

**Infections  
in the  
high-risk neutropenic host  
and  
strategies of  
antimicrobial therapy**

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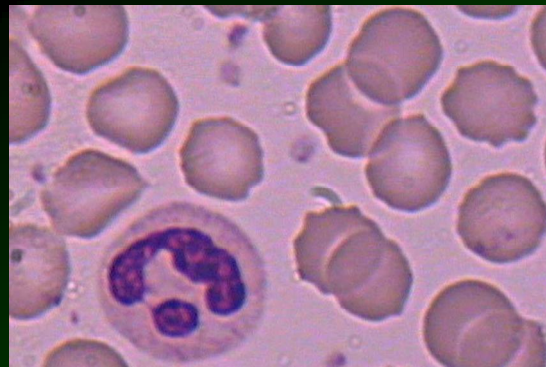
**Budapest**

**2005**

# Key points of discussion

- **The concept of febrile neutropenia**
- **Major pathogens**
- **Clinical spectrum of febrile neutropenia**
- **Risk assessment and initial therapy**
- **Problems in high-risk patients**
  - resistant bacteria
  - fungal infection
- **Future perspectives**

# Febrile neutropenia



# Febrile neutropenia

## NEUTROPHIL GRANULOCYTES:

$< 0,5 \times 10^9/\text{liter}$  (=500 / microliter)

OR

$< 1 \times 10^9/\text{liter}$  (=1000 / microliter) and  
expected to decrease

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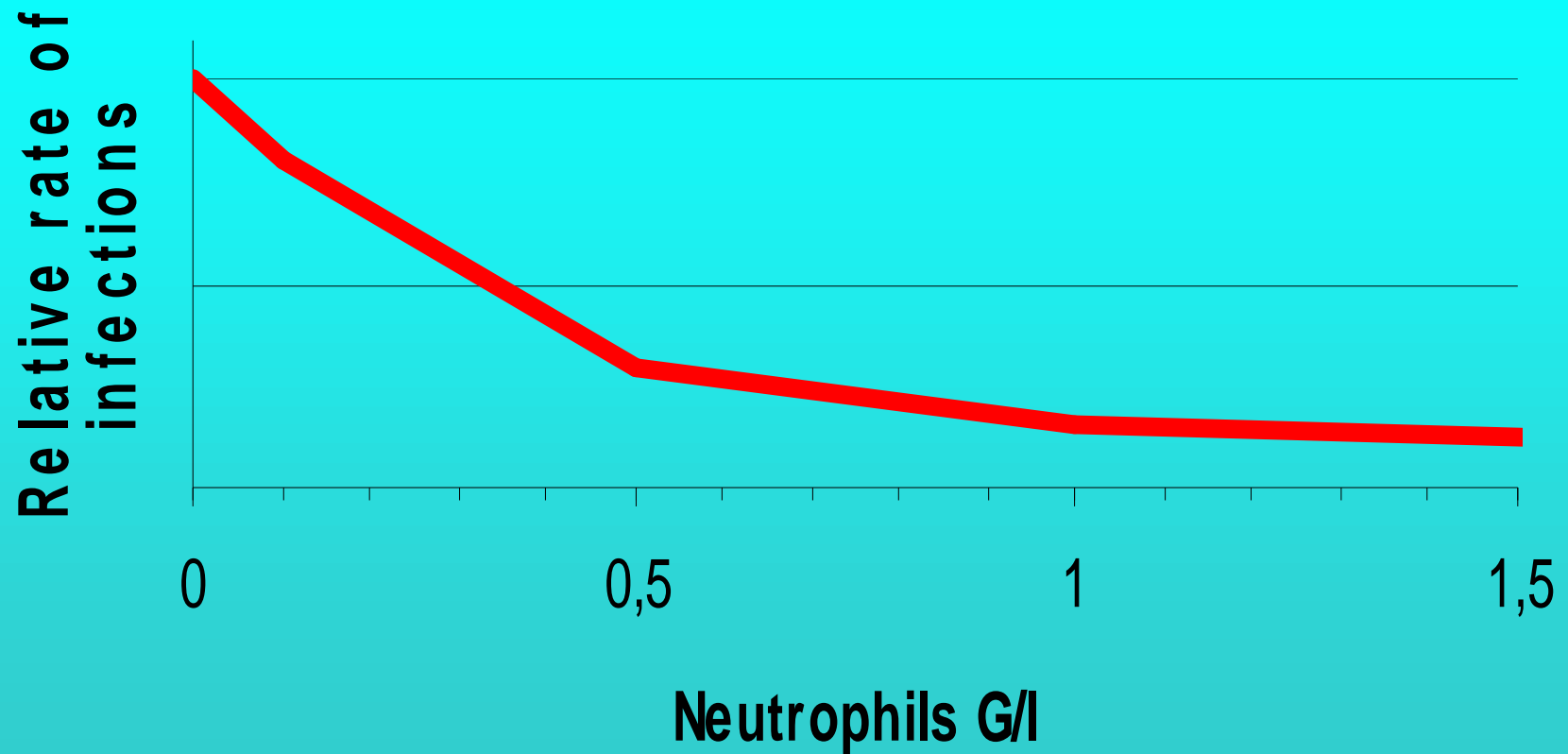
## FEVER:

Temp.  $> 38,5^\circ\text{C}$  (one occasion)

OR

$>38^\circ\text{C}$  (for one hour)

# Absolute neutrophil count and risk of infection

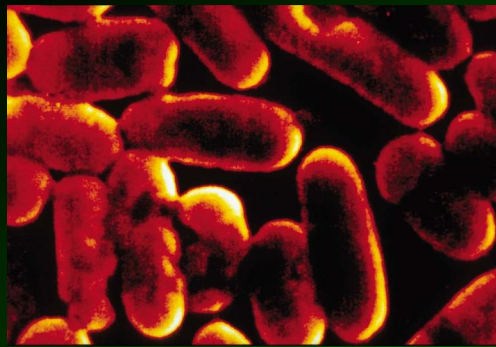


# **Febrile neutropenia**

- **Duration of neutropenia important**
- **Additional risk factors and comorbidity**
- **A medical emergency: fever may herald  
bacterial sepsis**

