

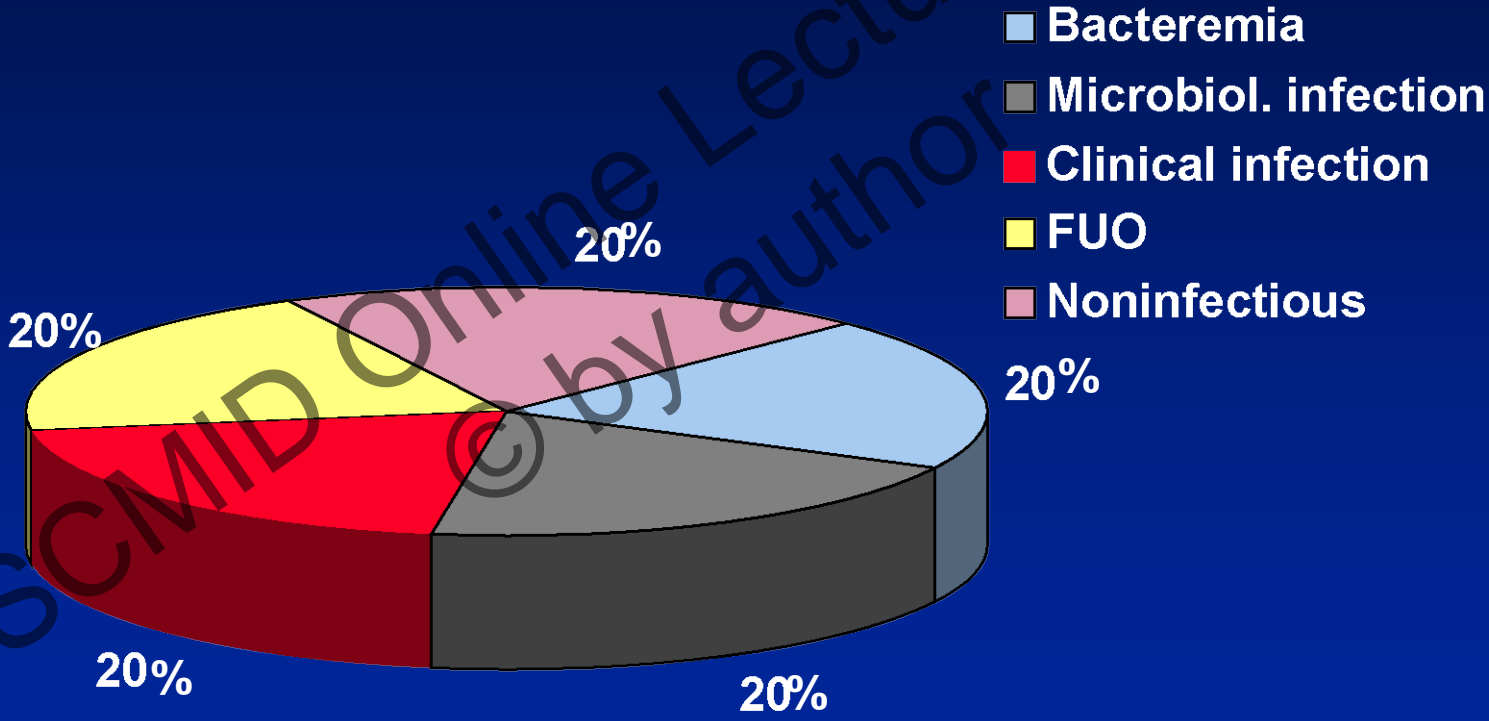
# What Should be the Duration of Empirical Antibiotic Treatment?

