1st European Conference on Infection in Leukemia

EMPIRICAL ANTIBACTERIAL TREATMENT: GLYCOPEPTIDES AND OTHER GRAM-POSITIVE ANTIBACTERIALS

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ELN European LeukemiaNet

EBMT

EORTC European Organisation for Research and Treatment of Cancer

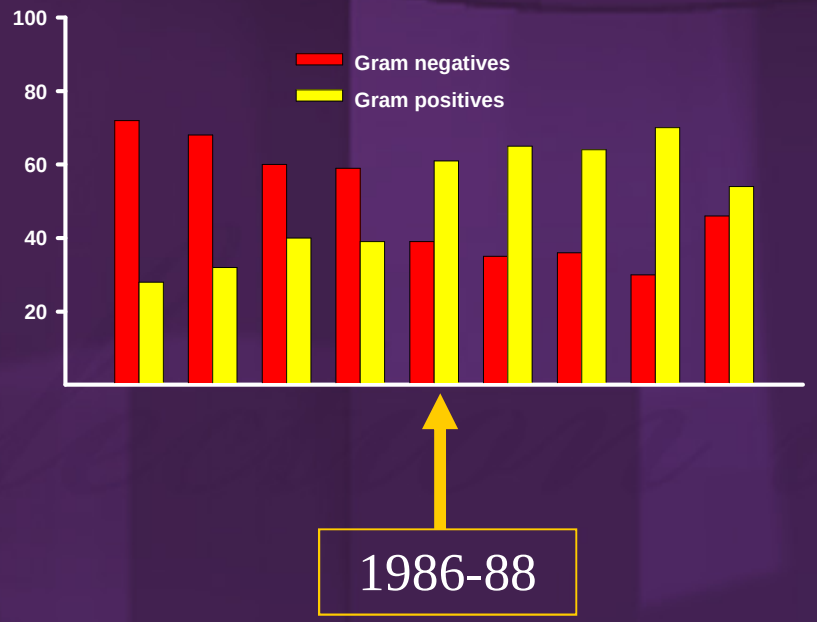
ICHS International Conference on Infection in Immunocompromised Host

BACKGROUND

1. **Epidemiological data in the mid 80’**

2. **Development of resistance to glycopeptides in 90’**

IATG-EORTC TRIALS 1973-2000



GLYCOPEPTIDES (GP) IN NEUTROPENIC PATIENTS: OBJECTIVES

1. **Should GP be given as upfront empirical therapy ?**

2. **Should GP be given in case of documented Gram positive MDI?**

3. **Should GP be given in case of persistent fever after initial broad spectrum empirical antibiotic therapy?**

GLYCOPEPTIDES IN NEUTROPENIC PATIENTS: METHODS

- **Literature review**
  - **Search**
    - **Medline**
    - **Cochrane**
    - **Pubmed**
    - **Manual search bibliography of referenced publications**
    - **ICAAC, ECCMID, ASH, ASCO, and EBMT 2002-2005**
- **CDC grading**
- **Questionnaire on European practices.**

GLYCOPEPTIDES IN NEUTROPENIC PATIENTS: METHODS

1. **Randomized controlled trials**

2. **Meta-analysis**
   1. **Paul et al JAC 2005; 55: 436-444**
   2. **Vardakas Lancet Infect Dis 2005; 5: 431-439**

3. **Published guidelines**

GLYCOPEPTIDES IN NEUTROPENIC PATIENTS

1. **Upfront empirical therapy**

2. **In case of persistent fever after initial broad spectrum empirical antibiotic therapy**

3. **In case of documented Gram positive MDI**

RANDOMIZED CONTROLLED TRIALS WITH THE SAME ANTIBIOTIC(S) IN THE 2 GROUPS (1)

Trial/year	N=	Antibiotic	Glycopeptide
Karp 1986	60	Ticar-genta	Vancomycin
Del Favero 1987	47	Cefta-amika	Teicoplanin
Micozzi 1990	46	Pipera-amika	Teicoplanin
De Pauw 1990	103	Cefta	Teicoplanin
EORTC 1991	747	Cefta-amika	Vancomycin

RANDOMIZED CONTROLLED TRIALS WITH THE SAME ANTIBIOTIC(S) IN THE 2 GROUPS (2)

Trial/year	N=	Antibiotic	Glycopeptide
Novakova 1991	103	Cefta	Vancomycin
Ramphal 1992	127	Cefta	Vancomycin
Martino 1992	158	Pipera-amika	Teicoplanin
Pico 1993	102	Cefta	Vancomycin

CA5 ComettaA; 21/09/2005

RANDOMIZED CONTROLLED TRIALS WITH DIFFERENT ANTIBIOTICS IN THE 2 GROUPS (1)

Trial/year	N=	Antibiotic- no GP	Antibiotic + GP
Shenep 1988	101	Ticar-amika	Ticar/clav-amika
Meunier 1990	75	Cefta-amika	Cefta
Viscoli 1991	193	Cefta-amika	Cefta
Riikonen 1991	89	Imipenem	Cefta
Bosseray 1992	87	Imipenem	Cefta

Diapositive 9

CA6 ComettaA; 21/09/2005

RANDOMIZED CONTROLLED TRIALS WITH DIFFERENT ANTIBIOTICS IN THE 2 GROUPS (2)