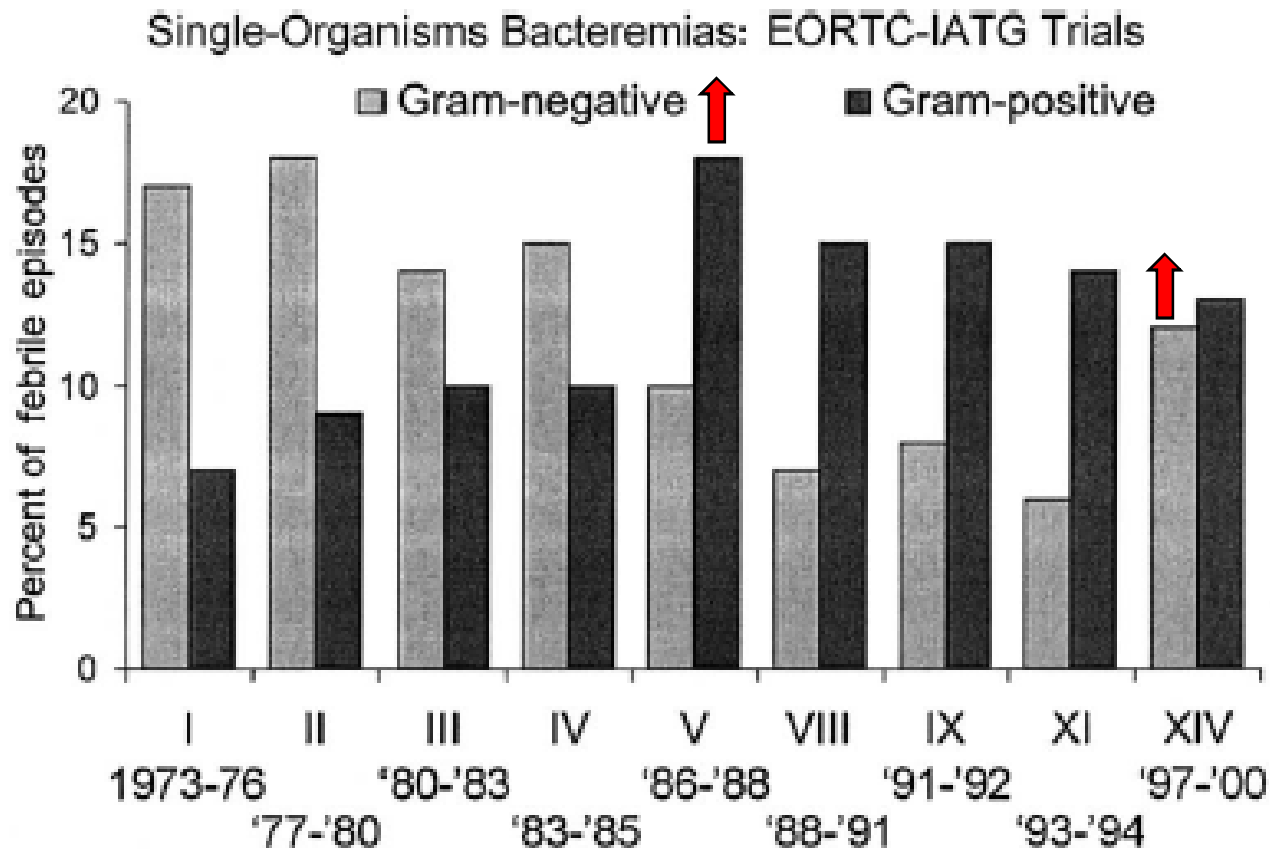


# Major pathogens



# Changes in the spectrum of bacterial bloodstream infections







Viscoli C, Castagnola E. Treatment of febrile neutropenia: what is new?  
Curr Opin Infect Dis 2002; 15:377–82.



# **Are Gram-positives predominant?**

- **Bloodstream infections : Gram-positives > Gram-negatives > (anaerobs, yeasts)**
- **Deep tissue infections (pneumonia, cellulitis, abdominal infections): Gram-negative or polymicrobial**

# Important Gram-positives

- *Staphylococcus epidermidis* 
- *Staphylococcus aureus* 
- *Corynebacterium* spp. 
- Streptococcus, viridans group 
- *Enterococcus* spp. 
- Other 

