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Review

Efficacy of oral prophylactic antibiotics in neutropenic afebrile oncology patients: A systematic review of randomised controlled trials

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Abstract

The use of oral prophylactic antibiotics in oncology patients is still a matter of debate. A systematic review was performed to assess the evidence for the effectiveness of oral prophylactic antibiotics to decrease bacteraemia and infection-related mortality in oncology patients during neutropenic episodes. Medline, Embase and the Cochrane register of controlled trials were searched from 1966 until 2002. The main outcome was the number of patients with documented bacteraemia (Gram-negative or Gram-positive bacteraemia) and infection related mortality. Data-extraction and quality assessment were performed independently by two reviewers. A total of 22 trials met the inclusion criteria. Seventeen trials compared prophylaxis (quinolones or Trimethoprim/sulfamethoxazole (TMP/SMZ)) to no prophylaxis. The incidence of Gram-negative bacteraemia decreased significantly (pooled OR 0.39, 95% CI 0.24–0.62) without an increase in Gram-positive bacteraemia. Quinolone-based regimens showed a stronger reduction in Gram-negative bacteraemia while TMP/SMZ based regimens were more effective in Gram-positive bacteraemia. Infection related mortality due to bacterial causes decreased with the use of prophylactic antibiotics (pooled OR 0.49, 95% CI 0.27–0.88). No increase in fungaemia or fungal related mortality was seen with the use of oral prophylaxis. In conclusion, this study has shown that oral prophylactic antibiotics decreased Gram-negative bacteraemia and infection related mortality due to bacterial causes during neutropenic episodes in oncology patients.

Keywords: Oral prophylactic antibiotics; TMP/SMZ (Trimethoprim/sulphamethoxazole); Quinolones; Prevention of infection

1. Introduction

Complications from infection remain a source of morbidity and mortality in oncology patients. With the intensified treatment of both solid and haematological malignancies, episodes of severe neutropenia are induced by cytotoxic chemotherapy, leading to increased chances of infectious complications. Treatment of infection has improved significantly since the 1970s when empiric antibiotic therapy was introduced at the onset of febrile neutropenia [1]. In recent years, the choice of antibiotics during febrile neutropenia has changed a lot, but routine hospitalisation and administration of parenteral broad spectrum antibiotics are still standard of care in most hospitals [2]. Even though the infection related mortality in these patients has decreased

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substantially (approximately 4–6% in adult patients and 0.4–1.0% in paediatric patients [2–4]), the prevention of infection remains extremely important in this group of patients. The pattern of infectious organisms has changed significantly over time. Gram-positive organisms are most prevalent and cause 60–70% of bacteraemias [5], 20% are caused by Gram-negative organisms and 10% by fungal organisms. Mortality due to infections is much higher for Gram-negative bacteraemia than for Gram-positive bacteraemia. Therefore, even though the prevalence of Gram-negative bacteraemia has decreased, it is essential to reduce infection related mortality due to Gram-negative organisms [6].

In the 1970s, van der Waaij and colleagues [7] developed a strategy to reduce the frequency of infections, especially by Gram-negative bacteria in the immunocompromised patient. By this strategy, named selective decontamination of the digestive tract (SDD) eliminates potentially pathogenic aerobic micro-organisms from the gastro-intestinal tract without affecting the non-pathogenic anaerobic flora [7]. SDD is achieved by administration of oral partly absorbable/non-absorbable antibiotics, often in combination with anti-fungal prophylaxis. For adequate use of prophylaxis, it is essential that the oral antibiotics are administered before the onset of neutropenia to achieve optimal eradication of the potential pathogenic aerobic micro-organisms in the digestive tract. Several randomised controlled trials have been conducted to assess if prophylaxis with Trimethoprim/sulfamethoxazole (TMP/SMZ) is a successful strategy to reduce the frequency of Gram-negative infections in neutropenic patients [8–17]. TMP/SMZ destroys aerobic Gram-negative bacteria in the colon without affecting the anaerobic flora and can significantly reduce the rate of bacterial infections [18]. Despite the reported successes of TMP/SMZ, several disadvantages were associated with its use, including hypersensitivity to the drugs, prolonged duration of neutropenia [14,19] and the occurrence of infections with resistant Gram-negative bacteria [20].

In the 1980s, fluoroquinolones were considered more promising drugs as prophylactic antibiotics since they had an increased activity against Gram-negative bacteria. Furthermore they were not as myelosuppressive as TMP/SMZ and were not associated with hypersensitivity. Many randomised controlled trials have been performed, assessing the effectiveness of fluoroquinolones that are summarised in two systematic reviews [21,22]. Although these trials show an important reduction in the incidence of Gram-negative infection, no reduction was found in infection related mortality.

Despite the considerable number of trials involving oral prophylactic antibiotics, there is still no consensus opinion as to whether the use of these antibiotics reduce infection-related mortality, and if it should be given to patients at risk. Our aim in this systematic review is to evaluate the efficacy of oral prophylactic antibiotics (TMP/SMZ or quinolones), started before the expected onset of neutropenia, in decreasing bacteraemia and infection related mortality in neutropenic oncology patients. We also aim to define a subgroup of patients who will benefit most from using this strategy.