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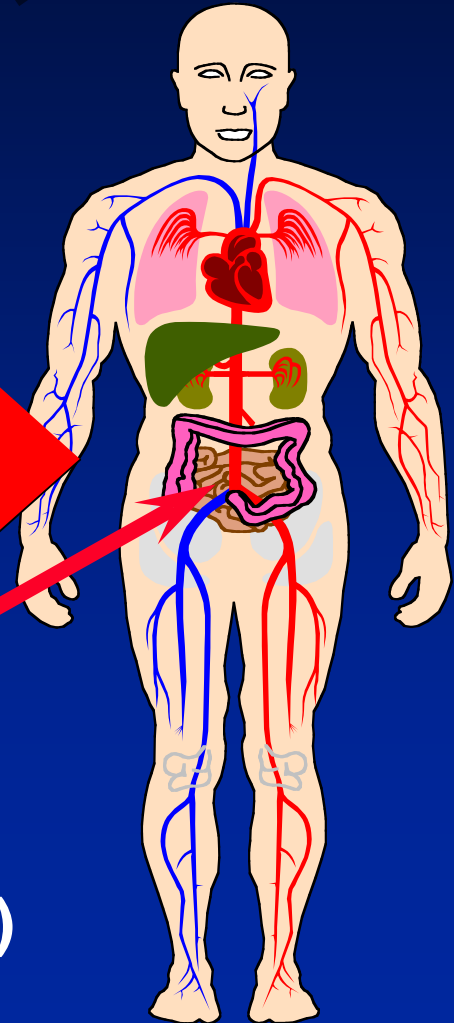
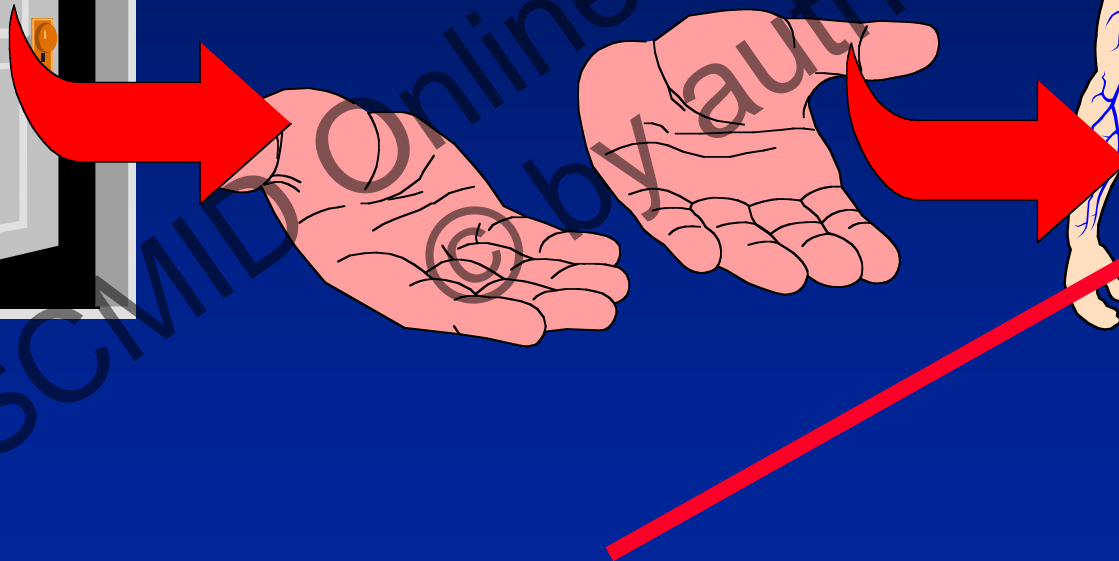
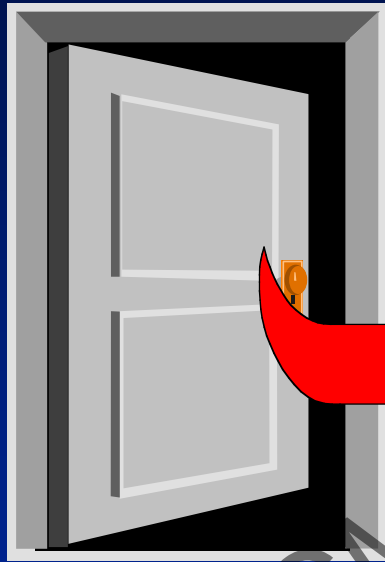
# Causes of Fever in Neutropenic Patients