# Important Gram-negatives

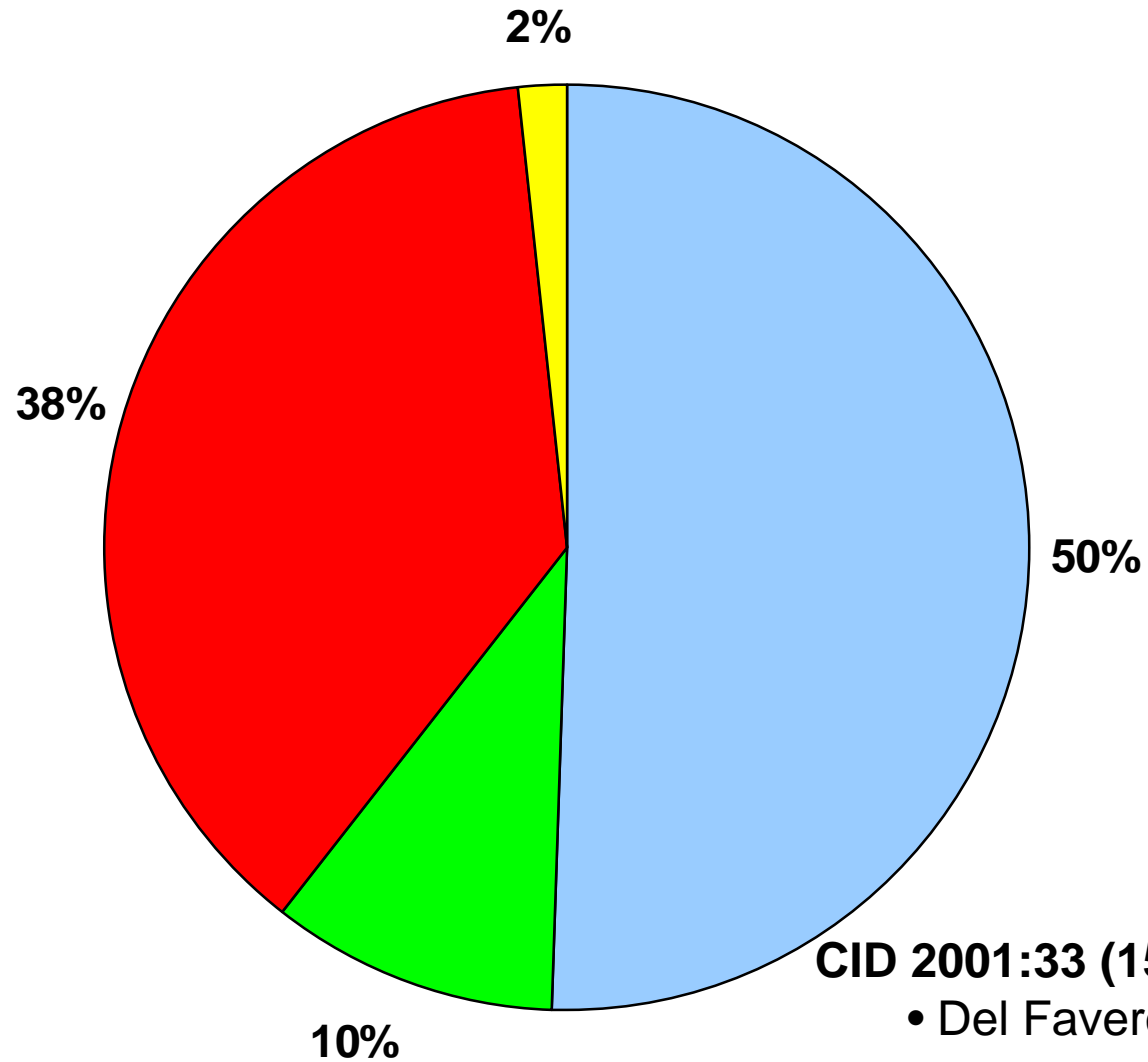
- *E. coli*
- *P. aeruginosa*
- *Klebsiella* spp.
- *Enterobacter* spp.
- *S. maltophilia*
- *Acinetobacter* spp.
- *Pseudomonas* spp.



# Clinical spectrum of febrile neutropenia



- Unexplained fever
- Clinically documented
- Bacteremia
- Other microbiologically documented



CID 2001:33 (15 October)  
• Del Favero et al.

# Initial evaluation

- **Medical history**
  - **Underlying disease**
  - **Cause of neutropenia**
  - **Other immunosuppressive factors**
  - **Comorbidity**



# **Initial evaluation**

- **Medical history**
  - **Recent infections**
  - **History of antimicrobial prophylaxis and/or therapy**
  - **Adverse events while on antimicrobials**

# Initial evaluation

- **Physical examination**
  - **General appearance**
  - **Blood pressure (shock?)**
  - **Do not forget: oral cavity, axillae, anogenital region**
  - **Lack of inflammatory response !**
- **Laboratory tests**

# Initial evaluation

- **Microbiology: two/three sets of blood cultures (vascular lines, each lumen)**
- **Other specimens as indicated**
  - **stool: C.difficile toxin**
  - **urine**
  - **CSF**
- **Imaging**
- **Biopsy (skin)**

**Mortality of Gram-negative bacteremia if untreated can exceed 50 % within 48 hours (Bodey GP)**



**Early empirical antimicrobial therapy based on agents with anti-Gram-negative and anti-Pseudomonas activity dramatically decreases mortality in febrile neutropenia. (Schimpff S et al, 1971)**

**Not all  
neutropenic patients  
are alike**



**Talcott JA, et al: The medical course of cancer patients with fever and neutropenia.**

**Arch Intern Med 1988;148:2561-68.**

**Risk assessment**

**HIGH RISK**

**Group 1.: Patients hospitalized at onset of fever**

**Group 2.: Outpatients with comorbidity**

**Group 3.: Patients with uncontrolled  
underlying disease (cancer)**

**LOW RISK**

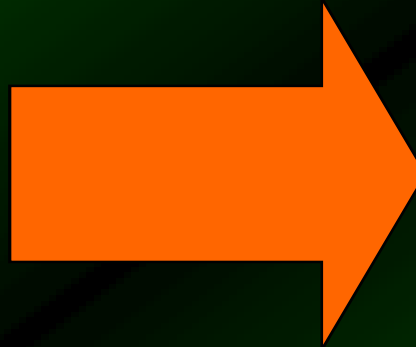
**Group 4.: Outpatients without comorbidity  
or uncontrolled underlying disease (cancer)**

# Multinational Association of Supportive Care in Cancer (MASCC) Risk Scoring Index

- **Burden of illness**
  - No symptoms 5
  - Mild symptoms 5
  - Moderate symptoms 3
- **No hypotension** 5
- **No chronic obstructive lung disease** 4
- **Solid tumor or no fungal infection** 4
- **No dehydration** 3
- **Outpatient at onset of fever** 3
- **Age < 60 yrs** 2

