Approaches to febrile neutropenia

2011 IDSA-ECIL guidelines

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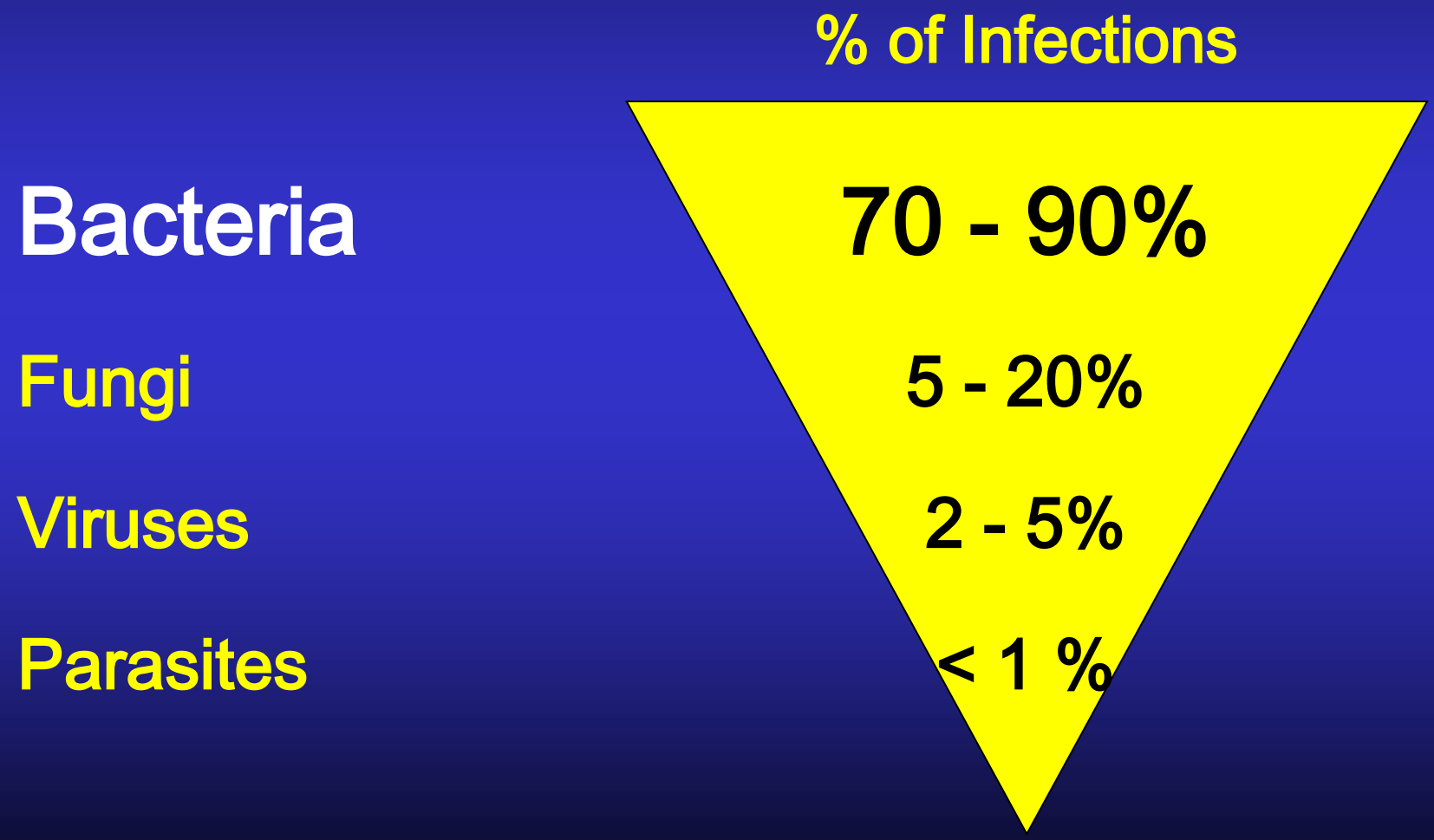
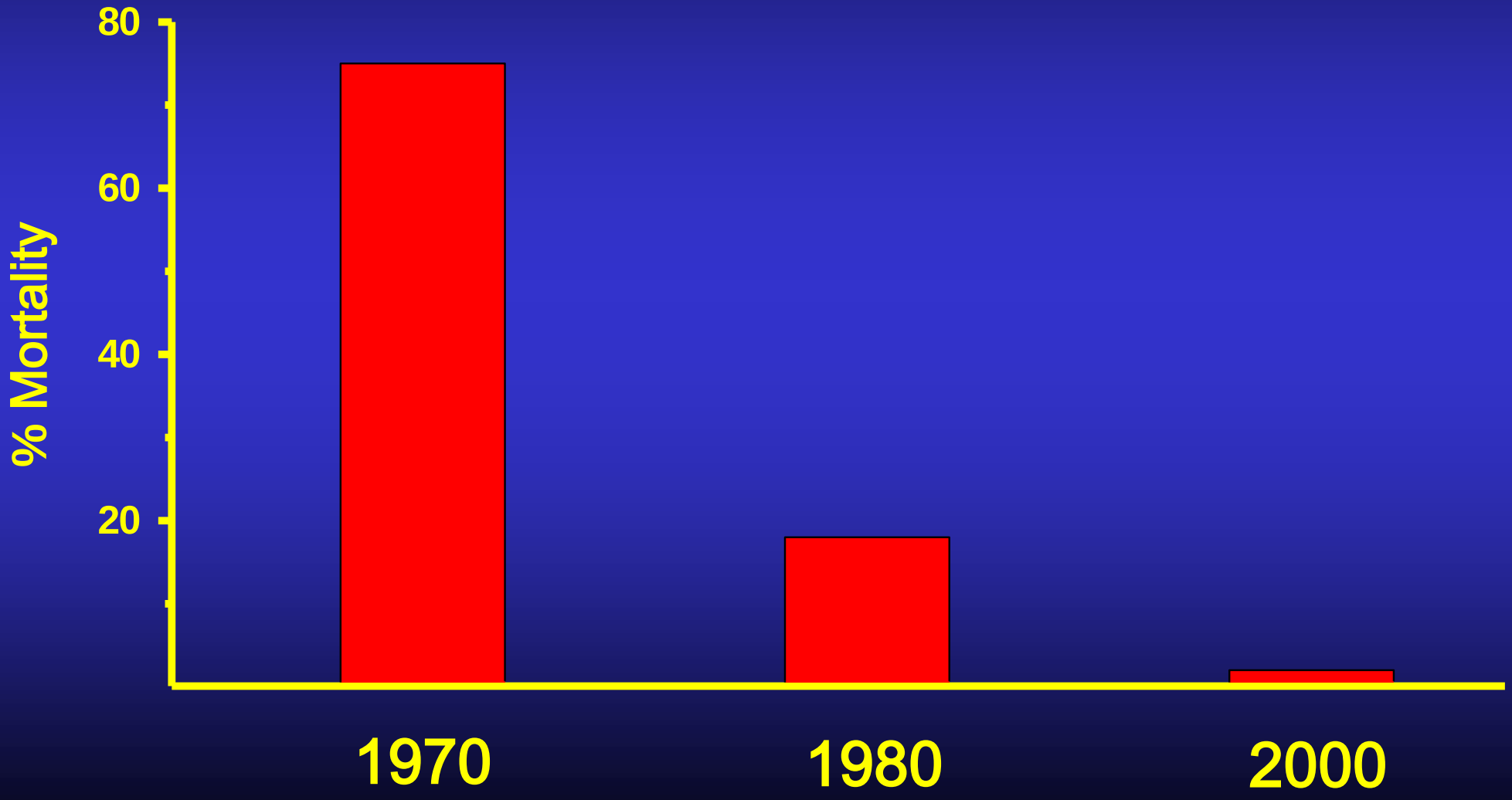
Febrile Neutropenia: Definition

