Η σήψη στον ανοσοκατεσταλμένο* ασθενή

**ουδετεροπενικο αιματολογικό ασθενή*

Καρολίνα Ακινόσογλου

Παθολόγος-Λοιμωξιολόγος

Επικουρη Καθηγήτρια

Πανεπιστημίου Πατρών

Some facts : Sepsis in the severely immunocompromised patient

- Increased risk of infection by common pathogens and opportunistic infections
- Increased risk of developing systemic inflammatory response including sepsis and septic shock
- Paradoxically, in some patients like SOT recipients, prognosis may not be worse – perhaps even better

Kalil AC et al (Clin Infect Dis 2015; 60:216-22)
Jeddi et al Hematology. 2010 Feb;15(1):28-32
Legrand et al Critical Care Medicine, 2012, 40(1):43-49

Some facts : Sepsis in the severely immunocompromised patient

Severe and prolonged neutropenia

- Cytoablative chemotherapy (e.g induction chemotherapy for acute leukemia and lymphoreticular leukemias)
- Delayed bone marrow recovery following allogenic hematopoietic stem cell transplantation (HSCT)
- Solid organ transplantation

Non-Severe and Short neutropenia

- Neutropenia of short duration chemotherapy in many solid malignancies

- Low risk of systemic infection and sepsis
- Excellent short-term prognosis generally managed as outpatients

Frienfield et al Clin Infect Dis. 2011 Feb 15;52(4):e56-93
Klastersky et al 2016 Annals of Oncology 27 (Suppl 5): v111–v118
Taplitz et al 2018 J Clin Oncol. 2018 May 10;36(14):1443-1453

Risk factors associated with neutropenic sepsis

HIGH RISK

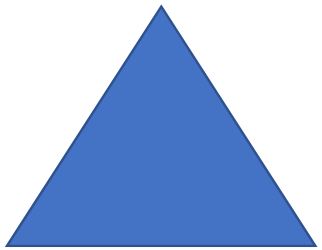
- Neutropenia (esp. if <500/µl)
- Duration > 7 days

- Acute leukemia
- Prolonged hospital stay
- Prior surgery
- Advanced disease
- Delay of ICU admission
- Hickman catheter
- Pre-treatment with antibiotics or chemotherapy

- Phosphate < 0.8 mmol/L),
- Protein < 62 g/L)
- Non-adapted antibiotic therapy

- Pneumonia
- Tachypnea
- PCT≥ 1.5 ng/Ml
- lactate> 3 mmol
- HCO3 < 17 mmol/L
- antithrombin (< 70%), or factor VIIa (<0.8 ng/mL)
- MASCC < 21

Infection / Bacteremia **Development of sepsis, severe sepsis & septic shock**



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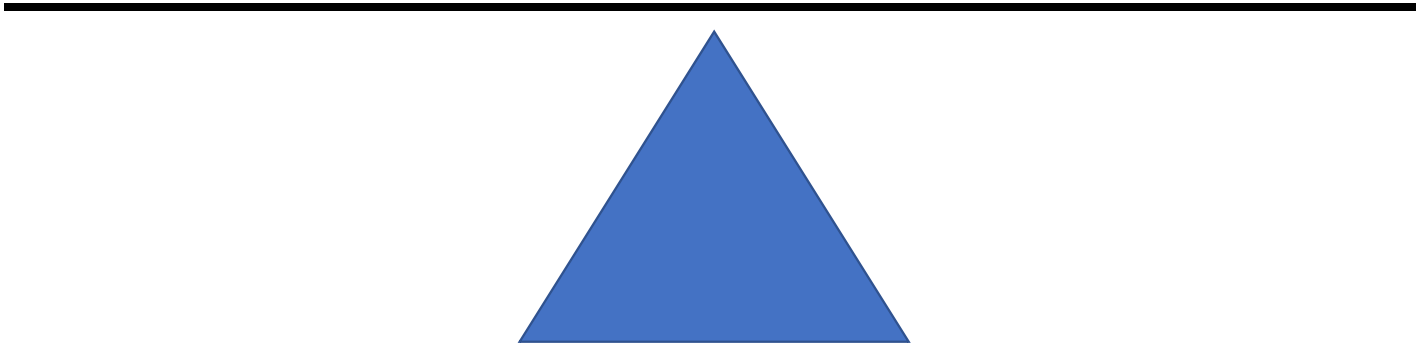
Bloodstream infection in hematological patients

- Incidence 20-60%
- Mortality 15-45%
- Appropriate empiric antibiotic is critical

- ↑ Resistance to antibiotics worldwide
- ↑ Use of broad-spectrum antibiotics
  ➔selection of carbapenem and multi drug resistant pathogens
- Fungal infections
- *Cl. Difficile* associated diarrhea



Risk factor for infection with MDR bacteria

- Patient's prior colonization or infection by resistant pathogens, particularly:
  - ESBL or carbapenemase – producing Enterobacteriaceae
  - Resistant non-fermenters *Acinetobacter, Pseudomonas, Stenotrophomonas*
  - MRSA, esp MIC>2mg/L
  - VRE
- Previous exposure to broad spectrum antibiotics, esp but not limited to 3rd gen cephalosporin
- Serious illness
- Nosocomial infection
- Prolonged hospital stay and/or repeated hospitalizations
- Urinary catheters
- Older age
- ICU

Averbruch et al Haematologica. 2013 Dec;98(12):1826-35.

Microbial resistance in hematology – oncology patients

Table II. National resistance rates, in percentage of invasive isolates, for *E. coli*, *K. pneumoniae* and *P. aeruginosa* in selected European countries 2013.

	Sweden %	United Kingdom %	Germany %	France %	Spain %	Italy %	Greece %
E. coli							
Quinolones	12	16	22	17	35	42	31
Third-generation cephalosporins	5	15	11	10	13	26	17
Carbapenems	<0·1	<0·1	0·1	0·1	0·7	0·6	1·4
K. pneumoniae							
Quinolones	4	9	15	29	22	54	68
Third-generation cephalosporins	4	14	16	28	20	55	70
Carbapenems	0	0·5	0·7	0·7	1·6	34	59
P. aeruginosa							
Quinolones	6	6	16	21	28	29	44
Piperacillin/tazobactam	7	5	18	15	9	31	30
Ceftazidime	7	4	10	12	9	24	28
Carbapenems	7	5	15	17	17	26	49

Created from data provided in ECDC (2014).

Br J Haematol. 2016 Feb;172(4):497-511.