2. Patients and methods

2.1. Identification of studies

A literature search was done using Medline from 1966 to October 2002, Embase from 1988 to October 2002 and the Cochrane Central Register of controlled trials issue 2, 2002. We used the following terms (MESH and textword):

(prevention OR infection control OR selective decontamination OR decontamination digestive tract OR prophylactic antibiotics OR framycetin OR colistin OR nystatin OR neomycin OR trimethoprim-sulfamethoxazole OR trimethoprim OR sulfamethoxazole OR cotrimoxazole OR nalidixic acid OR quinolone OR fluoroquinolone OR norfloxacin OR ciprofloxacin OR ofloxacin OR non-absorbable antibiotics OR rifampin OR roxithromycin)
AND
(leuk(a)emia OR cancer OR oncol* OR malignan* OR neoplasm* OR antineoplastic OR carcinoma)
AND
(agranulocytosis OR neutropeni* OR aplasia OR granulocytopeni* OR leukopeni*)
AND
(randomised controlled trial OR drug therapy OR therapeutic use OR random *(using a sensitive research methodology filter)).

We included German, French and English articles. The computer search was supplemented by checking the references of the articles for additional papers. Authors of included papers [23,24] were contacted.

2.2. Inclusion/exclusion criteria

We included randomised trials that compared oral based prophylactic antibiotics with either placebo or no prophylaxis and compared quinolone-based prophylaxis to TMP/SMZ-based regimens. Trials considering oncology patients (both adults and children) undergoing chemotherapy where oral prophylactic antibiotics were started before the expected onset of neutropenia were included. We excluded trials using total decontamination of the digestive tract, trials in which intravenous antibiotics were used as prophylactics, trials in which infection was present at the time of starting prophylactic

antibiotics, where prophylactic antibiotics were started at the onset of neutropenia and when prophylactic antibiotics were compared to other regimens of prophylactic antibiotics.

2.3. Data-extraction and outcome measures

Two reviewers (MvdW, MdW) independently abstracted the following data: year of publication, characteristics of the patients, including age and type of malignancy, type of prophylactic antibiotics used, the number of patients included in both treatment arms, the number of neutropenic episodes analysed, the number of patients with bacteraemia, the number of patients with fungaemia and the number of infection related deaths. Disagreements were resolved between the two reviewers by discussion.

We considered as a primary outcome documented bacteraemia (Gram-positive or Gram-negative bacteraemia) and mortality (infection related mortality and mortality due to bacterial causes) during febrile neutropenic episodes and as secondary outcome fungaemia and fungal related mortality. Bacteraemia had to be defined as two or more positive blood-cultures (each intravenous port and/or at least one peripheral blood culture). Blood cultures had to be repeated for persistent fevers or rigors. Catheter-related infections had to be defined according to the Hospital Infection control guidelines [25,26].

2.4. Quality assessment

Two reviewers independently assessed the following criteria regarding the methodological quality of the included trials: allocation concealment (adequate, not adequate, not clear), blinding of patients and outcome-assessors (yes, no, not clear) and the use of an intention to treat analysis (yes, no, not clear?) [27].

2.5. Meta-analysis

Trial specific odds ratios (ORs) were calculated. The ORs were combined according to the fixed effect method of Mantel–Haenszel if there was clinical homogeneity in both interventions and outcomes. Statistical heterogeneity was tested with the Chi square test of homogeneity. In addition, heterogeneity was quantified by the use of the I^2 statistic, describing the percentage of total variation across trials that are due to heterogeneity between trials. A value of 0% indicates no observed heterogeneity between the trials, a value of 50% may be considered substantial heterogeneity and 100% indicates only heterogeneity between the trials [28]. In case of heterogeneity the random effect model was applied for combining ORs [29]. Publication bias was looked at using the funnel plot.

Meta-analyses were performed for the following comparisons: prophylactic antibiotics *versus* placebo or no prophylaxis and for TMP/SMZ *versus* quinolones. Subgroup analyses were performed for trials with only conventional chemotherapy patients *versus* trials with only bone-marrow transplantation patients and for trials performed in the 1980s *versus* trials performed after 1990.

3. Results

3.1. Identification of trials

Our literature search revealed 330 eligible trials (Fig. 1). Of those, 293 trials were not included because these were trials on total gut decontamination, trials on using intravenous antibiotics as form of prophylaxis, fungal prophylaxis or trials comparing prophylactic antibiotics to other combinations of prophylactic antibiotics. A total of 37 articles were retrieved. A total of 15 trials did not fulfil the inclusion criteria while 21 trials were included. Of these, 18 trials addressed prophylactic antibiotics compared to no prophylaxis or placebo and 4 trials compared quinolones to TMP/SMZ (Tables 1 and 2).

A funnel plot of the outcome bacteraemia showed no publication bias (data not shown).

3.2. Quality of the included trials

Of the 22 included trials, 14 (64%) showed adequate concealment of allocation [8,9,12,14,15,23,24,30–37] and both patient and outcome-assessor were blinded [8–10,12–15,23,24,31,34–37]. Ten trials (47.5%) used an intention to treat analysis [9,12,14–17,31,34,37,38] (Tables 1 and 2).