- Definitions are not hard-and-fast rules
- Fever is a single oral temperature measurement of ≥38.3°C or a temperature of ≥38.0°C sustained for a 1-h period
  - Axillary temperature is discouraged
  - Rectal temperature measurements should be avoided
- Neutropenia is defined as an ANC of < 500 cells/mm^3 or an ANC that is expected to decrease to < 500 cells/mm^3 during the next 48 hours
  - "functional neutropenia" patients are also at risk
- Non-infectious causes of fever should be excluded: transfusion of blood products; chemotherapeutic agents; tumor lysis syndrome; diffuse intravascular coagulation; cerebral lesions; graft-versus-host disease; drug-fever . Beware of corticosteroids!

Frequency of Infectious Agents in Neutropenic Cancer Patients



Evolution of the Mortality due to Bacterial Infections in Neutropenic Cancer Patients



IDSA-ECIL 2011 Recommendations

1. Risk assessment and low-risk versus high risk
2. Specific tests and cultures
3. What empirical antibiotic therapy and in what setting?
4. Modification: when en how?
5. How long?
6. When should antibiotic prophylaxis be given?
7. Empirical antifungal therapy
8. Antifungal prophylaxis or preemptive therapy
9. Antiviral prophylaxis
10. Role of hematopoietic growth factors
11. Management of catheter-related infections
12. Environmental precautions

