Infection in cancer patients including neutropenic fever

פרופ' דפנה יהב

מקרה 1

- בן 45,
- DLBCL טיפול ראשון, נושא פיקליין
- מגיע למיון שבוע וחצי לאחר טיפול עם חום 39, יציב המודינמית ונשימתית
- בבדיקה ללא מקור לחום, מוקוזיטיס קלה, פיקליין נראה תקין
- ANC-0, צפוי לניוטרופניה של 10 ימים

איך נגדיר את החולה

- 1. Low risk neutropenic fever
- 2. High risk neutropenic fever
- 3. Vascular catheter related infection
- 4. Viral infection

Definition

- *Fever* is defined as a **single oral** temperature measurement of **>=38.3C** (101F) or a temperature of **>=38.0C** (100.4F) sustained over a **1-h** period
- *Neutropenia* is defined as an **ANC** of **<500** cells/mm3 or an ANC (<1000) that is expected to decrease to <500 cells/mm3 during the next 48 h

- Freifeld 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 Feb 15;52(4):e56-93.
- Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) 2017

NF - general

- **>80%** of patients with hematologic malignancies will develop NF during >1 chemotherapy cycle
- ~50% have clinically or microbiologically documented infection
- **Bacteremia 20-30%:**
- Gram-negative (30–67%)
- Gram-positive (32–68%)
- Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X

NF - general

- **Every patient** with fever and neutropenia should receive **empirical** antibiotic therapy urgently (ie, within **2 h**) after presentation, because infection may progress rapidly in these patients
- Neutropenic patients who are **not febrile** but who have new signs or symptoms that suggest infection (e.g., infiltrate) should have empirical antibiotics initiated
- Freifeld et al. IDSA Guidelines. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Risk for severe infection and death

- **High risk: any of:**
- Profound neutropenia (**ANC <100** cells/mm3) anticipated to extend **>7 days**
- Presence of any co-morbid medical problems including but not limited to:

➢ **Hemodynamic instability**

➢ Oral or gastrointestinal **mucositis** that interferes with swallowing or causes severe diarrhea

➢ Freifeld et al. IDSA Guidelines. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Risk for severe infection and death

- **Gastrointestinal** symptoms, including abdominal pain, nausea and vomiting, or diarrhea
- **Neurologic** or mental-status changes of new onset
- Intravascular **catheter infection**, especially catheter tunnel infection
- New **pulmonary** infiltrate or hypoxemia, or underlying chronic lung disease

- Freifeld et al. IDSA Guidelines. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Risk for severe infection and death

- Evidence of **hepatic insufficiency** (defined as aminotransferase levels >5 X normal values) or **renal insufficiency** (defined as a creatinine clearance of <30 mL/min)
- OR
- **MASCC** score <21
- Freifeld et al. IDSA Guidelines. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Table 3. The Multinational Association for Supportive Care in Cancer Risk-Index Score

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

NOTE. The maximum value of the score is 26. Adapted from [43]. Reproduced with permission of the American Society for Clinical Oncology.

[a] Burden of febrile neutropenia refers to the general clinical status of the patient as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score of 5); moderate symptoms (score of 3); and severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.

[b] Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.

[c] Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.

Our patient – anticipated ANC<100 for >7d -> High risk

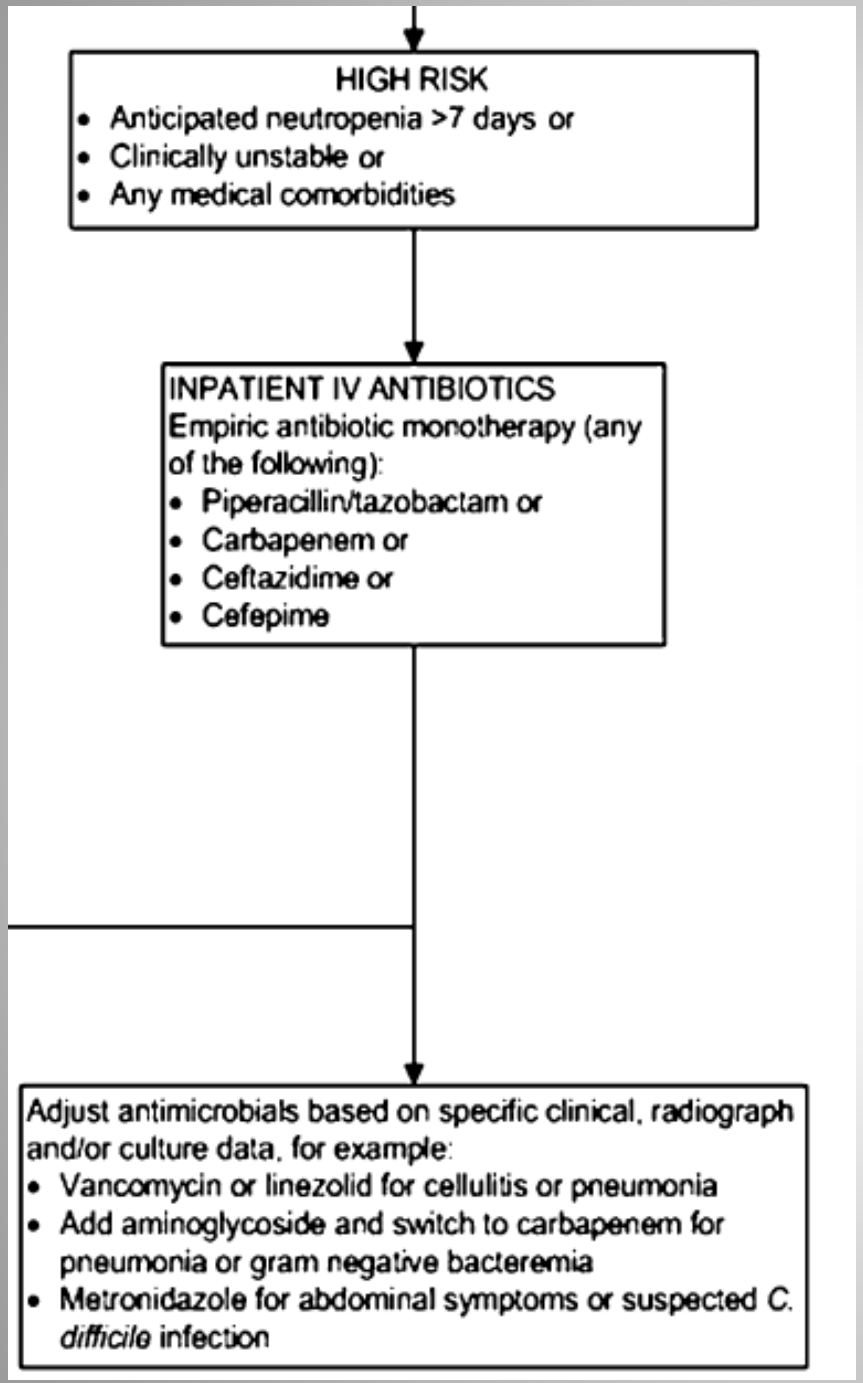
Your choice for treatment?

Choice for treatment

- 1. IV ceftazidime (fortum)
- 2. IV piperacillin/tazobactam (tazocin)
- 3. IV vancomycin + tazocin
- 4. IV vancomycin + tazocin + echinocandin
- 5. IV meropenem

Risk stratified personalized approach to EAT

- 1. Local prevalence of resistant Gram-negatives
- 2. Colonization of MDR/Previous infection with MDR
- 3. Hemodynamic stability
- <u>If all absent -> low risk setting:</u>
- ECIL recommendation: carbapenem-sparing empirical monotherapy - **piperacillin–tazobactam, ceftazidime, cefepime**, or cefoperazone–sulbactam
- Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X



Freifeld 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 Feb 15;52(4):e56-93.

	Recommendations
Low-risk clinical settings	
(1) Low local prevalence of resistant bacteria, and (2) no known colonisation or previous infection with resistant bacteria, and (3) haemodynamic stability	Carbapenem-sparing monotherapy with extended-spectrum penicillins or third-generation or fourth-generation cephalosporin (eg, piperacillin–tazobactam, cefepime, ceftazidime, or cefoperazone–sulbactam)

piperacillin–tazobactam, ceftazidime, cefepime, or cefoperazone–sulbactam

Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X

Resistance

- Vary substantially between centres
- Gram negative:
- 30–50% 3GC resistance (ESBL or other)
- 9–32% carbapenem resistance
- *Pseudomonas aeruginosa:*
- 20–37% multidrug resistant

- Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X

Ceftazidime?

- Decreasing potency against Gram-negative organisms – no coverage for **ESBL**s
- Poor activity against many **Gram-positive** pathogens, such as streptococci, staphylococci

Definitions

- MDR – resistant to at least 3 different groups (any GNR)
- DTR – resistant to all ‘routine’ drugs (p. aeruginosa)
- CRE – carbapenemase-resistant Enterobacterales
- CPE - carbapenemase-producing Enterobacterales: KPC, OXA, MBL (NDM, VIM)
- CRAB - carbapenem-resistant *Acinetobacter baumannii*

Allergy

- Most penicillin-allergic patients tolerate cephalosporins, but those with a history of an immediate-type hypersensitivity reaction (eg, hives and bronchospasm) should be treated with a combination that avoids b-lactams and carbapenems, such as **ciprofloxacin plus clindamycin** or **aztreonam plus vancomycin**
- Freifeld et al. IDSA Guidelines. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Common bacteria in NF?

Table 1. Common Bacterial Pathogens in Neutropenic Patients

Common gram-positive pathogens
Coagulase-negative staphylococci
Staphylococcus aureus, including methicillin-resistant strains
Enterococcus species, including vancomycin-resistant strains
Viridans group streptococci
Streptococcus pneumoniae
Streptococcus pyogenes

Freifeld et al. IDSA Guidelines. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Common gram-negative pathogens
Escherichia coli
Klebsiella species
Enterobacter species
Pseudomonas aeruginosa
Citrobacter species
Acinetobacter species
Stenotrophomonas maltophilia

Freifeld et al. IDSA Guidelines. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

מקרה 2

- בן 45,
- DLBCL טיפול ראשון, ללא פיקליין
- מגיע למיון כשבועיים לאחר טיפול עם חום 39, במיון ל"ד 80/50 אחרי נוזלים, טכיקרדי
- בבדיקה ללא מקור לחום
- ANC-0, צפוי לניוטרופניה של 10 ימים

הבחירה המתאימה ביותר לטיפול

- 1. IV fortum
- 2. IV tazocin
- 3. IV meropenem
- 4. IV vancomycin + IV meropenem

For discussion

- Vancomycin-tazocin
- Antifungals

High-risk clinical settings (any of the following)	
High local prevalence, colonisation, or previous infection with ESBL-producing *Enterobacterales* or Gram-negative bacteria resistant to first-line agents (but susceptible to carbapenems)*	Carbapenem
Colonisation or previous infection with carbapenem resistant Gram-negative bacteria	Refer to table 2 for specific recommendations by bacterial resistance type
Patient who is critically ill (eg, haemodynamic instability, sepsis, septic shock, or pneumonia): (1) without colonisation or previous infection with carbapenem-resistant Gram-negative bacteria, or (2) with colonisation or previous infection with resistant Gram-negative bacteria	Carbapenem with or without β-lactamase inhibitor; β-lactam plus aminoglycoside combination therapy (refer to table 2 for specific recommendations by bacterial resistance type)

1. Colonization/previous infection with first line resistant (or ESBL) – carbapenem
2. Colonization with CR – see table 2
3. Critically ill – carbapenem (+/-beta-lactamase) OR b-lactam+aminoglycodise (tazo+amikacin)

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Supplementary Table 4. Impact of colonization with resistant bacteria: invasive infections rates in patients with hematological malignancies or following hematopoietic cell transplantation.

Rate of infection	Any Gram-negatives	ESBL or 3GCSp-R	CRE	MDR *P. aeruginosa*	*Acinetobacter* spp	*Stenotrophomonas maltophilia*	Vancomycin-resistant enterococci	Methicillin-resistant *Staphylococcus aureus*
In colonized patients	289/1607 (18·0%) (29 studies)	86/753 (11·4%) (12 studies) [36, 38, 39, 41, 45, 54, 57, 60, 72, 76, 78, 79]	175/770 (22·7%) (11 studies) [38, 40, 45, 46, 54, 58, 62-64, 73, 92]	15/42 (35·7%) (4 studies) [38, 45, 50, 67]	2/9 (22·2%) (1 study) [38]	5/20 (25%) (1 study) [74]	202/1535 (13·2%) (13 studies) [33, 38, 42, 44, 49, 51, 53, 56, 57, 59, 61, 70, 75]	6/49 (12·2%) (3 studies) [43, 65, 69]
In non-colonized patients	116/9772 (1·2%) (14 studies)	87/4401 (2%) (8 studies) [39, 41, 45, 57, 72, 76, 78, 79]	16/3428 (0·5%) (2 studies) [45, 58]	12/1672 (0·7%) (2 studies) [45, 67]	No data	1/271 (0·4%) (1 study) [74]	39/3908 (1%) (10 studies) [33, 38, 42, 49, 51, 53, 57, 59, 61, 70]	11/1641 (0·7%) (2 studies) [65, 69]
In colonized Allo-HCT	82/338 (24·3%) (10 studies)	15/105 (14·3%) (2 studies) [45, 72]	43/173 (24·9%) (3 studies) [45, 46, 92]	13/30 (43·3%) (3 studies) [45, 50, 67]	No data	5/20 (25%) (1 study) [74]	129/892 (0·9%) (3 studies) [53, 59, 70]	No data
In non-colonized Allo-HCT	32/3791 (0·8%) (5 studies)	15/826 (1·8%) (1 study) [45]	4/1022 (0·4%) (1 studies) [45]	12/1672 (0·7%) (2 studies) [45, 67]	No data	1/271 (0·4%) (1 study) [74]	25/2864 (0·9%) (4 studies) [49, 53, 59, 70]	No data
In colonized Auto-HCT	37/211 (17·5%) (7 studies)	17/119 (14·3%) (2 studies) [45, 72]	19/87 (21·8%) (3 studies) [45, 46, 92]	2 cases (1 study) [45]	No data	No data	No data	No data
In non-colonized Auto-HCT	55/1197 (4·6%) (1 studies)	55/1197 (4·6%) (1 study) [45]	No data	No data	No data	No data	No data	No data
In colonized HM patients	68/437 (15·6%) (7 studies)	22/180 (12·2%) (2 studies) [38, 39]	43/238 (18·1%) (3 studies) [38, 62, 92]	1/10 (10%) (1 study) [38]	2/9 (22·2%) (1 study) [38]	No data	47/339 (13·9%) (5 studies) [33, 38, 42, 44, 51]	No data
Rate of previous colonization among patients with resistant infection	228/530 (43·0%) (19 studies)	94/215 (43·7%) (8 studies) [36, 37, 47, 48, 57, 76, 78, 79]	53/111 (47·7%) (5 studies) [40, 45, 58, 62, 73]	10/22 (45·5%) (2 studies) [45, 67]	No data	12/14 (85·7%) (2 studies) [32, 74]	180/219 (82·2%) (10 studies) [33, 42, 49, 51, 53, 57, 59, 61, 70]	4/15 (26·7%) (2 studies) [65, 69]

An increased risk of resistant infections, primarily bacteremia, was observed in patients colonized with resistant GNB and GPB.