3.3. Description of included trials

Eighteen trials compared oral antibiotic prophylaxis to placebo or no prophylactic antibiotics. Of those, 10 addressed TMP/SMZ and 8 trials addressed quinolones. The 18 trials included 1618 patients and took place from 1983 to 2002. Eight trials were done in patients with haematological malignancies [10,15–17,23,34,37,38], 3 trials in patients with solid tumours mostly undergoing high dose chemotherapy [9,24,31], 6 trials were done combining haematological and solid tumours [8,11–14,39] and one trial was performed with only allogenic bone marrow-transplant patients [35]. Three of the trials comparing prophylaxis to no prophylaxis also included paediatric patients [8,12,14]. In the control groups the incidence of bacteraemia ranged from 4.1% (in conventional chemotherapy) to 60% (in allogenic transplant patients), Gram-negative bacteraemia from 1.3% to 36% and Gram-positive bacteraemia from 2.7% to 38%. In six of the 17 trials, patients used prophylaxis during

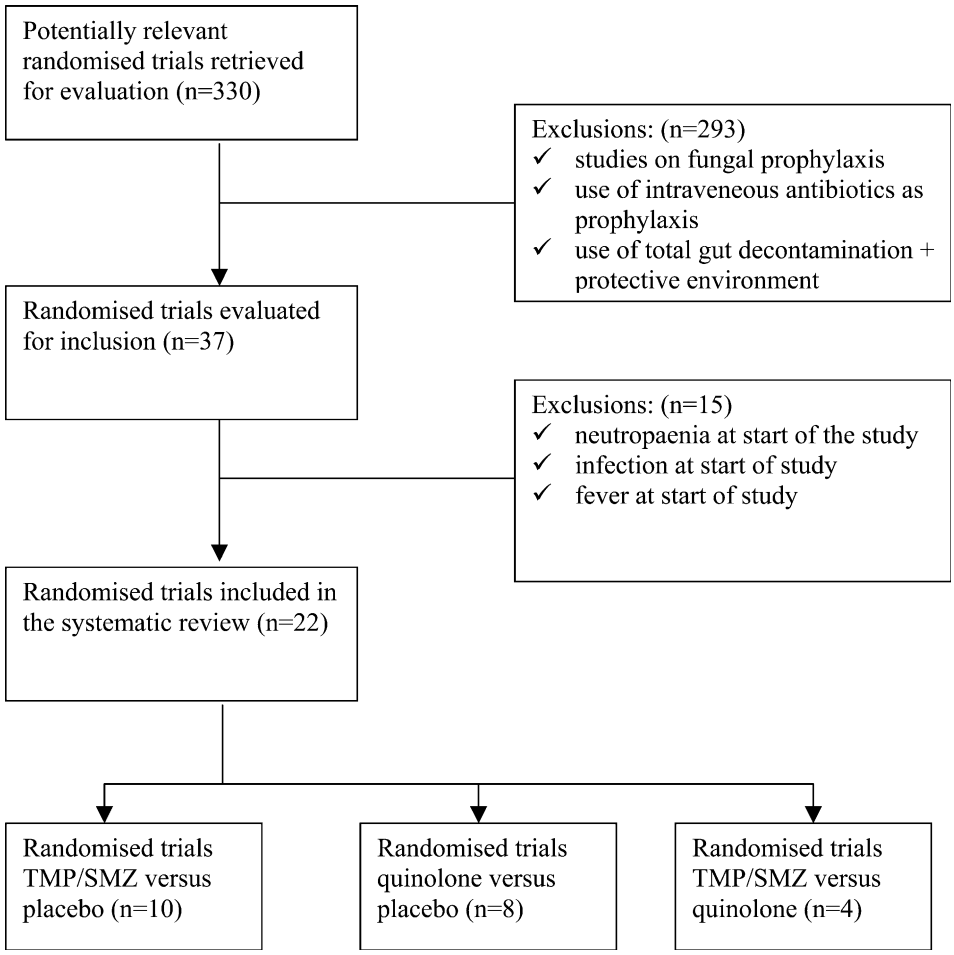

Fig. 1. All trials included in the search strategy with a breakdown of the articles, which were included for the analysis TMP/SMZ = Trimethoprim/sulfamethoxazole.

one neutropenic episode [8,10,17,34,35,38] and in 12 trials patients used prophylaxis during multiple neutropenic episodes [9,11–16,23,24,31,37,39]. Four trials compared quinolones to TMP/SMZ [30,32,33,36]. Of these, 3 trials included patients with haematological malignancies [30,32,33] and 1 trial included patients with both haematological and solid tumours [36]. All trials included patients who used prophylaxis during multiple neutropenic episodes. A total of 525 patients were included in these latter studies.

3.4. Meta-analyses

3.4.1. TMP/SMZ or quinolones versus placebo or no prophylaxis

This analysis included 18 trials. The characteristics of the included articles are shown in Table 1. Of the 18 included, 6 trials addressed the number of bacteraemic episodes compared to the total number of episodes [9,11,13,23,24,39] and 12 trials addressed the number of patients with bacteraemia compared to the total number of patients [8,10,12,14–17,31,34,35,37,38].

3.5. Effect on bacteraemia

Data on bacteraemia was extracted from 13 trials addressing 1305 patients (Fig. 2). Prophylaxis of any type reduced the occurrence of bacteraemia with 57% (OR = 0.48; 95% confidence interval [CI]: 0.34–0.66; $I^2 = 0\%$). For TMP/SMZ use only (Fig. 2) the OR was 0.51 (95% CI 0.33–0.79; $I^2 = 0\%$) and for quinolones used as prophylaxis the OR was 0.44 (95% CI 0.27–0.71; $I^2 = 0\%$). The Chi square test for heterogeneity was not significant in any of these comparisons (Fig. 2).