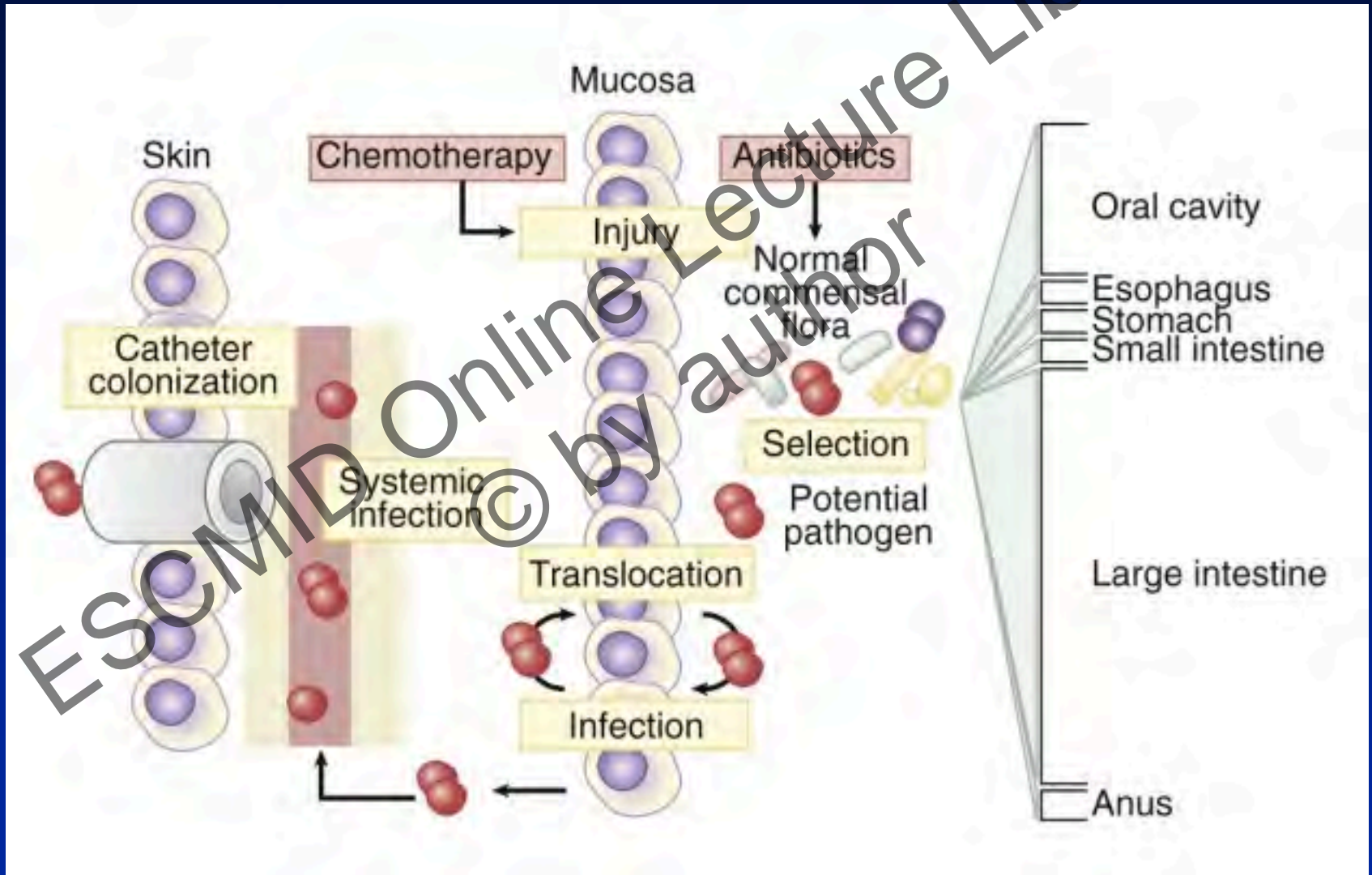
# Sources of Opportunistic Pathogens

Exogenous (%20)