Risk factors for blood stream infections mortality

TABLE 5. Analysis of Risk Factors for BSI Mortality

	Nonsurvivor	Survivor	Univariate	Multivariate	
	(n = 11)	(n = 74)	*P* Value	*P* Value	Relative Risk (95% CI)
Age, yr			0.45	/	/
≤35	5	46			
>35	6	28			
Gender			0.29	/	/
Male	7	39			
Female	4	35			
Type of BSI			0.053	0.69	/
Polymicrobial and/or secondary BSI	4	10			
Non	7	64			
Disease status			0.014	0.031	4.4 (1.306–20.800)
Standard risk	2	49			
High risk	9	25			
HSCT type			0.039	0.18	/
Autologous	0	22			
Allogenic	11	52			
Duration of neutropenia			<0.001	0.007	16.7 (4.81–58.00)
≤14 d	1	58			
≥15 d	10	16			
Drug resistance			<0.001	0.041	4.4 (1.14–17.28)
Non-MDR isolates	4	55			
Other MDR isolates	0	14			
Carbopenem-resistant MDR	7	5			

BSI = bloodstream infection; CI = confidence interval; HSCT = hematopoietic stem cell transplant; MDR = multiple drug resistance.

Medicine (Baltimore). 2015 Nov;94(45):e193

- **No significant pathophysiological differences between neutropenic and non-neutropenic patients**
- **qSOFA and SOFA score useful BUT**

(i) mental status may change independently.

(ii) Tumor-associated symptoms or complications can lead to neurological deficits

(iii) Platelet count cannot be used due to chemotherapy-associated or tumor-related thrombocytopenia,

(iv) chemotherapy-induced elevation of bilirubin and creatinine may influence the SOFA score calculation.

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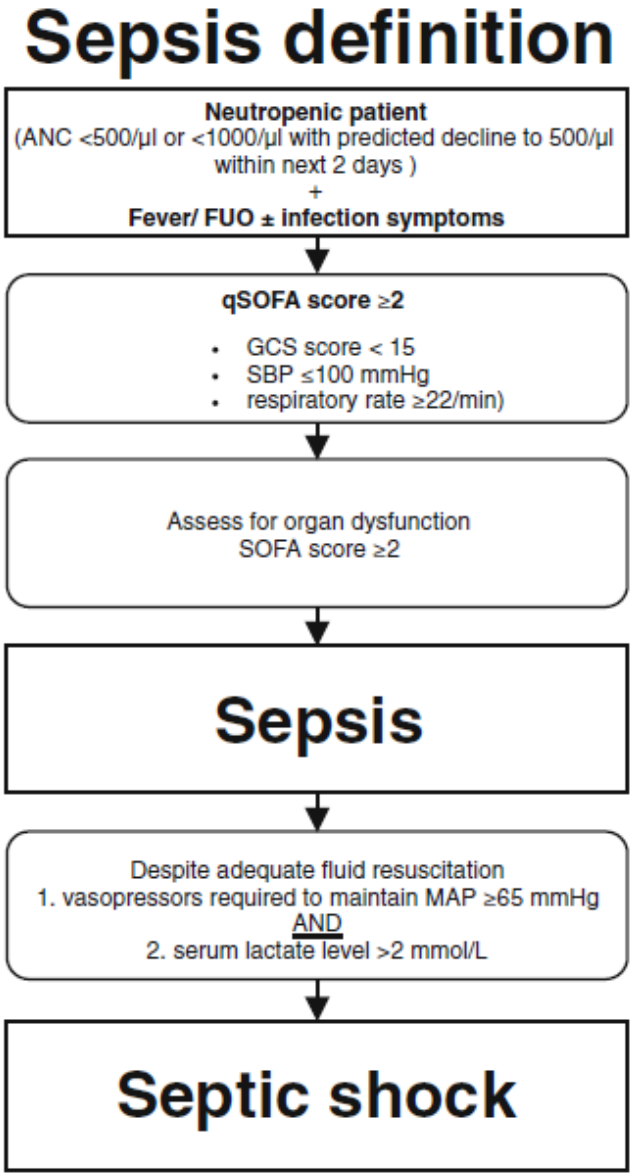

