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Empirical use of anti-Gram-positive antibiotics in febrile neutropaenic cancer patients with acute leukaemia ☆

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ABSTRACT

Gram-positive infections including those due to methicillin-resistant staphylococci occur frequently in febrile neutropaenic patients. Although few data support the empirical addition of a glycopeptide antibiotic to the standard broad-spectrum antibiotic regimen, these agents are often used in many cancer centres. The emergence of infections due to vancomycin-resistant enterococci and glycopeptide-intermediate staphylococci has led to recommendations for a restricted use of glycopeptide antibiotics. The objective of the present work was to formulate evidence-based guidelines for the empirical use of anti-Gram-positive antibiotics in neutropaenic patients with acute leukaemia.

1. Introduction

Early empirical administration of broad spectrum antibiotics has been shown to decrease the mortality due to bacterial infections in febrile granulocytopenic cancer patients.[1] Anti-pseudomonal beta-lactams with or without an aminoglycoside are standard antibiotic regimens for the initial therapy of febrile neutropenia in patients with haematological malignancies, i.e. with severe and prolonged neutropenia.[2,3]

Several studies performed in adults and pediatric neutropaenic patients have shown a shift towards an increased proportion of infections caused by Gram-positive bacteria. Indeed, single Gram-positive bacteraemias accounted for 30% of single organism bacteraemias before 1985 and increased to 60–70% in the 1990s.[4] With the increase in documented Gram-positive infections in febrile neutropaenic patients, including those due to methicillin-resistant staphylococci, the addition of a glycopeptide antibiotic to the standard regimen became controversial.[2] Over the last 10 years, the emergence of infections due to vancomycin-resistant enterococci and glycopeptide-intermediate staphylococci has led to recommendations to restrict the use of glycopeptide antibiotics.[5] The objective of the present work was to formulate evidence-based guidelines for the use of anti-Gram-positive antibiotics in neutropaenic patients with acute leukaemia.

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2. Materials and methods

2.1. Issues addressed in the guidelines

The following topics were addressed by the working group in a question and answer format:

(1) Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated for upfront empirical therapy of febrile neutropenia in patients with acute leukaemia?
(2) Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated for persistent fever in neutropaenic patients with acute leukaemia?
(3) Are there specific indications justifying the upfront use of anti-Gram-positive antibiotics as part of the empirical therapy?

2.2. Data source and review process

Medline was used to search articles published between 1st January 1966 and 1st September 2005. Medline searches and selections of articles were performed by one of the authors (O.M.). Medical Subject Heading (MeSH; http://www.nlm.nih.gov/mesh/meshhome.html) terms used in the Medline search included *leukaemia*, *neutropenia* and *agranulocytosis*. The Medline search was then narrowed by using the MeSH terms *anti-infective agents* (which was exploded to include glycopeptides such as vancomycin and teicoplanin, oxazolidinones such as linezolid and streptogramins such as quinupristin/dalfopristin), *clinical trials*, further limiting the search to human studies and English literature. Additional articles were retrieved from references of articles identified by the Medline search and of meta-analyses, guidelines and review articles on *antimicrobial agents in febrile neutropaenic patients*. Abstracts presented between 2002 and 2005 at international meetings of the American Society of Hematology (ASH), the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the American Society of Clinical Oncology (ASCO) and the European Bone Marrow Transplantation (EBMT) were screened using the following keywords: *neutropenia*, *agranulocytosis*, *empirical treatment*, *glycopeptides*, *oxazolidinones* and *streptogramins*.

2.3. Literature review and selection of articles

A study was considered eligible provided it was a randomised, controlled trial assessing the role of glycopeptides, oxazolidinones or streptogramins antibiotics given in addition to broad spectrum antibiotics for patients with acute leukaemia and febrile neutropenia. Abstracts and articles fulfilling the selection criteria were reviewed to exclude studies that were not relevant for the three issues addressed in the present guidelines (see the corresponding section). Exclusion criteria were (i) trials comparing two different glycopeptides without a placebo group, (ii) trials comparing two anti-Gram-positive antibacterial agents without a placebo group, (iii) trials comparing two different broad spectrum antibiotic regimens combined with the same glycopeptide, (iv) duplicate publications and (v) non-comparative studies. Meta-analyses assessing the role of glycopeptides in neutropaenic patients were also included. Articles were chosen by two independent reviewers (A.C. and O.M.) and reviewed until consensus was reached between the three authors about the selection of articles.