3.6. Effect on Gram-negative/Gram-positive bacteraemia and fungaemia

Data on Gram-negative bacteraemia could be extracted from 12 trials addressing 1210 patients (Fig. 3). There was a clear benefit shown for the use of prophylaxis (OR = 0.39; 95% CI 0.24–0.62; $I^2 = 4.8\%$). Seven trials used TMP/SMZ as prophylaxis. The meta-analysis showed a trend to the benefit of TMP/SMZ use, but it

Table 1
Included trials prophylactic antibiotics compared to no prophylaxis

Trial ID	Patients	Intervention	Allocation concealment	Blinding	Intention to treat
Weiser 1981 [16]	29 adult patients with leukaemia	TMP/SMZ 960 mg 2 × dd (n = 14) *vs* placebo (n = 15)	B	B	A
Gualtieri 1983 [10]	47 adult patients with leukaemia	TMP/SMZ 1920 mg 1 × dd (n = 24) *vs* placebo (n = 23)	B	A	B
Pizzo 1983 [14]	150 adults + children (Leukaemia + solid)	TMP/SMZ 10 mg/kg in 2 doses + erythro 30/mg/kg (n = 77) *vs* placebo (n = 73)	A	A	A
De Jongh 1983 [9]	61 adult patients with small lung cell carcinoma	TMP/SMZ 1040 mg 2 × dd (n = 32) *vs* placebo (n = 29)	A	A	A
EORTC 1984 [8]	342 adults and children haematologic and solid tumours	TMP/SMZ 960 mg 2 × dd (n = 177) *vs* placebo (n = 165)	A	A	B
Henry 1984 [17]	43 adult patients with leukaemia	TMP/SMZ 960 mg 2 × dd (n = 23) *vs* placebo (n = 20)	B	B	A
Kovatch 1985 [12]	91 children haematologic and solid tumours	TMP/SMZ (n = 43) *vs* placebo (n = 48)	A	A	A
Ward 1993 [15]	42 adult patients leukaemia	TMP/SMZ 960 mg 2 × dd (n = 22) *vs* placebo (n = 20)	A	A	A
Kauffman 1983 [11]	55 adult patients with haematologic or solid tumours	TMP/SMZ 480 mg 2 × dd (n = 29) *vs* placebo (n = 26)	B	B	B
Kramer 1984 [13]	45 adult patients with leukaemia or solid tumours	TMP/SMZ + erythro (29 episodes) *vs* placebo(27 episodes)	B	A	B
Karp 1986 [34]	68 adult patients, leukaemia or transplant	Norflox 400 mg 2 × dd (n = 35) *vs* placebo (n = 33)	A	A	A
Lew 1991 [35]	18 adult patients with BMT	Cipro 750 mg 2 × dd (n = 7) *vs* placebo (n = 11)	A	A	B
Maiche 1993	59 patients with leukaemia or solid tumours	G-CSF + ofloxacin 200 mg 2 × dd or ciproflox 750 mg 2 × dd (44 episodes) *vs* G-CSF (48 episodes)	C	B	B
Talbot 1993 [37]	119 adult patients ALL/ANLL	Enoxacin 400 mg 2 × dd (n = 62) *vs* placebo (n = 57)	A	A	A
Carlson 1997 [31]	90 adult patients with ovarian cancer	Cipro 500 mg 2 × dd (n = 45) *vs* no SDD (n = 45)	A	A	A
Thomas 2000 [23]	103 adult patients ALL and BMT	Pefloxacin 800 mg (n = 51) *vs* placebo (n = 52)	A	A	B
Tjan Heijnen 2001 [24]	161 adult patients small lung cell carcinoma	Cipro 750 mg 2 × dd + roxithro 150 mg 2 × dd (n = 82) *vs* placebo (n = 79)	A	A	B
Lee 2002 [38]	95 adult patients ANLL	Cipro 250 2 × dd + roxi 150 2 × dd (n = 46) *vs* placebo (n = 49)	B	B	A

(Cipro = Ciproxin, TMP/SMZ = Trimethoprim/sulphamethoxazole, Norflox = Norfloxacin, Erythro = erythromycin, Roxi = roxithromycin, ANLL = acute non-lymphocytic leukemia, ALL = acute lymphocytic leukemia, BMT = bone-marrow transplantation. Allocation concealment = A: adequate, B: not adequate C: not clear. Blinding = A: blinding done of patient and outcome-assessor, B: blinding not done, C: not clear. Intention to treat analysis = A: yes, B: no).

Table 2
Included trials quinolones *vs* TMP/SMZ

Trial	Patients	Intervention	Bacteraemia	Gram-negative bacteraemia	Allocation	Blinding	Intention to treat analysis
Bow 1988 [30]	63 adult leukaemia patients	Norflox 400 mg 2 × dd *vs* TMP/SMZ 960 2 × dd	9/31 *vs* 6/32	0/31 *vs* 4/32	A	B	B
Dekker 1987 [32]	65 adult leukaemia patients	Cipro 500 mg 2 × dd *vs* TMP/SMZ 960 + colistine	7/26 *vs* 4/26	4/26 *vs* 3/26	B	B	A
Donnelly 1992 [33]	230 adult leukaemia patients	Cipro 500 mg 2 × dd *vs* TMP/SMZ 960 mg	16/117 *vs* 12/113	1/117 *vs* 6/113	A	B	B
Lew 1995 [36]	167 adult patients all malignancies	Cipro 750 mg 2 × dd *vs* TMP/SMZ 960 2 × dd	10/75 *vs* 6/71	0/75 *vs* 1/71	A	A	B

(Cipro = Ciproxin, TMP/SMZ = Trimethoprim/sulphamethoxazole, Norflox = Norfloxacin, Allocation concealment = A: adequate, B: not adequate C: not clear. Blinding = A: blinding done of patient and outcome-assessor, B: blinding not done, C: not clear. Intention to treat analysis = A: yes, B: no).

did not reach 5% level of significance (OR = 0.65, 95% CI 0.36–1.17; $I^2 = 0\%$). From 5 trials data were extracted for quinolone use. There was a significant benefit for the use of quinolones (OR = 0.16; 95% CI 0.07–0.39; $I^2 = 0\%$) (Fig. 3).