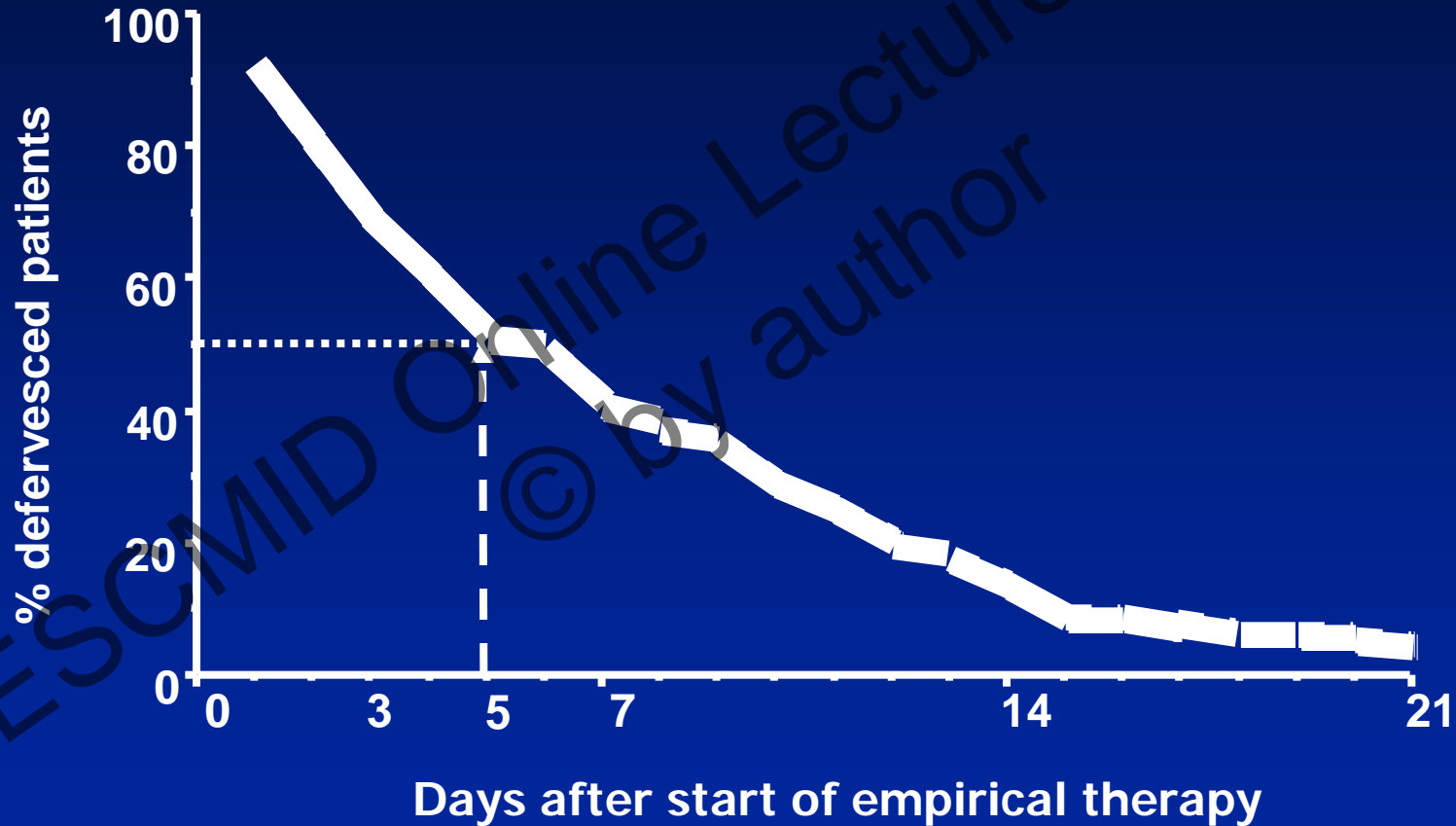
Endogenous flora (%80)