2.4. Data extraction and endpoints

The following data were extracted from each study: patient characteristics, underlying haematological disease, antimicrobial agent and doses used. The primary endpoints were the efficacy and safety of the empirical addition of anti-Gram-positive antibiotics to broad spectrum antibiotics.

Efficacy was assessed in terms of overall mortality and mortality related to infection, success rates without or with modification of empirical antimicrobial therapy, time to defervescence, breakthrough infections. Success without modification of the allocated regimen was defined as resolution of fever and clinical signs of infection, eradication of any infecting microorganism, absence of clinical deterioration, absence of breakthrough infection and survival during therapy. The following *adverse drug reactions* were analysed: *nephrotoxicity*, which was defined as a rise in serum creatinine (increase of more than 0.45 μmol/l or a two-fold increase over baseline) or a decrease of creatinine clearance (more than 50% from baseline value) and *skin rashes*.

Quality of evidence and level of recommendation were graded according to the CDC criteria.

2.5. Questionnaire on clinical practices in Europe

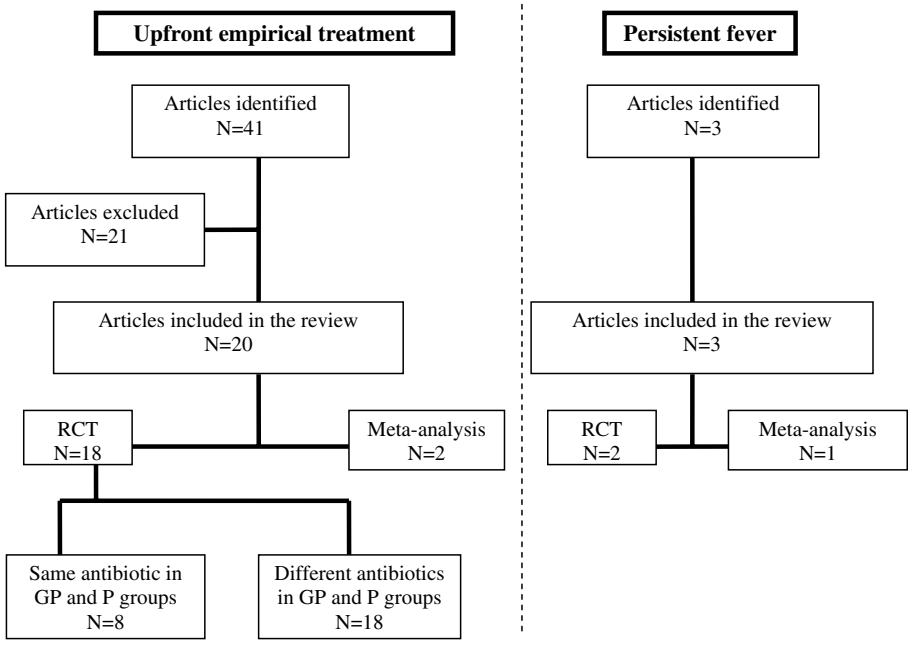
The questionnaire on clinical practices for the management of infections in neutropaenic patients with acute leukaemia comprised a section on the use of anti-Gram-positive antibiotics. The following information was collected: upfront empirical use of anti-Gram-positive antibiotics, addition of anti-Gram-positive antibiotics in persistently febrile neutropaenic patients and special conditions requiring the upfront addition of anti-Gram-positive antibiotics.

3. Results

3.1. Question 1: Is the use of anti-Gram-positive antibiotics (i.e. glycopeptides, oxazolidinones or streptogramins) indicated for upfront empirical therapy of febrile neutropenia in patients with acute leukaemia?

