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European  
Conference on  
Infection in  
Leukemia**

# **EMPIRICAL ANTIBACTERIAL TREATMENT: GLYCOPEPTIDES AND OTHER GRAM- POSITIVE ANTIBACTERIALS**

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**Sept. 30th / Oct. 1st 2005 Juan-les-Pins - France**

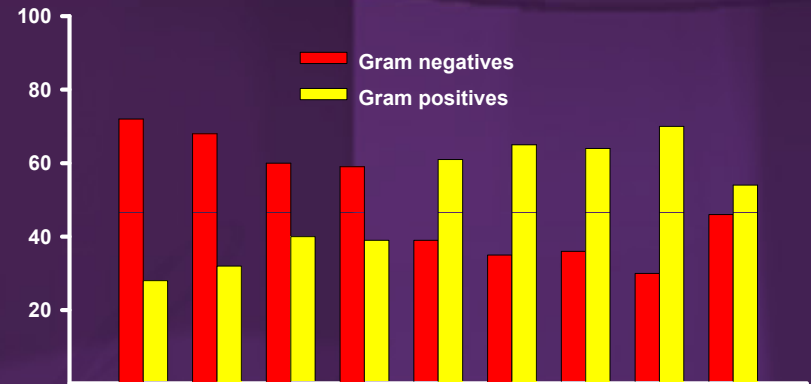


# BACKGROUND

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

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

IATG-EORTC TRIALS 1973-2000



1986-88

# **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)

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



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

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





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

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



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