# Multinational Association of Supportive Care in Cancer (MASCC) Risk Scoring Index

**Score  $\geq 21$**



**OUTPATIENT  
THERAPY**

**LOW RISK OF SEVERE COMPLICATIONS**

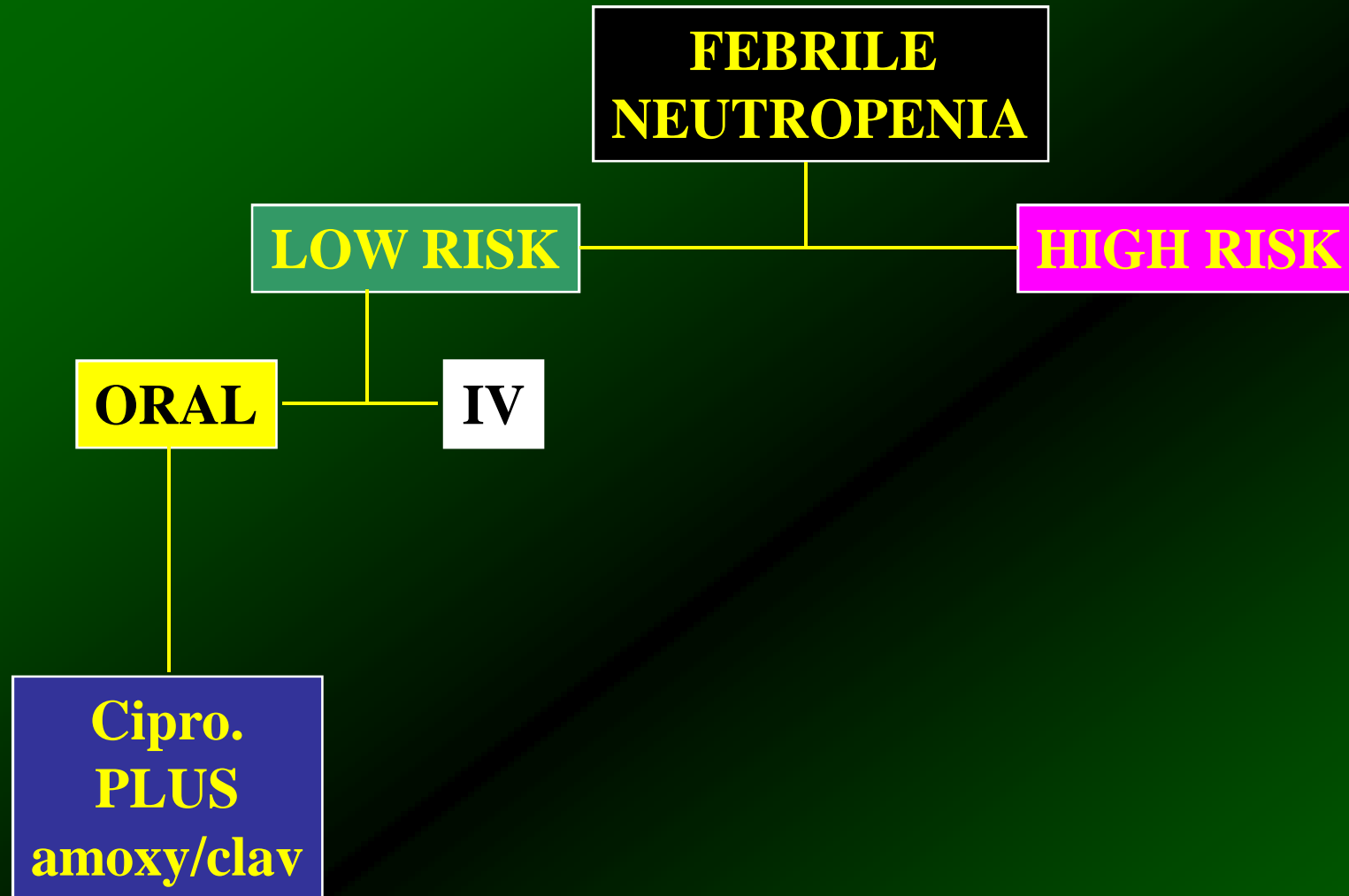
**Klastersky J et al. *J Clin Oncol.* 2000;18:3038–3051.**