# Source of Infection in Neutropenic Patients

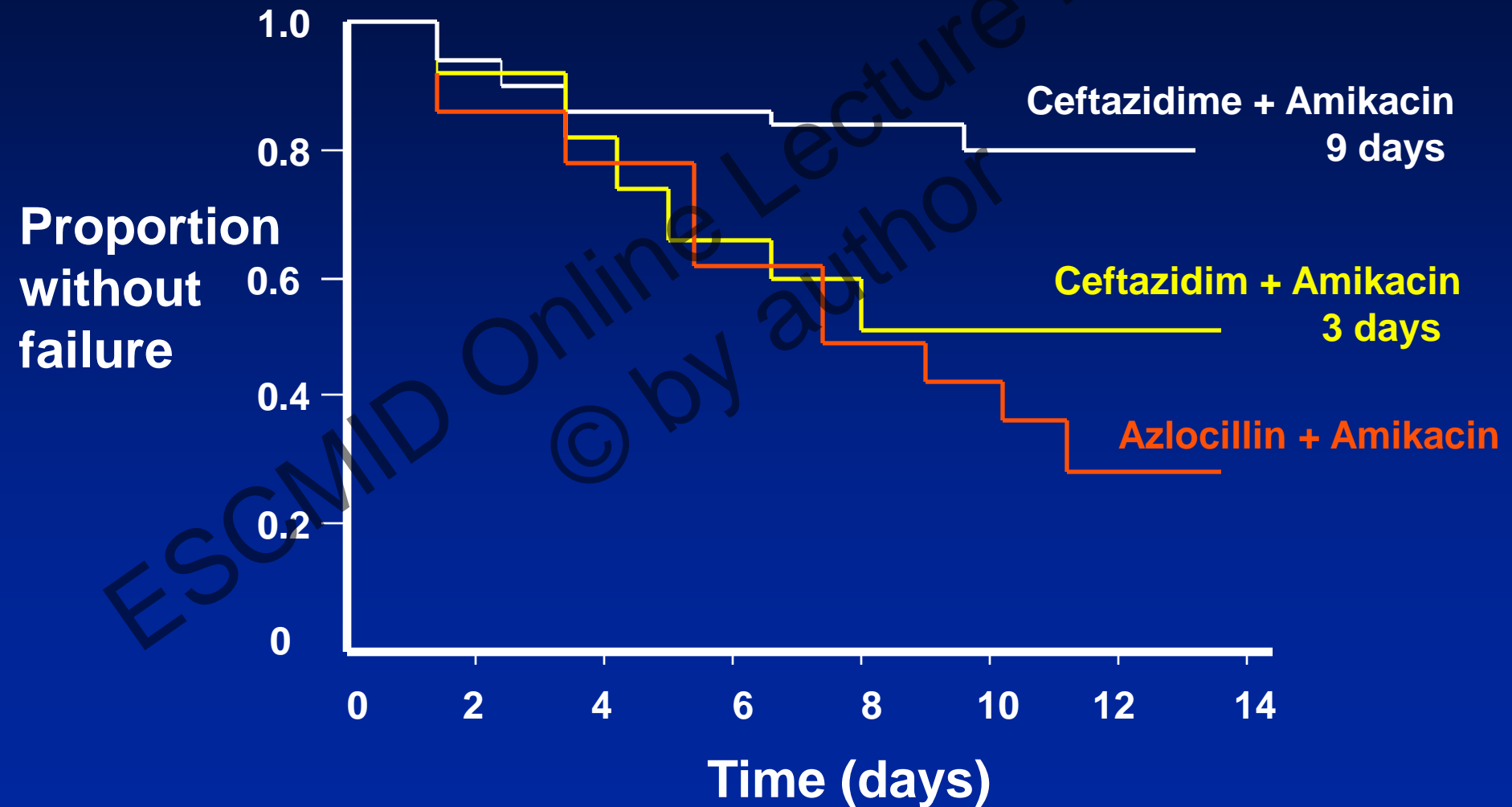


# Response to Empirical Antimicrobial Therapy



De Pauw BE, et al. Ann Int Med 1994;120:834

# Efficacy of Combinations in Bacteremic Patients



# Monotherapy

- **Advantages**

- Decreased toxicity
- Decreased cost
- Effective as combination therapy for the initial treatment
- May be the treatment of choice for “low-risk” patients

- **Disadvantages**

- Frequent modification required
- Selection of resistance
- Lack of activity against *S. epidermidis*, MRSA, some other gram-positives

