (−1·2 to 2·3)	0·53
Per-protocol population				
Number of patients (%)	66 (85%)	66 (84%)	..	..
Efficacy variable				
EAT-free days	16·9 (5·8)	13·0 (7·2)	−3·8 (−6·1 to −1·6)	0·0010
Safety variables				
Crude mortality	0 (0)	2 (3)	NA	0·49
Days of fever	5·9 (5·1)	6·7 (6·1)	0·86 (−1·1 to 2·8)	0·38

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2024 update of the AGIHO guideline on diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients with solid tumours and hematological malignancies

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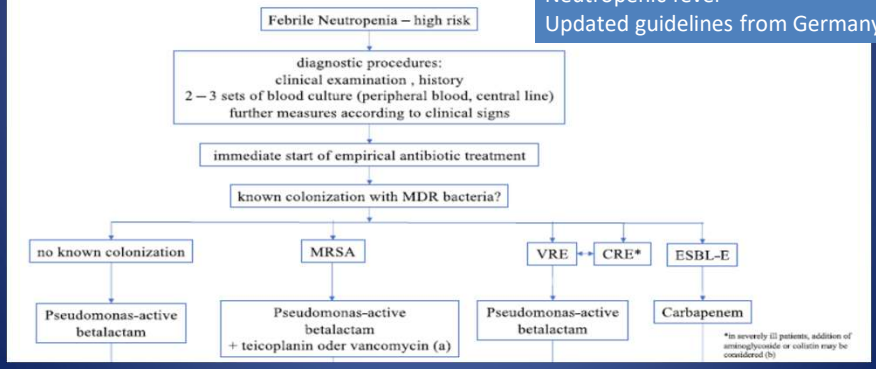
Neutropenic fever
Updated guidelines from Germany



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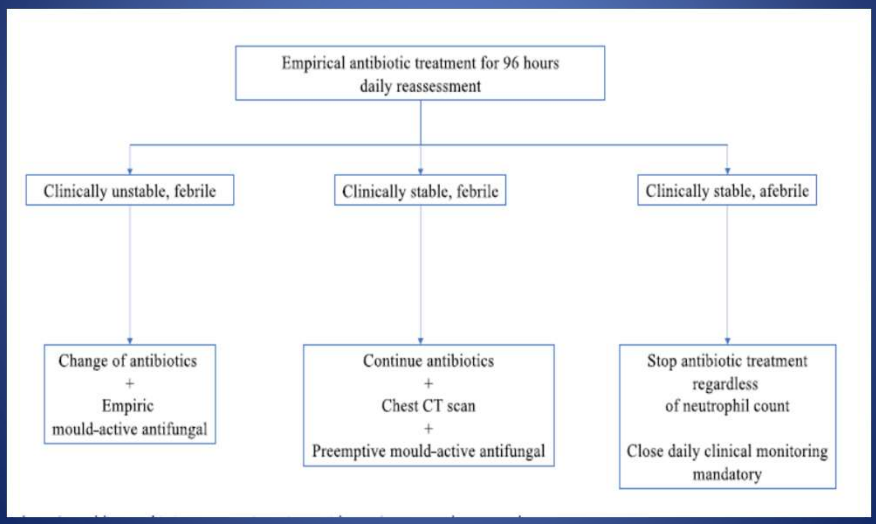
German approach to duration



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Summary

- Infectious complications are a major threat to immunocompromised patients
- Careful evaluation is needed to diagnose
- Likelihood of various infections can be predicted based on knowledge of immunosuppressive state and timeline

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Questions?

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