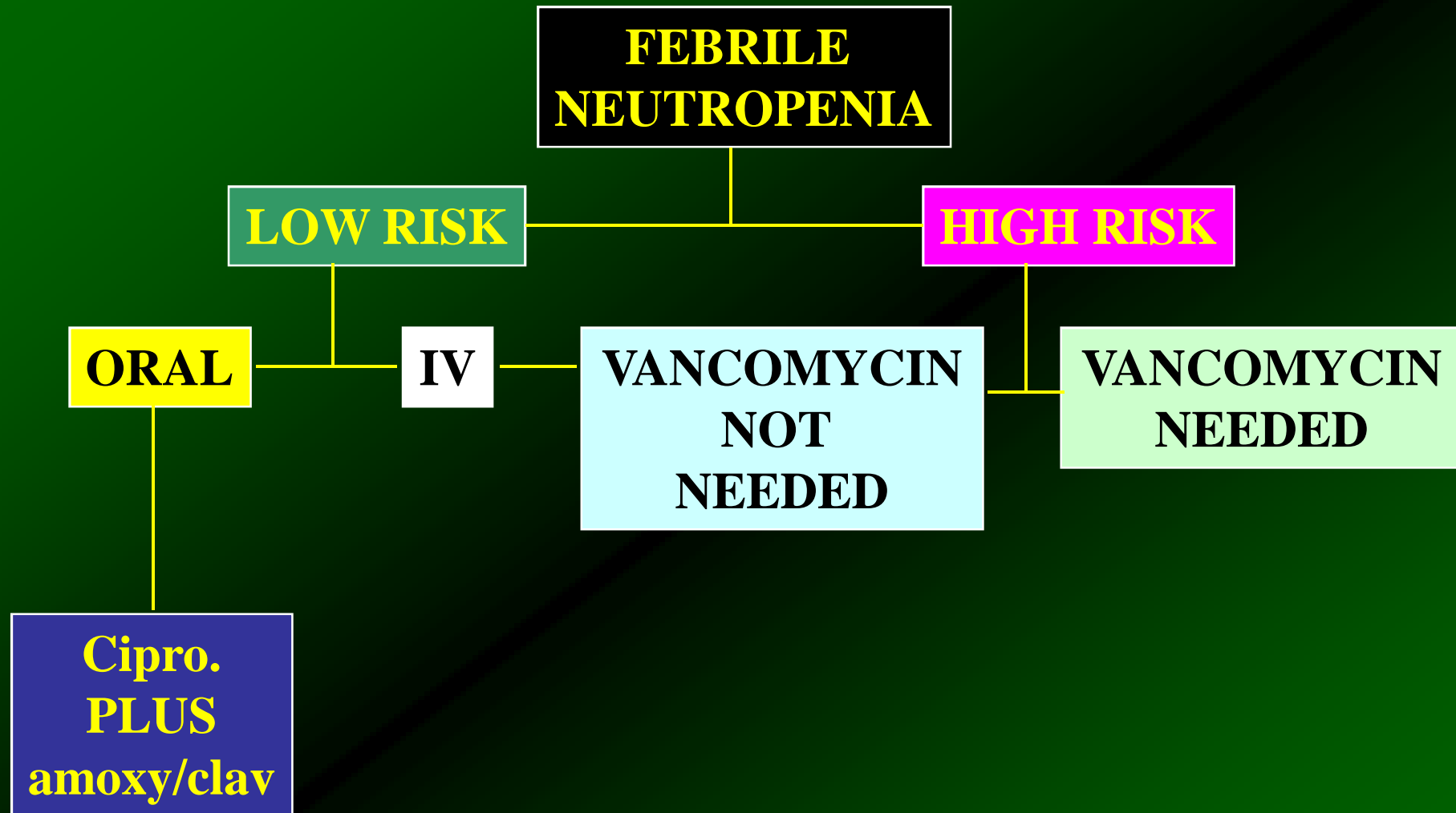
# Initial antimicrobial therapy



# Initial antimicrobial therapy



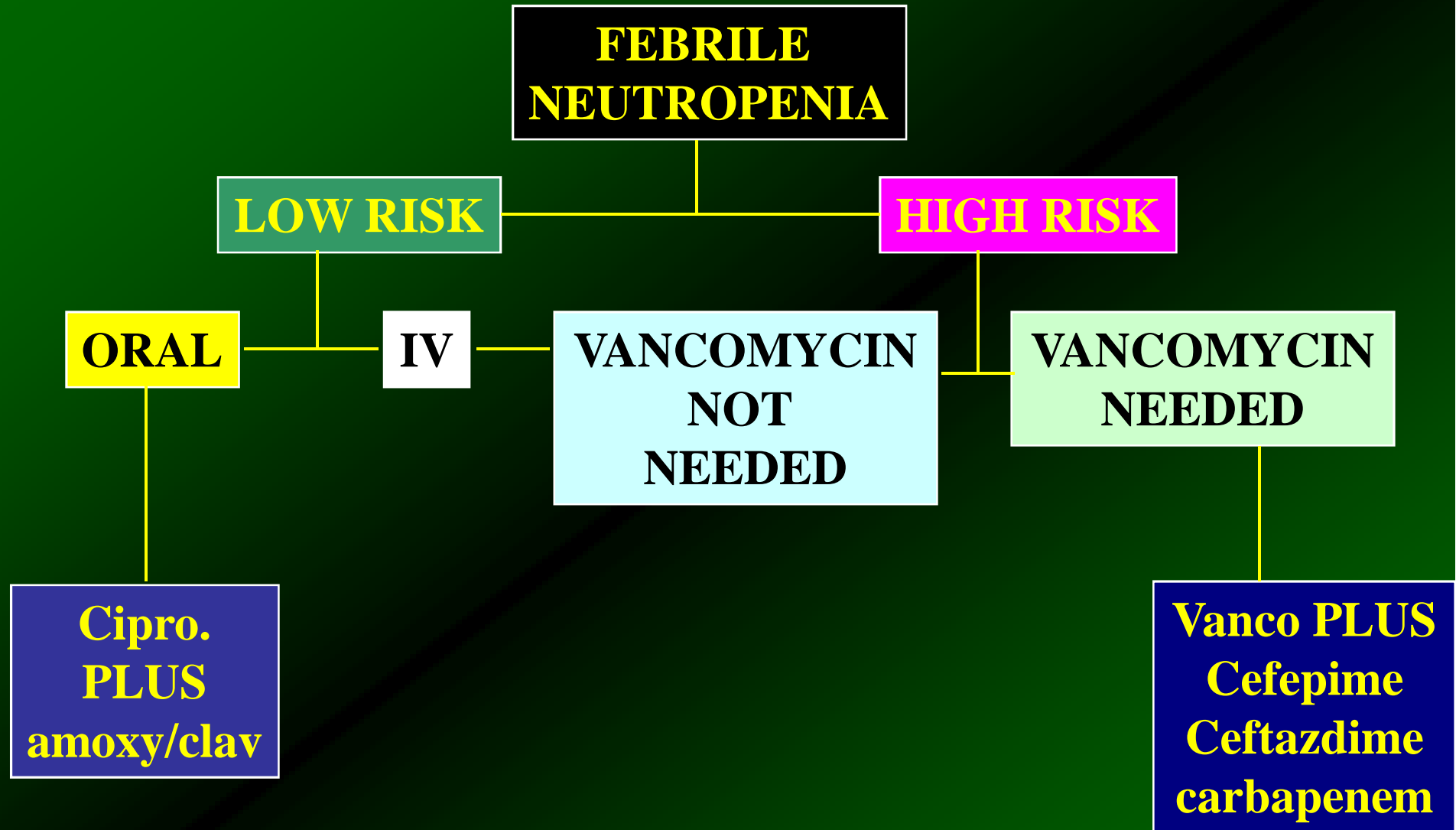
# Initial antimicrobial therapy



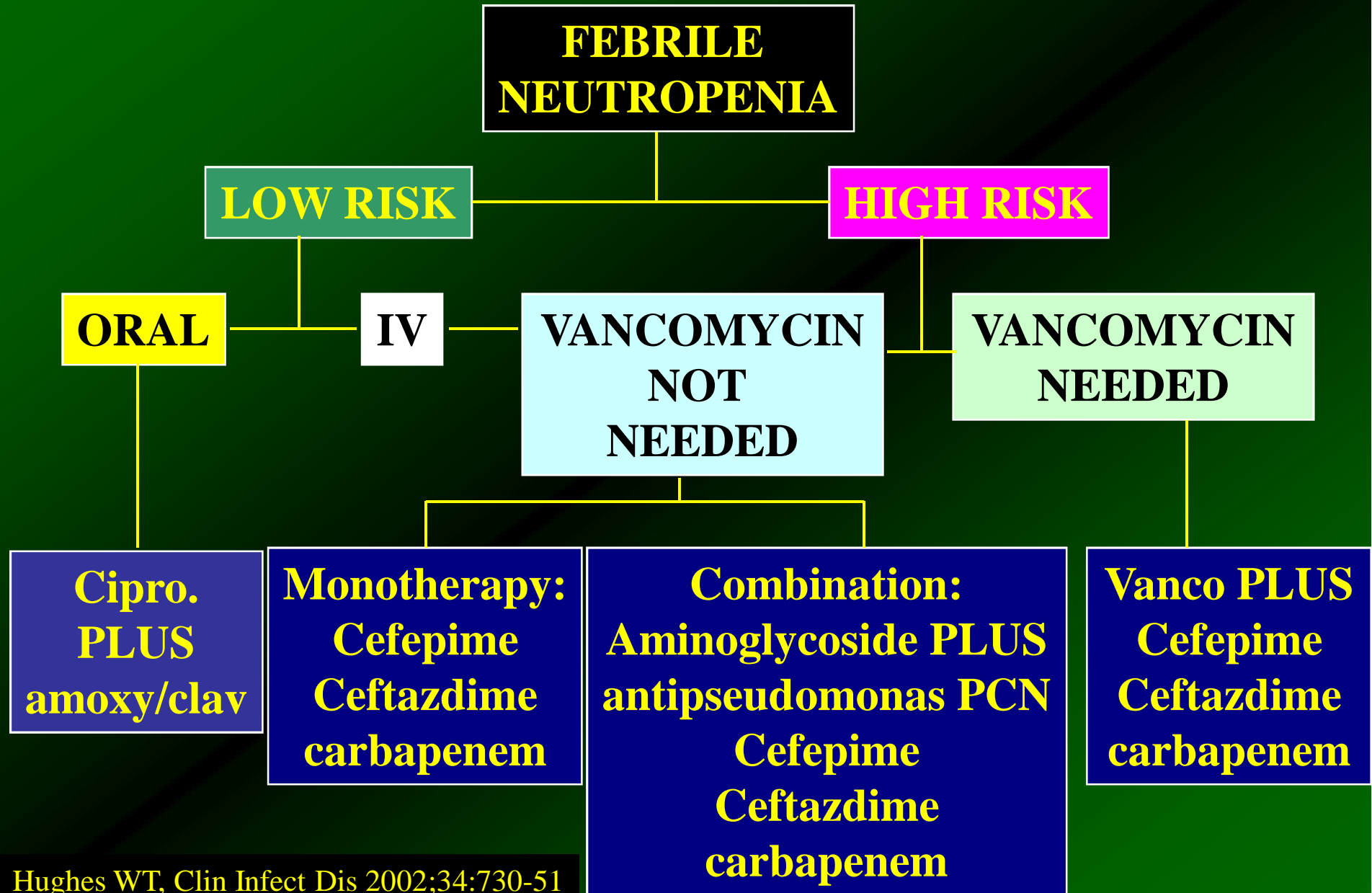
## **Initial antimicrobial combination containing vancomycin warranted**

- **Vascular device associated infection**
- **Hypotension**
- **Colonization with a betalactam-resistant organism (e.g.MRSA)**
- **Blood cultures: Gram-positive stain recovered (preliminary report)**

# Initial antimicrobial therapy



# Initial antimicrobial therapy



**Problems regarding  
the high-risk group of patients**

**Resistant bugs**

# **Do you have a resistance problem ?**

- **Be aware of**
  - **institutional epidemiology;**
  - **patients at specific risk for acquiring resistant pathogens;**
  - **local resistance patterns;**
  - **antimicrobial use.**



# Resistant Gram-positives

**Staph. coag. neg.**

**95 % resistant to  
methicillin, but low  
virulence**

***Staph. aureus***

**MRSA increasing.  
Initial vancomycin  
justified ?**

***Enterococcus spp.***

**VRE increasing.  
Initial linezolid in  
colonized pts ?**

# Resistant Gram-positives

**Strep. viridans  
group**

**In pts with mucosal  
damage and on  
quinolone  
prophylaxis.  
Penicillin resistance  
or tolerance not  
infrequent. Acute  
infection with  
hypotension and  
ARDS.**

# Resistant Gram-positives

*Leuconostoc* spp.  
*Lactobacillus* spp.  
*Pediococcus* spp.

Emerging. Resistant  
to vancomycin.

*Listeria*  
*monocytogenes*

In pts with impaired  
cell mediated  
immunity.  
Resistant to  
cephalosporins.