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



# GLYCOPEPTIDES AS UPFRONT THERAPY

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

Reference

Micozzi<sup>7</sup>

Pico<sup>8</sup>

Kelsey<sup>10</sup>

Martino<sup>11</sup>

Ramphal<sup>12</sup>

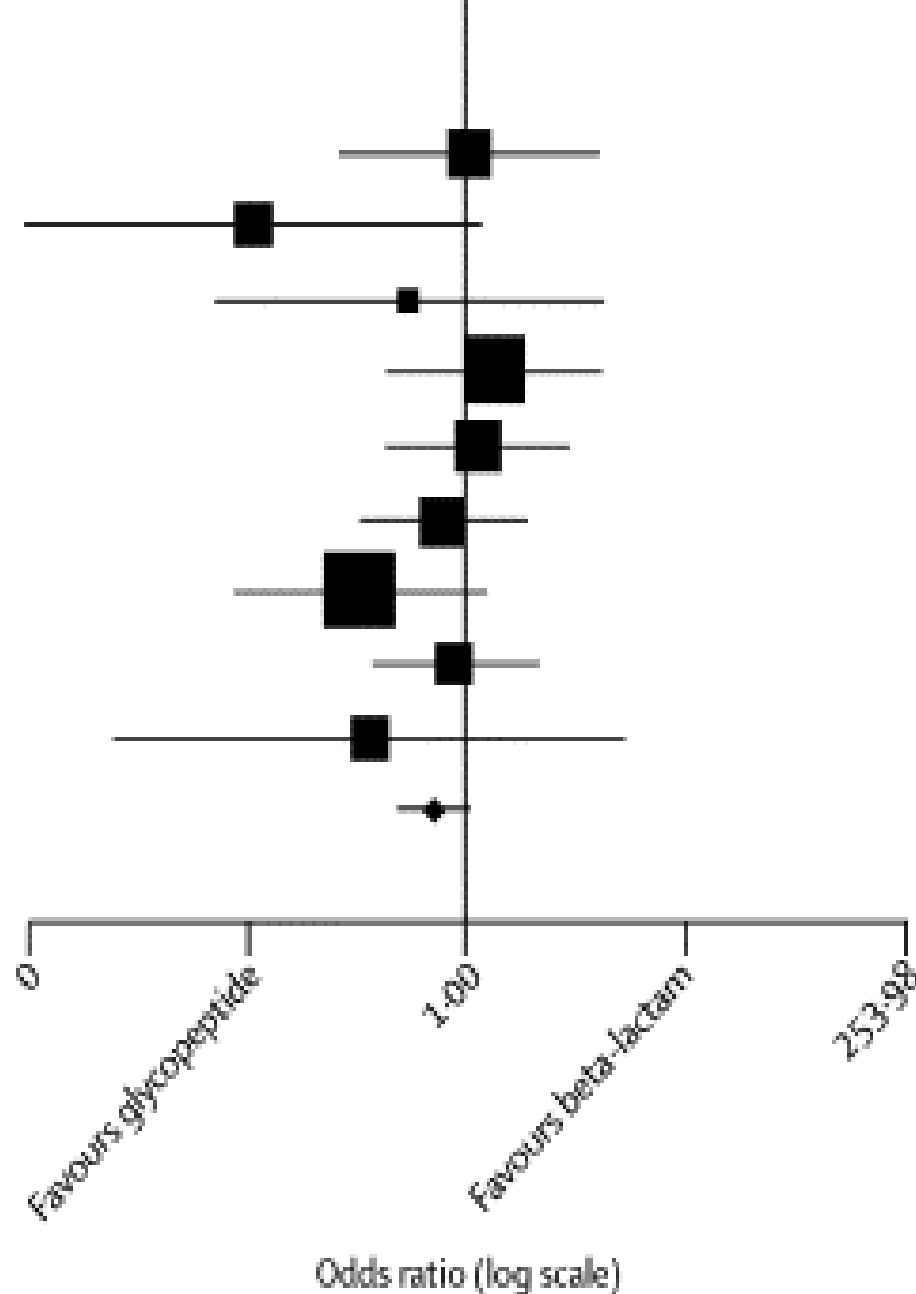
Novakova<sup>14</sup>

Viscoli<sup>16</sup>

Meunier<sup>17</sup>

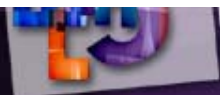
Shenep<sup>18</sup>

Combined



# 1. Odds ratios of mortality

Vardakas Lancet Infect Dis 2005; 5: 431-439



Infection in  
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# MORTALITY (1)

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



## MORTALITY ( 2 )

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

**\* Ceftazidime 1g q 8h**



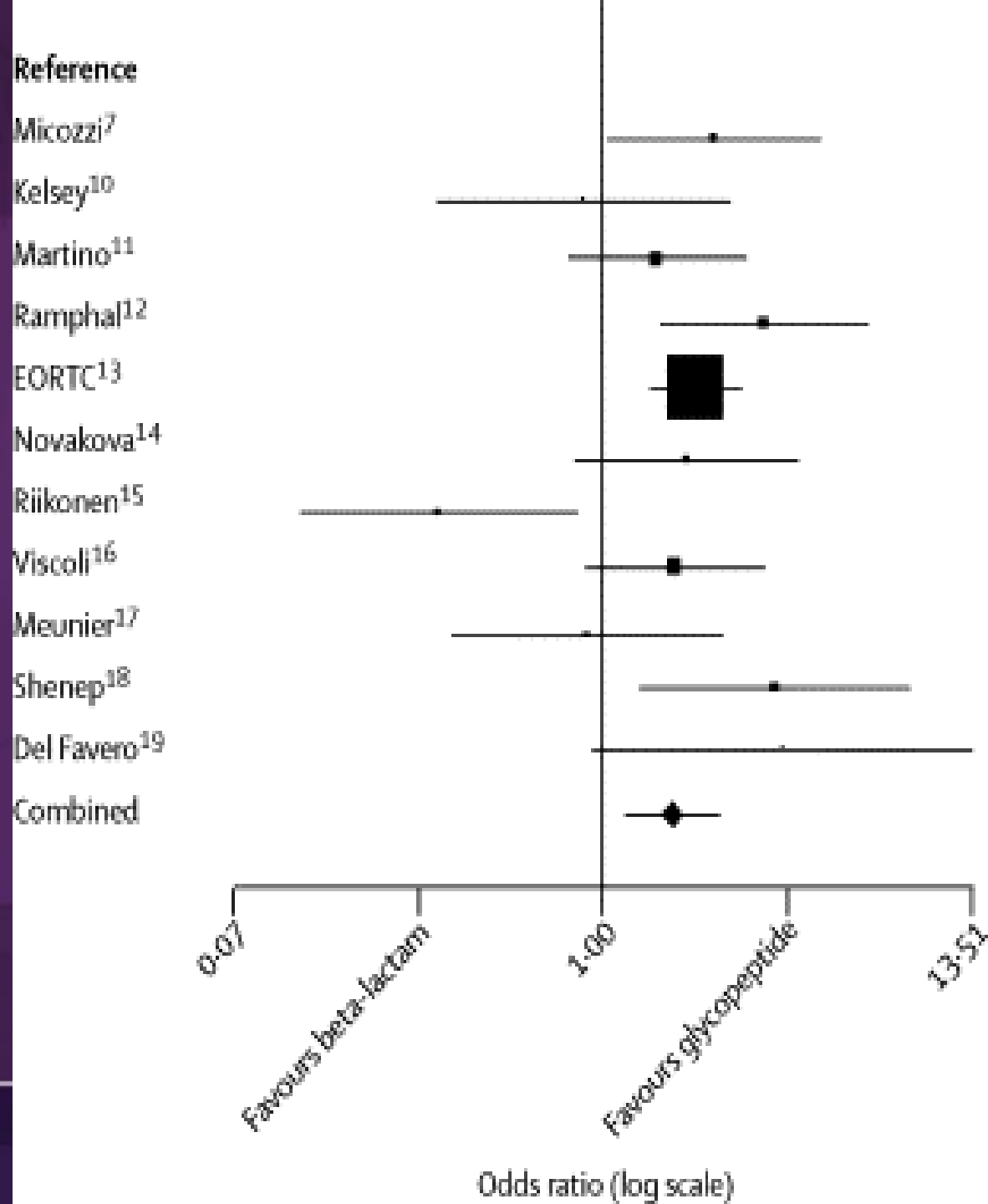
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# GLYCOPEPTIDES AS UPFRONT THERAPY