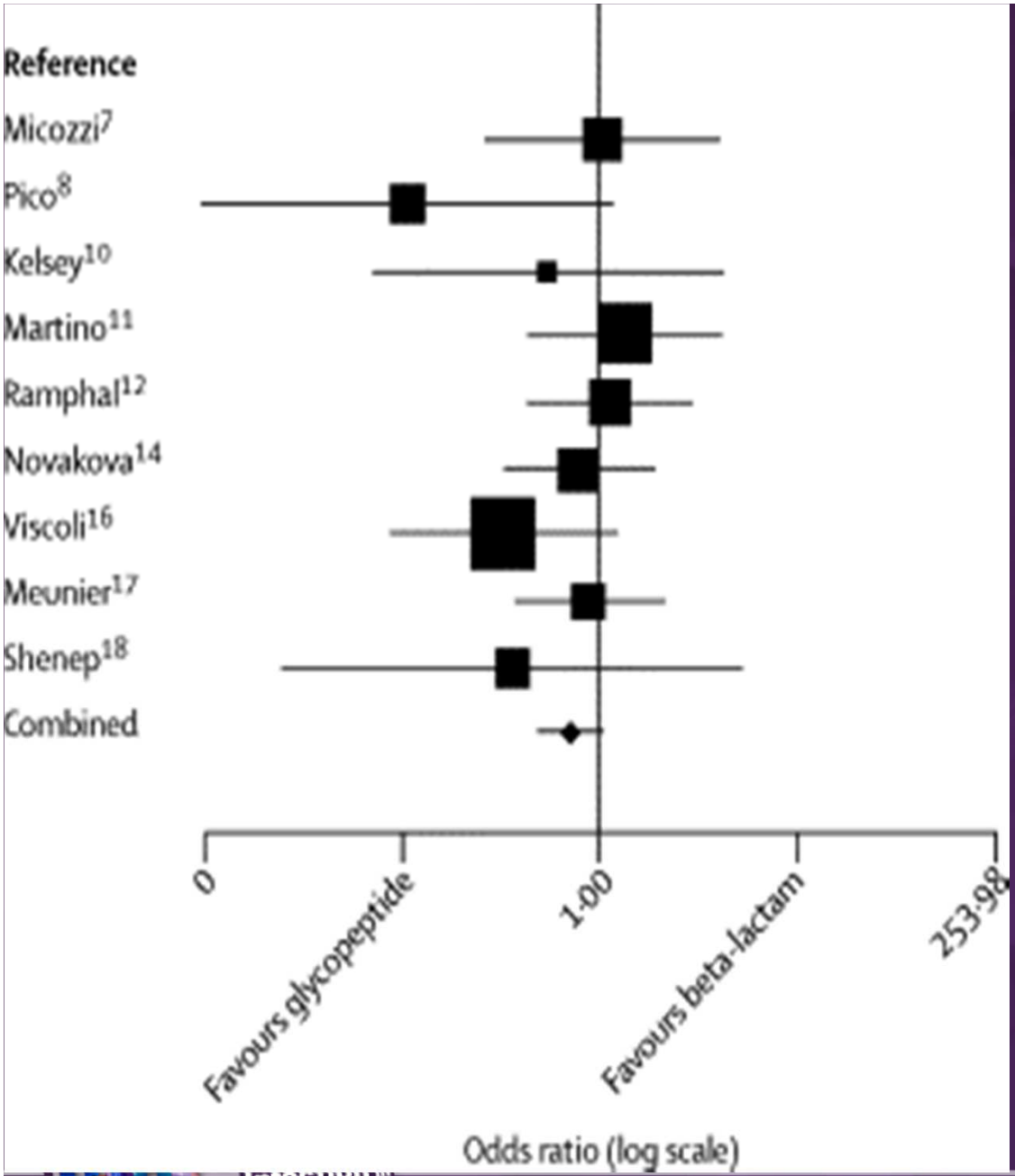
Trial/year	N=	Antibiotic-no GP	Antibiotic + GP
Spencer 1990	59	Pip-genta	Aztreonam
Kelsey 1992	71	Pip-genta	Cefta
Micozzi 1993	104	Pip-amika	Pip/tazo-amika
Granowetter 1988	151	Carbeni-cephalo-genta	cefta

Diapositive 10

CA7 ComettaA; 21/09/2005

GLYCOPEPTIDES AS UPFRONT THERAPY

1. **Mortality**
2. **Success, duration of fever, shock**
3. **Further infections, breakthrough bacteremia**
4. **Toxicity**



1. Odds ratios of mortality

Vardakas Lancet Infect Dis 2005; 5: 431-439

MORTALITY (1)

Trial/year	No Glycopeptide Death/total	Glycopeptide Death/total
Micozzi 1993	3/56	3/58
Kelsey 1992	2/29	1/29
Martino 1992	4/83	5/75
Ramphal 1992	6/63	7/64
Novakova 1991	9/60	7/60
Meunier 1990	9/50	8/50
Shenep 1988	1/48	0/53

MORTALITY (2)

Trial/year	No Glycopeptide Death/total	Glycopeptide Death/total
De Pauw 1990	6/51	4/52
EORTC 1991	19/370	24/377
Viscoli 1991	7/95	2/98
Pico 1993	10/69*	0/33