3.1.1. Glycopeptides

Using a search strategy including Medline, international meetings, 2 meta-analyses, 3 national guidelines and 39 clinical trials assessing the role of upfront use of glycopeptides in febrile neutropaenic patients have been identified (Fig. 1). Of the 39 clinical trials, 21 have been excluded for the following reasons: comparison of two different glycopeptides without a placebo group ($n = 7$), therapy with various broad-spectrum antibiotic regimens with the same glycopeptide in the treatment groups ($n = 6$), non-comparative studies ($n = 3$), dupli-



RCT: randomised clinical trial

GP: glycopeptide

P: placebo

Fig. 1 – Empirical use of anti-Gram-positive antibiotics in neutropaenic patients either as upfront treatment or in case of persistent fever: identification and selection of articles.

cate publication ($n = 2$), administration of two different beta-lactams in the group not receiving a glycopeptide ($n = 1$), use of historical controls ($n = 1$) and comparison of vancomycin to flucloxacillin without a placebo group ($n = 1$).

Therefore, 18 randomised controlled trials that have assessed the role of glycopeptides as upfront empirical therapy for febrile neutropaenic adult patients were reviewed (Table 1). All the studies had been published between 1986 and 1993 and examined the efficacy and toxicity of antibiotic regimens incorporating a glycopeptide antibiotic (vancomycin or teicoplanin) or not. Only 2 of 18 studies were double-blinded.[6,7] Three of 18 were multicentre studies.[8–10] The largest study that was conducted in 35 centres enrolled 747 patients, whereas the smallest study enrolled 46 patients.[8,11] In eight trials, both groups of patients were treated with the same broad spectrum antibiotic regimen, consisting either of ceftazidime monotherapy or of an anti-pseudomonal beta-lactam combined with an aminoglycoside.[6,8,9,11–15] In 10 studies, different broad-spectrum antibiotic regimens were used for patients who did or did not receive a glycopeptide.[7,10,16–23]

Two meta-analyses have been published on the role of glycopeptides in the initial empirical therapy of febrile neutropaenic cancer patients. Vardakas et al. performed a meta-analysis of 14 (i.e. Refs. 6–10,13–19,21,22) of the 18 randomized trials that included a total of 2413 patients.[24] A subgroup analysis was also performed on six studies in which the same broad-spectrum antibiotic regimen was used in both treatment arms (i.e. Ref. 6,8,9,13–15). The second meta-analysis was published by Paul et al. and included 13 studies (including Refs. 6,8–10,13,15,32,33) and 2392 patients.[25] Studies of flucloxacillin, sulphamethoxazole and cephalothin were also included in this meta-analysis as were two clinical trials (Refs. 32,33) in which glycopeptides were added for persistent fever. These meta-analyses extracted data on efficacy (including all-cause mortality, success without or with modification of empirical antibacterial therapy, duration of fever, breakthrough infections) and adverse events. After assessment of heterogeneity, pooled odds ratios or relative risk ratios were calculated by Maentel-Haenszel fixed effects (in absence of heterogenicity) or DerSimonian-Lard random effects models (in presence of heterogenicity), respectively.

Assessment of efficacy. As shown in Table 2, *all-cause mortality* which was reported in 11 of the 18 trials ranged between 0% and 18%. In one study performed in children, one death was reported in 101 patients.[7] In four studies, the mortality was higher than 10% (11–18%).[10,12,15,16] In 10 studies no significant difference in mortality between patients treated with or without a glycopeptide was observed. In only one study, in which a low dose of ceftazidime (1g q8h) had been used, was the mortality of glycopeptide-treated patients lower than that of control patients.[10] The largest study, performed by the EORTC, showed that the mortality in patients with Gram-positive bacteraemia was low (3 of 135 episodes) and that none of these deaths occurred within the first 3 days of therapy.[8] Thus, these results suggested that clinicians could wait for microbiological documentation of Gram-positive infection before adding a glycopeptide antibiotic. No study