Freifeld et al. Clin Infect Dis 2011; 52: e56-e93

1. Risk assessment

What distinguishes high-risk and low-risk patients

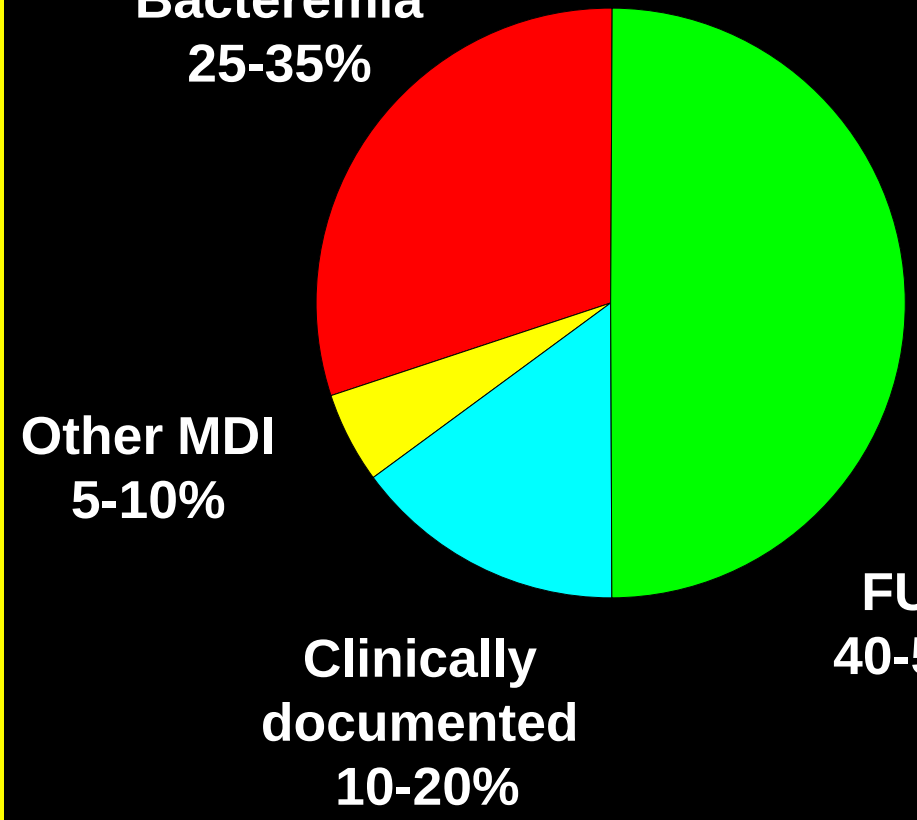
Incidence of Febrile Neutropenia → Febrile Mucositis

	LOW	HIGH
Type of chemotherapy	« Standard » chemotherapy for solid tumor, lymphoma, myeloma	Induction / consolidation chemotherapy for acute leukemia autologous or allogeneic HSCT
Disruption of mucous Membranes	+	+++
Duration of profound neutropenia < 0.1 G/L	≤ 7 days	≥ 7 days
FEBRILE NEUTROPENIA	5 – 20 %	80 – 100%

Etiology of Febrile Neutropenia

Low Incidence of FN

High Incidence of FN



The MASCC Risk Index for Prediction of the Absence of Serious Complications

Klastersky et al., J Clin Oncol, 2000; 18: 3038-51

Characteristic	Weight
Burden of illness: no or mild	5
moderate	3
No hypotension	5
No COPD	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age < 60 years	2
Maximum score	26