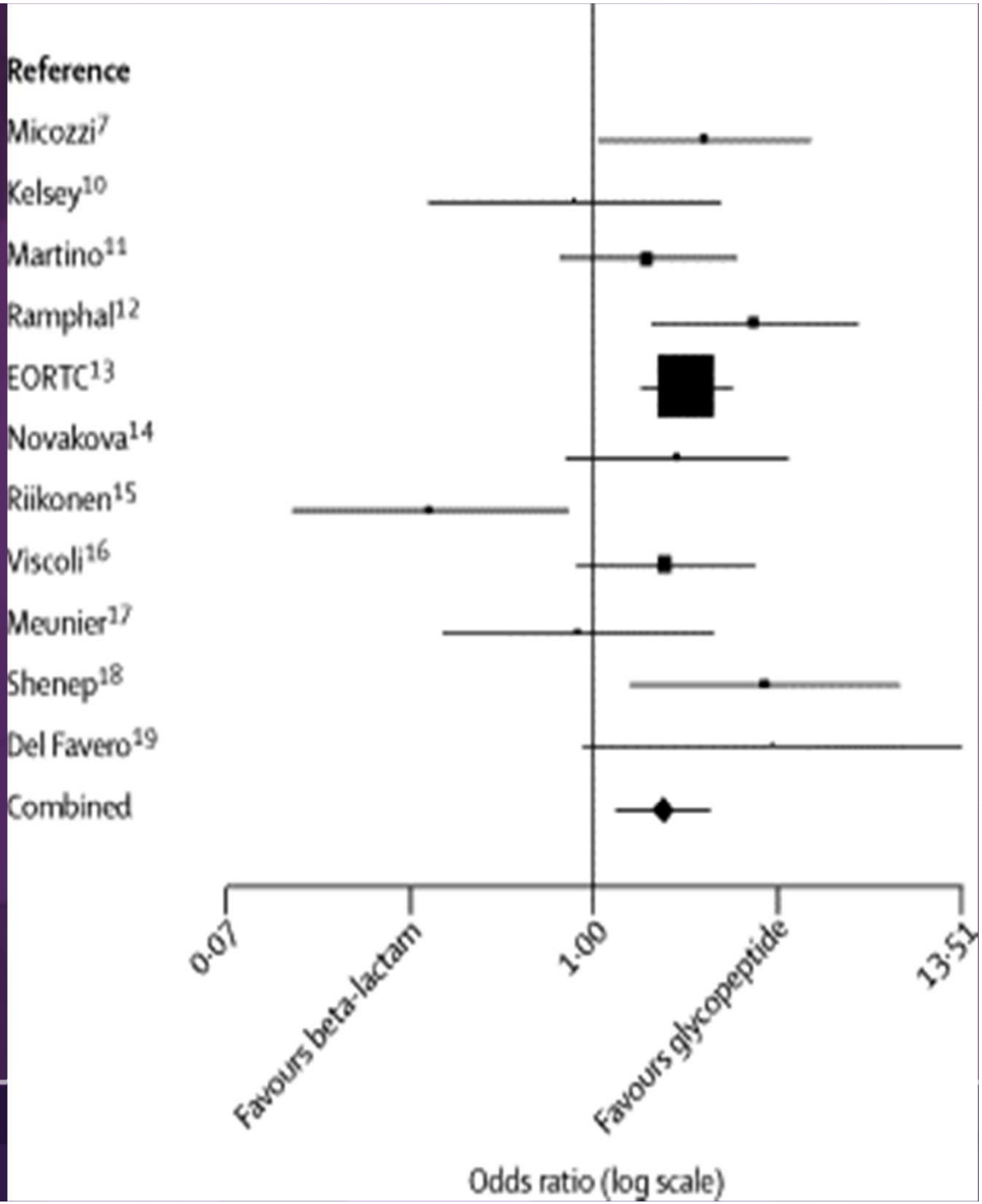
*** Ceftazidime 1g q 8h**

GLYCOPEPTIDES AS UPFRONT THERAPY

1. **Mortality**
2. **Shock, success, duration of fever**
3. **Further infections, breakthrough bacteremia**
4. **Toxicity**

2. Odds ratios of success without modification

Vardakas Lancet Infect Dis 2005; 5: 431-439



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Initial addition of vancomycin for the empirical treatment of Gram-positive bacteremia in neutropenic patients

Modification of initial empirical treatment	Cefta-amika (n = 68)	Cefta-amika + vancomycin (n = 67)	
Vancomycin	22%	0%	<0.001
Other antibiotic	10%	12%	
Amphotericin B	10%	21%	<0.001
Acyclovir	8%	11%	

EORTC-IATCG, J Infect Dis, 1991; 163: 951-958

2.Time to defervescence

- **EORTC : no difference**
- **Karp: significant difference (median 14 days in placebo group vs 9 days in GP group)**
- **Meta-analysis: pooling data from 2 trials: no difference**

3.BREAKTHROUGH INFECTION (1)

Trial/year	No Glycopeptide /total	Glycopeptide /total
EORTC 1991	50/370 (13.5%)	42/377 (11%)
Novakova 1991	6/51	8/52
Viscoli 1991	9/63	11/75
Kelsey 1992	2/35	3/36
Ramphal 1992	8/63	5/64
Micozzi 1993	9/58	7/56
Bosseray 1992	1/43	1/44