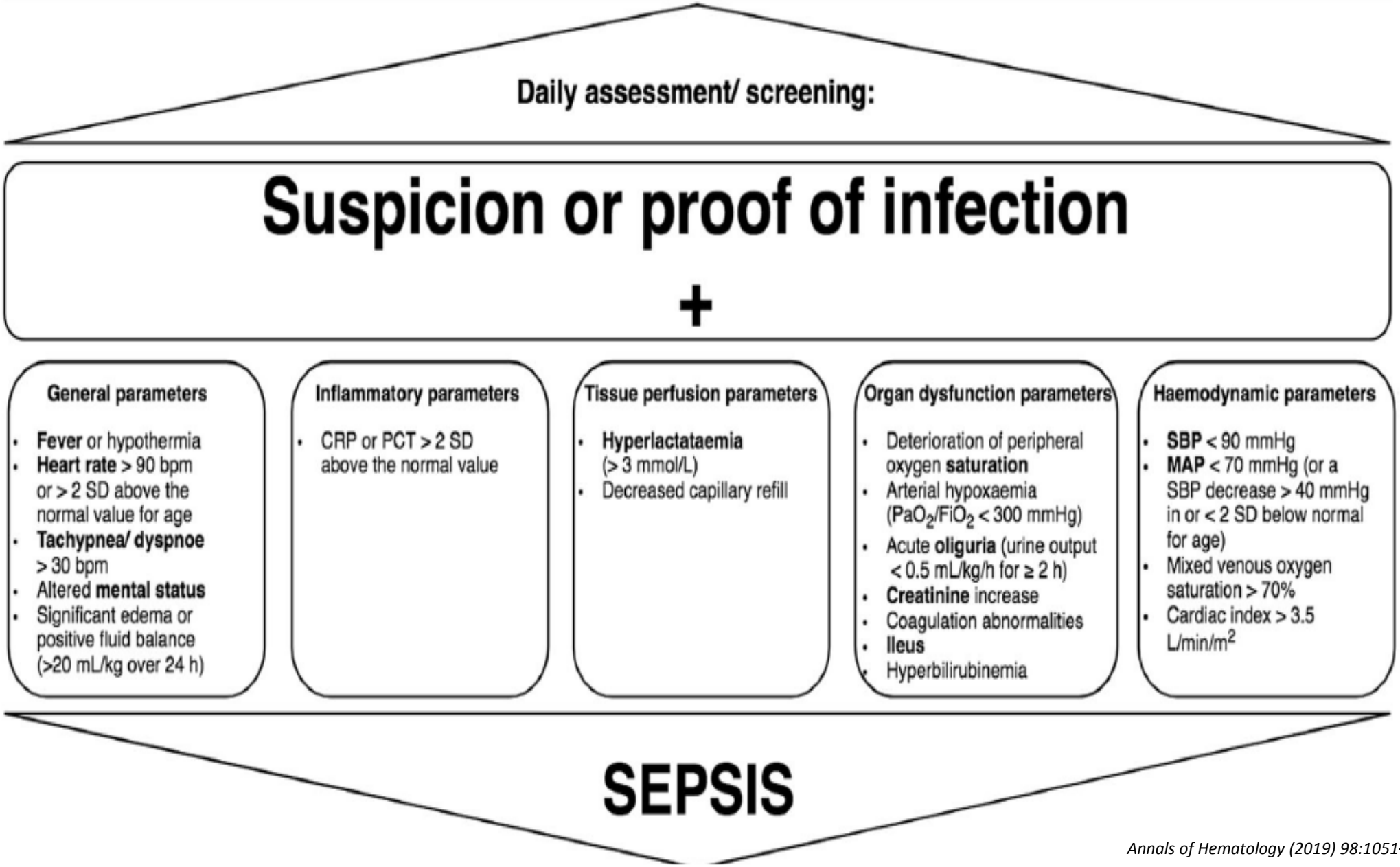

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Table 2. Initial assessment and investigations

1	Note the presence of indwelling i.v. catheters
2	Symptoms or signs suggesting an infection focus:
	Respiratory system
	Gastrointestinal tract
	Skin
	Perineal region/genitourinary discharges
	Oropharynx
	Central nervous system
3	Knowledge of previous positive microbiology results by checking clinical records
4	Routine investigations:
	Urgent blood testing to assess bone marrow, renal and liver function
	Coagulation screen
	C-reactive protein
	Blood cultures (minimum of two sets) including cultures from indwelling i.v. catheter
	Urinalysis and culture[a]
	Sputum microscopy and culture[a]
	Stool microscopy and culture[a]
	Skin lesion (aspirate/biopsy/swab)
	Chest radiograph
5	Further investigations (profound/prolonger neutropaenia/following allografts)
	High-resolution chest CT (if pyrexial despite 72 h of appropriate antibiotics)
	Bronchoalveolar lavage

i.v., intravenous; CT, computed tomography.
[a]Urinalysis, sputum and stool cultures only in case of suspected focus of infection at these sites.

Initial assessment and investigations : In quest of the source

- Neutropenic cancer patients with a suspicion or proof of an infection should be screened for signs of acute organ dysfunction (s) daily (AIII)
- Biomarkers can be used to support the diagnosis of bacterial/fungal infections but are unable to confirm or rule out an infection (BIIu-BIII).
- Modified multiplex PCR protocols might be used to support the diagnosis of infection leading to sepsis (CIIu).
- Early Warning Systems recommended (AIIht)

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Klastersky et al Annals of Oncology 27 (Supplement 5): v111–v118, 2016

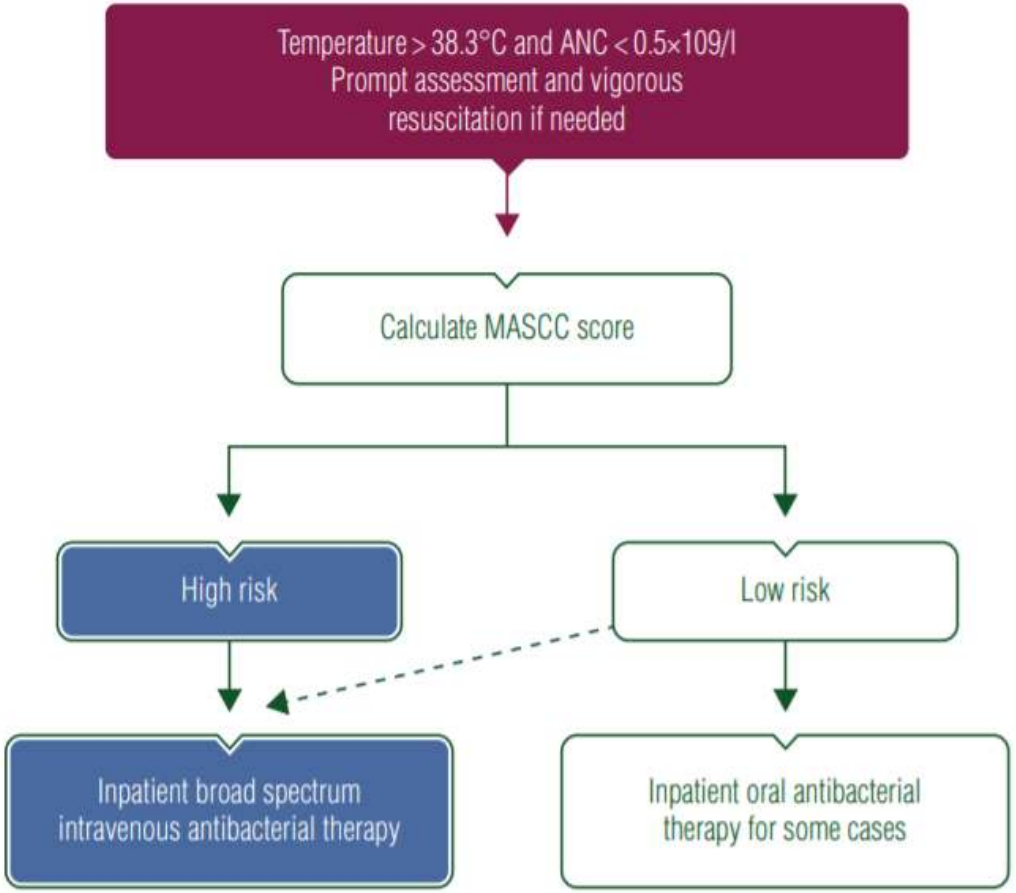
Outcome Risk Assessment

Table 1. MASCC febrile neutropaenia risk index

Characteristics	Score
Burden of illness: no or mild symptoms	5
Burden of illness: moderate symptoms	3
Burden of illness: severe symptoms	0
No hypotension (systolic BP > 90 mmHg)	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma with no previous fungal infection	4
No dehydration	3
Outpatient status (at onset of fever)	3
Age <60 years	2

Patients with score ≥21 at low risk for complications

- Haemodynamically stable
- No acute leukaemia or evidence of organ failure
- No pneumonia, an indwelling venous catheter or severe soft tissue infection [I, A].



Klastersky et al Annals of Oncology 27 (Supplement 5): v111–v118, 2016

In or Out ??