With the use of prophylaxis, Gram-positive bacteraemia was not reduced (OR = 0.75; 95% CI 0.49–1.14; $I^2 = 0\%$). However trials using TMP/SMZ as prophylaxis showed a benefit (OR = 0.47; CI 0.25–0.91; $I^2 = 0\%$). This was not shown for the quinolones (OR = 1.10; 95% CI 0.61–1.97; $I^2 = 0\%$) (data not shown).

Considering fungaemia no significant increase was seen in the number of events in the treatment group (14/531) as compared to the control group (9/521). The OR was 1.49 (95% CI 0.65–3.43; $I^2 = 0\%$).

3.7. Effect on reducing infection related mortality

Data on infection-related mortality could be extracted from 13 trials. Five trials [14,16,23,39,40] did not report on mortality data. A total of 966 patients were included in this analysis. A significant reduction in infection related mortality was shown with the use of prophylaxis (OR = 0.56; 95% CI 0.34–0.96; $I^2 = 0\%$) (data not shown). Excluding fungal causes of death, the OR was 0.49 (95% CI 0.27–0.88, $I^2 = 0\%$) (Fig. 4). Separate ORs for TMP/SMZ and quinolone trials did not reach significance. For TMP/SMZ use only the OR was 0.51 (95% CI 0.25–1.05; $I^2 = 0\%$) and for quinolones the OR was 0.43 (95% CI 0.15–1.27; $I^2 = 0\%$) (Fig. 4). Fungal related death was not significantly different in the two groups. The total number of events in the oral prophylaxis group was 8/487 and in the control group 10/479, the OR was 0.81 (95% CI 0.35–1.86, $I^2 = 0\%$).

3.8. Subgroup analyses

3.8.1. Conventional chemotherapy compared to bone marrow transplant

From 12 trials, data was abstracted to compare patients receiving conventional chemotherapy (9 trials) to patients who underwent a bone-marrow transplant (BMT) procedure (3 trials). In the 9 conventional chemotherapy trials a total of 712 patients were included. If we analysed the outcome bacteraemia, there were 72 patients with bacteraemia in the prophylactic antibiotic group ($n = 404$) and 109 patients in the control group ($n = 411$). A benefit was shown in favour of the use of oral prophylactic antibiotics in patients receiving conventional chemotherapy. The OR was 0.47 (95% CI: 0.32–0.71). There was no heterogeneity in this analysis (Chi square for heterogeneity $P = 0.58$, $I^2 = 0\%$) There were 3 trials only including BMT patients with a total of 436 patients. In the analysed outcome bacteraemia,

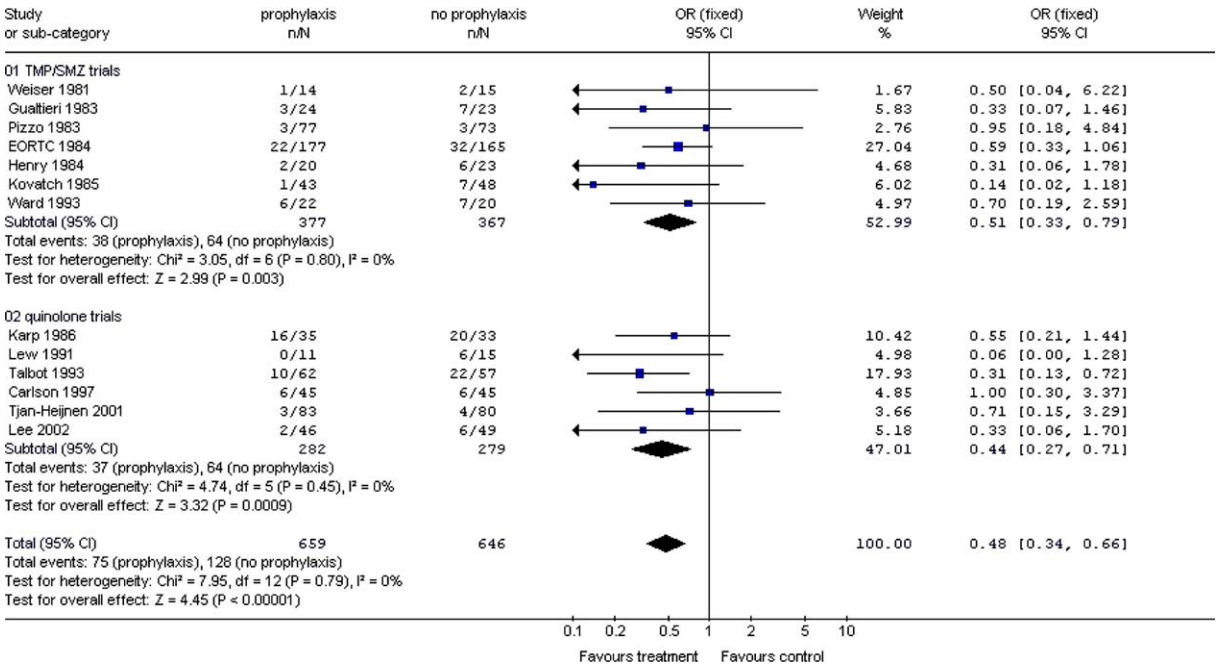

Fig. 2. Meta-analysis of oral prophylactic antibiotics compared to placebo or no prophylaxis for the outcome bacteraemia. The first 7 trials addressed trimethoprim/sulfamethoxazole (TMP/SMZ) and the last 6 trials quinolones. The odds ratio (OR) is presented with a 95% confidence interval.