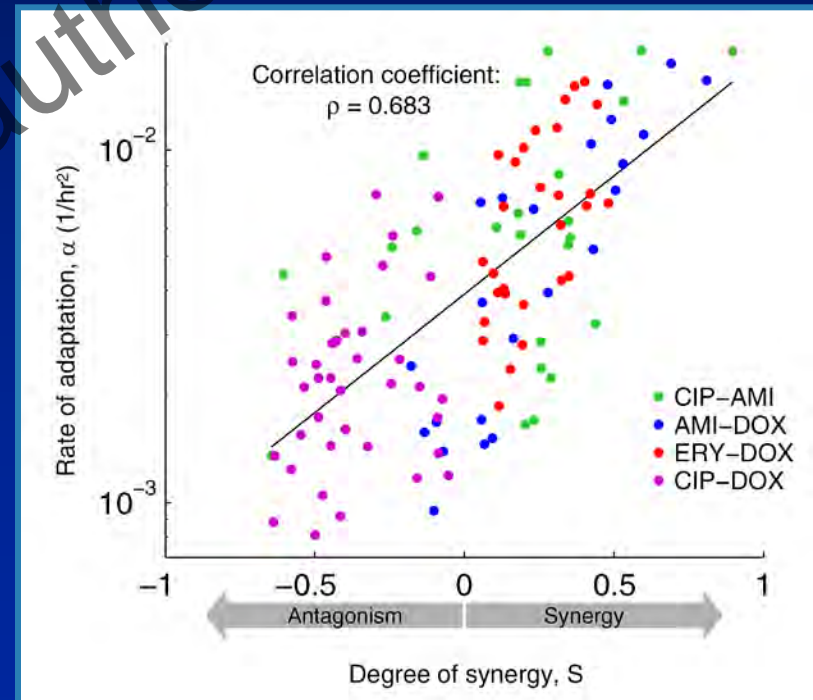
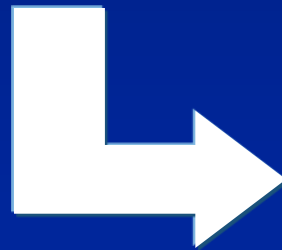
# Meta-analysis of Beta-Lactam Monotherapy vs Aminoglycosides Combinations

- 47 trials, 7807 patients
  - 9 trials compared the same beta-lactam
- No significant difference in all cause fatality (RR 0.85, 95% CI 0.72-1.02)
- Monotherapy was significantly successful (RR 0.92, 95% CI 0.85-0.99)
  - In trials comparing different beta-lactams
- Superinfection rates were similar
- Adverse events were more common with combination regimens



# Drug Combinations and the Development of Resistance

- A study of synergistic and antagonistic antibiotic combinations against *E. coli*
- Synergistic combinations facilitated development of resistance to both agents
- A high correlation between synergy and the rate of resistance adaptation was found