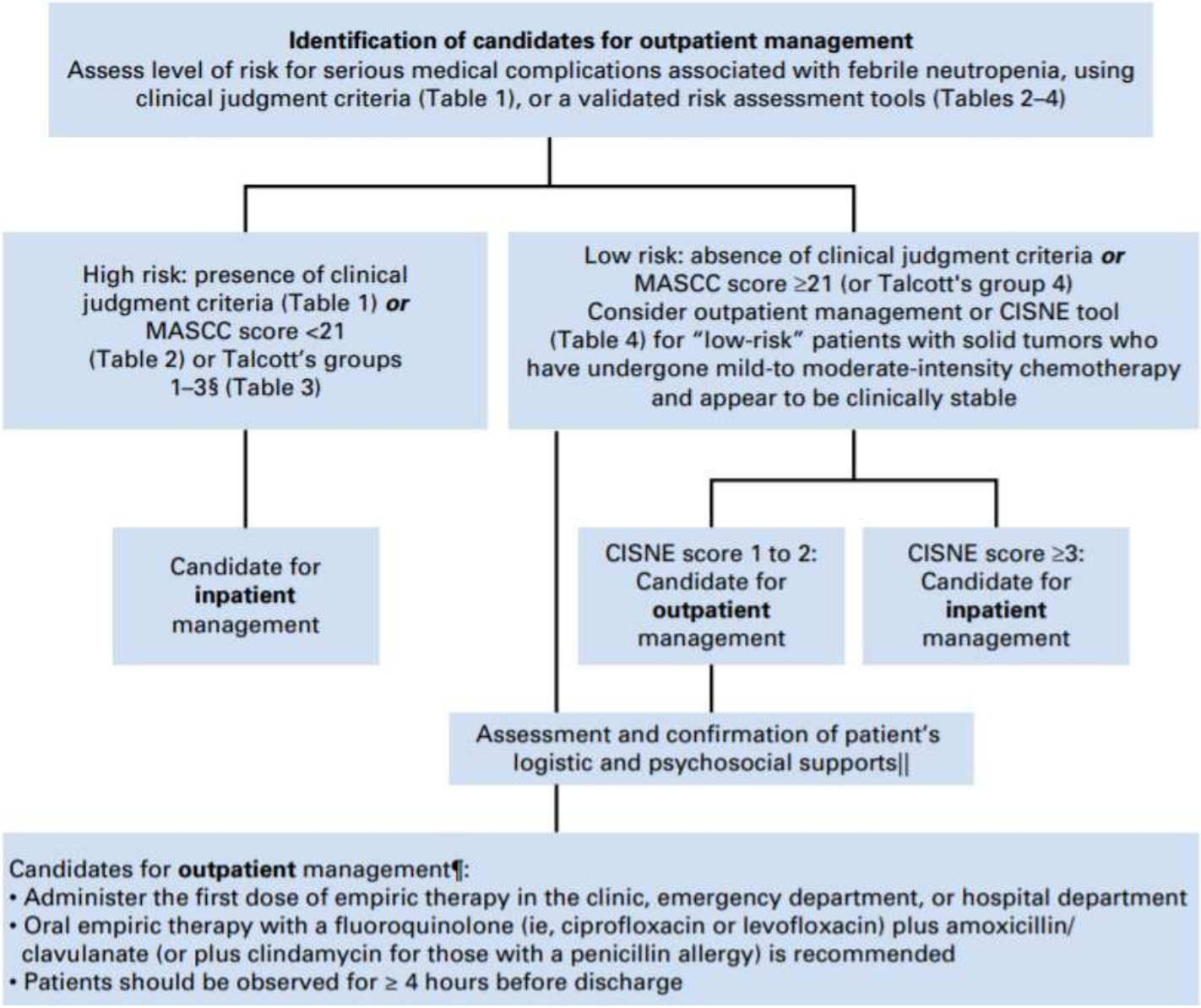


Table 4. The Clinical Index of Stable Febrile Neutropenia

Explanatory Variable*	No. of Points
Eastern Cooperative Oncology Group performance status ≥ 2	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
National Cancer Institute Common Toxicity Criteria mucositis of grade ≥ 2	1
Monocytes < 200/μL	1
Stress-induced hyperglycemia	2

*The six variables are integrated into a score ranging from 0 to 8, which classifies patients into three prognostic classes: low risk (0 points), intermediate risk (1 to 2 points), and high risk (≥ 3 points).

Taplitz et al 2018 J Clin Oncol 36 (14) 1443-1453

Sepsis resuscitation in hematological patients

Table 2 Proportion of neutropenic septic patients

Author, year of publication	Study title	Study period	Number of centers	Included patients (*n*)	Neutropenic patients *n* (%)
Soares 2006 [15]	Prognosis of critically ill patients with cancer and acute renal dysfunction	2000–2004	1	309	37 (12)
Soares 2008 [16]	Short- and long-term outcomes of critically ill patients with cancer and prolonged ICU length of stay	2000–2005	1	1090	81 (7)
Soares 2010 [17]	Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study	2007	28	717	52 (7)
Oeyen 2013 [18]	Long-term outcomes and quality of life in critically ill patients with hematological or solid malignancies: a single center study	2008–2009	1	483	32 (7)
Azoulay 2013 [1]	Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium	2010–2011	17	1011	289 (29)
Lee 2015 [19]	Effect of early intervention on long-term outcomes of critically ill cancer patients admitted to ICUs	2010–2012	1	525	237 (45)

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Sepsis resuscitation in hematological patients

Management of sepsis in neutropenic cancer patients:
2018 guidelines from the Infectious Diseases Working Party (AGIHO)
and Intensive Care Working Party (iCHOP) of the German Society
of Hematology and Medical Oncology (DGHO)

No evidence that sepsis and septic shock in patients with neutropenia need to be treated differently to nonneutropenic patients according to the sepsis guidelines 2016 (AIII)

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Choice of empirical antibiotic regimen

Local Epidemiology

- *Pseudomonas aeruginosa*
- ESBL producers
- MRSA
- etc

Patient Characteristics

- Opportunistic infections
- Prophylaxis and Previous Therapy
- Previous Colonization / MDR infection
- Previous Therapies
- Toxicity, Interaction, Allergies

Antimicrobial Therapy

- **Empirical antimicrobial treatment using anti-pseudomonal broad-spectrum antibiotics must be started immediately** (AIIrt)
- We recommend initial treatment with piperacillin/tazobactam or meropenem or imipenem/cilastatin (AIII)
- A combination treatment with an aminoglycoside may be considered in neutropenic patients with septic shock. (BIII)
- In case of clinically stabilizing patients or detection of pathogens sensitive to ß-lactam, ➔ stop aminoglycosides (AIII)
- Risk factors for invasive fungal infections and/or for uncontrolled cardiopulmonary instability, an antifungal therapy should be considered (AIII)