Table 1 – Clinical trials assessing the role of glycopeptide antibiotics as part of the empirical therapy of fever in neutropaenic cancer patients

First author and year	N	Type of study	Number of centres	Glycopeptide	Study endpoints
Karp, 1986	60	RCT-DB	Single	Vancomycin	Further Gram-positive infections, time to defervescence
Del Favero, 1987	47	RCT	Single	Teicoplanin	RR
Granowetter, 1988	101[a]	RCT	Single	Vancomycin	RR–RR′
Shenep, 1988	101	RCT-DB	Single	Vancomycin	RR, breakthrough bacteraemia, death
Micozzi, 1990	46	RCT	Single	Teicoplanin	RR–RR′, death
Spencer, 1990	59	RCT	Single	Teicoplanin	RR
Meunier, 1990	75	RCT	Single	Teicoplanin	RR, death
De Pauw, 1990	103	RCT	Single	Teicoplanin	RR–RR′
EORTC, 1991	747	RCT	35	Vancomycin	RR, RR in G+, time to defervescence, death
Novakova, 1991	103	RCT	Single	Teicoplanin	RR–RR′, time to defervescence, death
Viscoli, 1991	193	RCT	Single	Vancomycin	RR, death
Riikonen, 1991	89	RCT	Single	Vancomycin	RR, time to defervescence
Bosseray, 1992	87	RCT	Single	Vancomycin	RR
Martino, 1992	158	RCT	Single	Teicoplanin	RR, breakthrough bacteraemia, death
Kelsey, 1992	71	RCT	Single	Teicoplanin	RR, death
Ramphal, 1992	127	RCT	2	Vancomycin	RR–RR′, death, superinfections
Micozzi, 1993	104	RCT	Single	Teicoplanin	RR, time to defervescence, death
Pico, 1993	102	RCT	2	Vancomycin	Life-threatening infection

RCT, randomised controlled trial; DB, double-blinded; RR, response rate without modification of empirical antibiotic regimen; RR′, response rate with modification of empirical antibiotic regimen.
a Groups treated with ceftazidime or ceftazidime plus vancomycin included and group treated with cephalotin plus carbenicillin plus gentamicin excluded from the analysis.

Table 2 – Mortality and response rate without modification of therapy in clinical trials assessing the role of glycopeptide antibiotics as part of the empirical therapy of fever in neutropaenic cancer patients

First author and year	Mortality		Response rates without modification	
	Without glycopeptide	With glycopeptide	Without glycopeptide	With glycopeptide
Del Favero, 1987	NA	NA	56%	82%
Granowetter, 1988	NA	NA	75%	70%
Shenep, 1988	1/48 (2%)	0/53 (0%)	62%*	85%*
Micozzi, 1990	NA	NA	32%*	80%*
Spencer, 1990	NA	NA	47%	66%
Meunier, 1990	9/50 (18%)	8/50 (16%)	67%	67%
De Pauw, 1990	6/51 (12%)	4/52 (8%)	49%	63%
Viscoli, 1991	7/95 (7%)	2/98 (2%)	66%	77%
EORTC, 1991	19/370 (5%)	24/377 (6%)	63%*	76%*
Novakova, 1991	9/60 (15%)	7/60 (12%)	49%	63%
Riikonen, 1991	NA	NA	81%*	59%*
Ramphal, 1992	6/63 (10%)	7/64 (11%)	56%	61%
Bosseray, 1992	NA	NA	80%	80%
Martino, 1992	4/83 (5%)	5/75 (7%)	51%	60%
Kelsey, 1992	2/29 (7%)	1/29 (3%)	49%*	78%*
Micozzi, 1993	3/56 (5%)	3/58 (5%)	41%*	60%*
Pico, 1993	10/69* (14%)	0/33* (0%)	NA	NA

* Statistically significant difference.