However, data remained limited regarding non-fermenters (P. aeruginosa, Acinetobacter spp. and Stenotrophomonas maltophilia) and MRSA

ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol - limited activity for Gram+ and anarobes	Empirical therapy	Targeted therapy
CPE: KPC (ambler class A)		
Ceftazidime–avibactam	AIIu	AIItu
Meropenem–vaborbactam	BIItu	BIItu
Imipenem–cilastatin–relebactam	CIIt	CIIt
Cefiderocol	CIII	CIIt
CPE: OXA-48-like (ambler class D)		
Ceftazidime–avibactam	AIItu	AIItu
Cefiderocol	CIII	CIIt
CPE: MBL (eg, NDM, VIM, and IMP; ambler class B)		
Ceftazidime–avibactam plus aztreonam	AIItu	AIItu
Cefiderocol	CIII	BIIt
Combination therapy with a non-β-lactam agent is generally not recommended but it might be considered in the following clinical conditions: (1) patients who are critically ill with sepsis or septic shock until clinical improvement, or (2) difficult-to-treat infections (eg, pneumonia or uncontrolled infection source), or (3) infections due to CPE with MIC values near the resistance breakpoint (MIC can vary by one dilution)	..	CIII
Treatment of difficult-to-treat resistant *Pseudomonas aeruginosa*		
Ceftolozane–tazobactam (high dose of 9 grams per day)	AIItu	AIItur
Ceftazidime–avibactam	AIItu	AIItu
Imipenem–cilastatin–relebactam	BIIt	BIIt
Cefiderocol	CIII	BIItur
Addition of an active non-β-lactam antibiotic (eg, aminoglycoside, fluoroquinolone, or fosfomycin) can be considered in: patients who are critically ill (eg, sepsis, septic shock, or pneumonia) until clinical improvement, or *P aeruginosa* infections with MIC values near the resistance breakpoint (MIC can vary by one dilution), or uncontrolled infection source in combination with (1) ceftolozane–tazobactam, (2) ceftazidime–avibactam, (3) imipenem–cilastatin–relebactam, or (4) cefiderocol	..	(1) BIIr, (2) BIII, (3) BIII, (4) BIII

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Treatment of carbapenem-resistant *Acinetobacter baumannii*		
Sulbactam–durlobactam† plus high-dose imipenem	..	AIIt
High dose sulbactam (≥9 grams per day) plus other drug[1,2]	..	BIIt
Other combinations[3]	..	BIIt
Treatment of *Stenotrophomonas maltophilia*		
First-line therapy (whenever feasible), TMP–SMX in combination with levofloxacin‡, or high dose tetracycline derivatives (eg, minocycline or tigecycline) or cefiderocol	..	BIItu
If TMP–SMX not feasible (eg, resistance or intolerance) use one of the following two options§: (1) two-drug combination of levofloxacin (if susceptible), high dose tetracycline derivatives (eg, minocycline or tigecycline), or cefiderocol, or (2) triple combination of ceftazidime–avibactam plus aztreonam and one of levofloxacin (if susceptible) or high dose tetracycline derivatives (eg, minocycline or tigecycline)	..	(1) BIIu, (2) CIII
Duration of therapy for Gram-negative bacteraemia		
Antibiotics can be discontinued after at least 7 days of treatment when all symptoms and clinical signs of infection are resolved and infection is microbiologically eradicated: (1) with neutrophil recovery, or (2) without neutrophil recovery	..	(1) AIIu, (2) BIIu

For the ECIL-10 grades, see the appendix (p 23). CPE=carbapenemase-producing *Enterobacterales*. ECIL-10=10th European Conference on Infections in Leukaemia. IMP=metallo-β-lactamase active on imipenem. KPC=*Klebsiella pneumoniae* carbapenemase. MIC=minimal inhibitory concentration. MBL=metallo-β-lactamase. NDM=New Delhi metallo-β-lactamase. OXA-48-like=oxacillin-type 48 β-lactamase. TMP–SMX=trimethoprim–sulfamethoxazole. VIM=Verona integron-encoded metallo-β-lactamase. *Empirical therapy in patients colonised or previously infected with these Gram-negative bacteria. †Durlobactam is currently not approved for use in Europe by the European Medicines Agency. (1) in case sulbactam–durlobactam is not available; (2) in combination with any of the following agents: colistin (preferred agent whenever possible), cefiderocol, tigecycline, minocycline, and fosfomycin; or (3) combination of two of the following agents—preferably colistin and cefiderocol—if not possible or not available use tigecycline, minocycline, or fosfomycin. ‡Levofloxacin is likely not reliable empirical coverage for *Stenotrophomonas* in centres where levofloxacin is used for neutropenic prophylaxis. §Step down to monotherapy might be considered after clinical (and microbiological, if applicable) response is obtained and susceptibility to the single agent is confirmed.

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Why vancomycin?

Table 4. Indications for Addition of Antibiotics Active Against Gram-Positive Organisms to the Empirical Regimen for Fever and Neutropenia

• Hemodynamic instability or other evidence of severe sepsis
• Pneumonia documented radiographically
• Positive blood culture for gram-positive bacteria, before final identification and susceptibility testing is available
• Clinically suspected serious catheter-related infection (eg, chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site)
• Skin or soft-tissue infection at any site
• Colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae* (see text)
• Severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy

Freifeld et al. Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):e56-93.

Coverage of resistant Gram-positive bacteria†	Consider coverage for streptococcal infections when using agents with limited Gram-positive activity (eg, ceftazidime with or without avibactam or cefiderocol), particularly in patients with severe mucositis
Coverage of resistant Gram-positive bacteria†	Include anti-resistant Gram-positive coverage in patients with: (1) suspicion of catheter-related infection or skin and soft-tissue infection, or (2) sepsis, septic shock, or pneumonia (regardless of colonisation status)
Coverage of resistant Gram-positive bacteria†	Include methicillin-resistant *Staphylococcus aureus* coverage in colonised patients with: (1) haemodynamic instability (eg, sepsis or septic shock) or pneumonia, or (2) haemodynamic stability
Coverage of resistant Gram-positive bacteria†	In all other clinical conditions, the routine empirical use of agents targeting resistant Gram-positive bacteria is not recommended

† Vancomycin, linezolid, or daptomycin

1. ceftazidime, cefidrocol empiric therapy in patients with severe mucositis
2. SSTI/line infection
3. Septic shock, pneumonia
4. MRSA colonized with septic shock

Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X

1. **Neutropenia** is independently associated with sub-therapeutic serum concentration of **vancomycin**.

Choi MH, Choe YH, Lee SG, Jeong SH, Kim JH.
Clin Chim Acta. 2017 Feb;465:106-111. doi: 10.1016/j.cca.2016.12.021. Epub 2016 Dec 23.
PMID: 28025029
Similar articles

2. Augmented Renal Clearance in Patients With Febrile **Neutropenia** is Associated With Increased Risk for Subtherapeutic Concentrations of **Vancomycin**.

Hirai K, Ishii H, Shimoshikiryo T, Shimomura T, Tsuji D, Inoue K, Kadoiri T, Itoh K.
Ther Drug Monit. 2016 Dec;38(6):706-710.
PMID: 27681114
Similar articles

3. Augmented Renal Clearance in Pediatric Patients With Febrile **Neutropenia** Associated With **Vancomycin** Clearance.

Hirai K, Ihara S, Kinae A, Ikegaya K, Suzuki M, Hirano K, Itoh K.
Ther Drug Monit. 2016 Jun;38(3):393-7. doi: 10.1097/FTD.0000000000000270.

> Antibiotics (Basel). 2023 May 29;12(6):979. doi: 10.3390/antibiotics12060979.

Altered Pharmacokinetics Parameters of Vancomycin in Patients with Hematological Malignancy with Febrile Neutropenia, a Bayesian Software Estimation

Appropriate empirical and mortality

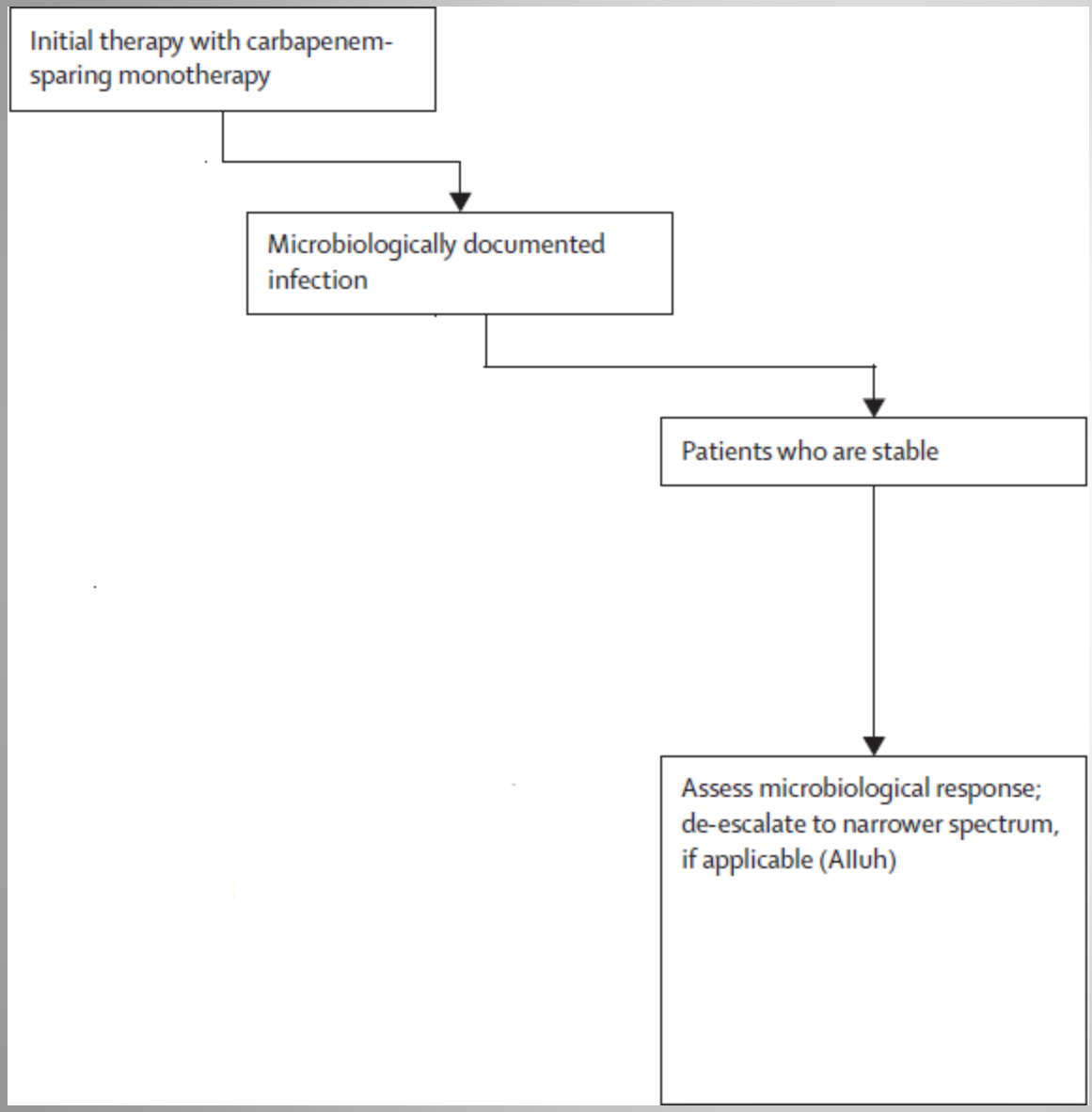
- In GPB bacteremia - no association was found between IEAT and mortality in patients with infections caused by CONS, enterococci, or penicillin-non-susceptible viridans group streptococcal (VGS) infections
- Not true for staph aureus – however, SAB is uncommon in NF (0–3%)
- Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X

מקרה 2 המשך

- יום 3 לטיפול בונקומיצין-טזוצין
- החולה יציב, בדם אי קולי רגיש לכל

- מה הלאה?
- להפסיק ונקומיצין
- לצמצם טיפול לפי צמיחה

72–96 h from the onset of fever



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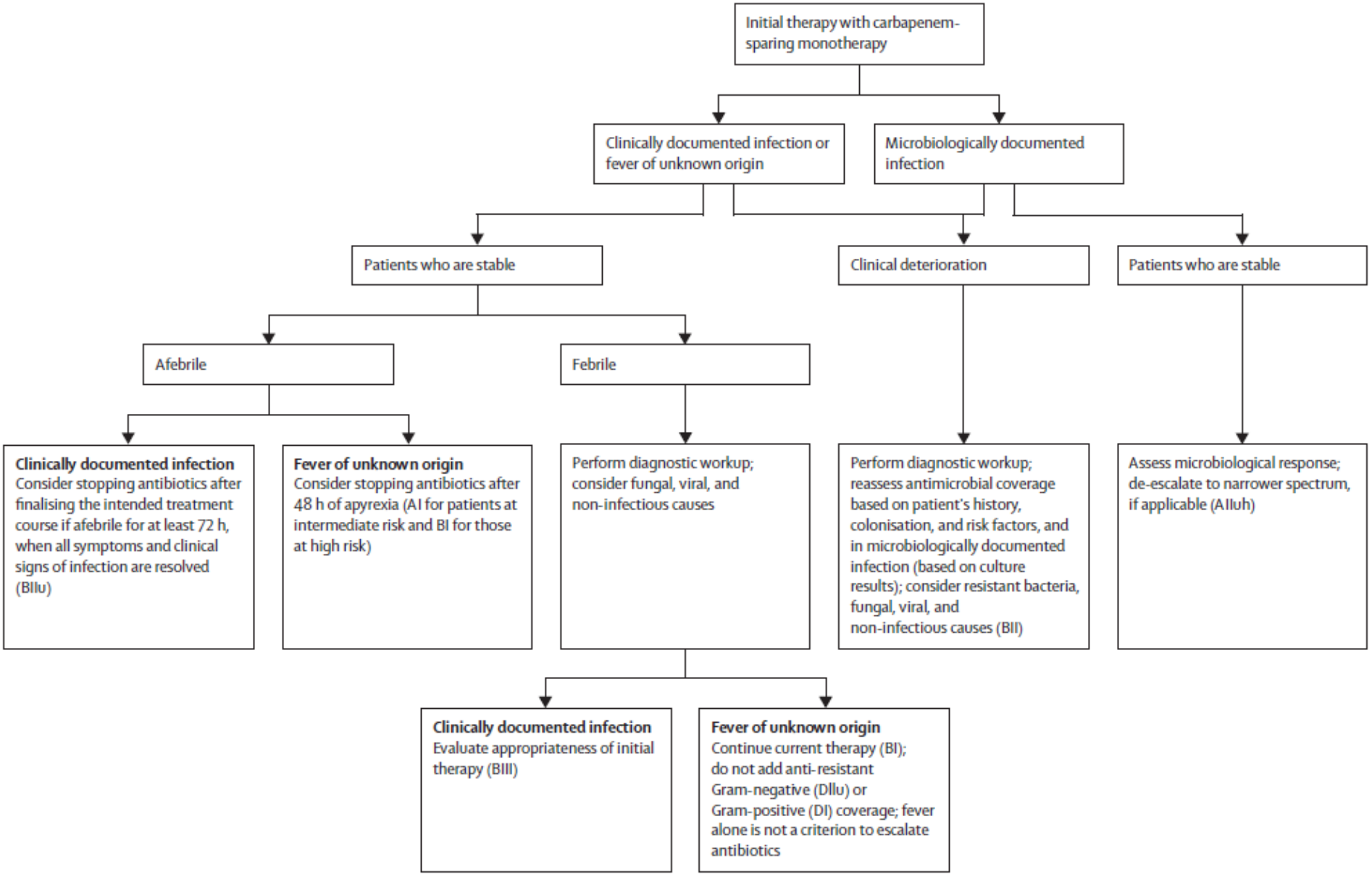
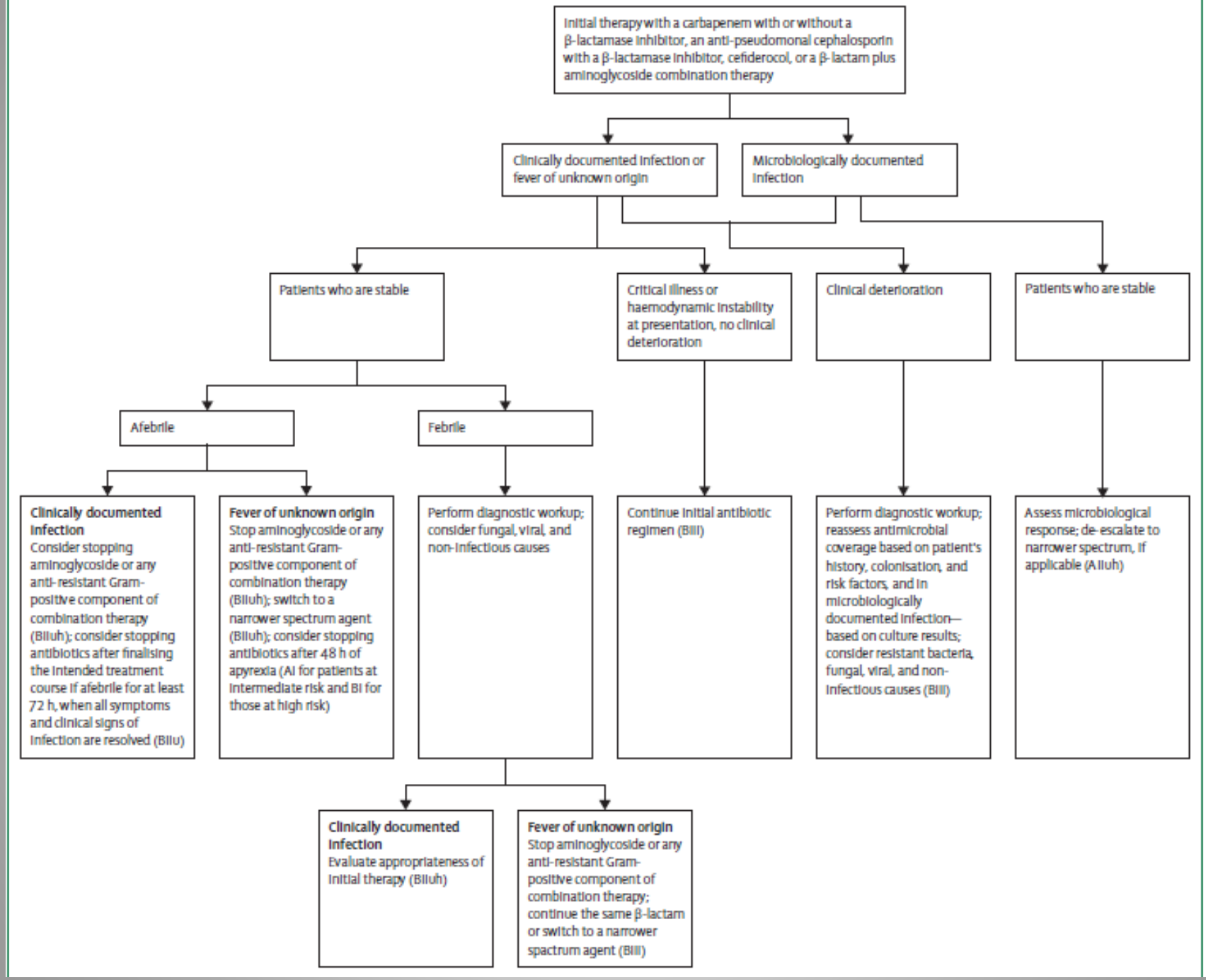
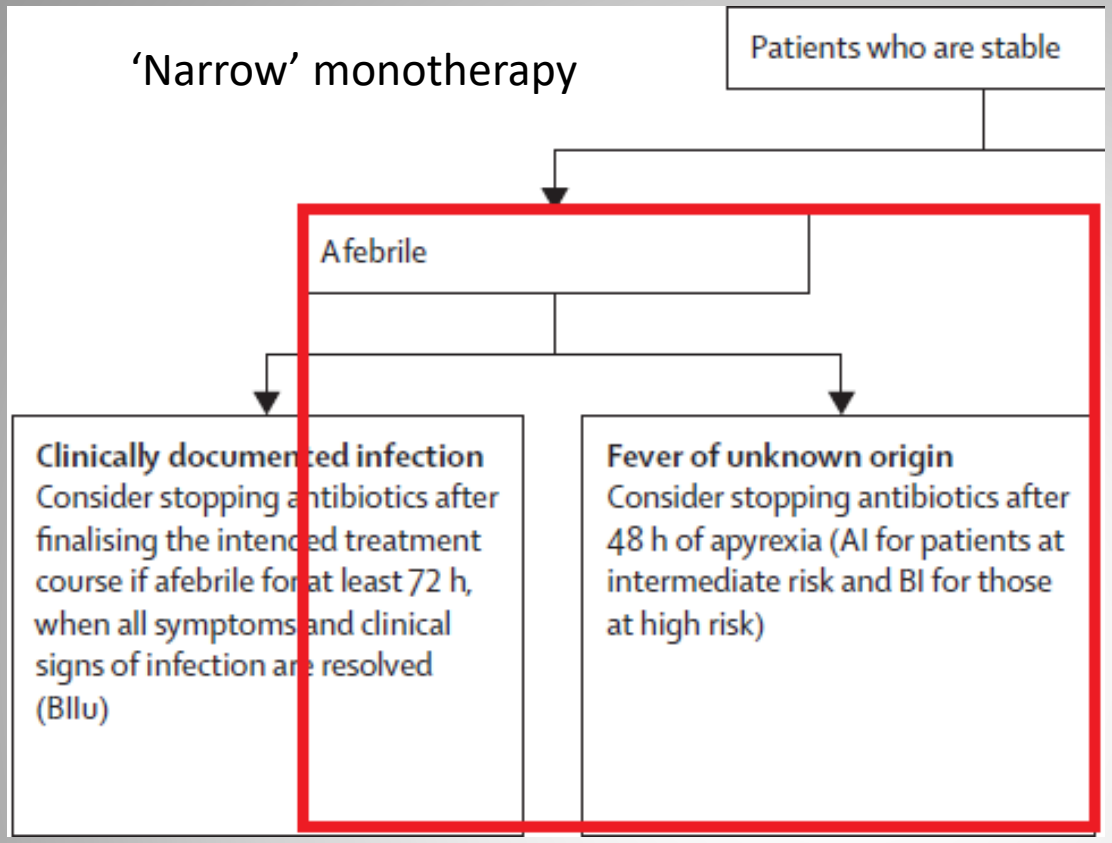
מקרה 2 אחר