3. BREAKTHROUGH INFECTION (2)

Trial/year	No Glycopeptide /total	Glycopeptide /total
Karp 1986	7 (32%)*	0
Marie/Pico 1993	35/146 (24%) G+ : 29/146	5/77 (6.5%) G+: 2/77

* Late onset G+ sepsis

3. G+ BREAKTHROUGH BACTEREMIA

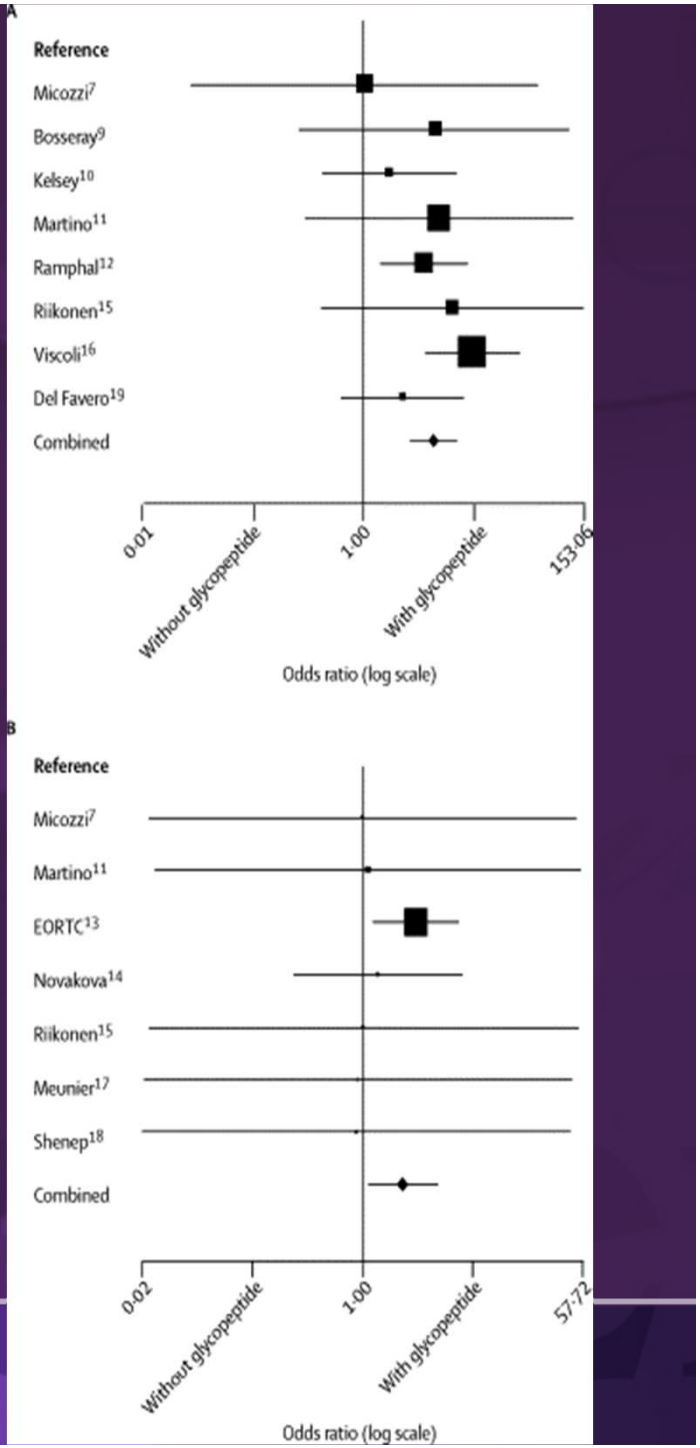
Trial/year	No Glycopeptide n/total	Glycopeptide n/total
Shenep 1988	9/48*	1/53
Riikonen 1991	1/45	0/44
Granowetter 1988	1/55	1/46
Kelsey 1990	0/35	1/38

* CNS: 5. Viridans streptococci: 4 (1 death due to shock)

4. Odds ratio of adverse effects

A. All adverse effects

B. nephrotoxicity



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Vardakas Lancet Infect Dis 2005; 5: 431-439

4. ADVERSE EFFECTS (1)

Trial/year	No Glycopeptide n/total	Glycopeptide n/total
Bosseray 1992	0/43	2/44
Kelsey 1992	8/35	8/36
Martino 1992	0/83	2/75
Ramphal 1992	6/63	19/64
Viscoli 1991	4/95	34/98
Riikonen 1991	0/45	3/44
Del Favero 1987	4/33	6/33

4.ADVERSE EFFECTS (2) EORTC 1991

Adverse effect	No Glycopeptide n=370	Glycopeptide n= 383
Nephrotoxicity	9 (2%)	24 (6%)
Hepatotoxicity	50 (13.5%)	85 (22%)
Hypokaliemia	35 (9%)	55 (14%)
Rash	12 (3%)	26 (7%)

EORTC-IATCG, J Infect Dis, 1991; 163: 951-958

4.ADVERSE EFFECTS (3): nephrotoxicity

Trial/year	No Glycopeptide /total	Glycopeptide /total
Karp 1986	23/29	22/31
Kelsey 1992	1/35	0/36
Martino 1992	0/83	0/75
Riikonen 1991	0/45	0/44
Del Favero 1987	0/33	0/33
Novakova 1991	3/51	4/52
Meunier 1990	0/36	3/39