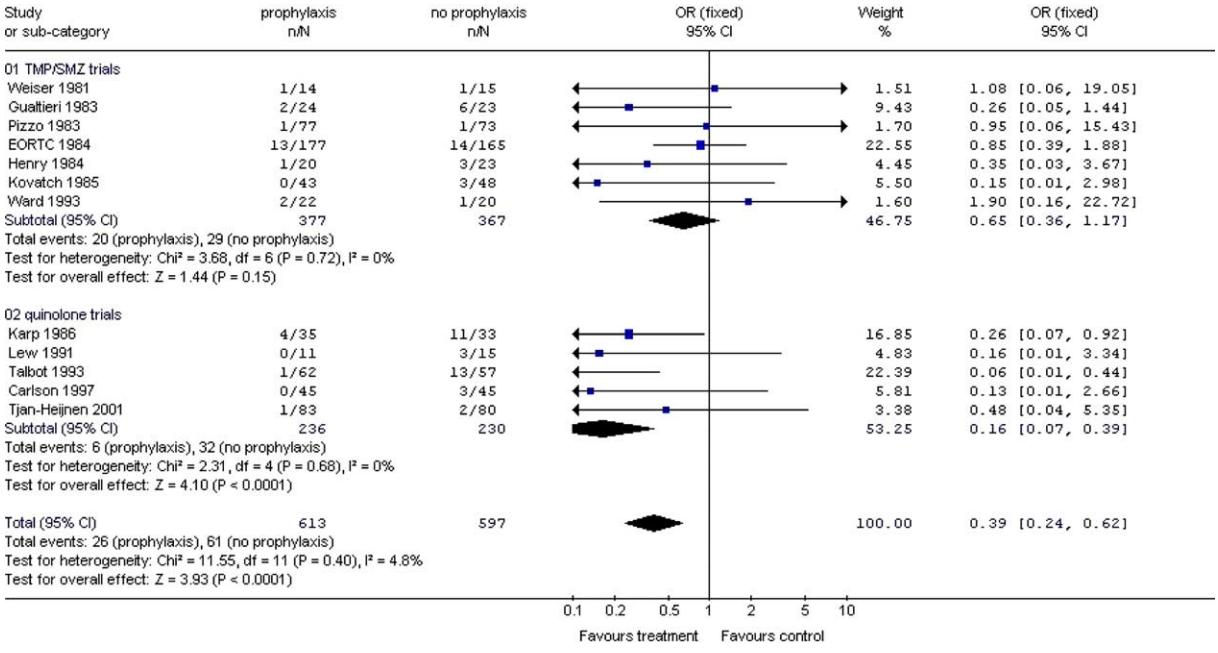

Fig. 3. Meta-analysis of oral prophylactic antibiotics compared to placebo or no prophylaxis for the outcome Gram-negative bacteraemia. The first 7 trials addressed trimethoprim/sulfamethoxazole (TMP/SMZ) and the last 5 trials quinolones. The odds ratio (OR) is presented with a 95% confidence interval.

there were 38 patients with bacteraemia in the prophylaxis group ($n = 223$) and 58 patients in the control group ($n = 213$). A benefit was shown in favour of the use of oral prophylactic antibiotics in patients receiving a BMT procedure. The OR was 0.52 (95% CI: 0.32–0.84). No heterogeneity was found in this analysis (Chi square for heterogeneity $P = 0.35$, $I^2 = 3.7\%$). In this subgroup analysis, both groups benefit equally from the use of oral prophylactic antibiotics (data not shown).