- יום 3 לטיפול בונקומיצין-טזוצין
- החולה יציב, אין צמיחה, אין מקור
- אין חום

- מה הלאה?
- להפסיק טיפול אנטיביוטי אחרי 48 שעות ללא חום (אם היה מרופנם אפשר לצמצם לטזוצין)


Initial therapy with carbapenem-sparing monotherapy
Clinically documented infection or fever of unknown origin
Microbiologically documented infection
Patients who are stable
Clinical deterioration
Patients who are stable
Afebrile
Febrile
Clinically documented infection
Consider stopping antibiotics after finalising the intended treatment course if afebrile for at least 72 h, when all symptoms and clinical signs of infection are resolved (BIIu)
Fever of unknown origin
Consider stopping antibiotics after 48 h of apyrexia (AI for patients at intermediate risk and BI for those at high risk)
Perform diagnostic workup; consider fungal, viral, and non-infectious causes
Perform diagnostic workup; reassess antimicrobial coverage based on patient's history, colonisation, and risk factors, and in microbiologically documented infection (based on culture results); consider resistant bacteria, fungal, viral, and non-infectious causes (BII)
Assess microbiological response; de-escalate to narrower spectrum, if applicable (AIIuh)
Clinically documented infection
Evaluate appropriateness of initial therapy (BIII)
Fever of unknown origin
Continue current therapy (BI); do not add anti-resistant Gram-negative (DIIu) or Gram-positive (DI) coverage; fever alone is not a criterion to escalate antibiotics


Initial therapy with a carbapenem with or without a β-lactamase inhibitor, an anti-pseudomonal cephalosporin with a β-lactamase inhibitor, cefiderocol, or a β-lactam plus aminoglycoside combination therapy
Clinically documented infection or fever of unknown origin
Microbiologically documented infection
Patients who are stable
Critical illness or haemodynamic instability at presentation, no clinical deterioration
Clinical deterioration
Patients who are stable
Afebrile
Febrile
Clinically documented infection
Consider stopping aminoglycoside or any anti-resistant Gram-positive component of combination therapy (BIIuh); consider stopping antibiotics after finalising the intended treatment course if afebrile for at least 72 h, when all symptoms and clinical signs of infection are resolved (BIIu)
Fever of unknown origin
Stop aminoglycoside or any anti-resistant Gram-positive component of combination therapy (BIIuh); switch to a narrower spectrum agent (BIIuh); consider stopping antibiotics after 48 h of apyrexia (AI for patients at intermediate risk and BI for those at high risk)
Perform diagnostic workup; consider fungal, viral, and non-infectious causes
Continue initial antibiotic regimen (BIII)
Perform diagnostic workup; reassess antimicrobial coverage based on patient's history, colonisation, and risk factors, and in microbiologically documented infection—based on culture results; consider resistant bacteria, fungal, viral, and non-infectious causes (BIII)
Assess microbiological response; de-escalate to narrower spectrum, if applicable (AIIuh)
Clinically documented infection
Evaluate appropriateness of initial therapy (BIIuh)
Fever of unknown origin
Stop aminoglycoside or any anti-resistant Gram-positive component of combination therapy; continue the same β-lactam or switch to a narrower spectrum agent (BIII)



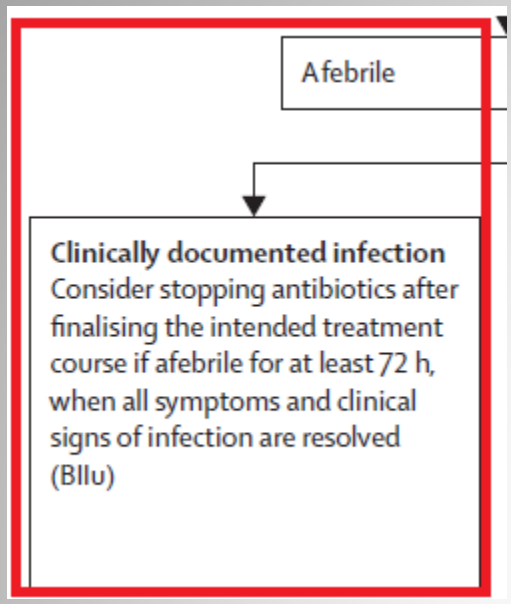
Broad

Fever of unknown origin
Stop aminoglycoside or any anti-resistant Gram-positive component of combination therapy (BIIuh); switch to a narrower spectrum agent (BIIuh); consider stopping antibiotics after 48 h of apyrexia (AI for patients at intermediate risk and BI for those at high risk)

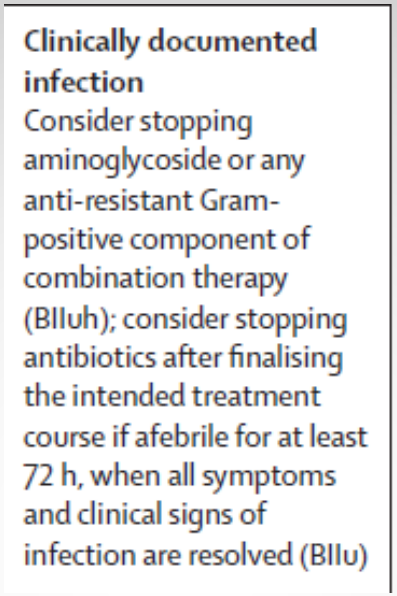
For patients with fever of unknown origin, discontinuation after confirming negative blood cultures is:

1. strongly recommended for patients at **intermediate risk** = auto-HSCT or lymphoma with an expected profound neutropenia of 7–10 days
2. moderately recommended for patients at **high risk** = allo-HSCT or acute leukemia with anticipated neutropenia lasting > 10 days

‘Narrow’ monotherapy



Broad



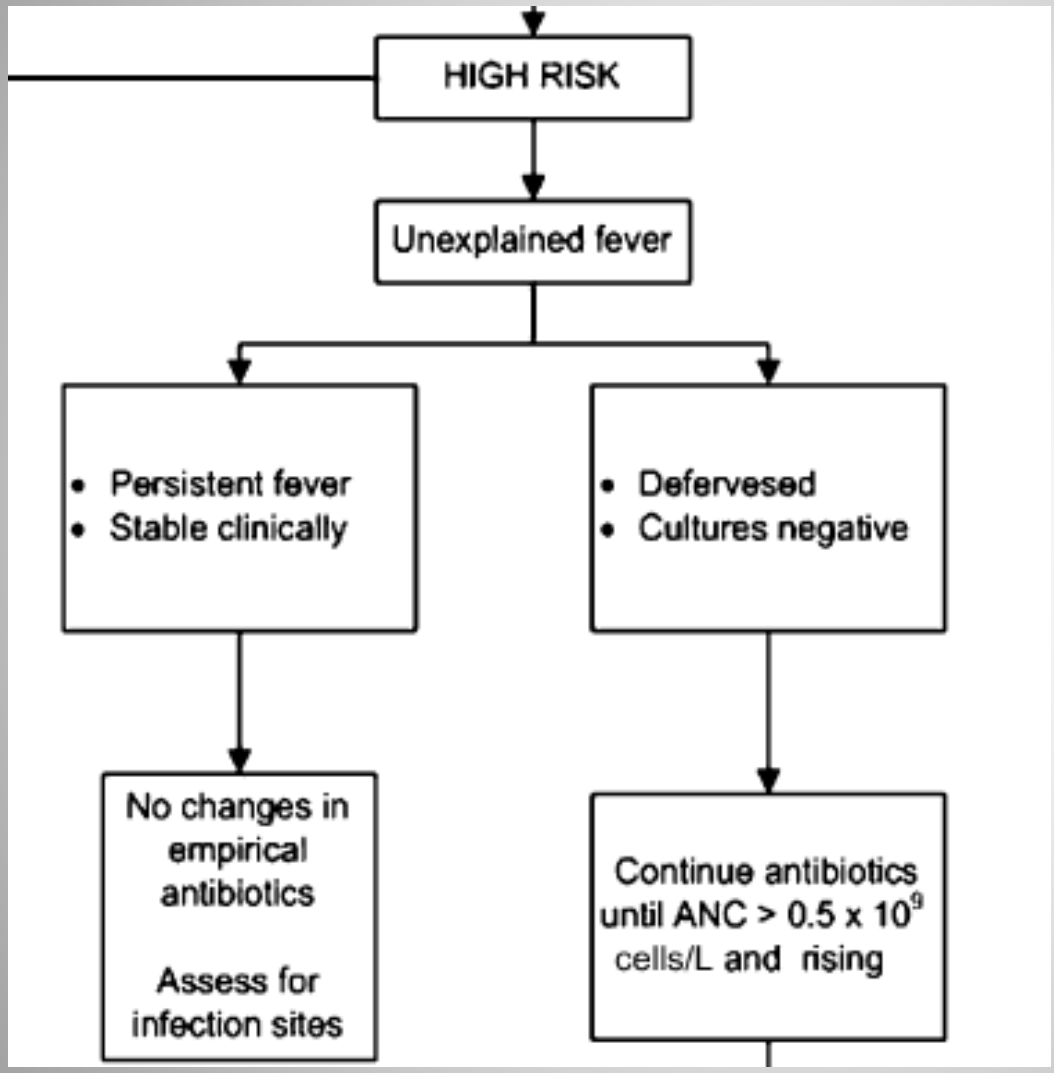
For patients with clinically or microbiologically documented infections, discontinuation can be considered after completing the intended treatment course with confirmed clinical and, if appropriate, microbiological resolution, if the patient is afebrile for at least 72 h

מקרה 2 אחר

- יום 3 לטיפול בונקומיצין-טזוצין
- החולה יציב, אין צמיחה, אין מקור
- עדיין חום

- מה הלאה?
- להפסיק ונקומיצין
- המשך טיפול בטזוצין

Day 2-4

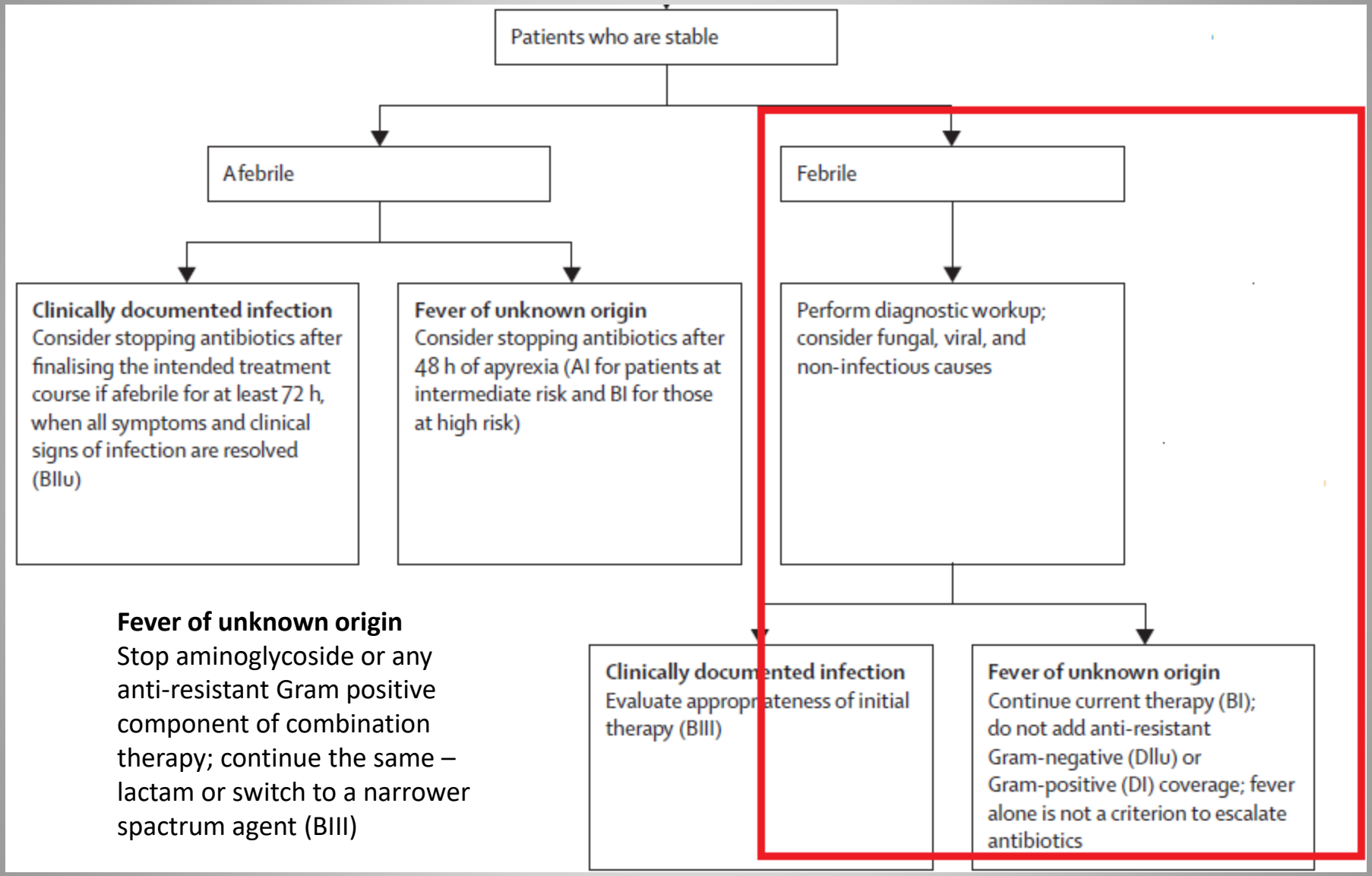


Freifeld et al. Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

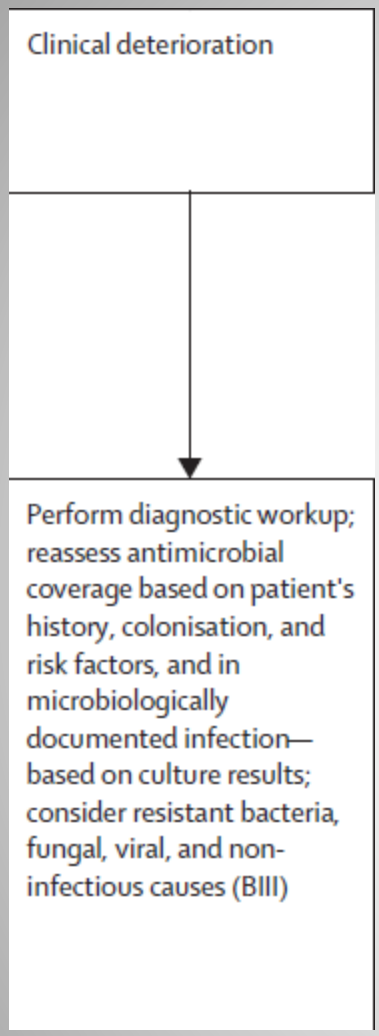
Modifications

- **Unexplained persistent fever** in a patient whose condition is otherwise **stable** rarely requires an empirical change to the initial antibiotic regimen
- If an infection is identified, antibiotics should be adjusted accordingly
- If vancomycin or other **coverage for gram-positive** organisms was started initially, it may be **stopped after 2 days** if there is no evidence for a gram-positive infection
- IDSA guidelines

piperacillin–tazobactam, ceftazidime, cefepime, or cefoperazone–sulbactam



Fever of unknown origin
Stop aminoglycoside or any anti-resistant Gram positive component of combination therapy; continue the same –lactam or switch to a narrower spactrum agent (BIII)