was designed with enough power to show a significant difference in all-cause mortality. However, the meta-analysis by Vardakas et al. provided some useful information on this issue.[24] Up-front addition of a glycopeptide antibiotic did not reduce all-cause mortality either in overall study population (odds ratio 0.67, 95% CI 0.42–1.05) or in the subgroup analysis, including six trials in which 405 patients received the same broad-spectrum antibiotic regimens in both treatment arms (odds ratio 1.05, 95% CI 0.52–2.00). The meta-analysis by Paul et al. confirmed these findings (relative risk 0.96, 95% CI 0.58–1.26).[25]

Success without modification of the initial antibiotic regimen was the second endpoint assessed in 16 of 18 trials (Table 2). Up-front use of a glycopeptide was associated with significantly higher success rates in five studies.[7,8,11,21,22] In addition, a trend in favour of the glycopeptide group was observed in seven other studies. The only trial performed in 89 febrile episodes in children reported response rates of

82% in patients treated with imipenem alone and 59% in those treated with a combination of ceftazidime and vancomycin.[18] In the meta-analysis by Vardakas et al. that comprised data from 11 trials and 1812 episodes of fever, the addition of a glycopeptide antibiotic to the empirical antibiotic regimen was associated with a higher success rate compared to that of regimens not including a glycopeptide (odds ratio 1.63, 95%CI 1.17–2.28).[24] The same difference was observed in sub-analyses of patients with microbiologically documented infections (odds ratio 2.03, 95% CI 1.39–2.97), in patients with bacteraemia (odds ratio 1.80, 95% CI 1.23–2.63) and in patients with neutropenia of less than 100 cells/μl (odds ratio 2.24, 1.15–4.39). However, the success rate without modification should be interpreted with great caution, especially in trials that were not double-blinded as there was an obvious bias towards an addition of a glycopeptide antibiotic in persistently febrile patient when it was not part of the initial antibiotic regimen.[8,15] Indeed, additional analyses did not show differences in terms of the *duration of fever* in patients treated with or without glycopeptides or in the proportion of patients with persistent fever at each day after initiation of empirical therapy suggesting that the modification of treatment might have been influenced by factors other than true microbiological or clinical failures.[8,9,15,22] The meta-analysis by Vardakas et al. also confirmed the observation that use of a glycopeptide did not reduce the time to defervescence.[24]

Success rates with modification of the empirical antibiotic regimen, which was assessed in five studies, were similar in patients who did or did not receive glycopeptides.[11,12,14,15,23] However, if modification of the allocated treatment is not evaluated as a failure, causes of failures are then limited to death and breakthrough bacteraemia and success rates are in the range of 90%. Therefore, the likelihood of showing a difference, if it exists, is very limited especially in studies with relatively small sample sizes (i.e. 100–150 patients).

Breakthrough infections occurred in 13–15% of febrile neutropaenic episodes (7 studies). The risk of breakthrough infections was unchanged in patients who had received a glycopeptide.[8,9,15,17,19,21,22] Data from the meta-analysis by Vardakas et al. based on four trials and 1188 episodes of febrile neutropenia confirmed that the addition of a glycopeptide did not exert any impact on the development of breakthrough infections (odds ratio 1.18, 95%CI 0.71–1.98).[24] In contrast, the meta-analysis by Paul et al. reported a reduction of bacterial breakthrough infections (relative risk 0.38, 95%CI 0.24–0.59) and of Gram-positive breakthrough infections (relative risk 0.21, 95%CI 0.11–0.37).[25] The occurrence of breakthrough bacteraemia was reported in four studies. Unfortunately, the low number of events (0–2 cases per group) that occurred in three of these four studies was insufficient to draw any conclusion.[18,21,23] One study performed in children in a single centre showed that the number of breakthrough bacteraemias due to Gram-positive bacteria was significantly higher in the group who did not receive a glycopeptide (9 of 48 patients) than in the group who did (1 of 53 patients).[7] Obviously, epidemiological data which may differ between cancer centres are essential when choosing an initial antibiotic regimen. None of these studies performed between 1985 and 1993 reported the emergence of vancomycin-resistant enterococci (VRE). However, by the end of the 1990s, VRE had become a significant concern in cancer patients, especially in US centres. Vancomycin use was shown to be a risk factor for VRE bloodstream infections.[26] An infection control policy reducing vancomycin use was associated with a decrease of the total incidence of VRE infections including VRE bloodstream infections.[27] Although VRE are less of a problem in Europe than in the US, there have been reports of VRE infections in European cancer centres, which strengthens the argument in favour of restricted use of glycopeptide antibiotics.