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%	



## 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)

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

### 3. BREAKTHROUGH INFECTION (2)

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

\* Late onset G+ sepsis

### 3. G+ BREAKTHROUGH BACTEREMIA

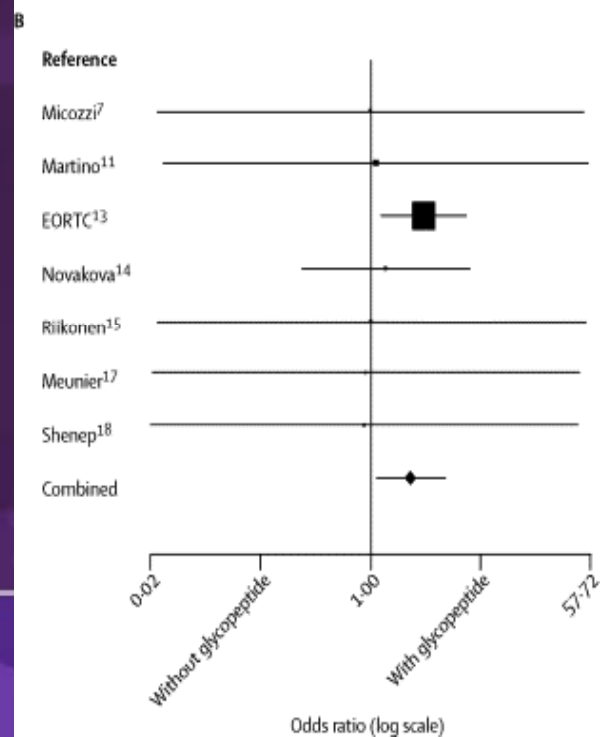
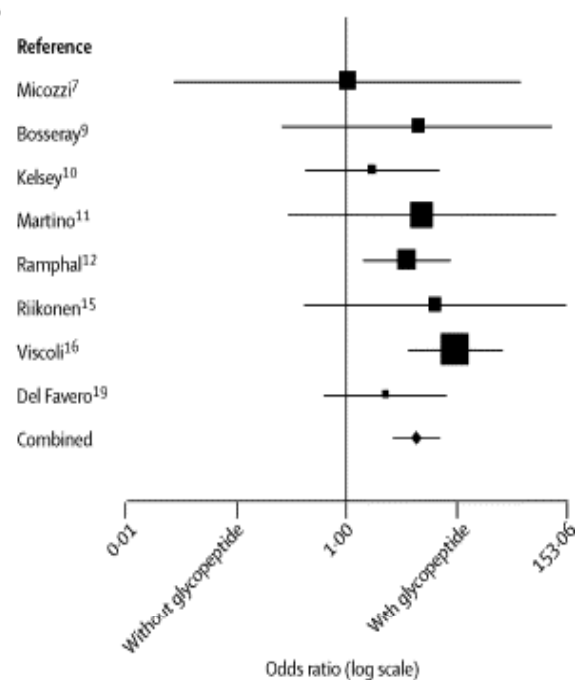
<b>Trial/year</b>	<b>No Glycopeptide n/total</b>	<b>Glycopeptide n/total</b>
<b>Shenep 1988</b>	<b>9/48*</b>	<b>1/53</b>
<b>Riikonen 1991</b>	<b>1/45</b>	<b>0/44</b>
<b>Granowetter 1988</b>	<b>1/55</b>	<b>1/46</b>
<b>Kelsey 1990</b>	<b>0/35</b>	<b>1/38</b>