Asses coverage for:
Gram positive
Gram negative
Fungi
(Viral)

Remember

- The median time to defervescence following the initiation of empiric antibiotics in patients with hematologic malignancies, including hematopoietic cell transplant (HCT) recipients, is **five days**

- IDSA guidelines

Duration

	Recommendations	ECIL-10 Grade
Fever of unknown origin		
Patients who are afebrile for at least 48 hours and remained haemodynamically stable since presentation	Discontinue empirical antibiotic therapy after at least 72 h, regardless of the neutrophil count or the anticipated duration of neutropenia	BI for patients at high risk* and AI for patients at intermediate risk*
Patients who are afebrile whose antibiotics were discontinued, particularly if neutropenia persists	Close inpatient or outpatient clinical observation is recommended	AIIu
Patients who are afebrile with antibiotics discontinued before neutrophil recovery in centres where prophylactic antibiotics are routinely used for neutropenia	Consider resuming antibiotic prophylaxis	CIII
Patients who develop recurrent fever after stopping antibiotics (after initial defervescence)	Antibiotics should be promptly restarted after clinical evaluation and appropriate microbiological workup	AIIu
Patients with persistent fever and haemodynamic stability (patients at high risk or intermediate risk)	(1) Continue empirical antibiotic therapy; or (2) continue diagnostic efforts to identify occult infections or alternative explanation of fever; discontinuation of empirical therapy can be considered at a later stage, once a bacterial source has been reasonably ruled out	(1) BI, (2) CIII

Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X

Duration

Microbiologically documented infections, clinically documented infections		
Patients who have completed the intended treatment course, are haemodynamically stable, afebrile for at least 72 h, have resolution of all symptoms and clinical signs of infection, and have microbiological eradication of infection (when re-sampling is feasible)	Consider discontinuing antibiotic therapy before neutrophil recovery	BIIu
Patients who are afebrile whose antibiotics were discontinued, particularly if neutropenia persists	Close inpatient or outpatient clinical observation is recommended	AIIu
Patients who are afebrile with antibiotics discontinued before neutrophil recovery in centres where prophylactic antibiotics are routinely used for neutropenia	Consider resuming antibiotic prophylaxis	CIII
Patients who develop recurrent fever after stopping antibiotics (after initial defervescence)	Antibiotics should be promptly restarted after clinical evaluation and appropriate microbiological workup	AIIu

Duration of therapy for Gram-negative bacteraemia		
Antibiotics can be discontinued after at least 7 days of treatment when all symptoms and clinical signs of infection are resolved and infection is microbiologically eradicated: (1) with neutrophil recovery, or (2) without neutrophil recovery	..	(1) AIIu, (2) BIIu

Averbuch et al. ECIL 10. Lancet Infect Dis. 2025 Nov 25:S1473-3099(25)00619-X

After discontinuation

- Close monitoring and prompt reinitiation of antibiotics at the first sign of a new infection
- Centres using antibiotic prophylaxis should consider restarting prophylaxis upon discontinuation
- Averbuch et al. 2025

RCT – Ram et al.

- Patients – allo/auto/CAR-T, 110p
- Intervention: ab 48-72h providing there was no evidence of clinical or microbiology documented infection VS until recovery of counts
- Outcomes: antibiotic-free-neutropenia days
- Results: less ab days, no difference in clinical success/mortality

- Ram et al. Early Antibiotic Deescalation and Discontinuation in Patients with Febrile Neutropenia after Cellular Therapy: A Single-Center Prospective Unblinded Randomized Trial. Transplant Cell Ther. 2023 Nov;29(11):708.e1-708.e8

Disadvantages of prolonged ab

- Increased risk for drug toxicity
- CDAD
- Superinfections (fungi or MDR bacteria)
- Resistance!
- Increased cost
- Prolonged hospitalization
- Decreased quality of life
- Delayed chemotherapy (next course)

RCT – de Jonge et al.

- 281p, high risk NF (hemato malignancy or HCST)
- 48-72h tx vs SOC
- Discontinuation even if patient febrile
- Outcomes: composite of treatment failure, defined as recurrent fever or a carbapenem-sensitive infection, and septic shock
- ***Lancet Haematol* 2022**

Added value of this study

Our study strengthens the current knowledge of optimal treatment duration of febrile neutropenia. Although many previous studies stopped empirical therapy after defervescence, our study aimed to show that a fixed, short duration of 3 days is feasible in all patients with unexplained fever at day 3. Although the treatment failure rate was non-inferior in the short treatment group, secondary analyses suggested that serious adverse events and mortality occurred more often in the short treatment group, especially in patients with persistent fever after day 3, mostly due to non-carbapenem susceptible causes.

Implications of all the available evidence

The results of our study acknowledge the recommendation that treatment can be safely stopped after 3 days in patients who are afebrile. In case of persistent fever, carbapenem can be stopped, but the clinician should be vigilant for non-carbapenem susceptible infections and restart or broaden the spectrum of antibiotics in case of clinical deterioration. Future research should explore reasons for the increased rate of adverse events in patients who received short empirical treatment.

Line removal

- Any line - when the CVC is the suspected source of infection
- Any line - complicated CVC-related bloodstream infection (ie, sepsis, suppurative thrombophlebitis, endocarditis, or possible metastatic seeding)
- Short-term CVC-related uncomplicated bloodstream infection due to any pathogen
- Long-term CVC-related uncomplicated bloodstream infection:
- Bacteremia > 72h appropriate therapy
- *S aureus, P aeruginosa*, fungi, or mycobacteria
- Averbuch et al. 2025

Follow up blood cultures (FUBC)

- Universal FUBC to document clearance – consider for:
- *S aureus*, *enterococci*, resistant GNR, *Candida* spp
- Endocarditis/endovascular infections
- In other clinical scenarios – FUBC unnecessary!
- Particularly in those who have defervesced and show clinical improvement
- The yield is very low in patients who are persistently febrile, except when evaluating for breakthrough pathogens resistant to current antibiotic therapy or in the setting of new clinical instability
- Averbuch et al. 2025

Infect Control Hosp Epidemiol. 2021 Sep;42(9):1090-1097. doi: 10.1017/ice.2020.1368. Epub 2021 Jan 25.

Reductions in vancomycin and meropenem following the implementation of a febrile neutropenia management algorithm in hospitalized adults: An interrupted time series analysis

Before after ITS analysis
Algorithm for management of NF implementation
Single center, USA
2,014 patients

Trinh et al. Reductions in vancomycin and meropenem following the implementation of a febrile neutropenia management algorithm in hospitalized adults: An interrupted time series analysis. Infect Control Hosp Epidemiol. 2021 Sep;42(9):1090-1097.

Management algorithm

- (1) empirical vancomycin - in hemodynamically unstable patients and/or those with MRSA
- (2) broadening from cefepime to meropenem - reserved for hemodynamically unstable patients after 24 hours
- (3) febrile neutropenia empirical antibiotic treatment (eg, cefepime) was continued for a defined duration of 10 days regardless of neutrophil recovery in patients with resolved fevers and no microbiologically documented infection or clinically documented infection

Management algorithm

- Broad-spectrum intravenous (IV) antibiotic use decreased by 5.7%
- Immediate reductions in meropenem and vancomycin use by 22 (P = .02) and 15 (P = .001) DOT per 1,000 patient days, respectively
- No differences in safety outcomes including C. difficile infection, ICU length of stay, and in-hospital mortality

Impact of decreasing vancomycin exposure on acute kidney injury in stem cell transplant recipients

Horace Rhodes Hambrick MD[1,2], Kimberly F. Greco MPH[3], Edie Weller PhD[3,4], Lakshmi Ganapathi MBBS[1,4,5,6], Leslie E. Lehmann MD[4,7] and Thomas J. Sandora MD, MPH[1,4,6]

[1]Department of Pediatrics, Boston Children's Hospital, Boston, Massachusetts, [2]Department of Pediatric Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, [3]Biostatistics and Research Design Center, Institutional Centers for Clinical and Translational Research, Boston Children's Hospital, Boston, Massachusetts, [4]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, [5]Division of Nephrology, Boston Children's Hospital, Boston, Massachusetts, [6]Division of Infectious Diseases, Boston Children's Hospital, Boston, Massachusetts and [7]Pediatric Stem Cell Transplant, Dana-Farber Cancer Institute, Boston, Massachusetts

Abstract

Objective: To evaluate the change in vancomycin days of therapy (DOT) and vancomycin-associated acute kidney injury (AKI) after an antimicrobial stewardship program (ASP) intervention to decrease vancomycin use in stable patients after hematopoietic stem cell transplantation (HSCT).

Design: Retrospective cohort study and quasi-experimental interrupted time series analysis. Change in unit-level vancomycin DOT per 1,000 inpatient days after the intervention was assessed using segmented Poisson regression. Subject-specific risk of vancomycin-associated AKI was evaluated using a random intercept logistic regression model with mediation analysis.

Setting: HSCT unit at a single quaternary-care pediatric hospital.

Participants: Inpatients aged 3 months and older who underwent HSCT between January 1, 2015, and March 31, 2019 (27 months before and after the intervention) who received any dose of vancomycin.

Intervention: An ASP intervention in April 2017 creating a new practice guideline to decrease prolonged (>72 hours) vancomycin courses for stable HSCT patients with febrile neutropenia.

Results: Overall, 439 vancomycin exposures (234 before the intervention and 205 after the intervention) occurring across 300 transplants and 259 subjects were included. The mean vancomycin DOT was 307 per 1,000 inpatient days (95% confidence interval [CI], 272–342) and decreased after the intervention to 207 per 1,000 inpatient days (95% CI, 173–240). In multivariable analyses, the odds of AKI in the postintervention period were 37% lower than in the preintervention period (adjusted OR, 0.63; 95% CI, 0.42–0.95; $P = .0268$); 56% of the excess risk was mediated by vancomycin DOT.

Conclusions: An ASP intervention successfully decreased vancomycin use after HSCT and resulted in a decrease in AKI. Reducing empiric antibiotic exposure for stable patients after HSCT can improve clinical outcomes.

(Received 30 May 2021; accepted 5 October 2021; electronically published 7 December 2021)

J Antimicrob Chemother. 2017 Mar 1;72(3):668-677. doi: 10.1093/jac/dkw459.

Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis.

Righi E[1,2], Peri AM[2,3], Harris PN[2], Wailan AM[2], Liborio M[4], Lane SW[5,6], Paterson DL[2].

Author information

Abstract

BACKGROUND: Carbapenem-resistant Gram-negative bacteria are recognized as a cause of difficult-to-treat infections associated with high mortality.

OBJECTIVES: To perform a systematic review of currently available data on distribution, characteristics and outcome associated with carbapenem-resistant bloodstream infections in adult neutropenic patients.

METHODS: Included studies were identified through Medline, Embase and Cochrane databases between January 1995 and April 2016. Random effect meta-analysis was used to quantify the association between carbapenem resistance and mortality and between carbapenem exposure and resistance.

RESULTS: A total of 30 studies from 21 countries were included. Overall carbapenem resistance varied from 2% to 53% (median 9%) among studies. Infections due to carbapenem-resistant Pseudomonas spp . were reported in 18 (60%) studies showing high median resistance rates (44% of all carbapenem-resistant Gram-negatives and 19% of Pseudomonas isolates). Resistance of Enterobacteriaceae was less commonly reported and bloodstream infections due to carbapenem-resistant Klebsiella spp. were mainly documented from endemic areas (Greece, Italy, Israel). Carbapenem resistance in Acinetobacter spp. was reported in 9 (30%) studies (median resistance 58% of Acinetobacter isolates). Mortality rates ranged from 33% to 71% (median 50%) in patients with carbapenem-resistant infections. Carbapenem resistance appeared to correlate with mortality (OR 4.89, 95% CI 3.30-7.26) and previous exposure to carbapenems (OR 4.63, 95% CI 3.08-6.96).

CONCLUSIONS: Carbapenem resistance represents a threat to neutropenic patients. In this group, resistance is likely promoted by previous carbapenem use and leads to high mortality rates. The knowledge of resistance patterns is crucial and can direct clinicians in the use of alternatives to carbapenem-based regimens.

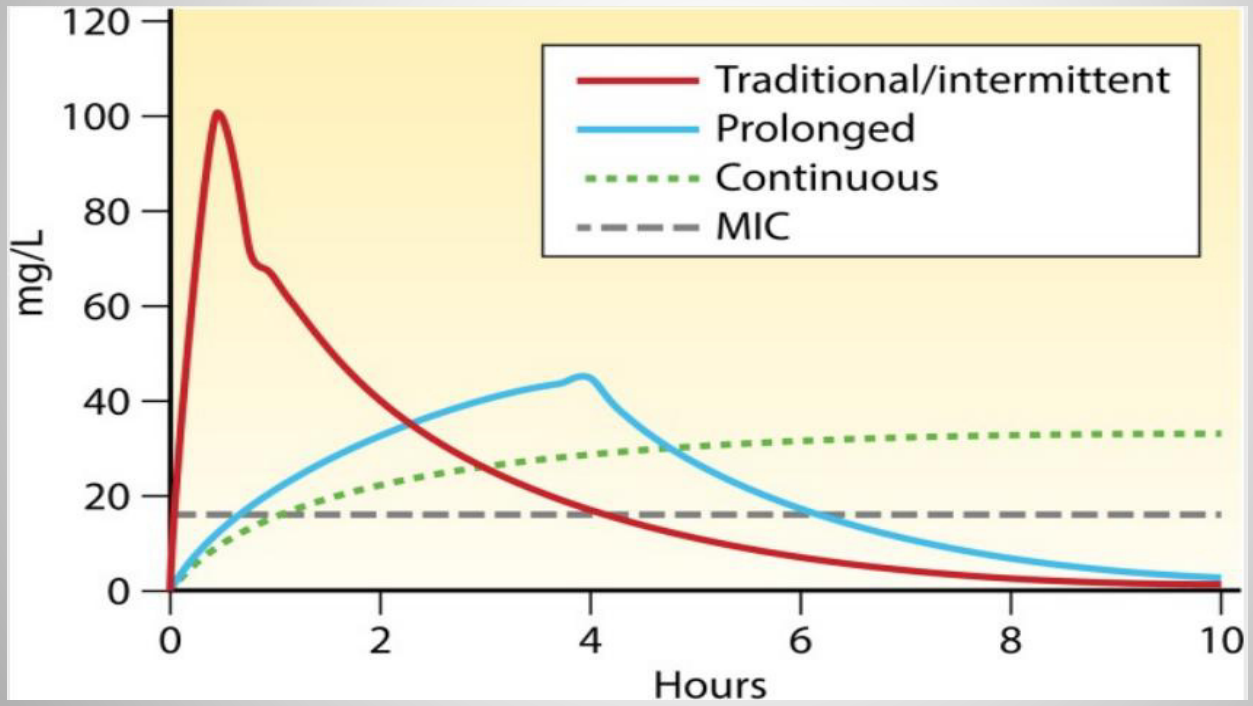
Acinetobacter bacteremia in hemato-oncology

- January 2010 and august 2018
- 46 patients with hematological malignancies
- Carbapenem resistant *acinetobacter baumannii* bacteremia
- Lymphoma – 19p; AML – 12p; ALL – 2p; HSCT – 16p
- Within 30 days of the bacteremia, only 2 of the 46 patients with bacteremia (4%) remained alive
- Shargian-Alon et al.