Assessment of adverse events. Most of the trials showed a trend towards an increased frequency of adverse events in patients treated with glycopeptides. This trend was confirmed in the meta-analyses by Vardakas et al. (odds ratio 4.98, 95% CI 2.91–8.55) and Paul et al. (relative risk 2.33, 95% CI 1.43–3.80).[24,25] In three studies there was a significantly higher incidence of skin rash in glycopeptide-treated patients.[8,9,17] Nephrotoxicity also occurred more often in glycopeptide-recipients, especially in patients who were treated simultaneously with an aminoglycoside (6% in the vancomycin group versus 2% in group not treated with vancomycin) or with amphotericin B.[8,9] However, no study reported the need of haemodialysis following the administration of glycopeptides. The meta-analyses confirmed that nephrotoxicity occurred more frequently in patients treated with a glycopeptide (Vardakas: odds ratio 2.10, 95% CI 1.12–3.95; Paul: relative risk 1.43, 95% CI 1.06–1.94).[24,25]

3.1.2. *Oxazolidinones and streptogramins*

A recent double-blind, multicentre study compared the safety and efficacy of linezolid to that of vancomycin in febrile, neutropaenic patients with cancer and proven or suspected Gram-positive infections.[28] The study, which enrolled patients at the onset of fever and patients with persistent fever, showed similar success rates in patients treated with linezolid and vancomycin (87.3% versus 85.2%, difference: 2.1%, 95% CI, −4.1 to 8.1). The safety of linezolid was comparable to that of vancomycin (serious adverse events in 12% and 16% of cases; treatment discontinuations related to adverse events occurred in 4% and 5% of cases; no difference in hematological adverse events or bone marrow recovery). Yet, given the absence of a placebo group, this study does not allow conclusions to be drawn on the questions addressed in these guidelines. No data have been reported on the use of streptogramins in neutropaenic cancer patients.

3.2. *Question 2: Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated in persistently febrile neutropaenic patients with acute leukaemia?*

Persistence of fever despite administration of broad-spectrum antibiotics is a common problem in neutropaenic patients. Antibiotic therapy is frequently modified in patients in whom fever persists after 72–96 h of empirical therapy despite the absence of clinical deterioration and documentation of an infection caused by a microorganism resistant to the allocated antibiotic regimen. With the increased frequency of

Gram-positive infections observed since the mid 1980s, adding glycopeptide antibiotics to the empirical regimen has been popular modification of therapy among physicians in charge of neutropaenic cancer patients.[29–31]

Two double-blinded studies with a similar design have examined whether there is an indication for adding a glycopeptide in neutropaenic cancer patients who remained febrile 48–96 h after initiation of broad-spectrum antibiotic therapy (Table 3). Both studies excluded patients with documented Gram-positive bacteria resistant to beta-lactam antibiotics and patients with catheter-related infections. In a large multicentre study conducted by the EORTC in 763 eligible patients treated empirically with piperacillin-tazobactam, 165 patients who remained febrile 48–60 h after initiation of therapy were randomized to receive either vancomycin (86 patients) or placebo (79 patients).[32] The time to defervescence, defined as a period of three consecutive days with a temperature below 38 °C, was similar in the 2 treatment groups. The number of patients who became afebrile under protocol therapy was 49% in the vancomycin group and 46% in placebo group. In addition, there was no difference in terms of mortality (5% in vancomycin group and 10% in placebo group), occurrence of breakthrough Gram-positive infections or proportion of patients for whom amphotericin B was added empirically. In the second study, conducted in a single centre, 114 patients who remained febrile 72–96 h after initiation of imipenem-cilastatin were randomized to receive either teicoplanin or placebo.[33] The number of patients who had defervesced 3 days after randomisation was 45% in the teicoplanin group and 47% in the placebo group. Mortality rates were also similar in both treatment groups (11% in the teicoplanin group and 7% in the placebo group). Taken together, the results of these two studies clearly indicate that the addition of a glycopeptide antibiotic did not have any impact on morbidity or mortality. This was confirmed by the meta-analysis of Paul et al. (relative risk of treatment failure 0.61, 95%CI 0.18–2.09).[25]