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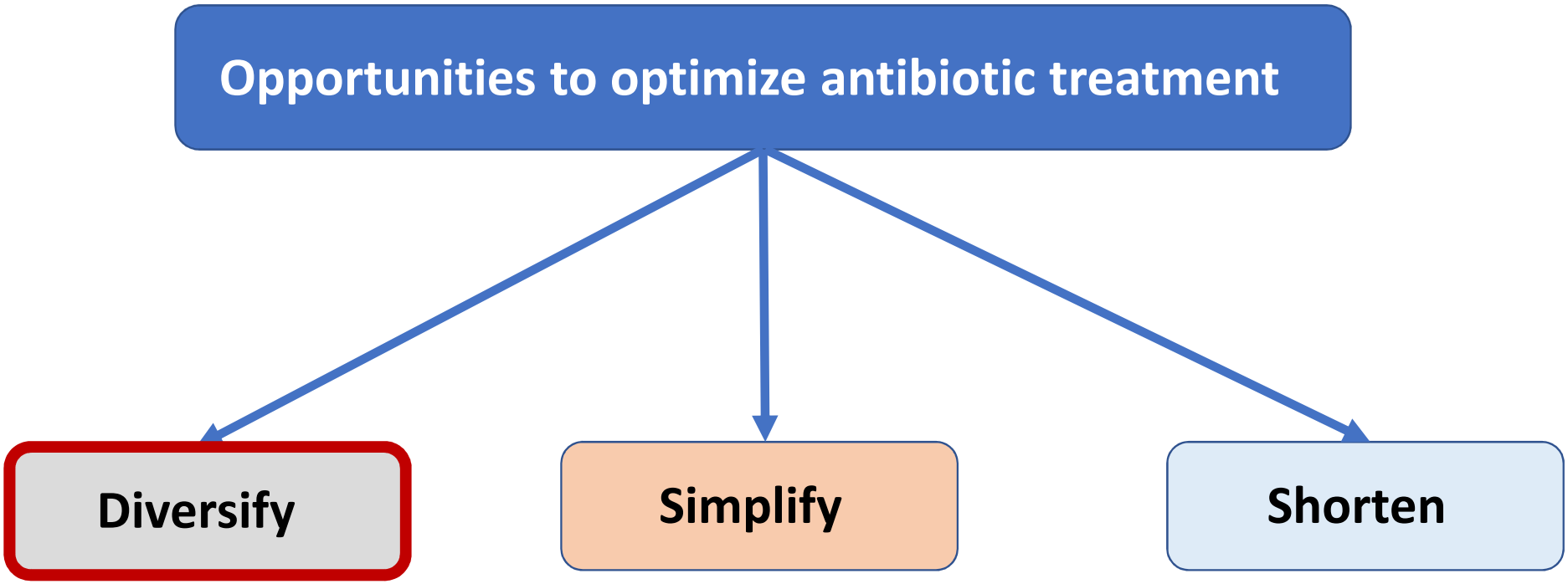

Opportunities to optimize antibiotic treatment
Diversify
Simplify
Shorten

Diversifying empirical antibiotic regimen : a possible approach

1. Use of cefepime or pip/tazo

- Local Epidemiology
- Associated site of infection
- Non-complicated illness
- No resistant bacteria colonization
- Fever with low probability of infectious aetiology (drugs, tumoral fever..)
- Low risk patients (CLL, myeloma, lymphoma)

2. Use of meropenem, other/new agents * as first line therapy

- Severely ill patients
- Fever and previous infection/colonization with resistant gram (-) pathogens (ESBL, KPC, etc)
- Neutropenic patients with recent therapy with pip/tazo and recurrent fever

** According to approved indications*

When to combine with aminoglycoside (BIII)

1. Seriously ill patients *(synergistic effect of benefit in pts with febrile neutropenia)*
2. If resistant non fermenters are likely based upon

- Local epidemiology
- Previous colonization / infection
- Previous use of carbapenems

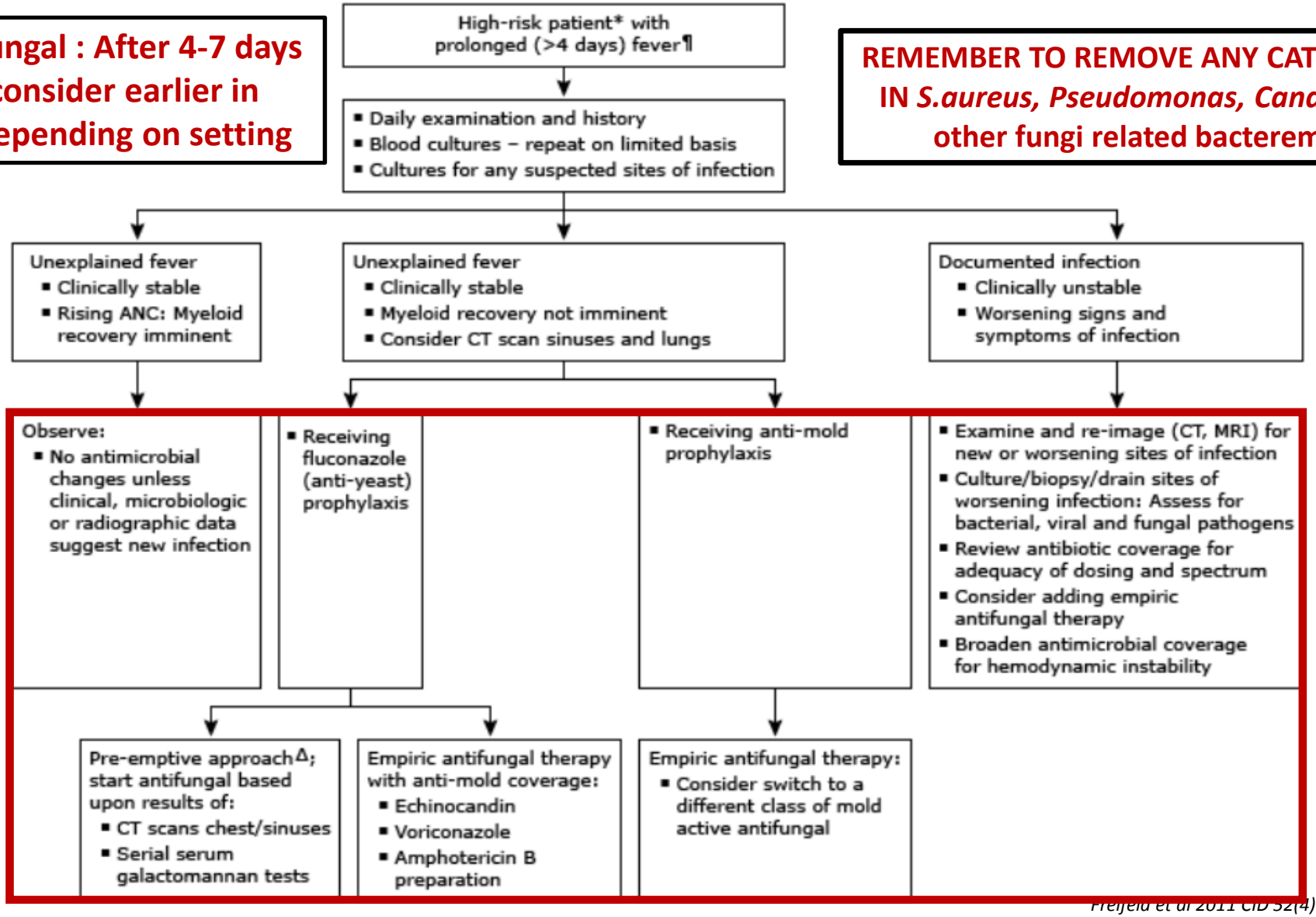
Freifeld et al 2011 CID 52(4) e56-93
Klastersky et al Annals of Oncology 27 (Supplement 5): v111–v118, 2016