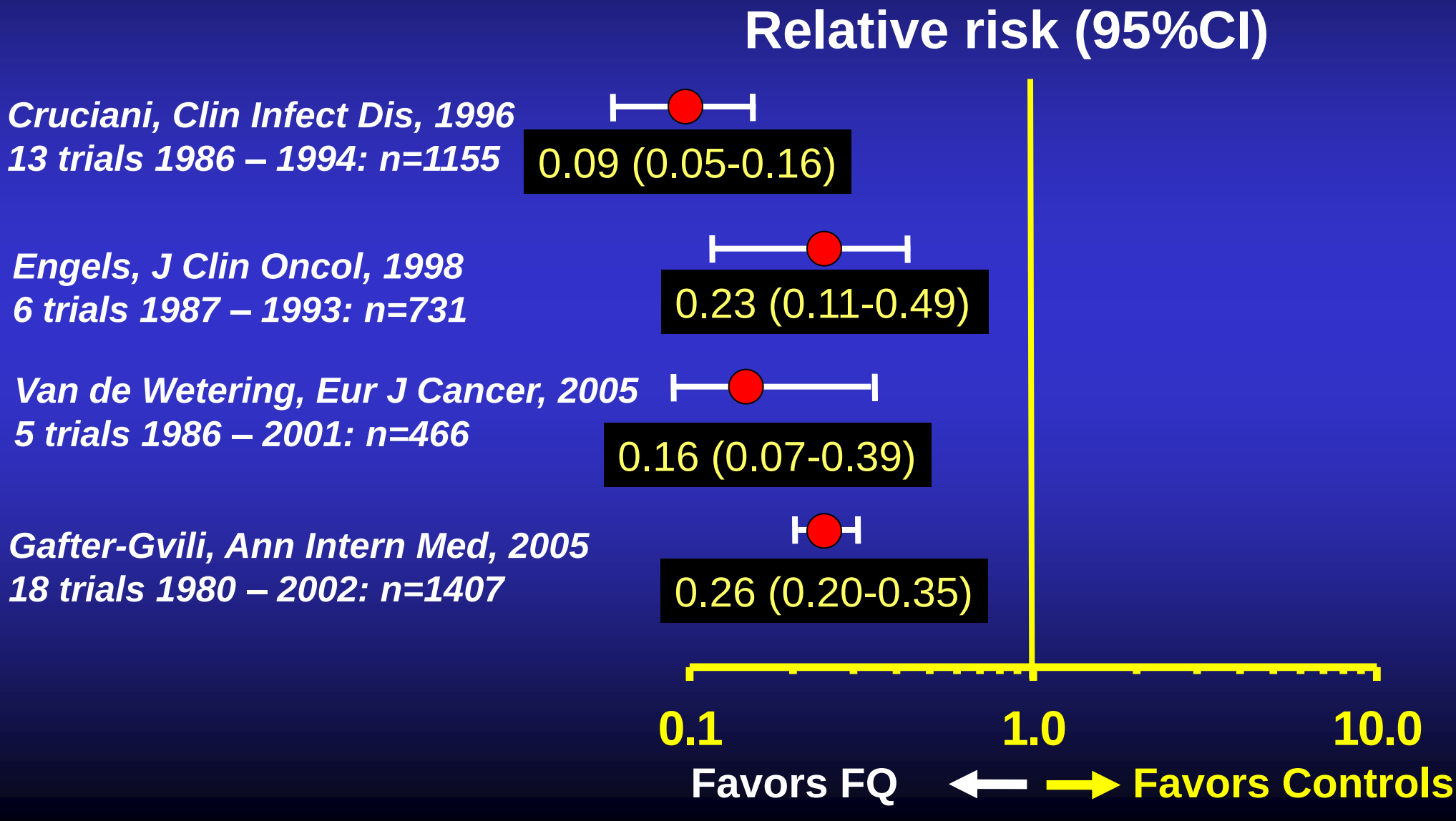
1. IDSA-ECIL 2011 Definition of High-Risk Patients

- MASCC score < 21
- Profound neutropenia (ANC ≤ 100 cells/mm^3) anticipated to extend > 7 days
- Presence of any co-morbid medical problem including but not limited to:
  - Hemodynamic instability
  - Oral of GI mucositis that interferes with swallowing or causes severe diarrhea
  - GI 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
- Evidence of hepatic insufficiency
  - Aminotransferase levels > 5 x ULN
- Evidence of renal insufficiency
  - Creatinine clearance of < 30 mL/min