3.3. *Question 3: Are there specific indications justifying the upfront use of anti-Gram-positive antibiotics as part of the empirical therapy?*

There are no data on specific indications (e.g. increased risk for resistant Gram-positive infections, severe sepsis/septic shock, suspected skin/soft tissue or catheter infections) for the upfront use of anti-Gram-positive antibiotics when combined with broad-spectrum antibiotics in febrile neutropaenic cancer patients.

3.3.1. *Questionnaire on clinical practice in Europe*

Of 37 experts, only one considered that anti-Gram-positive antibiotics should be given as up-front empirical therapy of fever in neutropaenic cancer patients. However, when there was suspicion of catheter-related infections and skin and soft tissue infections, use of an anti-Gram-positive antibiotics was favoured by 26 and 24 of the 34 consulted experts, respectively. Eighteen of the 34 experts also elected to use anti-Gram-positive antibiotics in patients with hypotension or shock. Finally, 11 of 34 experts favoured the use of an anti-Gram-positive antibiotic in patients with persistent fever.

4. Recommendations (Table 4)

4.1. *Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated for upfront empirical therapy of febrile neutropenia in acute leukemic patients?*

Answer: No, Grading I D.

Comments. The review of 18 studies performed between 1986 and 1993 as well as two recently published meta-analyses do not support the use of glycopeptides at the onset of fever in neutropaenic cancer patients. Although the up-front addition of a glycopeptide antibiotic was associated with better response rates without modification of the empirical antibiotic regimen, glycopeptides had no effects on several clinically relevant endpoints such as time to defervescence, occurrence of breakthrough infections and mortality. By contrast, the use of glycopeptides was associated with increased adverse events, mainly nephrotoxicity and skin rashes. Broad use of glycopeptides has been shown to be a risk factor for the development of bacteraemia due to vancomycin-resistant enterococci. Therefore, the absence of significant benefit and the risk of emergence of resistance to glycopeptides are important arguments favouring the restricted use of glycopeptides in these patients. No clinical data are available on oxazolidinones or streptogramins.

4.2. *Is the use of anti-Gram-positive antibiotics (i.e glycopeptides, oxazolidinones or streptogramins) indicated in persistently febrile neutropaenic patients with acute leukaemia?*

Answer: No, Grading I D.

Comments. The addition of a glycopeptide to broad-spectrum antibiotic is not recommended in neutropaenic patients with persistent fever as it has no impact on all-cause mortal-

Table 3 – Defervescence and all-cause mortality in clinical trials assessing the efficacy of glycopeptides in persistently febrile neutropaenic cancer patients

First author and year	Design	Regimens	Defervescence	All-cause mortality
Erjavec, 2000	Single centre, double-blinded	Teicoplanin, $n = 56$ versus Placebo, $n = 58$	44.6% versus 46.6%	10.7% versus 6.9%
Cometta, 2003	Multicentre, double-blinded	Vancomycin, $n = 86$ versus Placebo $n = 79$	49% versus 46%	5% versus 10%

Table 4 – CDC grading of evidence and level of recommendation for the use of glycopeptide antibiotic in neutropaenic cancer patients

Circumstances	Addition of glycopeptide	Quality of evidence and level of recommendation
Fever onset	Not recommended	I D
Persistent fever	Not recommended	I D
Predominance in the local epidemiology of resistant Gram-positive (e.g. methicillin-resistant *S. aureus*, penicillin-resistant *S. pneumoniae*)	Recommended	III C
Severe sepsis and septic shock	Recommended	III C
Skin and soft tissue infections (including catheter-related infections)	Recommended	III C

ity, on resolution of fever, on the time to defervescence or on the occurrence of breakthrough Gram-positive infections. No clinical data on oxazolidinones or streptogramins are available.