When to add a glycopeptide

- Haemodynamic instability or other evidence of severe sepsis, septic shock or pneumonia
- Colonization with MRSA or VRE
- Suspicious of catheter related infection
- Skin or soft tissue infection at any site in areas with ca-MRSA
- Severe mucositis in patients receiving quinolone prophylaxis or empirical therapy with cephalosporins

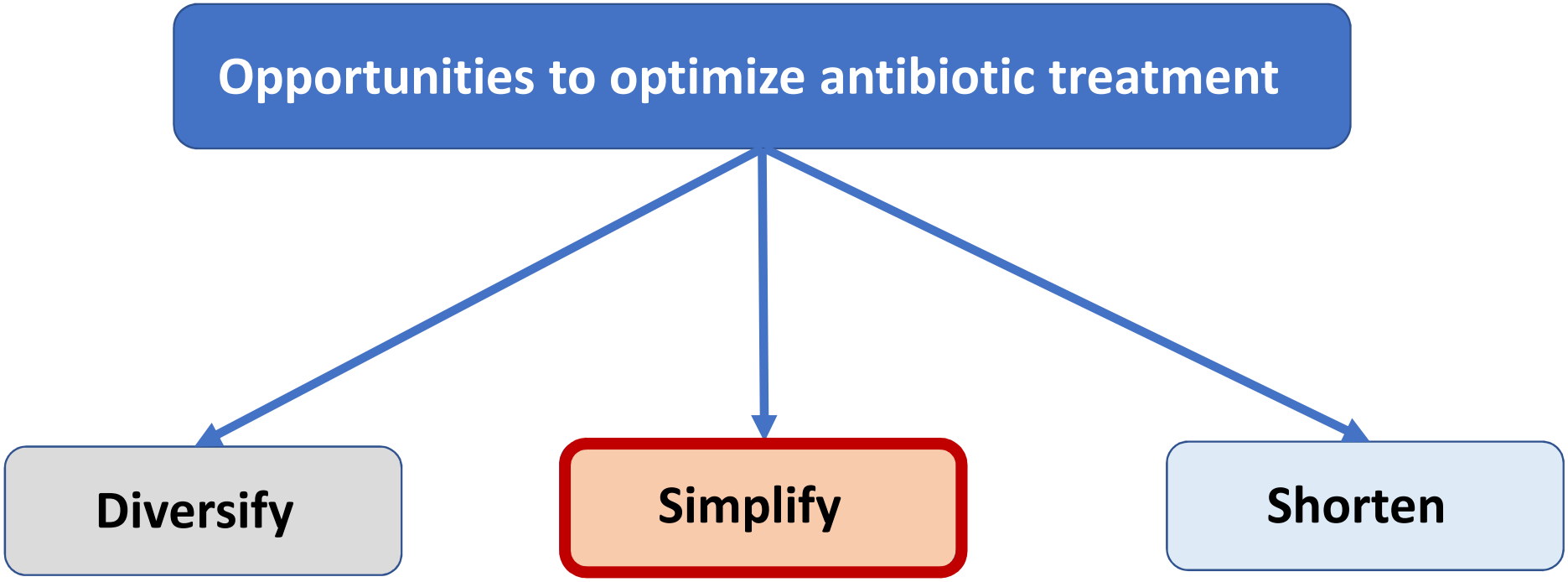
Freifeld et al 2011 CID 52(4) e56-93
Haematologica. 2013 Dec; 98(12): 1826–1835

Empiric antifungal : After 4-7 days of fever – consider earlier in critically ill depending on setting



REMEMBER TO REMOVE ANY CATHETERS IN *S.aureus, Pseudomonas, Candida* or other fungi related bacteremia