GLYCOPEPTIDES IN NEUTROPENIC PATIENTS

1. **Upfront empirical therapy**

2. **In case of documented Gram positive MDI**

3. **In case of persistent fever after initial broad spectrum empirical antibiotic therapy**

Bacteremia due to viridans streptococci in granulocytopenic cancer patients

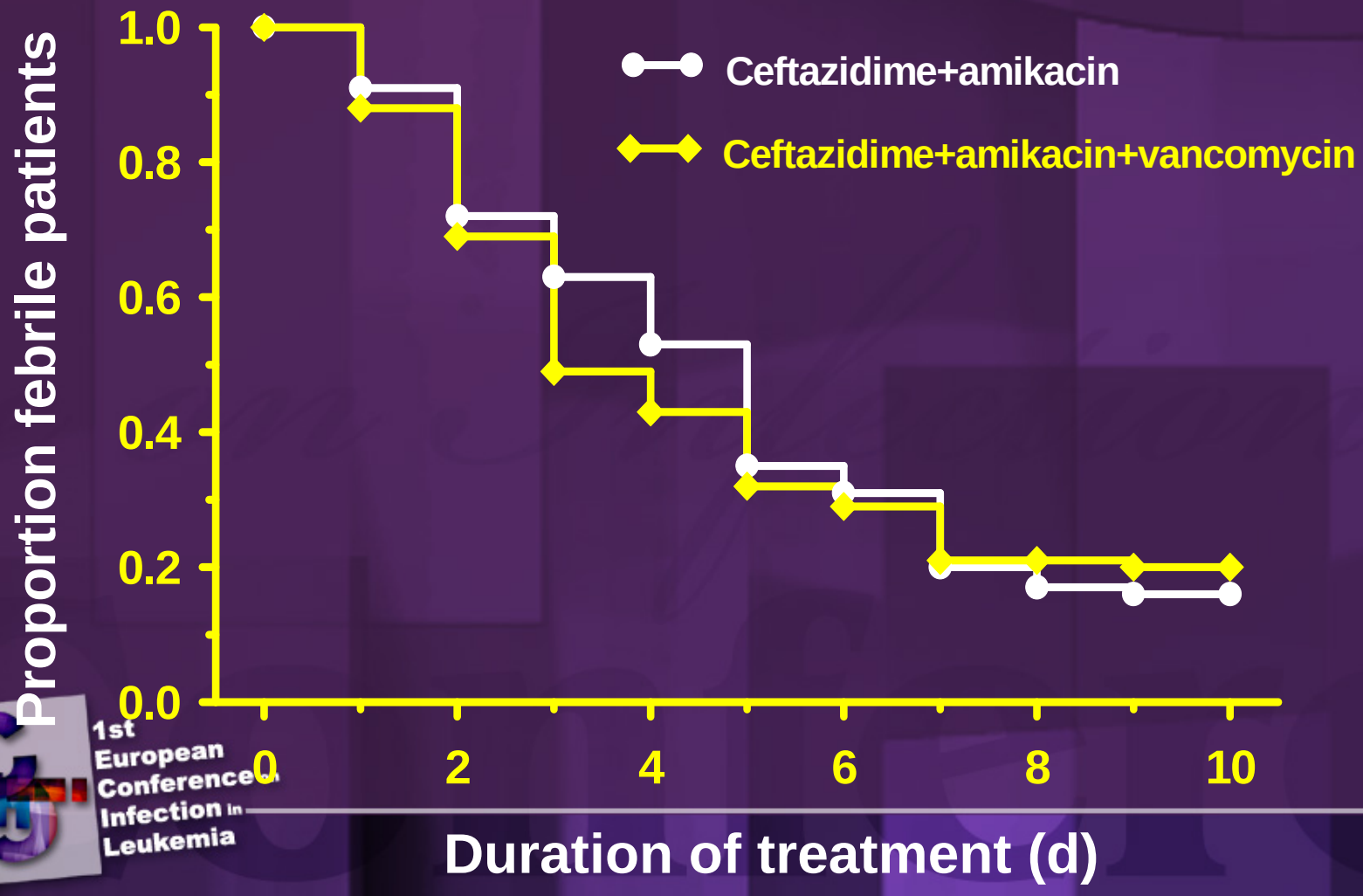
Trial/year	Pts number	Bacteremia due to S.viridans
Feld 2000	409	19 (4.6%)
Del Favero 2001	733	31 (4.3%)
Fleishback 2001	342	10 (2.9%)
Cordonnier 2003	513	24 (4.6%)
IATG-EORTC 2003	763	36 (4.7%)

EORTC-IATCG trial V: Gram-positive bacteremias

	Ceftazidime + Amikacin (n=68)	Ceftazidime + amikacin + vancomycin (n=67)
Streptococci	30	27
viridans	21	23
Coagulase-neg. staph.	28	21
S. aureus	4	16
Other	6	3

EORTC-IATCG, JID, 1991

Initial addition of vancomycin for the empirical treatment of Gram-positive bacteremia in neutropenic patients



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EORTC-IATCG, J Infect Dis, 1991; 163: 951-958