4.3. *Are there specific situations in which up-front empirical therapy with anti-Gram-positive antibiotics might be justified?*

Answer: Yes, Grading III C.

Specific situations. In centres where *resistant Gram-positive bacteria* (i.e. methicillin-resistant *S. aureus* or penicillin-resistant streptococci) are *predominant*, it is reasonable to include a glycopeptide in the empirical antibiotic regimen. The same reasoning also applies to patients known to be colonized with resistant microorganisms. However, *S. aureus* bacteraemias are rare in neutropaenic cancer patients, accounting only for 1–2% of febrile episodes in large clinical trials.[29,34,35] In case of colonisation with penicillin-resistant pneumococci, the doses of carbapenems, cefepime or piperacillin/tazobactam recommended for the treatment of neutropaenic patients should provide serum levels above the MIC of these microorganisms for prolonged periods of time (Recommendation: III C). If used for upfront therapy, glycopeptides should be stopped as soon as an infection due to resistant bacteria is ruled out, i.e. 48–72 h after initiation of therapy in most instances. Data from a single study suggest that linezolid may be an alternative to glycopeptides. No data on streptogramins are available.

Severe sepsis and septic shock occur in 1–2% of febrile neutropaenic episodes.[34,36] However, the incidence of these complications might be underestimated, as septic shock often is an exclusion criterion in many clinical studies. Although no data are available, it is recommended to use a glycopeptide antibiotic in patients in whom febrile neutropenia is accompanied by severe sepsis or septic shock. Indeed, in a logistic regression analysis of patient's outcome performed in 909 neutropaenic cancer patients with bacteraemia, the risk of fatal outcome was significantly increased in patients with hypotension (Recommendation III C).[37] Shock and respiratory distress syndrome have also been described in patients with viridans streptococcal bacteraemia.[38] Bacteraemias due to viridans streptococci accounted for 3–5% of all febrile episodes. Data showing a decreased susceptibility of viridans streptococci to penicillin have led some authors to recommend the administration of glycopeptides to febrile neutropaenic patients at increased risk of infections caused by these microorganisms.[39] The clinical complications of shock or respiratory distress syndrome have been typically observed in patients with severe mucositis who have received fluroquinolone prophylaxis and have been treated with ceftazidime monotherapy for empirical therapy of febrile neutropenia.[40] However, shock or respiratory distress syndrome associated with viridans streptococcal infections have occurred much less frequently in recent clinical trials using cefepime, piperacillin-tazobactam or carbapenems as these antibiotics exhibit better activity than ceftazidime against viridans streptococci.[34,35,41–44] These observations therefore suggest that the use of a glycopeptide is not justified for prevention of complications associated with infections due to viridans streptococci.

Clinical evidence of *skin and soft tissue infections, including catheter tunnel infections*, would also justify the empirical addition of a glycopeptide antibiotic since the majority of these infections are due to methicillin-resistant coagulase-negative staphylococci. However, no data support this recommendation (Recommendation III C).

5. Conclusions

Despite the frequency of Gram-positive infections in neutropaenic cancer patients, neither the individual studies nor the two meta-analyses performed on these studies support the empirical use of glycopeptide antibiotics either at fever onset or in the case of persistent fever despite empirical broad-spectrum antibiotic therapy. However, clinical conditions that may justify the up-front use of a glycopeptide include the predominance in the local epidemiology of resistant Gram-positive bacteria, severe sepsis or septic shock, or a high suspicion of skin and soft tissue infections, including catheter tunnel infections. A survey among experts suggested that practices in Europe are in line with these recommendations. In recent years, several new antibiotics with Gram-positive coverage have been licensed, such as oxazolidinones or streptogramins. However, little or no information, respectively, is available on the efficacy and safety of these agents in neutropaenic cancer patients.

Conflict of interest statement

A. Cometta has received grants and research supports from Bayer and Wyeth.

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