Way of administration and dosing

Loading dose -> extended/continuous infusion

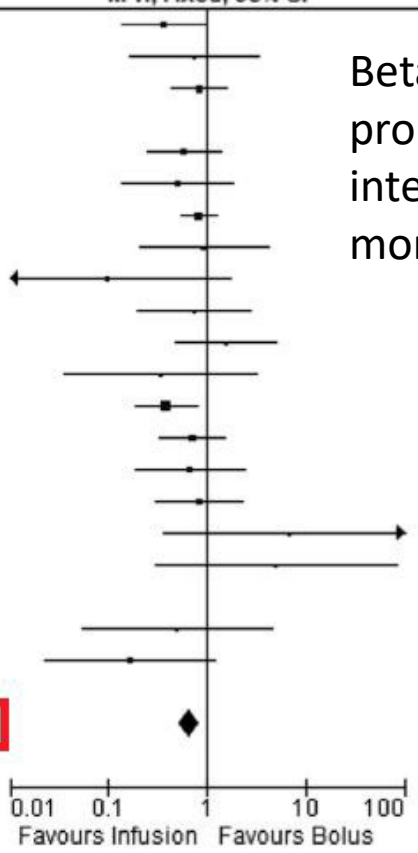
Beta-lactams: loading dose -> extended/continuous infusion



Study or Subgroup	Prolonged Infusion Events	Total	Intermittent Bolus Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Angus 2000	3	10	9	11	6.1%	0.37 [0.14, 0.98]
Buijk 2001	3	12	2	6	1.9%	0.75 [0.17, 3.35]
Chytra 2012	14	106	17	108	12.0%	0.84 [0.44, 1.61]
De Jongh 2008	0	6	0	6		Not estimable
Dow 2011	8	67	11	54	8.6%	0.59 [0.25, 1.35]
Dulhunty 2012	3	30	6	30	4.3%	0.50 [0.14, 1.82]
Fahimi 2012	17	31	20	30	14.4%	0.82 [0.55, 1.24]
Georges 2005	3	26	3	24	2.2%	0.92 [0.21, 4.14]
Grant 2002	0	47	5	51	3.7%	0.10 [0.01, 1.73]
Hughes 2009	6	78	3	29	3.1%	0.74 [0.20, 2.78]
Lagast 1983	5	20	4	25	2.5%	1.56 [0.48, 5.06]
Lau 2006	1	130	3	132	2.1%	0.34 [0.04, 3.21]
Lodise 2007	9	102	21	92	15.7%	0.39 [0.19, 0.80]
Lorente 2009	8	37	14	46	8.9%	0.71 [0.33, 1.51]
Patel 2009	4	70	5	59	3.9%	0.67 [0.19, 2.40]
Rafati 2006	5	20	6	20	4.3%	0.83 [0.30, 2.29]
Roberts 2007	3	29	0	28	0.4%	6.77 [0.37, 125.32]
Roberts 2009	2	5	0	5	0.4%	5.00 [0.30, 83.69]
Roberts 2010	0	8	0	8		Not estimable
Sakka 2007	1	10	2	10	1.4%	0.50 [0.05, 4.67]
Wang 2009	1	15	6	15	4.3%	0.17 [0.02, 1.22]
Total (95% CI)		**859**		**789**	**100.0%**	**0.66 [0.53, 0.83]**
Total events	96		137			

Heterogeneity: $Chi^2 = 16.20$, $df = 18$ ($P = 0.58$); $I^2 = 0\%$

Test for overall effect: $Z = 3.54$ ($P = 0.0004$)



Beta-lactams prolonged vs intermittent MA - mortality

Teo et al. Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis. Int J Antimicrob Agents. 2014 May;43(5):403-11.

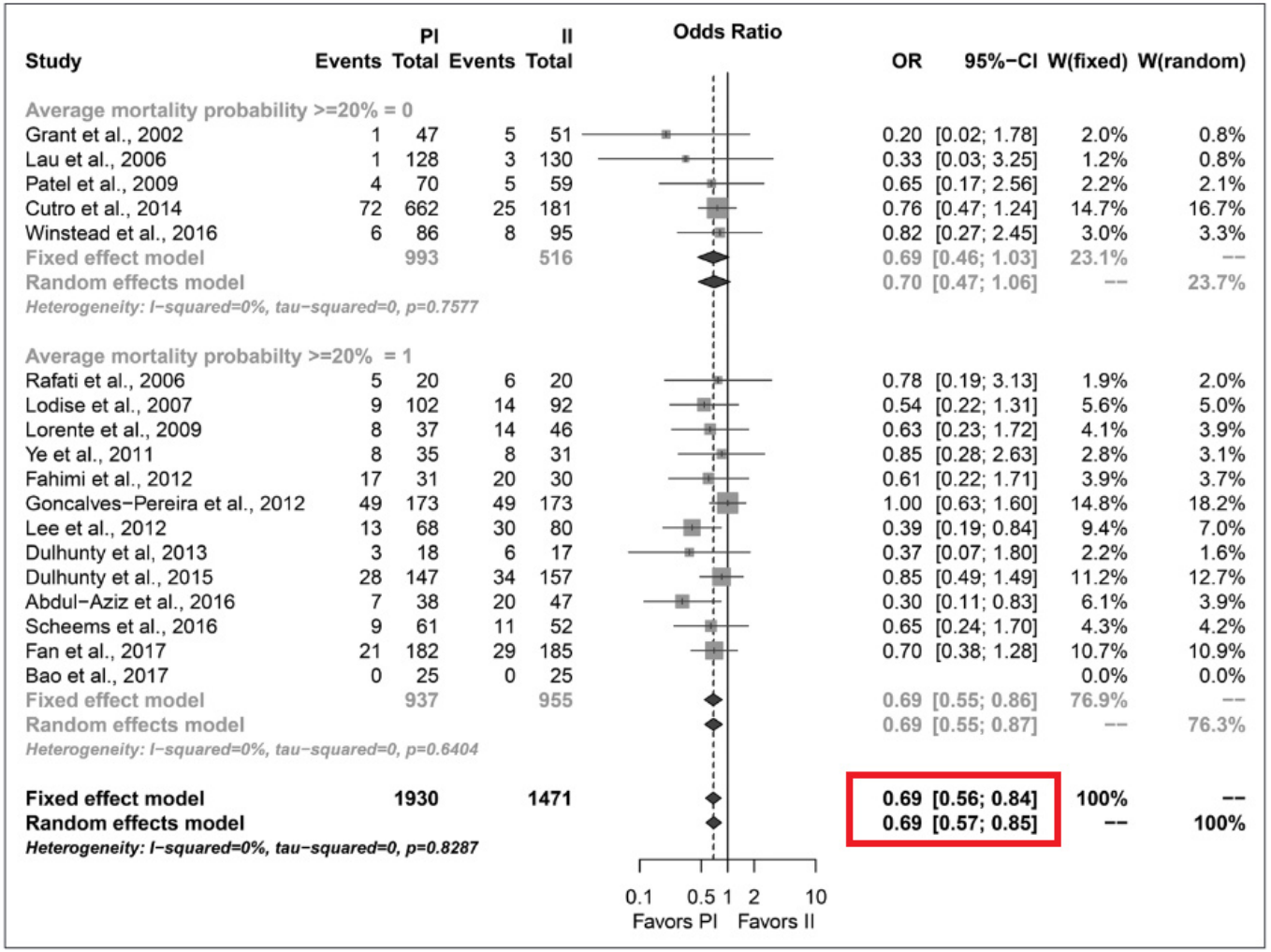


Figure 2. Meta-analyses of mortality benefit of piperacillin-tazobactam infusion scheme. II = intermittent infusion, OR = odds ratio, PI = prolonged infusion, tau-squared = between-study variance estimate, W = study weight in fixed- or random-effects model.

Pip/taz prolonged vs intermittent MA - mortality

Rhodes et al. Prolonged Infusion Piperacillin-Tazobactam Decreases Mortality and Improves Outcomes in Severely Ill Patients: Results of a Systematic Review and Meta-Analysis. Crit Care Med. 2018 Feb;46(2):236-243

Susceptible dose dependent

- Susceptibility of the isolate depends of the dosage regimen used
- **Higher dose** and more **frequent** dosing/**extended** needed to achieve a drug concentration that is effective
- Pip-taz for Enterobacterales:
- ≤8/4 µg/mL – susceptible
- ≤ 16/4 µg/mL – SDD
- ≥32/4 µg/mL - resistant

- Tamma et al. Breaking Down the Breakpoints: Rationale for the 2022 Clinical and Laboratory Standards Institute Revised Piperacillin-Tazobactam Breakpoints Against Enterobacterales. Clin Infect Dis. 2022 Aug 24:ciac688.

High dose, extended/cont. infusion – pip/taz

Interpretive Categories and MIC Breakpoints, µg/mL				Comments
S	SDD	I	R	
≤ 8/4	16/4		≥ 32/4	(21) Breakpoints for susceptible are based on a dosage regimen of 3.375-4.5 g administered every 6 h as a 30-minute infusion. Breakpoints for SDD are based on a dosage regimen of 4.5 g administered every 6 h as a 3-h infusion or 4.5 g administered every 8 h as a 4-h infusion.

Clinical and Laboratory Standards Institute (CLSI) 2022

Surviving Sepsis Campaign recommendation

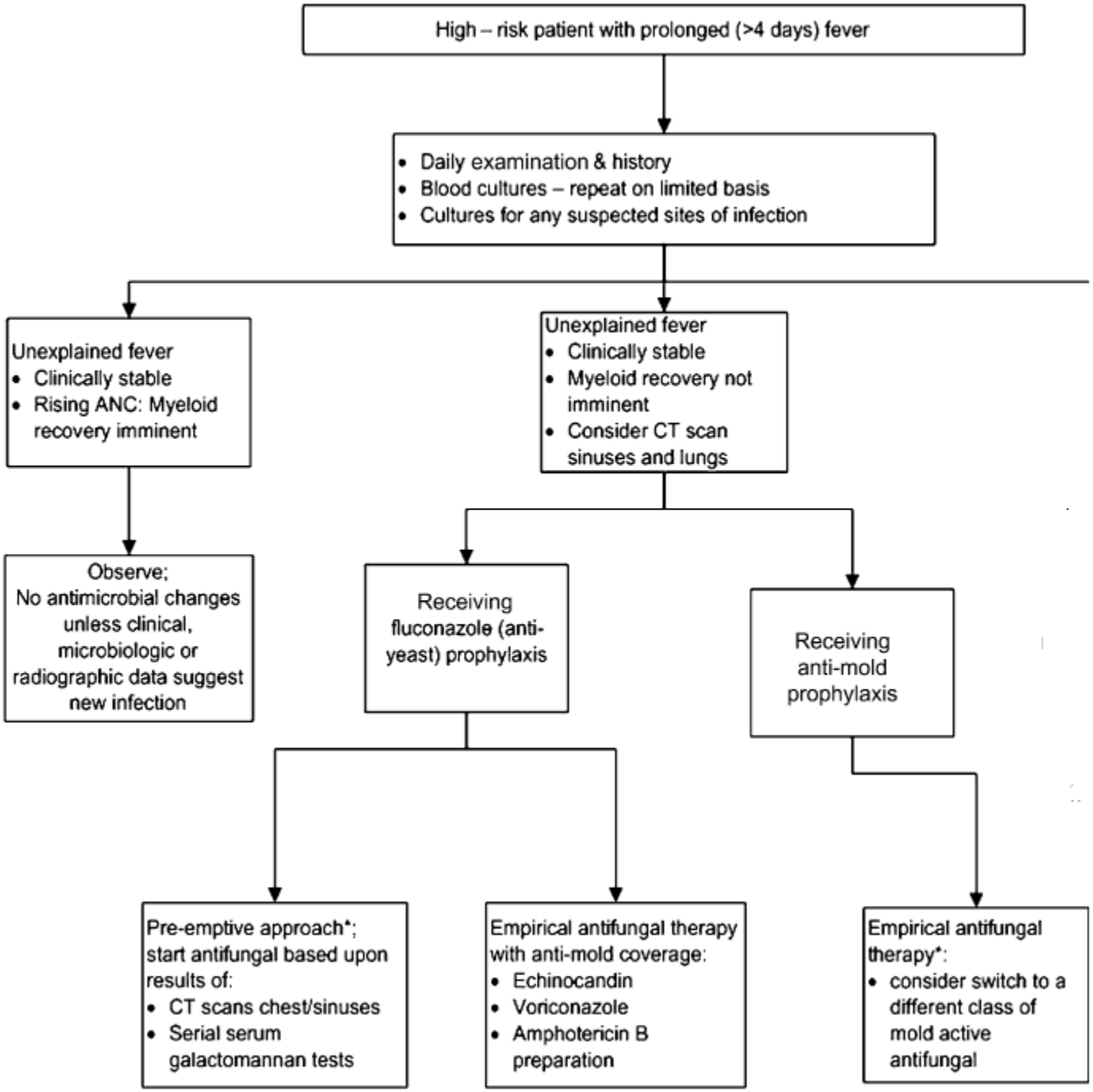
Delivery of Antibiotics

Recommendation
25. For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion.
Weak recommendation, moderate quality of evidence.

Evans et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Crit Care Med. 2021 Nov 1;49(11):e1063-e1143

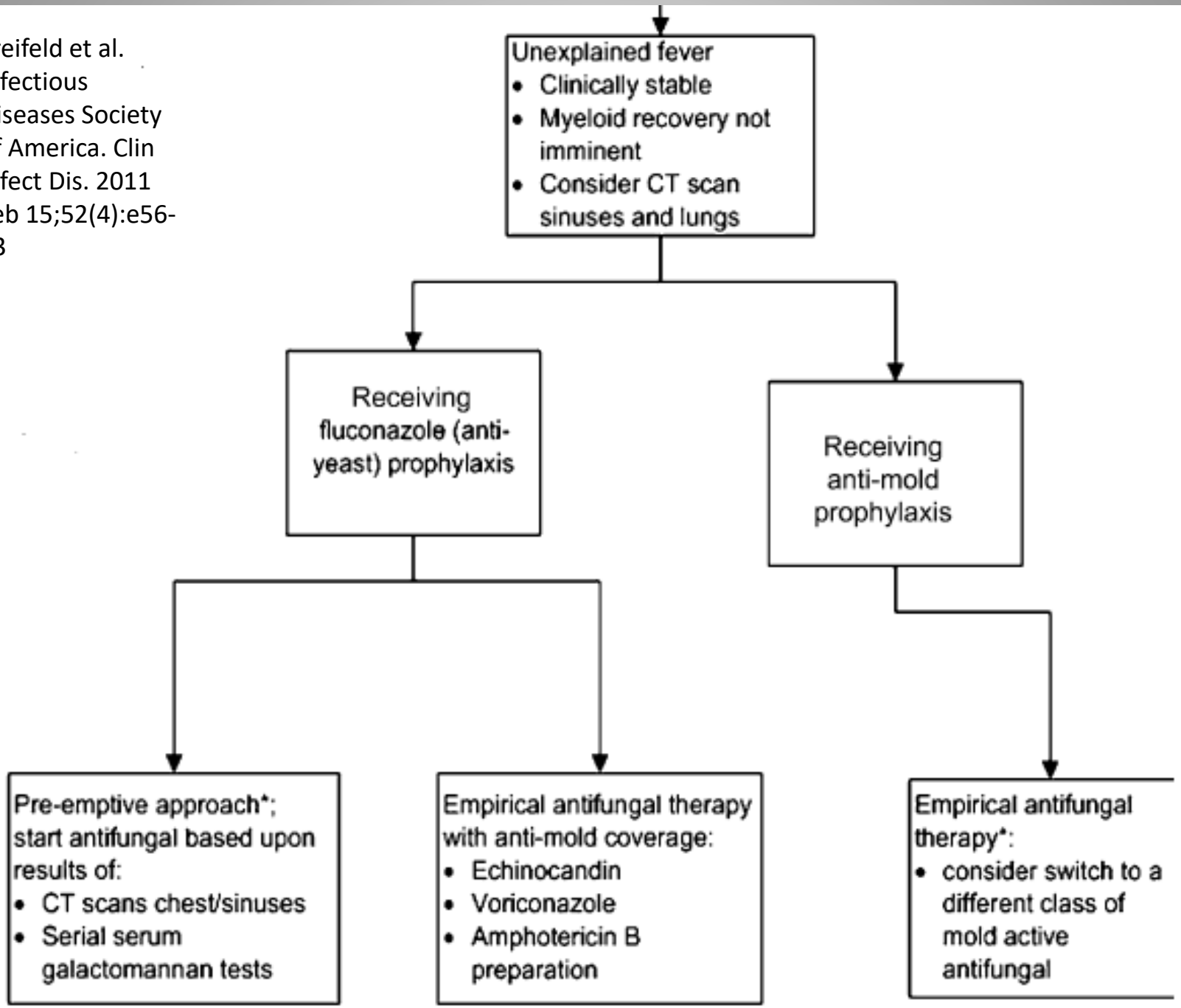
מקרה 3

- AML באינדוקציה
- תחת טיפול מונע בפלוקונזול-ציפרופלוקססין
- חום ניוטרופני ללא מקור, מטופל בטזוצין, יציב, נראה טוב
- תחת טזוצין החום נמשך
- לאחר 5 ימים ללא שינוי במצב החולה (עדיין חום, ניוטרופניה 0, יציב) – מה לעשות



Freifeld et al. Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Freifeld et al. Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):e56-93



Empirical anti-fungal

- If no antifungal prophylaxis -> Candida spp are the most likely
- If fluconazole prophylaxis -> C. glabrata and C. krusei or invasive mold infections, particularly Aspergillus spp
- If antimold prophylaxis -> change class

- Freifeld et al. Infectious Diseases Society of America. Clin Infect Dis. 2011 Feb 15;52(4):e56-93

Empirical anti-fungal

- → if no pulmonary nodules -> echinocandin
- → if pulmonary nodules -> BAL + antimold:
- Amphotericin (/liposomal) – aspergillus + mucor
- Posaconazole, isavuconazole - aspergillus + mucor
- Voriconazole – aspergillus