PATIENTS WITH SKIN AND SOFT TISSUE INFECTIONS

	Mono N=367	Comb N=355	Mono + V N=53	Comb + V N=43
Success (%)	35	33	42	42
Infectious mortality (%)	6	8	6	7
Days to defervescence	7.6	7.5	7.7	8.0
Superinfection (%)	10	10	15	8

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Dompeling Eur J Cancer 1996; 8: 1332

GLYCOPEPTIDES IN NEUTROPENIC PATIENTS

1. **Upfront empirical therapy**

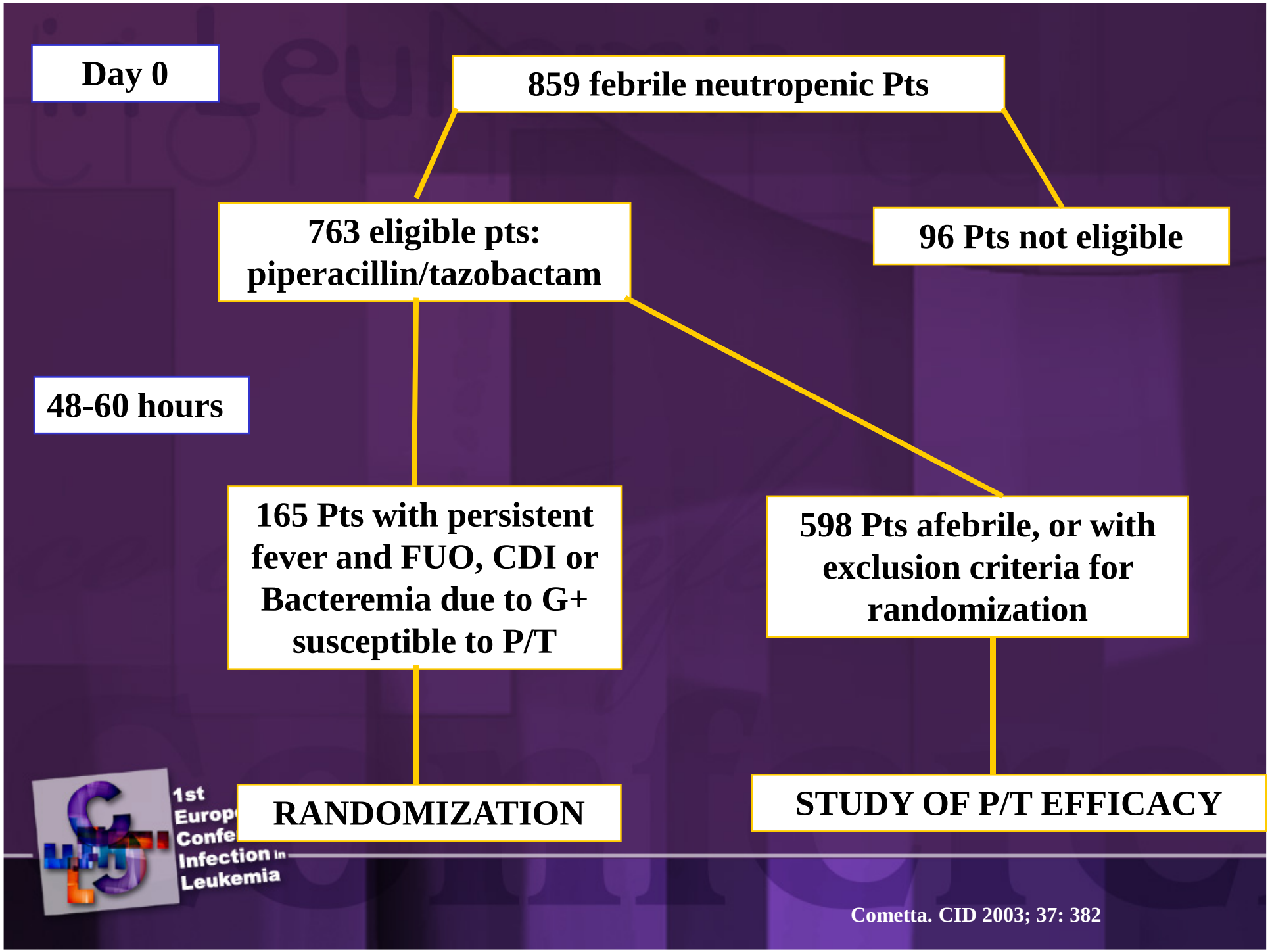
2. **In case of documented Gram positive MDI**

3. **In case of persistent fever after initial broad spectrum empirical antibiotic therapy:**

- **Cometta et al CID 2003; 37: 382**
- **Erjavec et al JAC 2000; 45: 843**

Addition of glycopeptides in neutropenic cancer patients

Trial/year	Pts number	pts with addition of glycopeptides
De Pauw 1994	722	26 %
IATG-GIMEMA 1996	987	36%
Winston 2001	541	31%
Sanz 2002	867	45%
Peacock 2002	471	62%