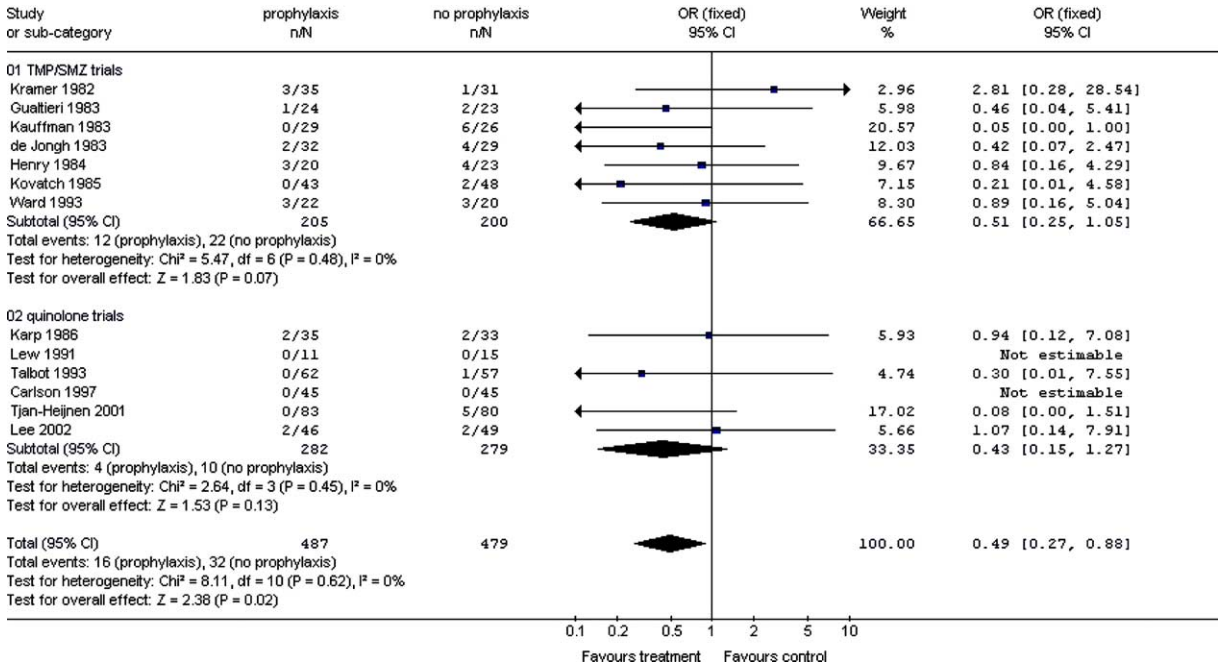

Fig. 4. Meta-analysis of oral prophylactic antibiotics compared to placebo or no prophylaxis for the outcome infection-related mortality due to bacterial causes. The first 7 trials addressed trimethoprim/sulfamethoxazole (TMP/SMZ) and the last 5 trials quinolones. The odds ratio (OR) is presented with a 95% confidence interval.

3.8.2. Trials performed in the 1980s compared to trials performed after 1990

Most TMP/SMZ trials were performed in the 1980s whereas, the quinolone trials were performed after 1990. The OR for bacteraemia in the older trials was 0.50 (95% CI 0.33–0.76; $I^2 = 0\%$). In the newer studies, a similar OR was found (OR = 0.44, 95% CI 0.26–0.74; $I^2 = 0\%$) (Fig. 5). For infection-related mortality, the same comparable results were found. In the older trials an OR of 0.50 was found (95% CI 0.24–1.05; $I^2 = 0\%$) and in the newer trials the OR was 0.49 (95% CI 0.17–1.26; $I^2 = 0\%$) (Fig. 6).

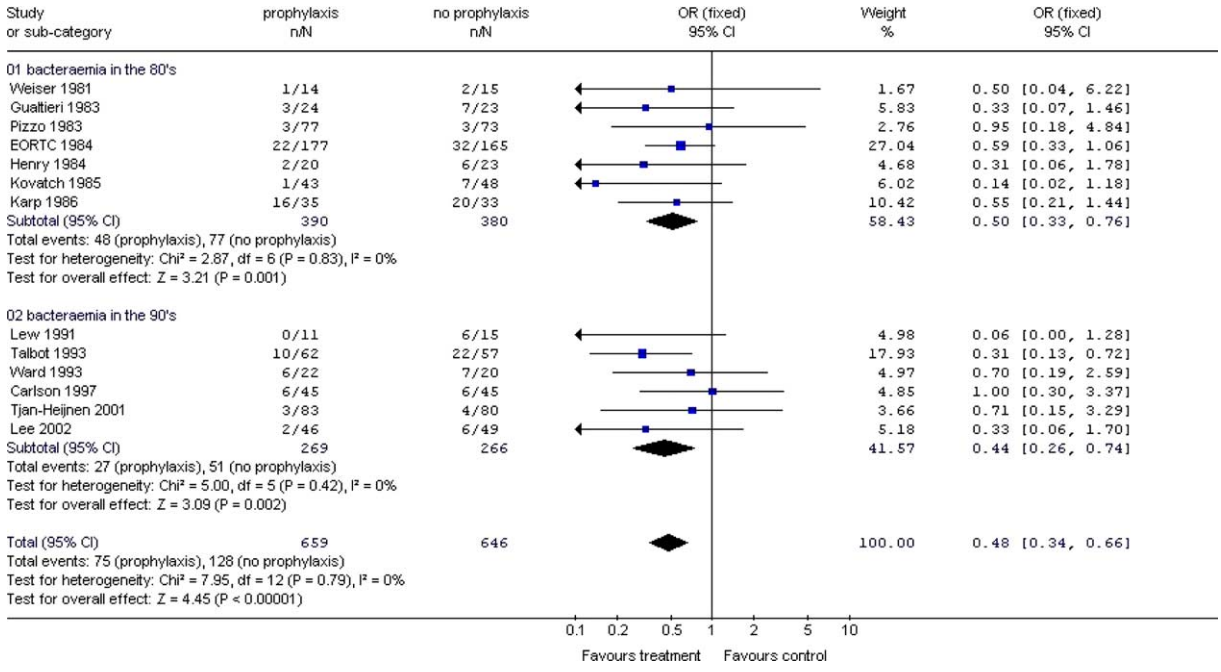

Fig. 5. Meta-analysis of oral prophylactic antibiotics compared to placebo or no prophylaxis for trials performed in the 1980s (7 trials) and trials performed in the 1990s (6 trials) with outcome bacteraemia. The odds ratio (OR) is presented with a 95% confidence interval.