Empirical anti-fungal

- Echinocandin –
- Salvage therapy for aspergillus (higher failure compared to azoles/ampho)
- NO coverage for:
- Fusarium
- Cryptococcus, Trychosporon
- Not considered monotherapy for mucor

Empirical anti-fungal

- Monitor drug levels:
- Voriconazole (1-5.5, better 2-3)
- Posaconazole (>0.7 prophylaxis, >1 treatment)

Vori

Timing of first trough sample
After 2-5 days; (repeat sampling recommended)

Posa

Tablet/IV: after 3 days: Suspension: 5-7 days.*

ECIL-6. Triazole antifungal therapeutic drug monitoring. https://www.ecil-leukaemia.com/images/resources/2015/5_ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf

- Caspofungin – Loading dose of 70 mg IV on day 1, then 50 mg IV once daily
- Micafungin – 100 mg IV daily
- Anidulafungin – Loading dose of 200 mg on day 1, followed by 100 mg once daily
- Voriconazole – Loading dose of 6 mg/kg IV every 12 hours on day 1, followed by 4 mg/kg IV every 12 hours
- Isavuconazole – 200 mg (equivalent to isavuconazonium sulfate 372 mg) IV every 8 hours on days 1 and 2, then 200 mg once daily from day 3 onwards
- Posaconazole – 300 mg IV or PO BID on day 1, then 300 mg daily thereafter
- Amphotericin B lipid complex – 5 mg/kg IV once daily
- Liposomal amphotericin B – 3 to 5 mg/kg IV once daily

Pre-emptive therapy

- No empirical antifungal
- Serial screen :
- Galactomannan antigen
- High resolution chest CT
- If one of them positive -> empirical antifungal
- Best for patients on fluco prophylaxis

גלקטומנאן

- באופן כללי רגישות: 58-65%, ספציפיות: 65-95%
- בחולים המטואונקולוגים רגישות וספציפיות ~80% (pre test probability)
- פולס פוזיטיב:
- טזוצין
- פטריות אחרות (פניציליום, היסטופלזמה, פוסריום)

Pre-emptive vs empirical

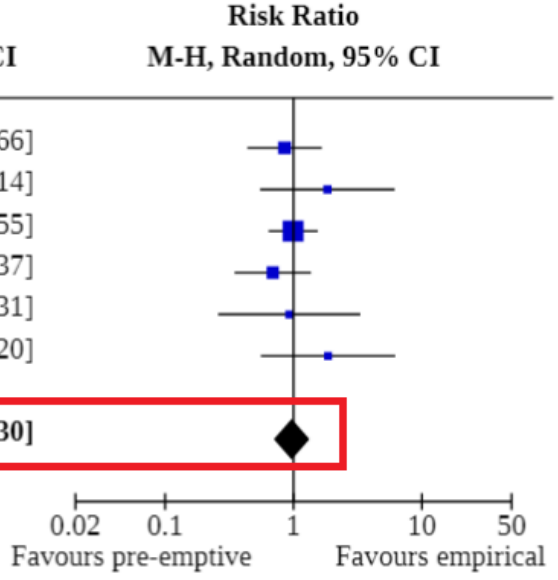
Analysis 1.1. Comparison 1: Pre-emptive versus empirical antifungal therapy, Outcome 1: All-cause mortality

Study or Subgroup	Pre-emptive Events	Pre-emptive Total	Empirical Events	Empirical Total	Weight	Risk Ratio M-H, Random, 95% CI
Aguado 2015	13	96	17	107	19.5%	0.85 [0.44 , 1.66]
Cordonnier 2009	7	143	4	150	6.0%	1.84 [0.55 , 6.14]
Hebart 2009 (1)	32	196	34	207	44.6%	0.99 [0.64 , 1.55]
Morrissey 2013	12	118	18	122	18.5%	0.69 [0.35 , 1.37]
Tan 2011	4	27	4	25	5.4%	0.93 [0.26 , 3.31]
Yuan 2016	7	130	4	138	6.0%	1.86 [0.56 , 6.20]
Total (95% CI)		**710**		**749**	**100.0%**	**0.97 [0.72 , 1.30]**
Total events:	75		81			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.31$, df = 5 (P = 0.65); $I^2 = 0\%$

Test for overall effect: Z = 0.22 (P = 0.82)

Test for subgroup differences: Not applicable



Uneno et al. Pre-emptive antifungal therapy versus empirical antifungal therapy for febrile neutropenia in people with cancer. Cochrane Database Syst Rev. 2022 Nov 28;11(11):CD013604

Pre-emptive vs empirical

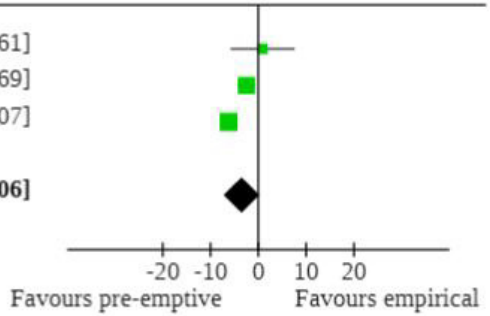
Analysis 1.4. Comparison 1: Pre-emptive versus empirical antifungal therapy, Outcome 4: Duration of antifungal use (days)

Study or Subgroup	Pre-emptive Mean	Pre-emptive SD	Pre-emptive Total	Empirical Mean	Empirical SD	Empirical Total	Weight	Mean Difference IV, Random, 95% CI
Aguado 2015	12.7	24.2	96	11.8	24.5	107	16.8%	0.90 [-5.81 , 7.61]
Cordonnier 2009	4.5	7.3	143	7	8.5	150	40.2%	-2.50 [-4.31 , -0.69]
Yuan 2016	13.8	4.7	130	20	4.7	138	43.1%	-6.20 [-7.33 , -5.07]
Total (95% CI)			**369**			**395**	**100.0%**	**-3.52 [-6.99 , -0.06]**

Heterogeneity: Tau² = 6.94; Chi² = 14.64, df = 2 (P = 0.0007); I² = 86%

Test for overall effect: Z = 1.99 (P = 0.05)

Test for subgroup differences: Not applicable



Uneno et al. Pre-emptive antifungal therapy versus empirical antifungal therapy for febrile neutropenia in people with cancer. Cochrane Database Syst Rev. 2022 Nov 28;11(11):CD013604

Pre-emptive vs empirical

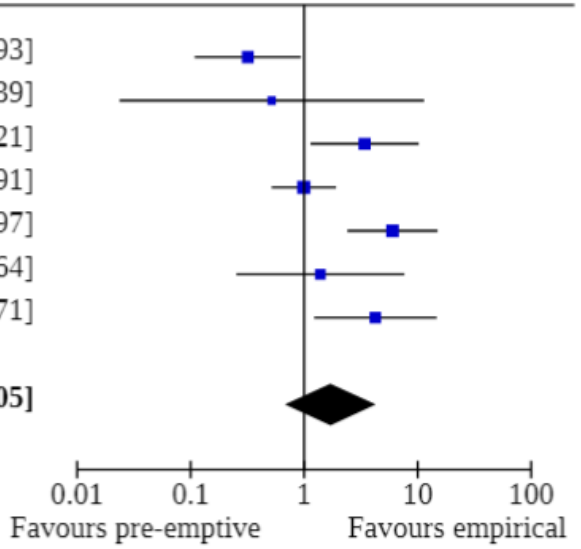
antifungal therapy, Outcome 5: Invasive fungal infection detection

Study or Subgroup	Pre-emptive Events	Pre-emptive Total	Empirical Events	Empirical Total	Weight	Risk Ratio M-H, Random, 95% CI
Aguado 2015	4	96	14	107	16.0%	0.32 [0.11 , 0.93]
Blennow 2010	0	8	1	13	5.8%	0.52 [0.02 , 11.39]
Cordonnier 2009	13	143	4	150	15.8%	3.41 [1.14 , 10.21]
Hebart 2009	16	196	17	207	18.9%	0.99 [0.52 , 1.91]
Morrissey 2013	29	118	5	122	17.1%	6.00 [2.40 , 14.97]
Tan 2011	3	27	2	25	11.7%	1.39 [0.25 , 7.64]
Yuan 2016	12	130	3	138	14.8%	4.25 [1.23 , 14.71]
Total (95% CI)		**718**		**762**	**100.0%**	**1.70 [0.71 , 4.05]**
Total events:	77		46			

Heterogeneity: $Tau^2 = 0.93$; $Chi^2 = 23.54$, df = 6 (P = 0.0006); $I^2 = 75\%$

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable



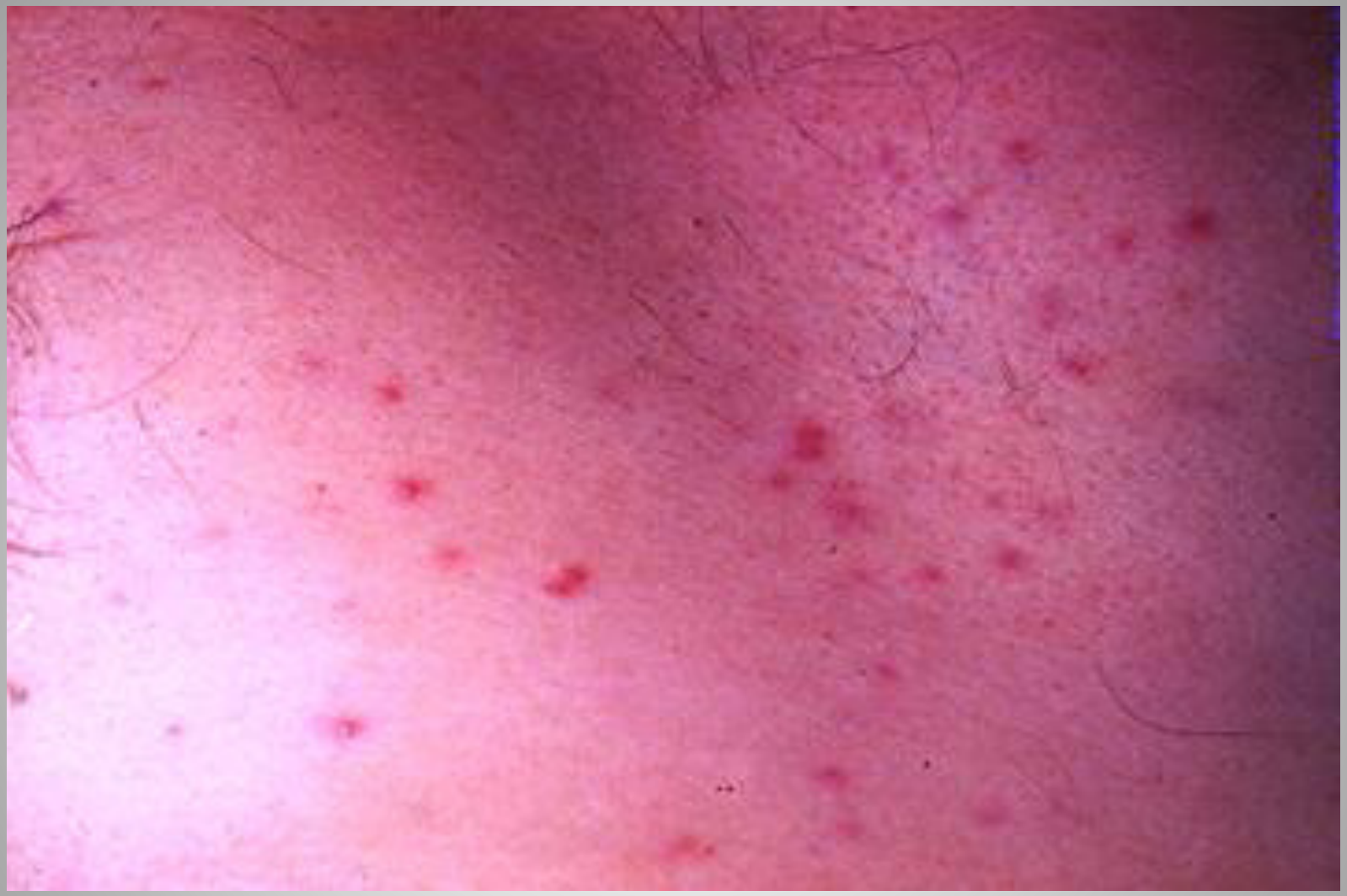
Uneno et al. Pre-emptive antifungal therapy versus empirical antifungal therapy for febrile neutropenia in people with cancer. Cochrane Database Syst Rev. 2022 Nov 28;11(11):CD013604

מקרה 3 - המשך

- CT חזה-סינוסים תקין, גלקטומנאן שלילי
- ללא טיפול אנטיפונגלי מעבר לפלוקונזול
- בימים הבאים החום ירד
- המשיך טזוצין 5 ימים נוספים ללא חום ואז -
- Breakthrough fever
- ירידת לחצי דם, כאבי שרירים
- ?

מקרה 4

- טיפול? בירור?
- טופל במרופנם, ונקו ואנידולפונגין
- בירור – בדיקה גופנית
- בבדיקה פריחה
- בירור – תרביות דם, דגימה של הפריחה למיקרוביולוגיה ופתולוגיה



אבחנה מבדלת

- זיהום חיידקי מפושט
- זיהום מיקובקטריאלי
- נוקרדיה
- זיהום בשמרים – קנדידה או קריפטוקוק
- זיהום עובשי מפושט (פוסריום)
- לוקמיה קוטיס


628310638

מקרה 4

- למחרת הודעה על צמיחה של שמרים בדם
- בדיקת פונדוס: חשד לרטיניטיס
- אקו לב: Mild-moderate LV dysfunction, באבחנה מבדלת קנדידה מיוקרדיטיס

Invasive candidiasis

- Invasive candidiasis = candidemia or deep-seated tissue candidiasis
- The most common fungal disease in hospitalized
- 40% mortality, even with antifungals
- Candidemia - the more common type of disease
- Deep-seated candidiasis - arises from either hematogenous dissemination or direct inoculation of candida species to a sterile site, such as the peritoneal cavity

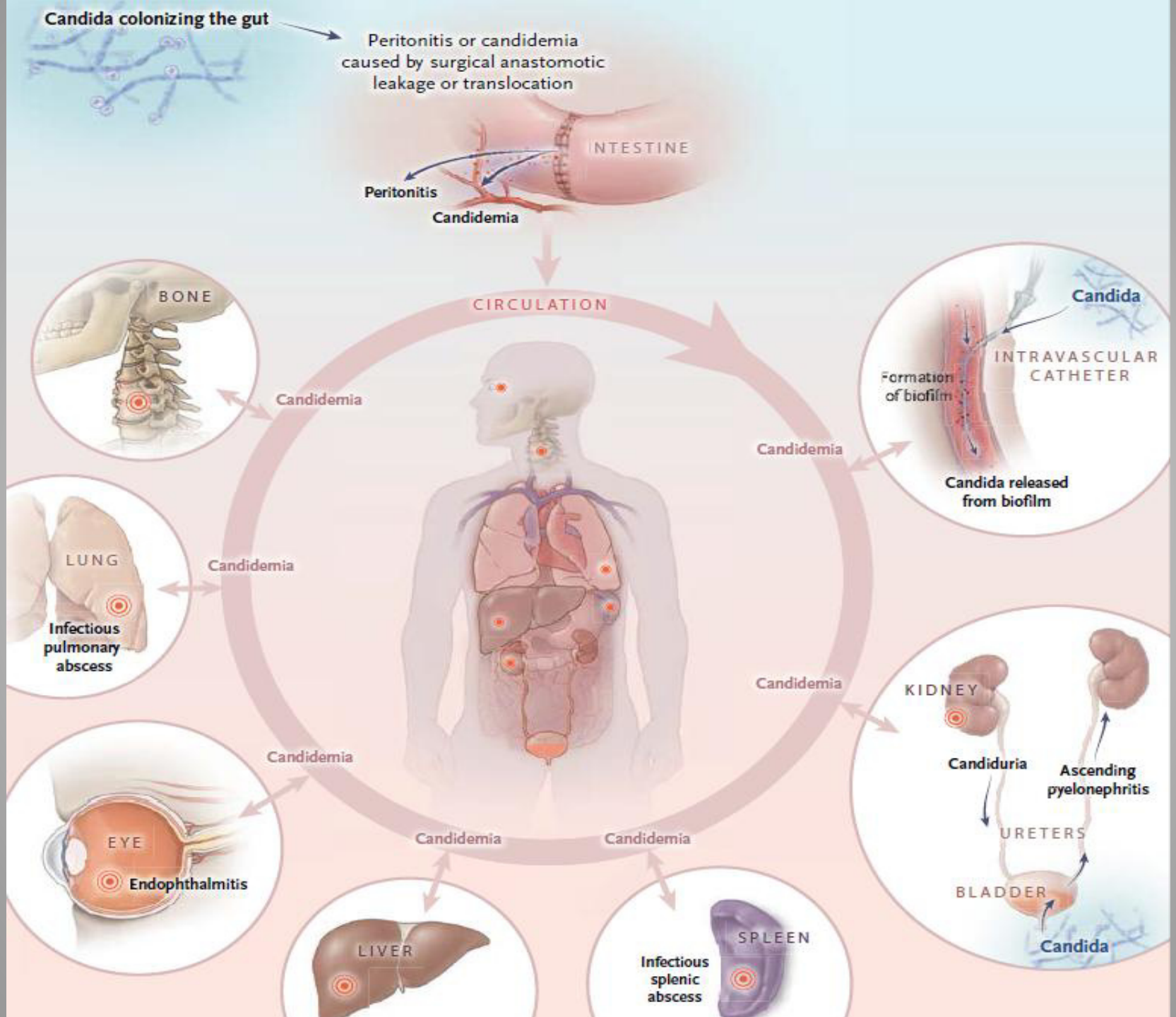

Candida colonizing the gut
Peritonitis or candidemia caused by surgical anastomotic leakage or translocation
INTESTINE
Peritonitis
Candidemia
CIRCULATION
BONE
Candidemia
Candida
INTRAVASCULAR CATHETER
Formation of biofilm
Candida released from biofilm
Candidemia
LUNG
Candidemia
Infectious pulmonary abscess
Candidemia
KIDNEY
Candiduria
Ascending pyelonephritis
URETERS
BLADDER
Candida
Candidemia
EYE
Endophthalmitis
Candidemia
Candidemia
LIVER
SPLEEN
Infectious splenic abscess