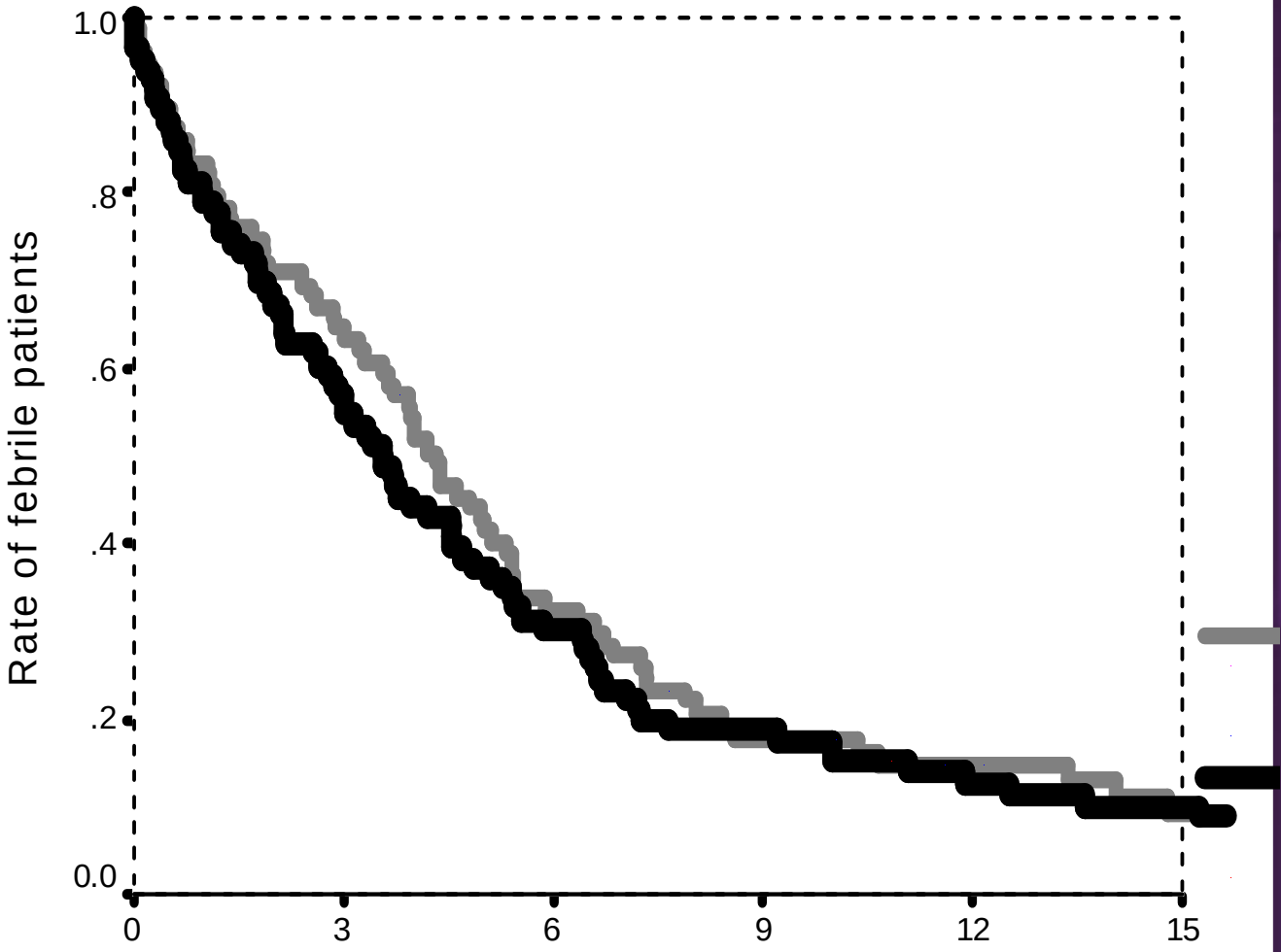

Day 0
859 febrile neutropenic Pts
763 eligible pts: piperacillin/tazobactam
96 Pts not eligible
48-60 hours
165 Pts with persistent fever and FUO, CDI or Bacteremia due to G+ susceptible to P/T
598 Pts afebrile, or with exclusion criteria for randomization
RANDOMIZATION
STUDY OF P/T EFFICACY
1st Europ Confe Infection in Leukemia
Cometta. CID 2003; 37: 382

Randomized patients: defervescence

	Placebo N = 79	Vancomycin N = 86
Pts with defervescence	73 (92%)	82 (96%)
Pts with defervescence under protocol therapy	36 (45%)	42 (49%)
Pts with defervescence after change of protocol therapy	37 (47%)	40 (47%)
Median time to defervescence (Days; 95% C.I.)	4.3 (3.3-4.7)	3.5 (2.7-4.4)

Cometta. CID 2003; 37: 382

Overall time to defervescence



Time zero : administration of vancomycin or placebo

Cometta. CID 2003; 37: 382

Outcome of the patients

	Placebo N = 79	Vancomycin N = 86
Further G+ bacteremia	4	3
Pts given ampho B	30 (37%)	31 (36%)
Pts with AE definitely or probably related to AB	3	9
Death related to infection (Day of death)	2 (15, 35)	1 (14)