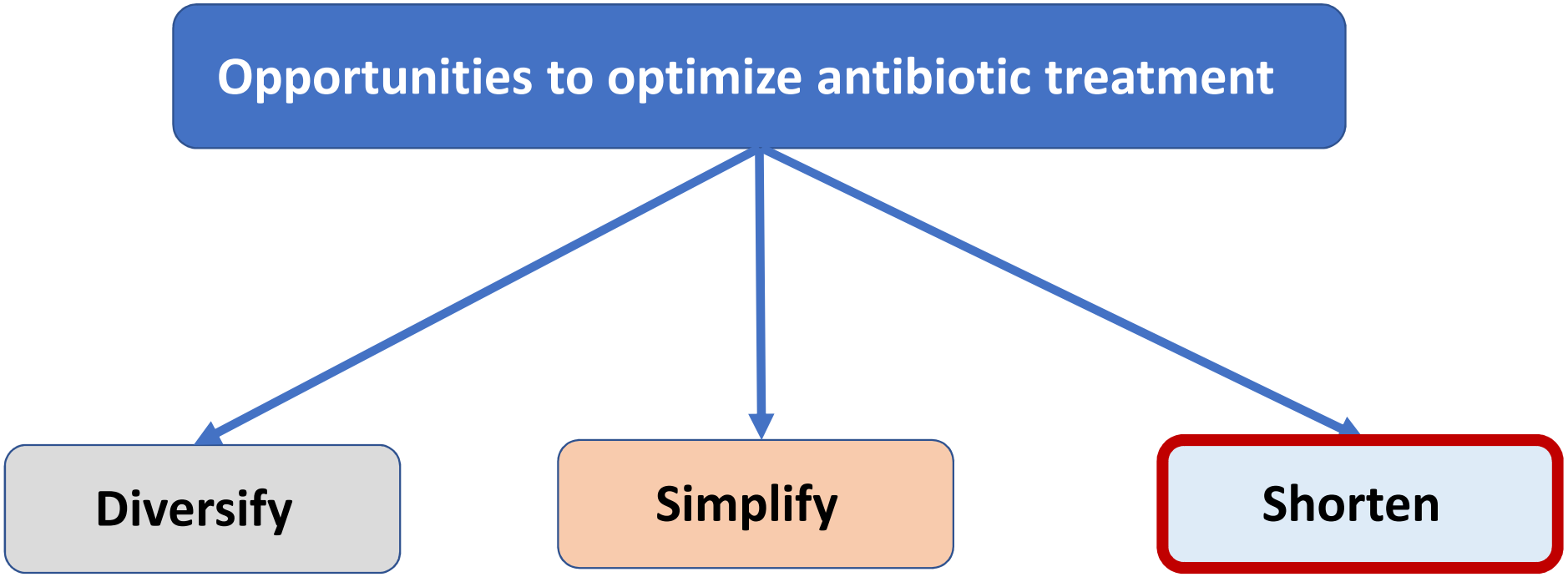
Freifeld et al 2011 CID 52(4) e56-93
Haematologica. 2013 Dec; 98(12): 1826–1835


Opportunities to optimize antibiotic treatment
Diversify
Simplify
Shorten

Choice of empirical antibiotic regimen : Simplify

	Escalation approach	De-escalation approach
Indication B-II for all		
	1) Uncomplicated presentation; 2) No known colonization with resistant bacteria; 3) No previous infection with resistant bacteria; 4) In centers where infections due to resistant pathogens are rarely seen at the onset of febrile neutropenia;	1) Complicated presentations; 2) Known colonization with resistant bacteria; 3) Previous infection with resistant bacteria; 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia.
Options for initial antibiotic therapy		
	1) Anti-pseudomonal cephalosporin (cefepime*, ceftazidime*) **AI** 2) Piperacillin-tazobactam **AI** 3) Other possible options include†: - Ticarcillin-clavulanate‖ - Cefoperazone-sulbactam‖ - Piperacillin + gentamicin‡	1) Carbapenem monotherapy **BII**§ 2) Combination of anti-pseudomonal β–lactam + aminoglycoside or quinolone‖ (with carbapenem as the β–lactam in seriously ill patients) **BIII** 3) Colistin + β–lactam ± rifampicin **BIII**¶ 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) CIII

Haematologica. 2013 Dec; 98(12): 1826–1835


Opportunities to optimize antibiotic treatment
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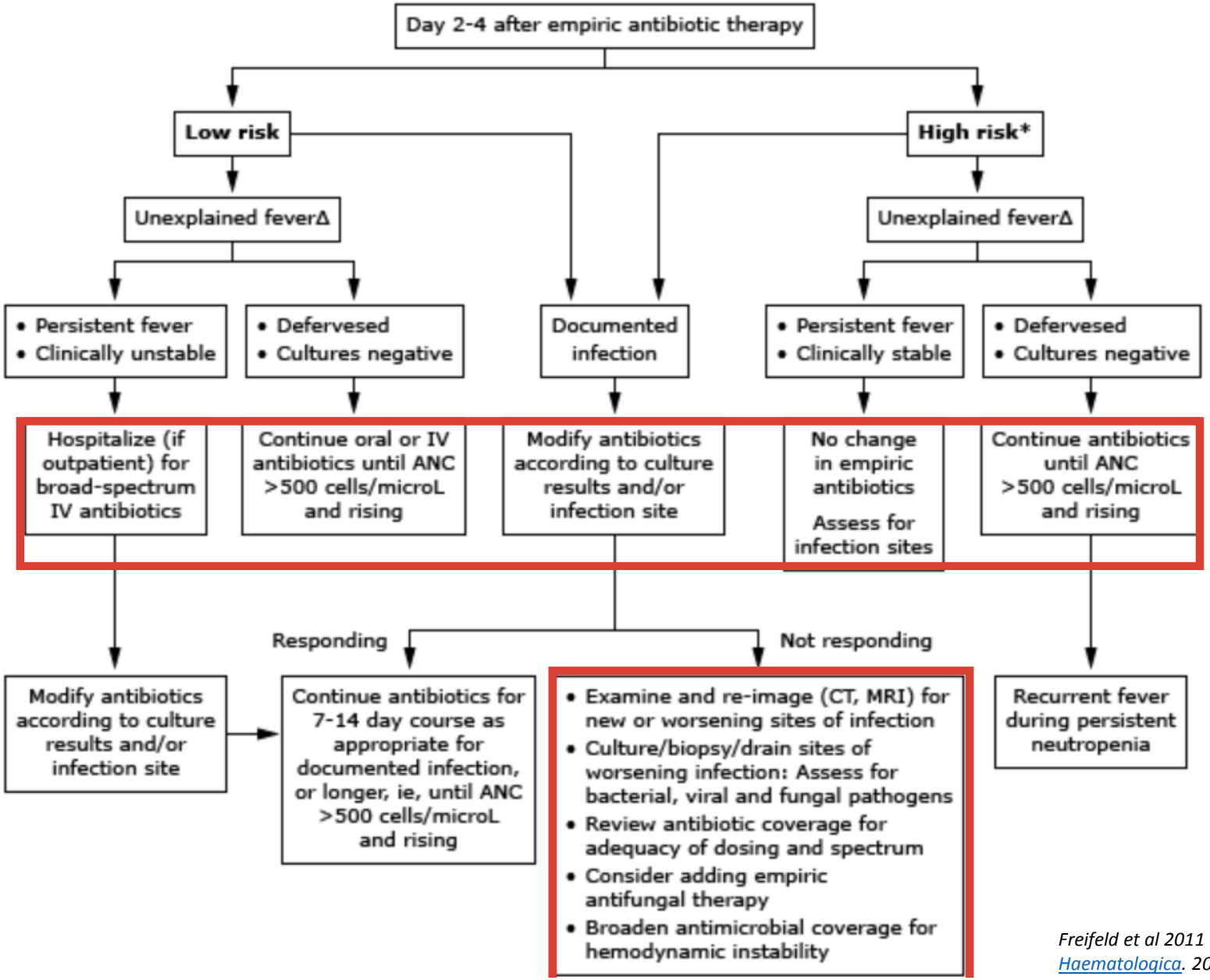

Freifeld et al 2011 CID 52(4) e56-93
Haematologica. 2013 Dec; 98(12): 1826–1835

Duration of Treatment

- If ANC is ≥0.5 × 109/l, pt asymptomatic and has been afebrile for 48 h and blood cultures are negative ➔ stop antibacterials [II, A].
- If ANC is ≤0.5 × 109/l, pt no complications and afebrile for 5–7 days, ➔ discontinued except in certain high-risk cases with acute leukemia and following high-dose ChT (continued for up to 10 days, or until the ANC is ≥0.5 × 109/l) [II, A].
- Patients with persistent fever despite neutrophil recovery should be assessed by an ID physician or clinical microbiologist and antifungal therapy considered [II, A].