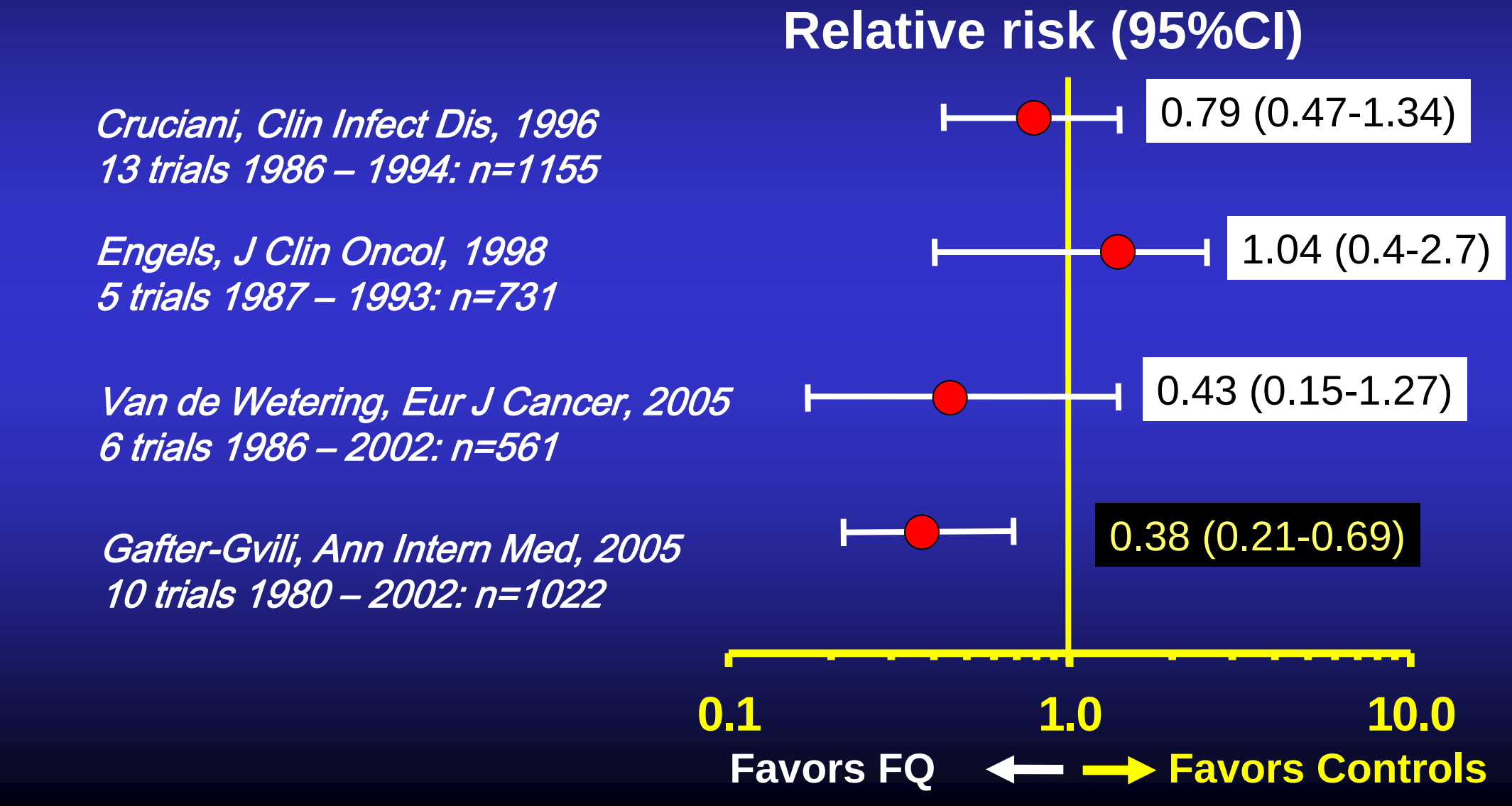
These patients should initially receive IV empirical antibiotic therapy in the hospital (B-I)

2. When should Antibiotic Prophylaxis be given, and with what Agents

Meta-Analyses of First-Generation Fluoroquinolone (FQ) Prophylaxis vs. Placebo/No Prophylaxis
ENDPOINT: GRAM-NEGATIVE BACTEREMIA



Meta-Analyses of First-Generation Fluoroquinolone Prophylaxis vs. Placebo or No Prophylaxis
ENDPOINT: INFECTION-RELATED MORTALITY



Evolution of Resistance and Fluoroquinolone Prophylaxis
EORTC-IATG Trials

Cometta, New England J Med, 1994; 330: 1240-1
EORTC-IATG Database

	1983-1985	1991-1993	1997-2000
Number of patients	219	706	763
FQ-prophylaxis	1%	45%	↓ 33%
Gram-negative bacteremia	12%	8%	↑ 12%
FQ-resistant *E. coli* bacteremia	0%	28%	↓ 20%
Infectious mortality	2%	1%	→ 1%

2. IDSA-ECIL Recommendations on Prophylaxis

- FQ prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (IDSA B-I)
  - Levofloxacin
  - Ciprofloxacin
  - European guidelines: A-I
- A systematic strategy for monitoring the development of FQ resistance among gram-negative bacilli is recommended (A-II)
- Addition of a gram-positive active agent to FQ prophylaxis is not recommended (A-I).
- Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for < 7 days (A-III)

3. What Empiric Antibiotic therapy is Appropriate and in what Venue

Empirical Antibiotic Therapy in Granulocytopenic Cancer Patients

Schimpff SC et al., N Engl J Med 1971; 284: 1061-5

Pseudomonas aeruginosa bacteremia

1968-69: Combination carbenicillin + gentamycin started after results of blood cultures