# Resistant Gram-negatives

*E. coli*

Fluoroquinolone  
resistance. May be  
community acquired.

*Klebsiella* spp.  
(*Enterobacter* spp.,  
*E. coli*)

ESBL-producing  
stains.

*Stenotrophomonas  
maltophilia*

Intrinsic resistance  
to carbapenems.

# Resistant Gram-negatives

*Pseudomonas  
aeruginosa,  
Acinetobacter  
baumannii*

**Multi /panresistant  
stains increasing.  
Resistance to  
betalactams,  
fluoroquinolones,  
aztreonam, less  
frequently to  
amikacin.  
Susceptible to  
colistin.**

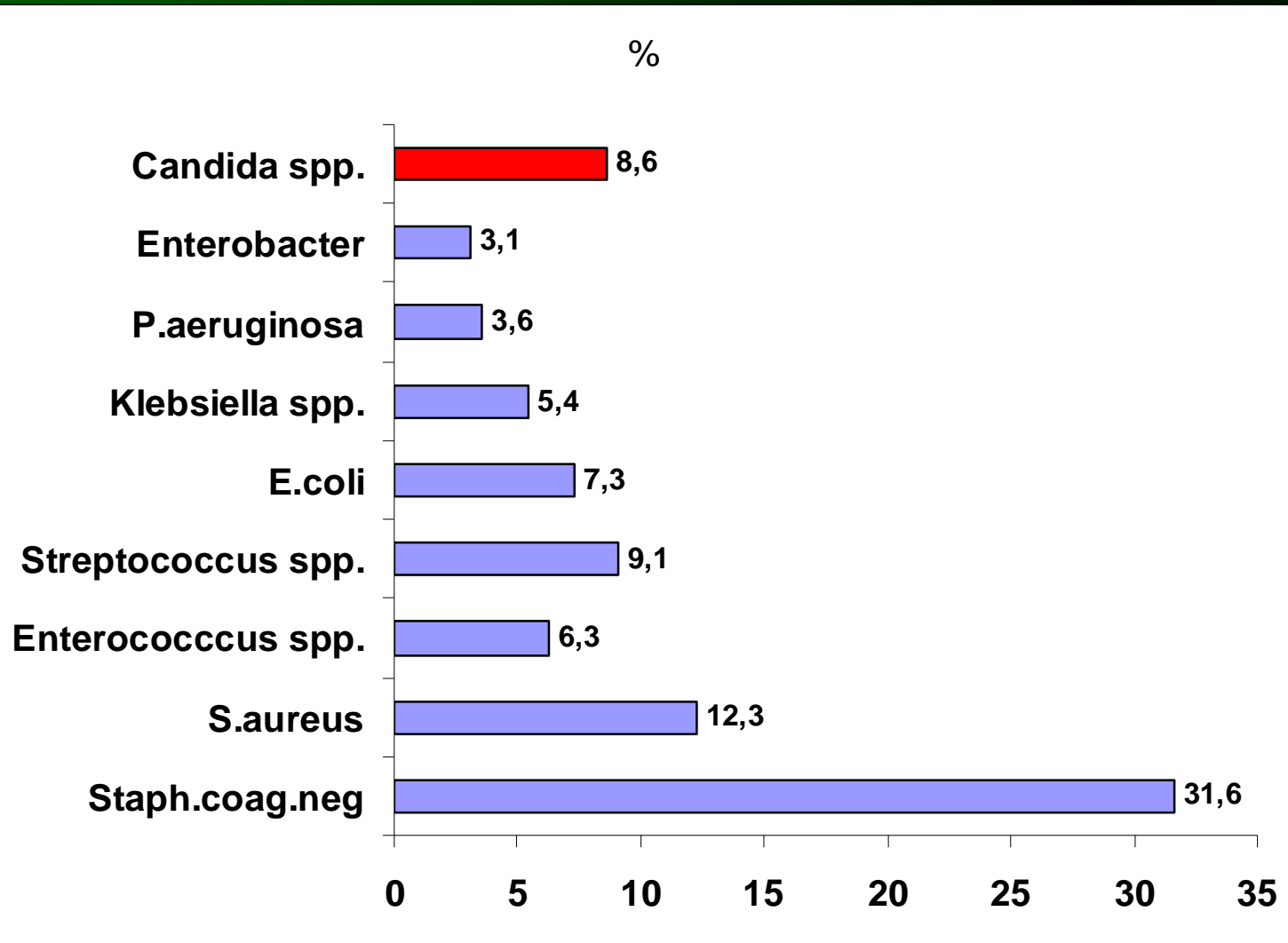
**Problems regarding  
the high-risk group of patients**

**Fungal infection**

# Species distribution of predominant pathogens in bloodstream infections in neutropenic patients.

Wisplinghoff H et al.