Annals of Oncology 27 (Supplement 5): v111–v118, 2016

Source control

- There is no evidence that source control is different in septic neutropenic patients than non-neutropenic patients (AIII)
- A source control (e.g., surgery or CT-controlled puncture) should be done asap (AIIt)
- **If possible, all intravascular devices should be removed in case of suspected infection**. (AIIt)

Fluid therapy

- There is no evidence that septic neutropenic patients need to be treated differently to non-neutropenic (AIII)
- Balanced crystalloids should be used for intravenous fluid administration. (AIIt)

Vasoactive medications

- There is no evidence that septic neutropenic patients need to be treated differently to non-neutropenic (AIII) (*consider however screening for underlying cardiac insufficiency*)

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Corticosteroids

- There is no evidence that septic shock in patients with neutropenia needs to be treated differently than non-neutropenic patients (AIII)
- The continuation of a cortisone therapy should be evaluated individually.(AIII)

** Even though, in chronic disseminated candidiasis : For patients who have debilitating persistent fevers, short-term (1–2 weeks) treatment with nonsteroidal anti-inflammatory drugs or corticosteroids can be considered (weak recommendation; low-quality evidence)*

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Clin Infect Dis. 2016 Feb 15;62(4):e1-50.

Blood products

- There is no evidence that sepsis and septic shock in patients with neutropenia require different treatment than non-neutropenic patients (AIII)
- RBC transfusion: **RBC transfusion only when Hb < 7.0 g/dL** in adults i**n the absence of particular circumstances,** such as myocardial ischemia, severe hypoxemia, or acute hemorrhage. No RBC transfusions should be performed for Hb ≥ 7 g/dL in the absence of risk factors.(DIIt)
- Granulocytes transfusion: there is low-grade evidence that **patients do not benefit from therapeutic granulocyte transfusions** in terms of clinical resolution of infection.(CIII)
- Platelet transfusion: in the absence of other risk factors for bleeding prophylactic, **platelet transfusions should be given ≤ 10 × 109/L (BI-Iitr)**. For neutropenic septic patients **or** prior to an intervention with an increased risk of bleeding, platelet transfusions should be **indicated individually** (AIII)

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Hematopoietic growth factors	• We **do not recommend the routine additional use of G-CSF or GM-CSF** to standard treatment of sepsis and septic shock in patients with neutropenia (DI-Iir) • G-CSF–induced neutropenia recovery carries a risk of respiratory status deterioration with acute lung injury or ARDS.
Immunoglobulins	• There is **marginally degree of evidence to support the use of IVIG** in sepsis and septic shock in patients with neutropenia (CIIrt)
Blood purification	• **Cytokine adsorption cannot be recommended** at this time for sepsis and septic shock in patients with neutropenia.(DIIt-III)

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Anticoagulants

- **No studies supporting the use of heparin** in sepsis and septic shock in patients with neutropenia.(DIII)
- Insufficient evidence to support antithrombin substitution in any category of critically ill participants (including pts with sepsis and DIC)(DIItr)

Venous thromboembolism prophylaxis

- **We recommend pharmacologic prophylaxis with unfractionated heparin or low-molecular-weight heparin for venous thromboembolism prophylaxis in the absence of contraindications. AIIt**

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Mechanical ventilation

- No evidence that septic neutropenic pts need to be treated differently to non-neutropenic (AIII)
- NIV should not be used in patients with a respiratory failure & a PaO2/FiO2 <150 mmHg. DIIt
- NIV did not improve survival compared to oxygen only. AIIrt
- High-flow nasal cannula (HFNC) oxygen when compared with standard oxygen did not reduce intubation or survival rates and may be used in special circumstances.(AIIt)
- Prone position recommended in severe ARDS. (BIItr)

Sedation and analgesia

- No evidence that sepsis and septic shock in patients with neutropenia need to be treated differently than non-neutropenic pts. (AIII)
- A strategy for whole-body physiotherapy—consisting of interruption of sedation and physical and occupational therapy in the earliest days of critical illness—is recommended. (AIII)
- The use of standardized weaning protocols is recommended. AIItr

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Management of renal dysfunction—renal replacement therapy (RRT)	• There is no evidence that sepsis and septic shock in pts with neutropenia need to be treated differently to non-neutropenic pts (AIII)
Bicarbonate therapy	• No evidence that septic shock in pts with neutropenia needs to be treated differently than non-neutropenic pts AIII
Glucose control	• No evidence that septic shock in pts with neutropenia needs to be treated differently than non-neutropenic pts AIII
Stress ulcer prophylaxis	• No evidence that septic shock in pts with neutropenia needs to be treated differently than non-neutropenic pts AIII
Nutrition	• No evidence that sepsis and septic shock in pts with neutropenia need to be treated differently than non-neutropenic pts. AIII • In patients with severe neutropenic enterocolitis, severe viral or bacterial gastrointestinal infections, or severe gastrointestinal graft-versus-host disease (GVHD**), enteral nutrition should be paused or, at least, carried out** with caution. AIII • Concomitant cancer-associated cachexia should not result in hyperalimentation. AIII • **Enteral nutrition is preferred over parenteral nutrition**, BIIt

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Treatment Goals and ICU admission

- Treatment goals and the short- and long-term prognosis of intensive care should be discussed with the patient and the relatives before admission to the ICU (AIII).
- **Full-code ICU management (without limitations of ICU resources) should be offered to all critically ill cancer patients** if long-term survival may be compatible with the general prognosis of the underlying malignancy (AIIu).

- Especially neutropenic septic patients benefit from a timely and targeted therapy.
- Typically, full-code management (without limitations of ICU resources) applies to patients with curative therapeutic options and those in remission of their malignancy, as well as to patients in whom cure is not likely but the expected life span is substantial (1 year ? *Arbitrary*)

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Thank you for your patience