↓

MORTALITY 50%

1970-71: Same antibiotics started with development of fever

↓

MORTALITY 26%

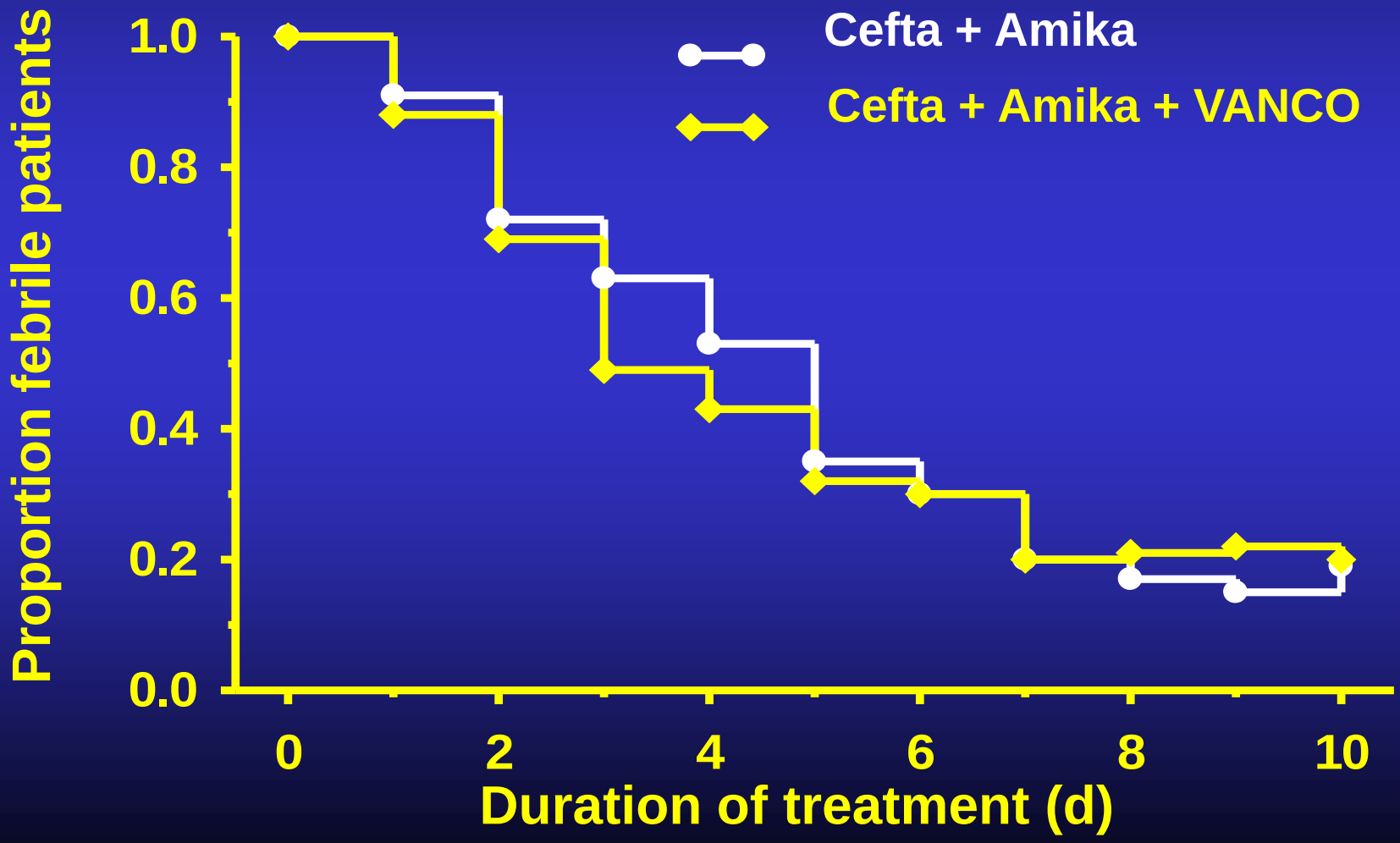
IMMEDIATE EMPIRICAL COMBINATION ANTIBIOTIC THERAPY (anti-Pseudomonal penicillin + aminogylcoside) AT ONSET OF FEVER is the CORNERSTONE of management of neutropenic cancer patients

***MONOTHERAPY* with bactericidal broad-spectrum beta-lactam antibiotics *IS AS AFFECTIVE AS* the *COMBINATION* of beta-lactam + aminoglycoside**

First-Line Use of Vancomycin for the Empirical Treatment of Febrile Neutropenic Patients ?