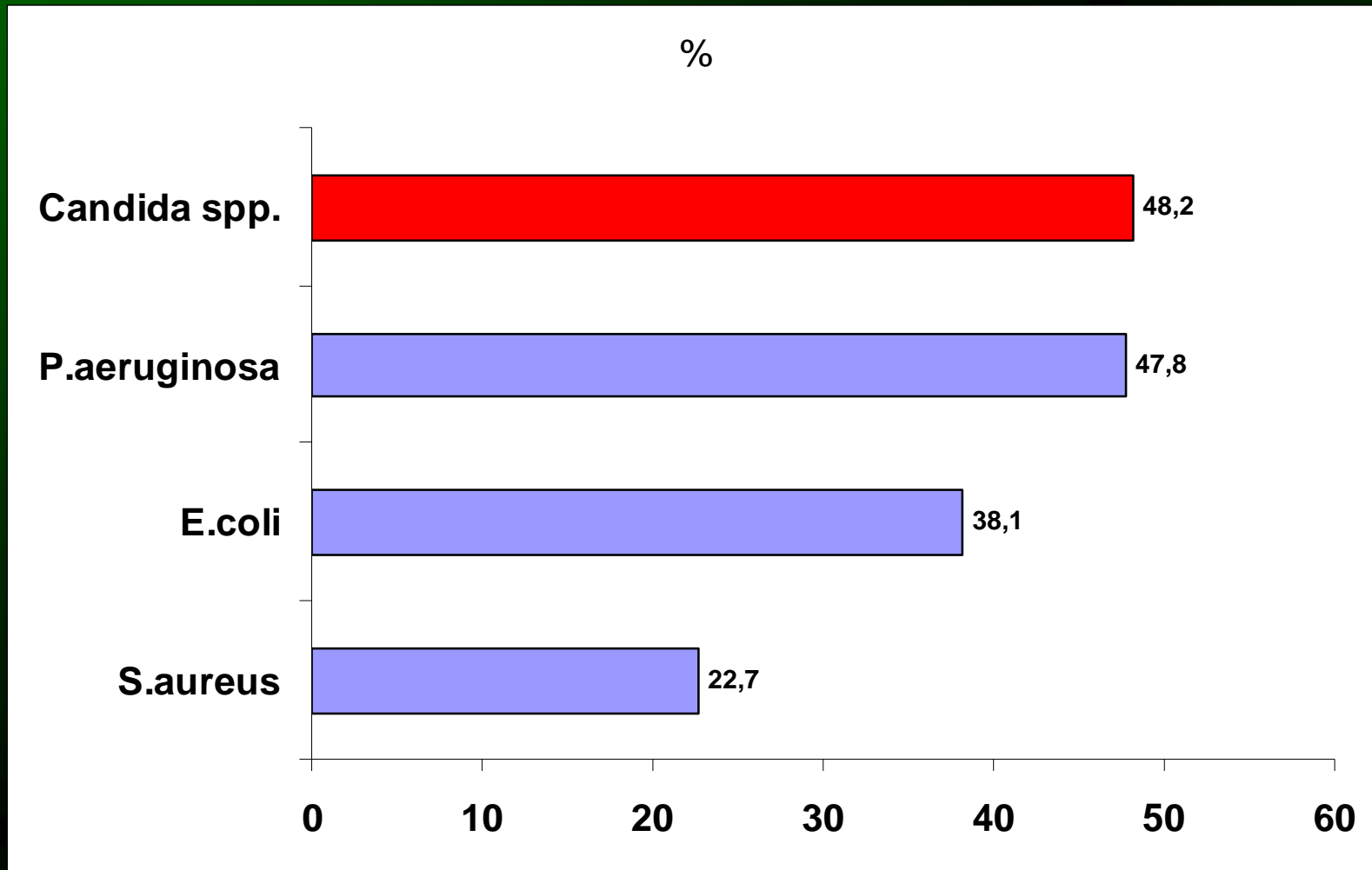
Clinical Infectious Diseases 2003; 36:1103–10



# Crude mortality rate for neutropenic patients with monomicrobial bloodstream infections, stratified by pathogen.

Wisplinghoff H et al.

Clinical Infectious Diseases 2003; 36:1103–10





# Diagnostic workup - Candida

- **Patients with persistent fever in spite of broad spectrum antibacterials.**
- **Consider risk factors, colonization and local epidemiology.**
- **First line diagnostic tool: blood cultures. But: sensitivity 50-90 %.**
- **Isolation from a sterile site: identification to species level, *in vitro* resistance to antifungals.**

# Fungal pathogens - Candida

- *Candida* spp
  - *C. albicans*: most common, low incidence of fluconazole-resistance
  - *C. tropicalis*: virulent
  - *C. parapsilosis*: nosocomial/CVC related infections
  - *C. glabrata*: less susceptible to fluconazole and amphotericin B
  - *C. krusei*: intrinsic resistance to fluconazole, less susceptible to amphotericin B

# Treatment of invasive candidosis

- **All candidemias must be treated.**
- **Options:**
  - **amphotericin B + fluconazole**
  - **caspofungin**
  - **amphotericin B /including lipid formulations /**
  - **fluconazole**
  - **voriconazole**

# Fungal pathogens - *Aspergillus*

- *Aspergillus* spp.

- *A. flavus*

- *A. fumigatus*

- *A. niger*

- *A. terreus*: resistant to amphotericin B

# Diagnostic workup - Aspergillus

- **Fungemia very rare.**
- **In high-risk patients:**
  - **Regular aspergillus antigen testing**
  - **High-resolution CT of the lungs**
- **If not contraindicated:**  
**bronchoscopy, BAL, biopsy**

# Treatment of invasive aspergillosis

- **Proven or probable cases must be treated without delay.**
- **Options:**
  - voriconazol
  - amphotericin B /including lipid formulations /
  - if refractory or intolerant: caspofungin
- **Combination therapy?**

# **Empirical antifungal treatment**

- **Diagnostic problems**
- **High mortality**
- **Trials**
  - **Pizzo PA 1993**
  - **Walsh TJ 1999, 2002, 2004**

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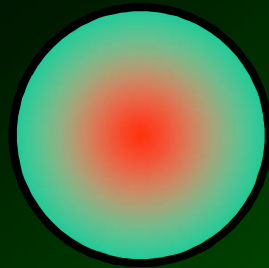
- **Infection not proven**
- **Toxicity**
- **Costs**
- **Selection of resistant pathogens**



## Other fungi

- *Cryptococcus neoformans*
- Zygomycetes (mucormycosis)
- *Pneumocystis jiroveci* (*carinii*)
- *Fusarium* spp.
- *Scedosporium* spp.
- .....

**What will come next ?**



# Future perspectives

- **Global changes in epidemiology**
- **Better understanding of risk factors and differences between patient groups**
- **Better (faster) diagnostic tools**
- **Therapy rather pre-emptive than empirical (except bacteria)**
- **Some new antimicrobials (no magic bullets expected)**