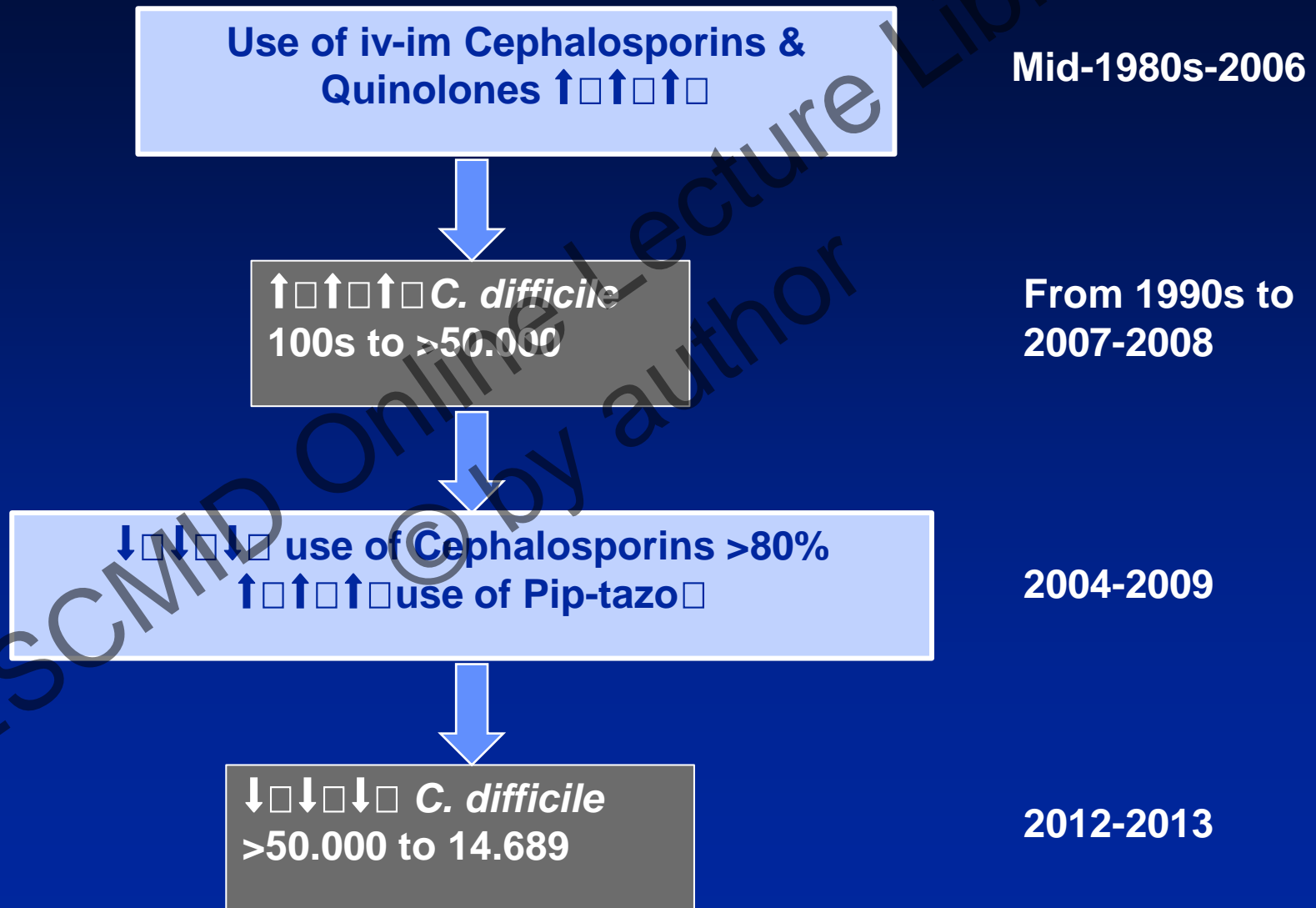


## **Problems of Prolonged Hospitalization in Patients with Neutropenia and Fever**

- **A large percentage have negative blood cultures & exhibit prompt defervescence**
- **Toxicities of antimicrobials**
- **High cost**
- **Exposure to nosocomial pathogens**
- **Increased risk of fungal infection**
- **Suboptimal quality of life**
- **Continued absence from work, school, home**

# Antibiotic Stewardship

## A British Example



# Additional Results...

- **Expected**

- Cephalosporin and quinolone R stabilized in *E. coli* and decreased in *Klebsiella* and *Enterobacter* spp.

- **Somewhat expected**

- No increase in pip-tazo resistance

- **Unexpected**

- Increase in carbapenamase-producing Enterobacteriaceae

- Highly-R to pip-tazo, MIC >128 mg/L
- Less R to carbapenems

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

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

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# Duration of Empirical Therapy

- In all settings until recovery of neutropenia ( $>500/\text{mm}^3$ ) (B-II)
  - In documented settings, longer if necessary (B-III)
  - If signs and symptoms of a documented infection resolve with appropriate duration of therapy, neutropenic patients may switch to oral quinolone prophylaxis until recovery



# Introduction to ECIL

*from ECIL1 to ECIL 4*

ESCMID



4<sup>th</sup> European Conference on Infections in Leukemia

## Duration of antibacterial treatment in FUO: Key points

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- Relapse of fever and bacterial infection are independent of discontinuing antibiotic therapy during neutropenia or after its resolution
- With appropriate antibiotic therapy, FUO has low mortality, unless patient is in septic shock