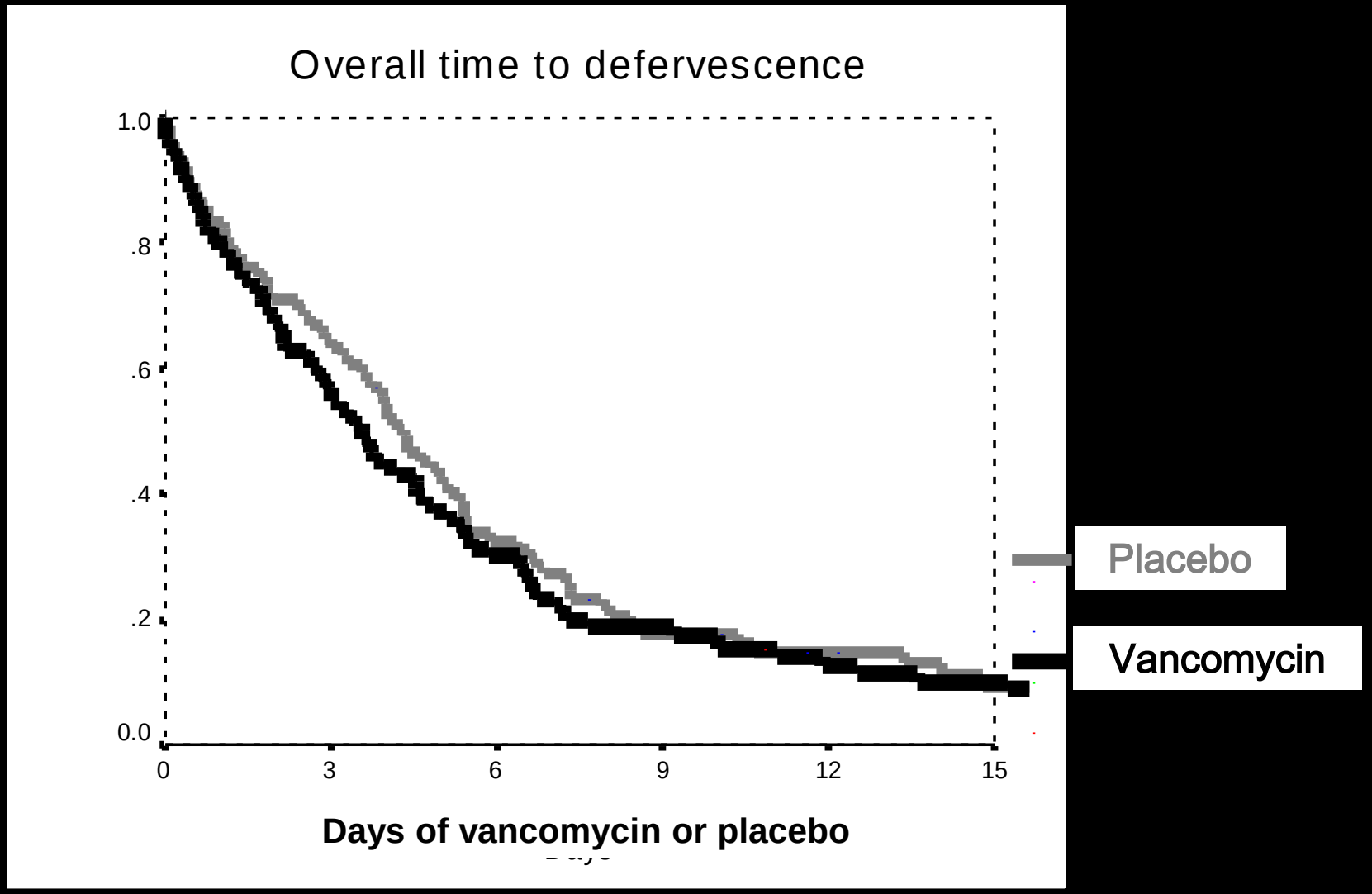
Not recommended (A-I)