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

## 4. Odds ratio of adverse effects

### A. All adverse effects

### B. nephrotoxicity



## 4. ADVERSE EFFECTS (1)

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



## 4.ADVVERSE EFFECTS (2) EORTC 1991

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

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

## 4. ADVERSE EFFECTS (3): nephrotoxicity

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

# 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**

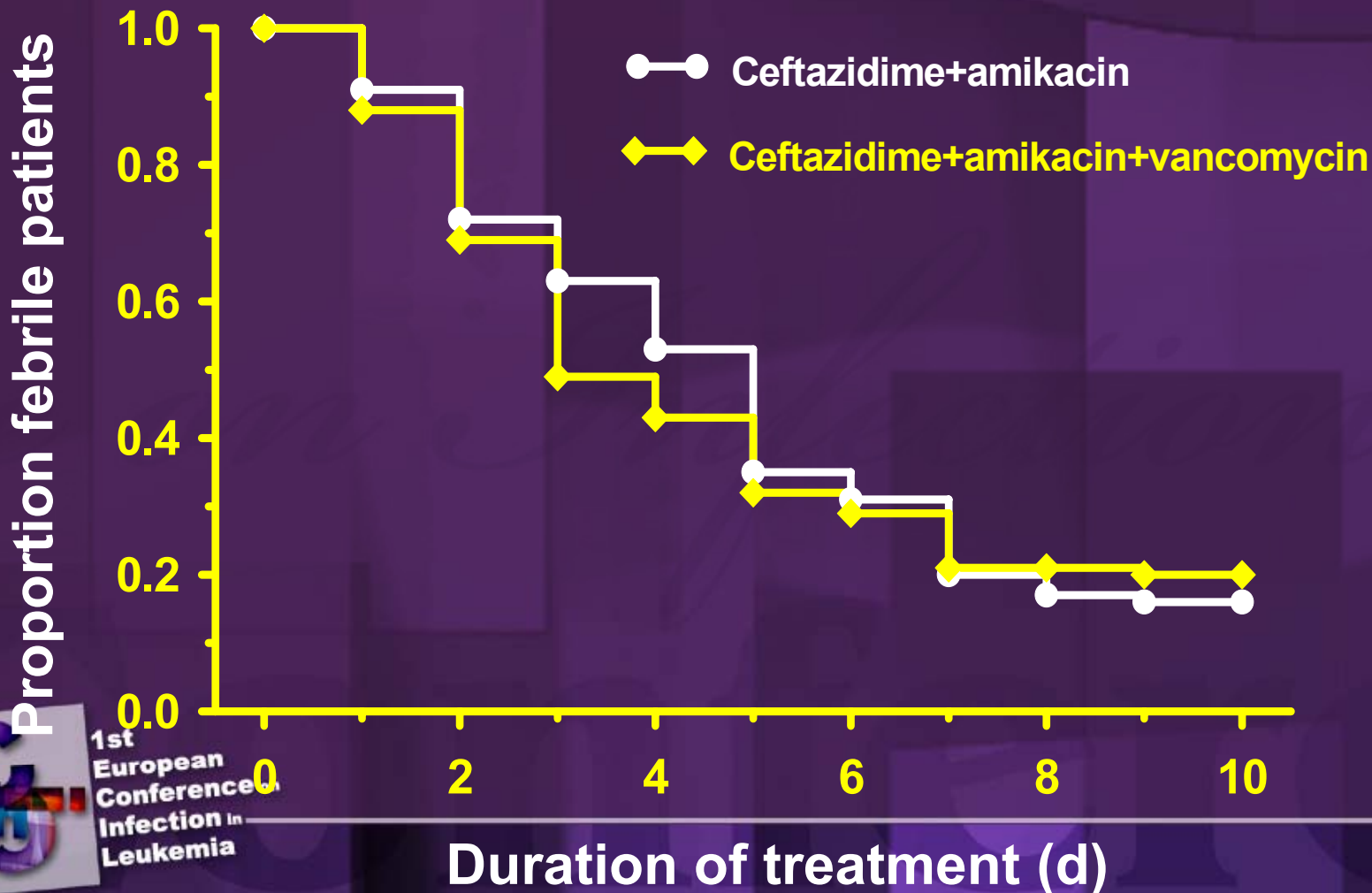
## Bacteremia due to viridans streptococci in granulocytopenic cancer patients