Table 1. Risk Factors for Invasive Candidiasis.*

Critical illness, with particular risk among patients with long-term ICU stay
Abdominal surgery, with particular risk among patients who have anastomotic leakage or have had repeat laparotomies
Acute necrotizing pancreatitis
Hematologic malignant disease
Solid-organ transplantation
Solid-organ tumors
Neonates, particularly those with low birth weight, and preterm infants
Use of broad-spectrum antibiotics
Presence of central vascular catheter, total parenteral nutrition
Hemodialysis
Glucocorticoid use or chemotherapy for cancer
Candida colonization, particularly if multifocal (colonization index >0.5 or corrected colonization index >0.4)

* ICU denotes intensive care unit. For further information see Cleveland et al.,[2] Arendrup et al.,[6] and Lortholary et al.[7]

Susceptibilities

- *C. albicans* –
- Only **1.5%** resistance to fluconazole
- Most susceptible to the echinocandins, although resistance has been reported
- Vast majority susceptible to AmpB

C. krusei

- Intrinsically resistant to fluconazole
- Higher rates of susceptibility for vori
- Usually susceptible to posaconazole, echinaocandins
- Decreased susceptibility to amphotericin B, requiring higher doses (1 mg/kg daily of AmpB or 5 mg/kg daily of lipid-based formulations)
- Usually resistant to flucytosine

General patterns of susceptibility of *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Echinocandins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R*
Candida glabrata	S-DD to R	S-DD to R	S to R	S to R	S	S to I	S to R*
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S

C. glabrata

- **Many** isolates are resistant to the **azoles**
- **Cross-resistance** among the azoles is common
- Isolates that are resistant to fluconazole are generally resistant to voriconazole as well
- Echinocandin resistance **~5-10%**
- Decreased susceptibility to amphotericin B, requiring higher doses

General patterns of susceptibility of *Candida* species

Species	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Flucytosine	Amphotericin B	Echinocandins
Candida albicans	S	S	S	S	S	S	S
Candida tropicalis	S	S	S	S	S	S	S
Candida parapsilosis	S	S	S	S	S	S	S to R*
Candida glabrata	S-DD to R	S-DD to R	S to R	S to R	S	S to I	S to R*
Candida krusei	R	S-DD to R	S	S	I to R	S to I	S
Candida lusitaniae	S	S	S	S	S	S to R	S

C. parapsilosis

- Highly susceptible to most antifungal agents
- The MICs for all the echinocandins are higher than for other species
- Clinical significance unknown

הנחיות לטיפול בקנדידמיה

- אכינוקנדין
- אפשר פלוקונזול כשהחולה יציב ואין חשד לקנדידה עמידה
- הוצאת ליין בהקדם
(ניוטרופנים – לא חובה)
- ת.ד מדי יום-יומיים
- פונדוס (בניוטרופנים – לאחר ניוטרופניה)
- אקו לב

I. What Is the Treatment for Candidemia in Nonneutropenic Patients?

Recommendations

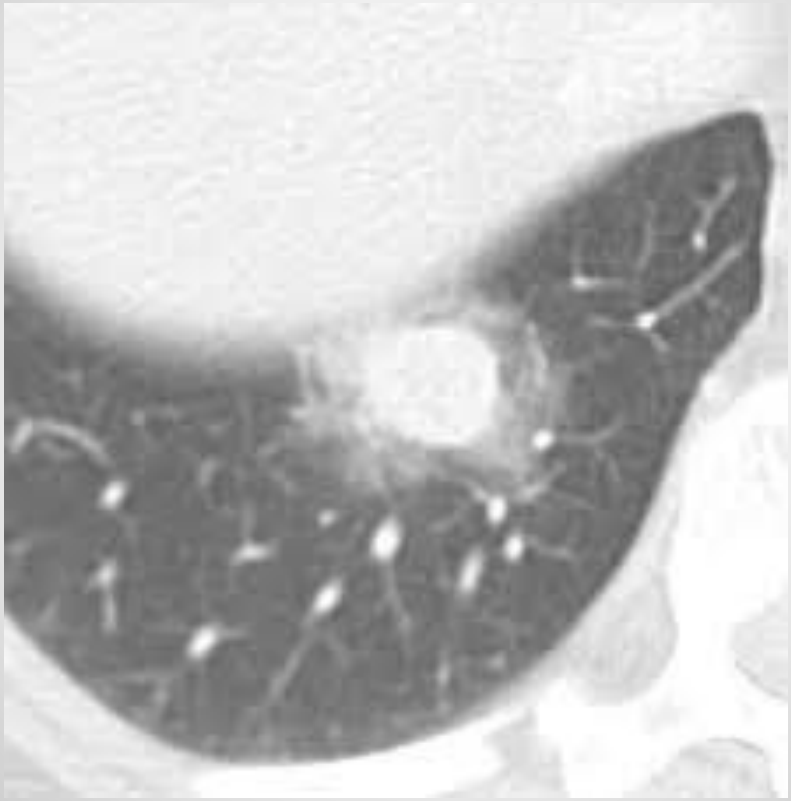
1. An echinocandin (caspofungin: loading dose 70 mg, then 50 mg daily; micafungin: 100 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily) is recommended as initial therapy *(strong recommendation; high-quality evidence).*
2. Fluconazole, intravenous or oral, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative to an echinocandin as initial therapy in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species *(strong recommendation; high-quality evidence).*

Pappas et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases

מקרה 4

- אינדוקציה לAML
- ניוטרופניה עמוקה וממושכת של שבועיים
- חום ללא תגובה לכיסוי אנטיביוטי רחב טווח
- מעל 4 ימים:
- הדמית חזה-סינוסים:

CT



Invasive aspergillosis

- Bronchoscopy – culture, GM
- IDSA guidelines: “We recommend performing a bronchoscopy with BAL in patients with a suspicion of IPA (strong recommendation; moderate-quality evidence)

Proven IA

Table 1. Criteria for Proven Invasive Fungal Disease

Fungus	Microscopic Analysis: Sterile Material	Culture: Sterile Material	Blood	Serology	Tissue Nucleic Acid Diagnosis
Molds[a]	Histopathologic, cytopathologic, or direct microscopic examination[b] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage	Recovery of a hyaline or pigmented mold by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process, excluding BAL fluid, a paranasal or mastoid sinus cavity specimen, and urine	Blood culture that yields a mold[c] (eg, *Fusarium* species) in the context of a compatible infectious disease process	Not applicable	Amplification of fungal DNA by PCR combined with DNA sequencing when molds are seen in formalin-fixed paraffin-embedded tissue
Yeasts[a]	Histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or biopsy from a normally sterile site (other than mucous membranes) showing yeast cells, for example, *Cryptococcus* species indicating encapsulated budding yeasts or *Candida* species showing pseudohyphae or true hyphae[d]	Recovery of a yeast by culture of a sample obtained by a sterile procedure (including a freshly placed [<24 hours ago] drain) from a normally sterile site showing a clinical or radiological abnormality consistent with an infectious disease process	Blood culture that yields yeast (eg, *Cryptococcus* or *Candida* species) or yeast-like fungi (eg, *Trichosporon* species)	Cryptococcal antigen in cerebrospinal fluid or blood confirms cryptococcosis	Amplification of fungal DNA by PCR combined with DNA sequencing when yeasts are seen in formalin-fixed paraffin-embedded tissue

Table 2. Probable Invasive Pulmonary Mold Diseases

Host factors
Recent history of neutropenia (<0.5 × 10^9 neutrophils/L [<500 neutrophils/mm^3] for >10 days) temporally related to the onset of invasive fungal disease
Hematologic malignancy[a]
Receipt of an allogeneic stem cell transplant
Receipt of a solid organ transplant
Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a therapeutic dose of ≥0.3 mg/kg corticosteroids for ≥3 weeks in the past 60 days
Treatment with other recognized T-cell immunosuppressants, such as calcineurin inhibitors, tumor necrosis factor-a blockers, lymphocyte-specific monoclonal antibodies, immunosuppressive nucleoside analogues during the past 90 days
Treatment with recognized B-cell immunosuppressants, such as Bruton's tyrosine kinase inhibitors, eg, ibrutinib
Inherited severe immunodeficiency (such as chronic granulomatous disease, STAT 3 deficiency, or severe combined immunodeficiency)
Acute graft-versus-host disease grade III or IV involving the gut, lungs, or liver that is refractory to first-line treatment with steroids

Diagnosis of IA – clinical

Clinical features
Pulmonary aspergillosis
The presence of 1 of the following 4 patterns on CT:
Dense, well-circumscribed lesions(s) with or without a halo sign
Air crescent sign
Cavity
Wedge-shaped and segmental or lobar consolidation
Other pulmonary mold diseases
As for pulmonary aspergillosis but also including a reverse halo sign
Tracheobronchitis
Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis
Sino-nasal diseases
Acute localized pain (including pain radiating to the eye)
Nasal ulcer with black eschar
Extension from the paranasal sinus across bony barriers, including into the orbit
Central nervous system infection
1 of the following 2 signs:
Focal lesions on imaging
Meningeal enhancement on magnetic resonance imaging or CT

Diagnosis of IA – microbiological

- Culture or microscopic detection of fungal elements
- Galactomannan (serum/plasma, BAL, CSF)
- PCR x 2 (serum/plasma, BAL)

Invasive pulmonary aspergillosis – therapy

Primary	Alternative
llus	
Voriconazole (6 mg/kg IV every 12 h for 1 d, followed by 4 mg/kg IV every 12 h; oral therapy can be used at 200–300 mg every 12 h or weight based dosing on a mg/kg basis); see text for pediatric dosing	Primary: Liposomal AmB (3–5 mg/kg/day IV), isavuconazole 200 mg every 8 h for 6 doses, then 200 mg daily Salvage: ABLC (5 mg/kg/day IV), caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), micafungin (100–150 mg/day IV), posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, itraconazole suspension (200 mg PO every 12 h)

Primary regimen

- Voriconazole (Herbrecht et al. Voriconazole versus amphotericin B for primary therapy of IA. NewEngl J Med 2002; 347: 407–15)
- Liposomal AmpB
- Isavuconazole (Maertens et al. Isavuconazole versus phase 3, randomised-controlled, non-inferiority trial. Lancet 2016; voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a 387: 760–9)
- Posaconazole (Maertens et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet 2021; 397: 499–509)
- Voriconazole + anidulafungin (Marr et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial.Ann InternMed 2015; 162: 81–9)

Voriconazole AEs

- Transient visual disturbances
- Hepatotoxicity, which may be dose limiting (elevated serum bilirubin, alkaline phosphatase, and hepatic aminotransferase enzyme levels)
- Skin rash, erythroderma, photosensitivity, and perioral excoriations;
- GI - nausea, vomiting, and diarrhea
- Visual or auditory hallucinations
- Cardiovascular events including tachyarrhythmias and QT interval prolongations
- Periostitis
- Squamous cell skin cancer or melanoma

	Enzyme/ transporter inhibition*
Fluconazole	CYPs 2C19 (strong), 2C9 (moderate), 3A4 (moderate; more consistently observed with fluconazole ≥200 mg/day)
Isavuconazole (formulated as prodrug isavuconazonium sulfate)	CYP3A4 (moderate); P-gp efflux (weak to moderate)
Itraconazole	CYP3A4 (strong); P-gp efflux
Posaconazole	CYP3A4 (strong); P-gp efflux
Voriconazole	CYP2C19 (moderate); 3A4 (strong)

All prolong QT, except isavuconazole

Table 2. Commonly Encountered Drug–Drug Interactions During Treatment of Aspergillosis

Agent/Class	Interaction	Comment
CNI and mTOR inhibitor immunosuppressive agents	Significant increase in CNI levels by azole	CNI and mTOR agents should be reduced (approximately 30%–50% for CNI and greater for rapamycin) at the time of initiating azole therapy and serum levels for both agents monitored until steady state is reached. Stopping of CNI or mTOR may provoke graft rejection.
Corticosteroids	Levels are increased by azoles	May exacerbate immunosuppression favorable for fungal growth. Prolonged coadministration may elicit signs of excessive steroid exposure.
Antiretroviral agents for HIV	Variable effects	Frequently used in combination with other classes of agents; monitoring of azole levels recommended, and bidirectional drug–drug interactions common.
Rifampin/rifabutin	Decreased levels of azole agents while rifampin/rifabutin levels are increased	Combined use of voriconazole, posaconazole, isavuconazole, or itraconazole with rifampin/rifabutin should generally be avoided. Some combinations are considered contraindicated; others may be managed by TDM and dose adjustment.
Agents that cause QTc interval prolongation (fluoroquinolone and macrolide antimicrobials, quinine, quinidine, digoxin, amiodarone and other antiarrhythmic drugs, calcium channel blockers, psychiatric drugs, antihistamines, and other agents)	QT interval prolongation, torsades de pointes, and other cardiac arrhythmias have been observed with azoles in combination with other agents or preexisting conditions that have these effects	Assess risk benefit and administer with caution to patients with cardiac disorders that increase the risk of arrhythmias.
Vincristine and other vinca alkaloid agents	Neurotoxicity including peripheral neuropathy and seizures in combination with azoles; azole levels also increased	Given the potential for serious toxicity, vincristine and other vinca alkaloids should generally not be coadministered with mold-active azoles. Alternative antifungal therapy (eg, amphotericin B formulation or echinocandin) should be used.
Cyclophosphamide	Increased levels with coadministration of some azoles	Increased renal, hepatic, or genitourinary dysfunction

High risk of QTc prolongation						
Arsenic trioxide	Ivosidenib	Ribociclib	Toremifene*			
Imatinib	Nilotinib	Thiotepa	Vandetanib			
Moderate risk of QTc prolongation						
Abirateron	Capecitabine	Encorafenib	Ixazomib	Pralatrexate	Talazoparib	Dolasetron*
Aflibercept	Ceritinib	Eribulin	Lapatinib*	Romidepsin	Tegafur	Domperidone*
Apalutamide	Cladribine	Enzalutamide	Melphalan	Rucaparib	Tivozanib	Ondansetron*
Axitinib	Crizotinib	5-Fluorouracil	Nilutamide	Selpercatinib*	Trifluridine	
Avapritinib	Darolutamide	Flutamide	Osimertinib	Sorafenib	Vemurafenib	
Bicalutamide	Dasatinib	Gilteritinib	Panobinostat	Sotorasib		
Cabozantinib*	Duvelisib	Glasdegib*	Pazopanib	Sunitinib*		

Giraud et al. The QT interval prolongation potential of anticancer and supportive drugs: a comprehensive overview. Lancet Oncol 2022; 23: e406–15

https://crediblemeds.org/

	Itraconazole	Posaconazole	Voriconazole	Isavuconazole
Acalabrutinib	Avoid or reduce the dose of acalabrutinib to 100 mg/day			No dose titration. Monitor adverse effects
Bortezomib	Caution (1)			Probably without risk
Bosutinib	Avoid. Risk of QT prolongation due to elevated bosutinib concentrations			Caution. (2) Reduce the dose by 50%
Carfilzomib	Caution. Risk of QT prolongation			Without risk
Cyclophosphamide	Caution: May increase cyclophosphamide levels with potential risk of QT prolongation			Risk of potential ineffectiveness (3)
Cyclosporine	Caution. Elevated cyclosporine levels	Reduce cyclosporine dose by 75%	Reduce cyclosporine dose by 50 %	Caution (4)
Dasatinib	Avoid. Risk of QT prolongation due to elevated dasatinib concentrations			No dose titration. Monitor adverse effects
Doxorubicin	No dose titration. Monitor adverse effects			
Duvelisib	Reduce duvelisib dose to 15 mg twice daily			No dose titration. Monitor adverse effects
Etoposide	No dose titration. Monitor adverse effects			
Gilteritinib	Avoid or closely monitor			No dose titration. Monitor adverse effects
Glasdegib	Avoid. Risk of QT prolongation due to elevated glasdegib concentrations			Without risk
Ibrutinib	Avoid	Caution (5)		Caution (6)
Idelalisib	Without risk			
Imatinib	Caution (7)			
Lenalidomide	No dose titration. Monitor adverse effects (8)			No dose titration
Midostaurin	Caution. Alternative drugs that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.			Monitor adverse effects
Nilotinib	The administration of nilotinib with drugs that are strong CYP3A4 inhibitors should be avoided (9)			No dose titration. Monitor adverse effects
Oxaliplatin	No dose titration. Monitor adverse effects (8)			No dose titration
Pomalidomide	No dose titration. Monitor adverse effects			
Ponatinib	Caution, consider reducing the starting dose of ponatinib to 30 mg			No dose titration. Monitor adverse effects
Prednisone	Caution (10)			Caution (11)
Ruxolitinib	Caution	Reduce ruxolitinib dose by 50%		No dose titration. Monitor adverse effects
Selinexor	No dose titration. Monitor adverse effects			
Sirolimus	Avoid			Caution (4)
tacrolimus	Caution (12)	Reduce tacrolimus dose by one third		Caution (4)
All-transretinoic acid	Caution (13)			No dose titration. Monitor adverse effects
Arsenic trioxide	Caution (8)			Without risk
Venetoclax	Avoid (14)			Reduce the daily dose by 50%
Vinblastine	Avoid	Caution (15)	Caution (16)	Caution (16)
Vincristine	Avoid	Caution (15)	Caution (16)	Caution (16)