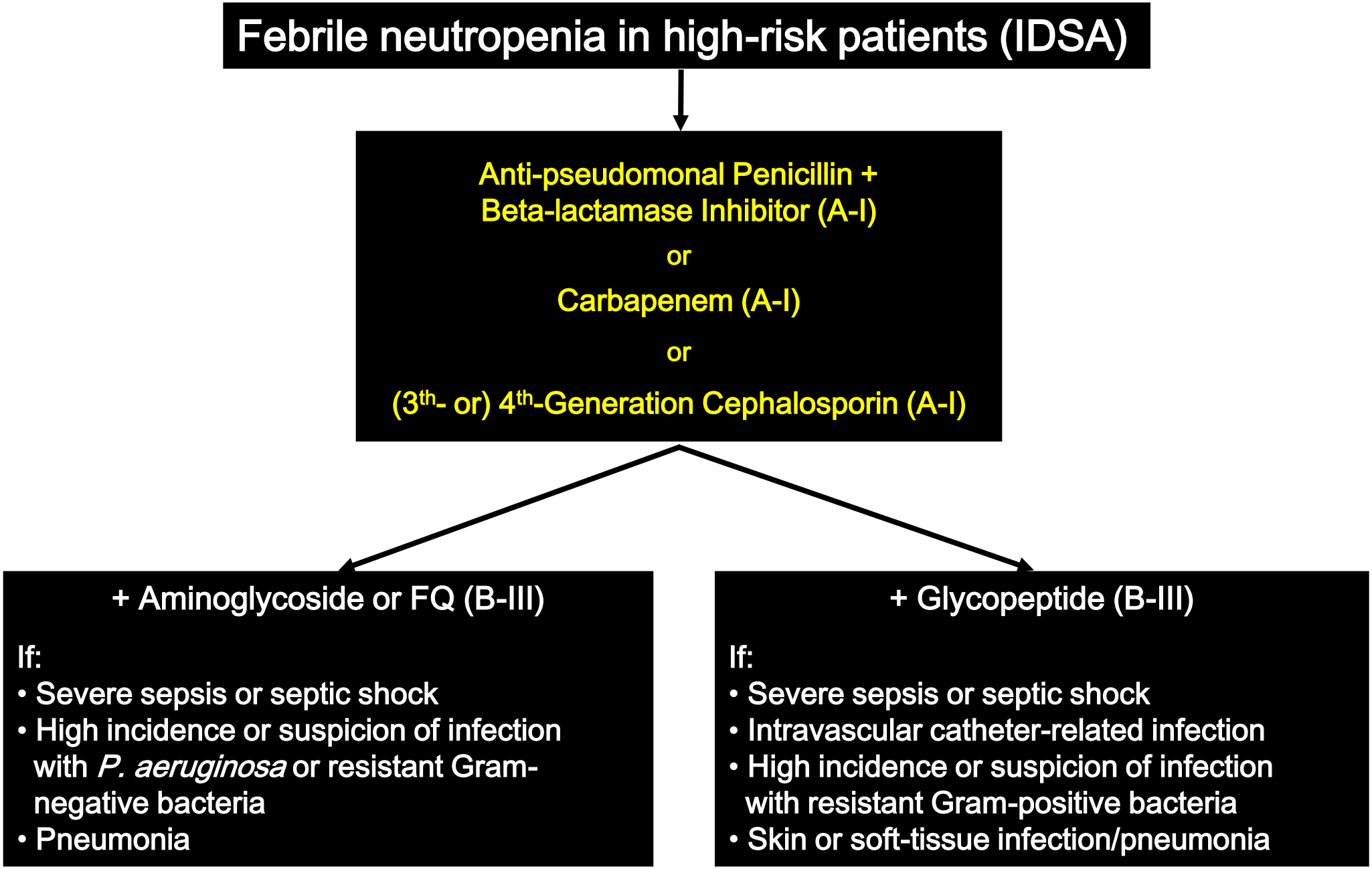
EORTC-IATCG, J Infect Dis, 1991; 163: 951-8



Second-Line Use of Empirical Vancomycin for Persistent Fever (>72h) in Neutropenic Cancer Patients ?

Cometta et al. for the EORTC-IATG, Clin Infect Dis, 2002; 37: 382-9




Febrile neutropenia in high-risk patients (IDSA)
Anti-pseudomonal Penicillin +
Beta-lactamase Inhibitor (A-I)
or
Carbapenem (A-I)
or
(3th- or) 4th-Generation Cephalosporin (A-I)
+ Aminoglycoside or FQ (B-III)
If:
• Severe sepsis or septic shock
• High incidence or suspicion of infection with P. aeruginosa or resistant Gram-negative bacteria
• Pneumonia
+ Glycopeptide (B-III)
If:
• Severe sepsis or septic shock
• Intravascular catheter-related infection
• High incidence or suspicion of infection with resistant Gram-positive bacteria
• Skin or soft-tissue infection/pneumonia

Empirical therapy for febrile neutropenia

Escalation vs. De-escalation approach (ECIL)

- Escalation: initial antibacterial regimen targeted to the more frequent bacteria identified in a given centre, then an adaptation of that regimen in a given patient, 24-72 h later, once a pathogen is known.
- De-escalation: initial broad-spectrum empirical therapy talking into account the worst expected scenario of resistant bacteria in a given centre. 24-72 h later, the antibacterial therapy should be stepped down when possible according to the clinical course and the microbiological results

ECIL 4 guidelines: Approach to initial regimens in escalation and de-escalation approaches

- Escalation
  - 4th generation cephalosporin
  - Piperacillin-tazobactam
  - No anti-resistant Gram-positive coverage
  - No combination with aminoglycosides/quinolones
- De-escalation
  - Carbapenem
  - Combination beta-lactam with aminoglycoside or quinolones
  - Combination beta-lactam with colistin
  - Early anti-resistant Gram-positive coverage with vancomycin or a new anti-Gram positive agent