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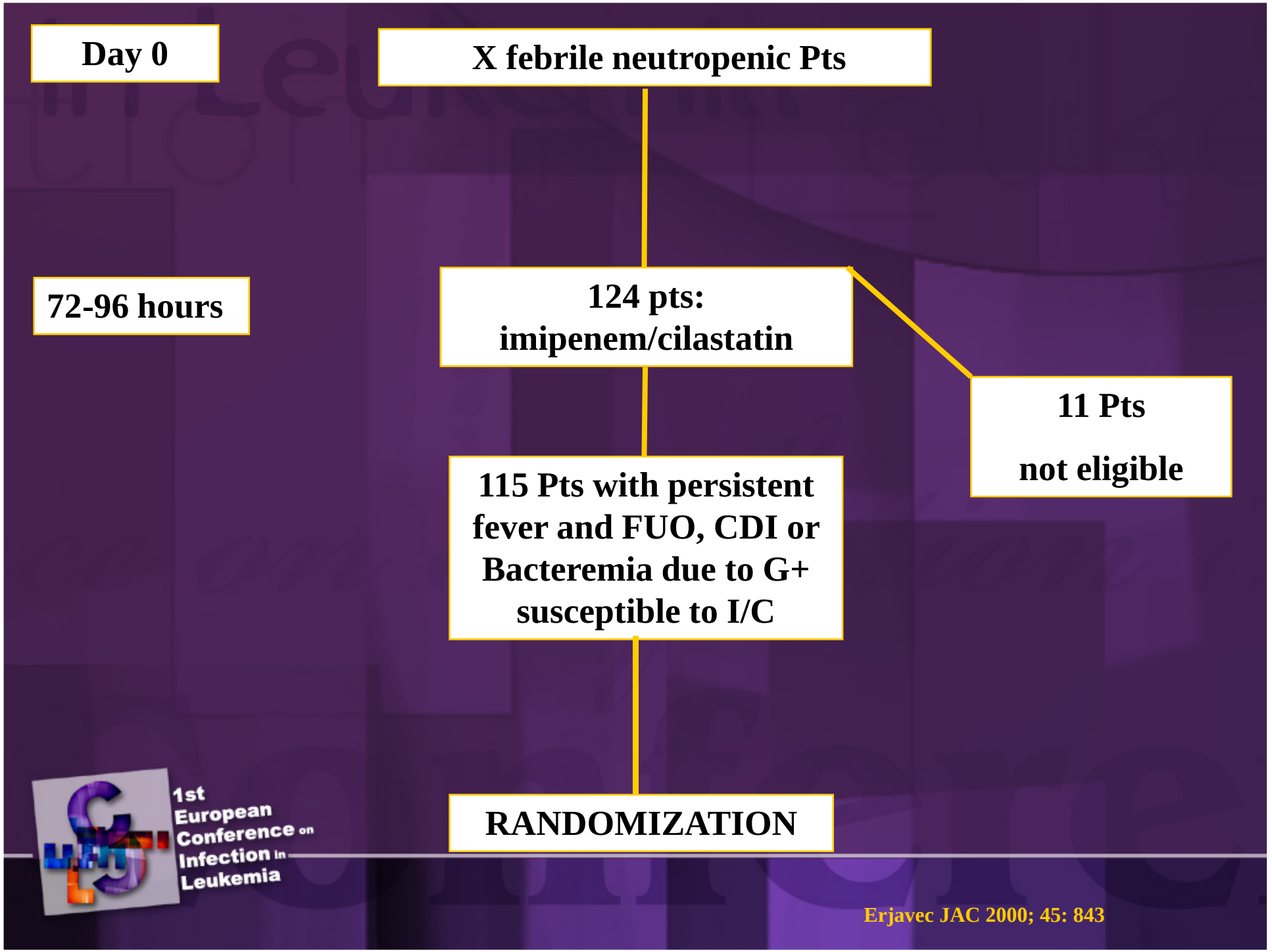
Cometta. CID 2003; 37: 382


Day 0
X febrile neutropenic Pts
72-96 hours
124 pts: imipenem/cilastatin
11 Pts not eligible
115 Pts with persistent fever and FUO, CDI or Bacteremia due to G+ susceptible to I/C
RANDOMIZATION
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Erjavec JAC 2000; 45: 843

Erjavec et al
outcome of the patients

	Placebo N = 58	Teicoplanin N = 56
Pts with defervescence	27 (46.6%)	25 (44.6%)
Death	4 (6.9%)	6 (10.7%)

Erjavec JAC 2000; 45: 843

1. Initial empirical glycopeptide in neutropenic patients (IDSA 2002)

- Development of hypotension or shock
- Known colonisation with MRSA or Peni-R Pneumococcus
- Positive results for G+ before identification
- Clinically suspected serious cath-related infection (cellulitis)
- (Institutions with high rate of infections due to MRSA or Peni-R viridans streptococci)

RANDOMIZED CLINICAL TRIALS: PROBLEMS

- **No double-blind trial except Karp's and Shenep's trials: addition of GP more frequent in the group initially treated without GP**
- **More trials with different antibiotics in the 2 groups: role in the occurrence of adverse effects and further infections?**
- **Various doses of vancomycin and teicoplanin**
- **No randomized controlled trial assessing the use of streptogramin or linezolid**

CONCLUSION 1

	Glycopeptide	CDC grading system
At onset of fever	Not recommended	I D
Persistent fever	Not recommended	I D

CONCLUSION 2

	Glycopeptide	CDC grading system
Known colonisation with MRSA	recommended	III C
Hypotension or shock	recommended	III C
Skin and soft tissue infections including cath-related infections	recommended	III C