Azanza et al. Recommendations on the use of azole antifungals in hematology-oncology patients. Revista Española de Quimioterapia 2023

Voriconazole TDM-guided dosing algorithm

voriconazole	dosage each 12 hrs (oral)			
trough level	200mg*	250mg*	300mg*	400mg*
<0,1mg/L	400mg	400mg	400mg	500mg
0.1-0.4mg/L	400mg	400mg	400mg	500mg
0.5-1mg/L	300mg	300mg	400mg	450mg
1-1,5mg/L	250mg	300mg	450mg	450mg
1.5-2mg/L	250mg	300mg	350mg	450mg
2-3.5mg/L	200mg	250mg	300mg	400mg
3.5-5mg/L	150mg	200mg	250mg	300mg
> 5mg/L	100mg	150mg	150mg	200mg

voriconazole	dosage each 12 hrs (intravenous)			
trough level	4mg/kg*	5mg/kg*	6mg/kg*	7mg/kg*
<0,1mg/L	6mg/kg	7mg/kg	8mg/kg	8,5mg/kg
0.1-0.4mg/L	6mg/kg	7mg/kg	8mg/kg	8,5mg/kg
0.5-1mg/L	5mg/kg	6mg/kg	7mg/kg	8mg/kg
1-1,5mg/L	5mg/kg	6mg/kg	7mg/kg	8mg/kg
1.5-2mg/L	4,5mg/kg	5,5mg/kg	6,5mg/kg	7,5mg/kg
2-3.5mg/L	4mg/kg	5mg/kg	5mg/kg	6mg/kg
3.5-5mg/L	3mg/kg	4mg/kg	4mg/kg	5mg/kg
> 5mg/L	2mg/kg	3mg/kg	3mg/kg	4mg/kg

* = dosage given to patient at time of concentration measurement

ECIL-6. Triazole antifungal therapeutic drug monitoring. https://www.ecil-leukaemia.com/images/resources/2015/5_ECIL6-Triazole-TDM-07-12-2015-Lewis-R-et-al.pdf

Duration of treatment -IPA

- Minimum of 6–12 weeks
- Largely dependent on the degree and duration of immunosuppression and response
- For patients with successfully treated IPA who require subsequent immunosuppression, secondary prophylaxis should be initiated to prevent recurrence

Follow up

- Follow-up chest CT scan to assess response of IPA after a minimum of 2 weeks of treatment
- In neutropenic patients, pulmonary lesions usually increase in size during the first week following initiation of therapy and while the patient recovers from neutropenia
- The size of lesions can increase up to 4-fold during the first week and then remain stable for another week
- Serial monitoring of serum GM

I. Breakthrough IA on mould-active prophylaxis

- ~ **5%–10%** of patients on mould-active prophylaxis (posaconazole, other triazoles, micafungin) develop probable or proven IA
- Definition: after > **3 days** of therapy
- When suspecting breakthrough:
- 1 . Ensure adequate drug levels prior to stopping prophylaxis ->
- a. Low -> adjust
- b. Appropriate -> consider changing drug
- 2. Investigate for breakthrough
- Slavin et al. J Antimicrob Chemother 2022; 77: 16–23

Aggressive attempts to confirm the pathogen

Particularly if susp:

1. Mucormycosis
2. Triazole-resistant Aspergillus species
3. Rare mould with unpredictable susceptibility

- *Exclude other causes of infection or other non-infectious pathologies*

Table 1. Investigation of refractory or breakthrough infection

Investigation	Details
Serum/plasma or blood samples	GM
	β-d-glucan
	PCR
Therapeutic drug monitoring	Titrate drug dose to therapeutic levels
Fibreoptic bronchoscopy	BAL from infected lobe
	Biopsy lesion if practical
	Microscopy (using optical brighteners) and cytology
	Culture
	GM
	LFD
	PCR—positive samples can be tested further for the presence of genetic markers of resistance.
	Antifungal susceptibility on positive cultures
CT-guided biopsy or biopsy of peripheral lesion	Microscopy
	Culture
	Antifungal susceptibility on positive cultures
	Non-culture methods of identification (tissue-based molecular sequencing, immunohistochemistry, cytology)

BAL, bronchoalveolar lavage; GM, galactomannan; LFD, lateral flow device.

Slavin et al. J Antimicrob Chemother 2022; 77: 16–23

Mucormycosis suspected

- Pleural effusion
- More than 10 nodules
- Reversed halo signs
- Concomitant sinusitis
- Voriconazole prophylaxis

- Chamilos et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis. 2005;41(1):60.

II. IA failing treatment with a triazole: ‘refractory disease’

- **~10%–15%** of patients receiving a triazole for primary therapy of acute IA might require a change due to inadequate response
- Primary therapy, with confirmed therapeutic drug levels, should be given for **at least 8 days** to show an effect
- Indications for change:
- **Rising serum GM ≥8d**
- **Radiological increase in size of the initial lesion ≥ 15d**
- **A lesion arising in a new site (clinically/radiologically) ≥8d**
- **Culture of a resistant organism**
- Slavin et al. J Antimicrob Chemother 2022; 77: 16–23

Table 2. Reasons for changing first-line antifungal treatment

Days since initiation of therapy		Clinical and diagnostic findings compared with baseline
At any time	1	Identification of a pathogen resistant to primary antifungal therapy
8 to 14		On the basis of changes in GM:
	2	(i) Serum: The serum GM index has not fallen by either 1 unit or to <0.5 units based on measurements taken at least 7 days apart (ii) BAL: Positive GM from BAL in a patient with a previous BAL test that did not meet the definition of positive (too low or entirely negative) without regard for the interval of time between samples. Note that there is not a definition for rising GM index values from BAL as these values are subject to sampling error
		Or
	3	Clinical deterioration consistent with persisting or progressive invasive fungal disease with no other identifiable aetiology
		Or
	4	New distinct site of infection detected clinically or radiologically
≥15		Any of the above criteria
		Or
	5	Progression of original lesions on CT (or other imaging) based on >25% growth of initial lesions in the context of no change in immune status

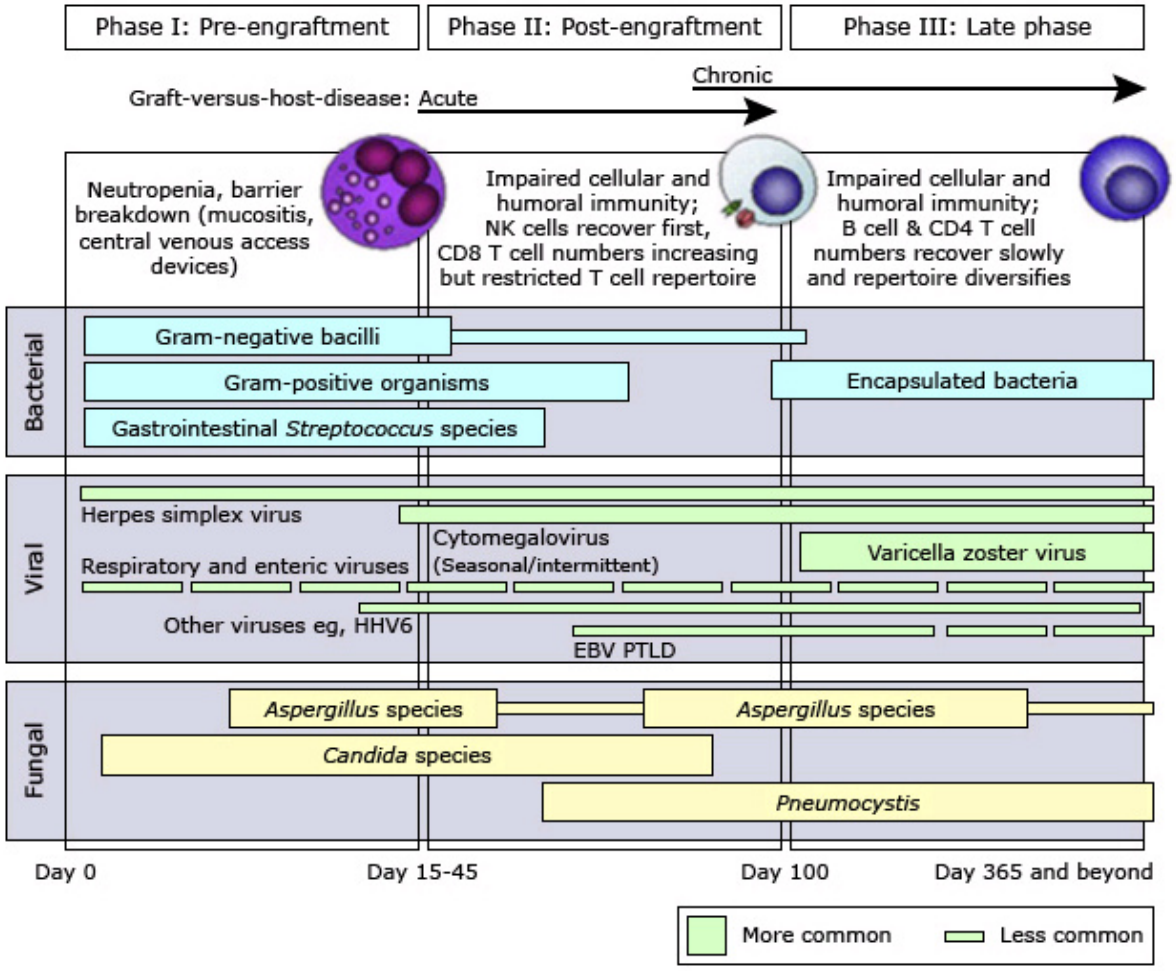
Slavin et al. J Antimicrob Chemother 2022; 77: 16–23

II. IA failing treatment with a triazole: ‘refractory disease’

- Change: from a triazole to LAmB
- In some cases, the addition of an echinocandin
- or a switch to another triazole
- might be considered if inadequate drug exposure was thought to be the reason for therapeutic failure
- Poorly responsive/progressive malignancy -> unlikely that change in antifungal therapy would improve the life expectancy

Infections in HSCT

Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients



EBV: Epstein-Barr virus; HHV6: human herpesvirus 6; PTLD: posttransplant lymphoproliferative disease.

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Allo-HSCT

Bacterial

- As in neutropenic fever in the pre-engraftment (extra-cellular bacteria)
- *Bacillus cereus* – rare, early after transplantation, can cause meningitis
- *Clostridium difficile* - Chemotherapy, antibiotics
- Prolonged hospitalization – MDR bacteria
- Late posttransplantation - encapsulated (pneumococc, haemophilus)

Bacterial special

- Post engraftment
- TB
- Non-tuberculous mycobacteria
- Nocardia

Fungal

- As in neutropenic fever in the pre-engraftment (candida, aspergillus)
- In patients with GVHD (glucocorticoids, other immunosuppressives) - high risk of fungal infection (candida or aspergillus) even after engraftment and resolution of neutropenia

Fungal

- PCP - prophylaxis trimethoprim-sulfamethoxazole (TMP-SMX) starting at engraftment and continuing for at least 1 year

- Some protection against toxoplasmna, *Listeria monocytogenes* and nocardia

Parasitic

- Toxoplasmosis – TMP-SMX prophylaxis for patients seropositive for *T. gondii*
- Toxo encephalitis (brain lesions)
- Pneumonia
- Day 60-150 post allo HSCT

Viral - herpesviruses

Virus	Reactivation Disease
Herpes simplex virus type 1	Oral lesions
	Esophageal lesions
	Pneumonia (primarily HSC transplant recipients)
	Hepatitis (rare)
Herpes simplex virus type 2	Anogenital lesions
	Hepatitis (rare)
Varicella-zoster virus	Zoster (can disseminate)
Cytomegalovirus	Associated with graft rejection
	Fever and malaise
	Bone marrow failure
	Pneumonitis
	Gastrointestinal disease
Epstein-Barr virus	B cell lymphoproliferative disease/lymphoma
	Oral hairy leukoplakia (rare)

Viral - herpesviruses

Human herpesvirus type 6	Fever
	Delayed monocyte/platelet engraftment
	Encephalitis (rare)
Human herpesvirus type 7	Undefined
Kaposi's sarcoma–associated virus	Kaposi's sarcoma
	Primary effusion lymphoma (rare)
	Multicentric Castleman's disease (rare)
	Marrow aplasia (rare)

Viral CMV

- CMV usually begins 30–90 days after HSC transplantation (14d-120d)
- Risk is different than in SOT – R+D- most risky
- CMV retinitis – common in HIV, not in transplanted patients
- Serious CMV disease (pneumonia) is much more common among allogeneic than autologous

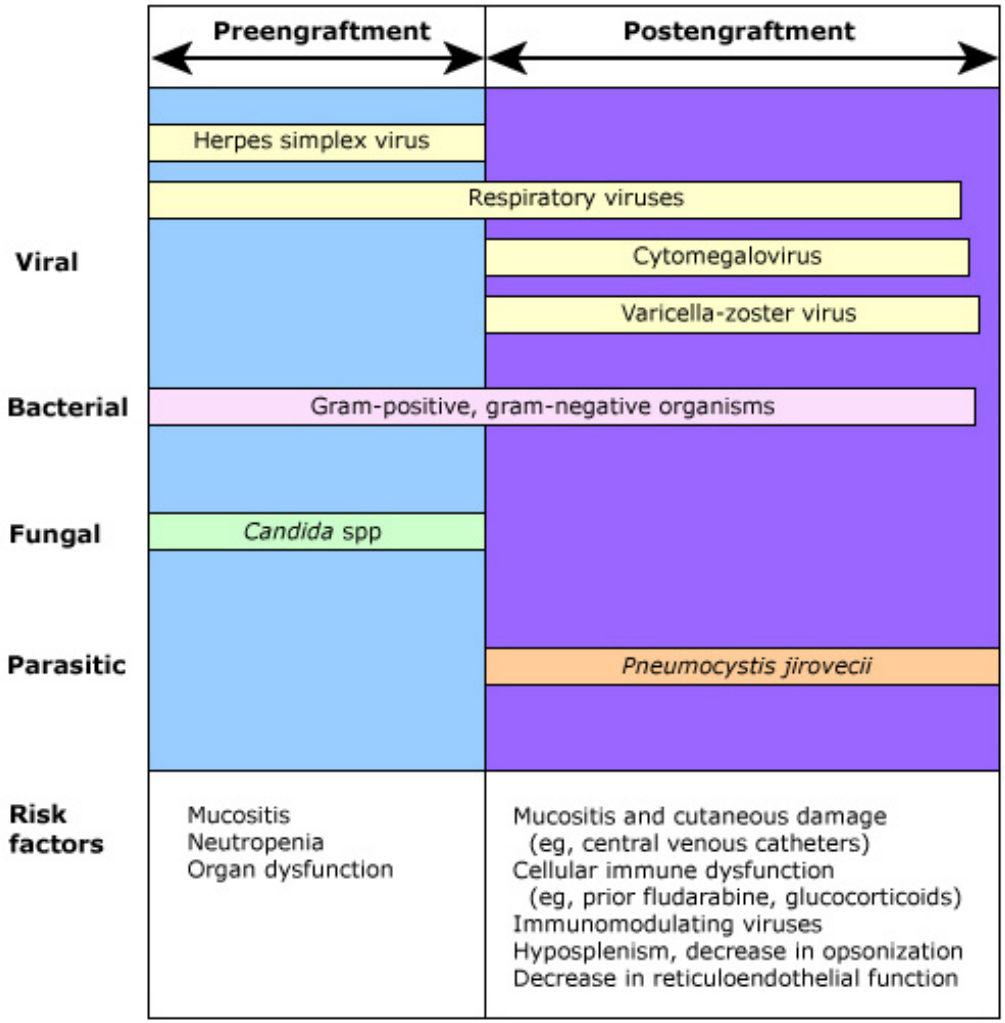
CMV - prevention

- Prophylaxis (engraftment to 120d)
- Ganciclovir/valganciclovir - dose-related bone marrow suppression
- Pre-emptive – PCR CMV – treat any positive value

EBV - PTLD

- Incidence among allogeneic HSC transplant recipients is 0.6–1%
- Can become apparent as early as 1–3 months after engraftment
- High fevers and cervical adenopathy (IMN), but more commonly - extranodal mass

Typical timing of infections among autologous hematopoietic cell recipients receiving antimicrobial prophylaxis

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Call!