# Duration of antibiotics in FUO: Evidence & Recommendations

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- Discontinue **iv** empirical antibacterials after  $\geq 72$ h
  - *If patient has been afebrile  $\geq 48$ h and is **stable***
  - *Irrespective of neutrophil count or **expected** duration of neutropenia **BII***

Joshi *et al.*, *Am J Med* 1984  
Jones *et al.*, *J Pediatr* 1994  
Cornelissen *et al.*, *Clin Infect Dis* 1995  
Horowitz *et al.*, *Leuk Lymphoma* 1996  
Santoloya *et al.*, *Clin Infect Dis* 1997  
Lehmbecher *et al.*, *Infection* 2002  
Cherif *et al.*, *Scand J Infect Dis* 2004  
Slobbe *et al.*, *Eur J Cancer* 2009

58



4<sup>th</sup> European Conference on Infections in Leukemia

## **With few Precautions...**

- **If still neutropenic, the patient should be kept hospitalized**
  - **Close observation further 24-48 h**
- **If fever recurs antibiotics should be re-started urgently**
- **Centers using prophylactic antibiotics should consider renewing this regimen after stopping therapy**

# Relaps and Death After Discontinuation of Antibiotic Therapy During Persistent Neutropenia

Study	Year	Design	Duration of neutropenia	Continuation of antibacterial therapy		Discontinuation of antibacterial therapy during persistent neutropenia	
				Relapsing neutropenic fever	Death due to bacterial infection	Relapsing neutropenic fever	Death due to bacterial infection
Pizzo <i>et al.</i>	1979	Open randomization: continue vs. stop antibiotics	12 days (median)	1/16 (6%)	0 (0%)	7/17 (41%)	2/17 (12%)
Joshi <i>et al.</i>	1984	Observational	20.5 days (mean)	NA	NA	8/16 (50%)	0 (0%)
Pizzo <i>et al.</i>	1987	Observational	>14 days	35/93 (38%)	3/95 (3%)	NA	NA
Cornelissen <i>et al.</i>	1995	Observational	7 days (median)	NA	NA	7/85 (8%)	2/85 (2%) <sup>a</sup>
Horowitz <i>et al.</i>	1996	Observational	17 days (mean)	NA	NA	3/10 (33%)	0 (0%)
Santolaya <i>et al.</i>	1997	Open randomization: continue vs. stop antibiotics	9 days (mean)	3/39 (8%)	0 (0%)	2/36 (6%)	0 (0%)
IDG-EORTC—Cometta <i>et al.</i> and Viscoli <i>et al.</i> (unpublished)	2003 2006	Post hoc observational analysis	17.5 days (median)	49/114 (43%)	1/114 (1%)	NA	NA
Cherif <i>et al.</i>	2004	Observational	NA	NA	NA	9/49 (18%)	0 (0%)
Slobbe <i>et al.</i>	2009	Observational	20.5 days (mean)	NA	NA	NR	1/169 (0.5%) <sup>a</sup>

FUO, fever of unknown origin; NA, not analysed or not applicable.

<sup>a</sup>Secondary ciprofloxacin prophylaxis.

# Early Cessation of Empirical Therapy in Patients with Neutropenia and FUO

January 2010-June 2014  
283 neutropenia episodes (214 pts)

80 (28%)  
Inf. documented

203 (72%)  
FUO

8 (4%)  
Died under tx  
4 remained neutropenic

163 (80%)  
Defervesced & survived  
up to 10 months

32 (16%)  
Fever reappeared  
in median 5 days (1-23)

10 (6%)  
Died after 23d-10m

# Outcome in 32 Episodes with Relapsed Fever

32 episodes  
6 d median tx (5-22 d)  
5 d median after defervesced (1-23 d)

20 (63%) relapsed as FUO

No mortality

12 (37%) relapsed as documented infection

2 died (6%)  
- CR-Kp bacteremia  
- Inv. aspergillosis

10 (94%) survived up to a year

# Conclusions

- **Short duration of empirical therapy in patients with neutropenia and FUO is safe and effective**
- **Unnecessarily long duration of treatment may cause**
  - **Emerging resistance**
  - **Increased toxicity**
  - **High cost**

**Thank you....**

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