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

## EORTC-IATCG trial V: Gram-positive bacteremias

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

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



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# PATIENTS WITH SKIN AND SOFT TISSUE INFECTIONS

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

# 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

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

**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**

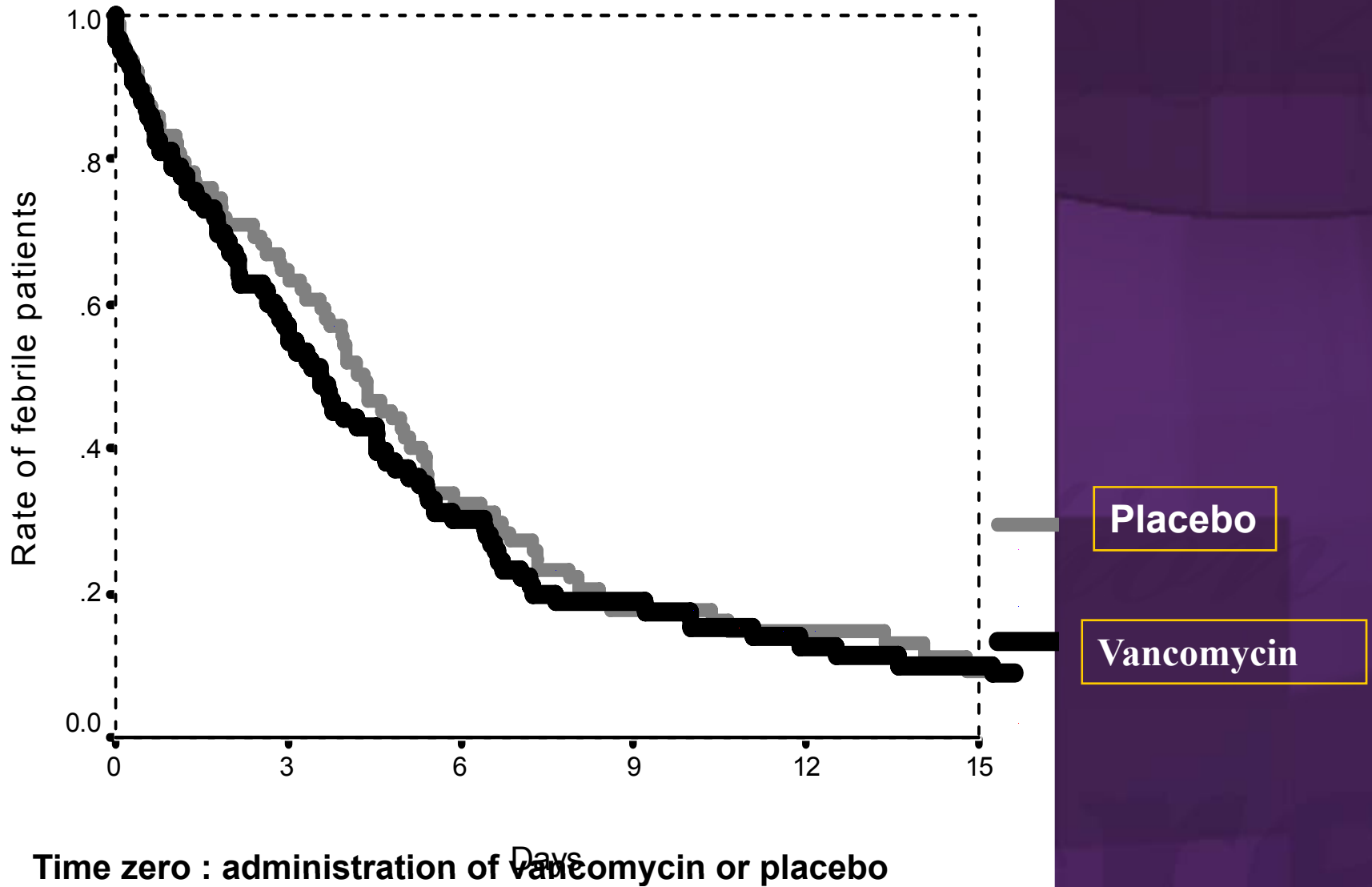


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## Randomized patients: defervescence

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

# Overall time to defervescence



## Outcome of the patients

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

**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**

# Erjavec et al outcome of the patients

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

# 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

	<b>Glycopeptide</b>	<b>CDC grading system</b>
<b>At onset of fever</b>	<b>Not recommended</b>	<b>I D</b>
<b>Persistent fever</b>	<b>Not recommended</b>	<b>I D</b>

## CONCLUSION 2

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