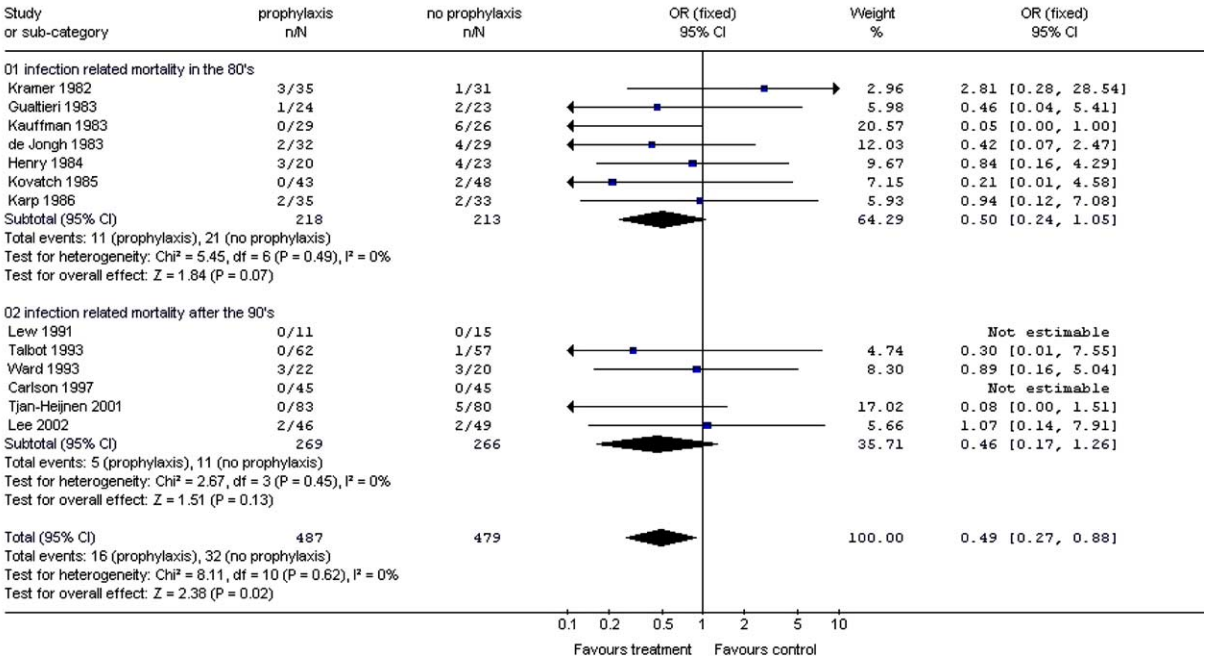

Fig. 6. Meta-analysis of oral prophylactic antibiotics compared to placebo or no prophylaxis for trials performed in the 1980s (7 trials) and trials performed in the 1990s (6 trials) with outcome infection-related mortality. The odds ratio (OR) is presented with a 95% confidence interval.

4. Discussion

This systematic review showed a significant reduction in Gram-negative bacteraemia with the use of prophylactic antibiotics especially the quinolone-based regimen and a decrease in mortality due to bacterial infections using pooled OR. Separate ORs for the TMP/SMZ trials and the quinolone trials did not reach significance. This review also showed no increase in fungaemia or fungal related mortality with the use of prophylactic antibiotics.

Previous systematic reviews [21,22] showed a significant reduction of Gram-negative bacteraemia with quinolone-based regimens but failed to show a reduction in infection-related mortality. This review differs from the previous ones on several aspects. First, we included trials both on TMP/SMZ and quinolones. Cruciani and Engels [21,22] only focused on quinolone regimens. Both TMP/SMZ and quinolone trials with or without additional Gram-positive cover decreased the anaerobic pathogenic flora without affecting the non-pathogenic flora. It therefore, seems justified to combine the trials for the outcome Gram-negative bacteraemia and infection related mortality. Second, in our analyses we compared TMP/SMZ or quinolone based regimens with no treatment or placebo while the previous reviews also included trials with other antibiotics in the comparison groups. Third, we excluded trials on the intravenous use of prophylactic antibiotics, as the original SDD concept focused on the use of oral antibiotics. Fourth, we focused on trials in which patients started prophylactic antibiotics before the onset of neutropenia (which is essential for the appropriate use of prophylaxis) and in which patients had no infections at the time of inclusion. Fifth we only extracted data from trials where the number of patients with bacteraemia (Gram-negative or Gram-positive) could be compared to the total number of patients per treatment group.

The incidence of bacteraemia is reduced by the use of both TMP/SMZ and quinolone prophylaxis. Due to the high risk of mortality, one aim of oral prophylaxis is to reduce Gram-negative bacteraemia. This systematic review showed that quinolone based prophylaxis was more effective in reducing Gram-negative bacteraemia than TMP/SMZ based regimens. Concerning Gram-positive bacteraemia, our systematic review showed that with TMP/SMZ based regimens, the incidence of Gram-positive bacteraemia was reduced. However, this was not evident for quinolone based regimens. It is well known that quinolones offer inadequate coverage for Gram-positive infections [41]. Addition of antibiotics covering Gram-positive microorganisms, could address this problem. Cruciani and colleagues [41] summarised all RCTs performed on the addition of Gram-positive prophylaxis to fluoroquinolones in a systematic review and concluded that there is lack of clear cut benefit on morbidity and mortality. This treatment strategy, however, should be valuable in subgroups of patients at high risk of streptococcal infections. This has yet to be shown. Although there is an increase over time of

Gram-positive organisms 60–70% [5], the mortality due to infections is much higher for Gram-negative than for Gram-positive bacteraemia. Celkan and co-workers [6] describe the infection related mortality in oncology patients as 8% due to Gram-positive septicaemia and 20% due to Gram-negative septicaemia. It is therefore of primary importance to focus on the elimination of Gram-negative organisms.

One issue of great concern in the oncology patient is the occurrence of resistant isolates. Strains that have been shown to develop quinolone resistance are *Escherichia coli* and coagulase negative staphylococcus [42]. The percentage of emerging resistance differs from more than 25% reported in the EORTC trials to less than 10% in the Memorial Sloan Kettering Centre. It is likely that the increasing resistance to fluoroquinolones among isolates from cancer patients reflects the pressure put on the endogenous flora, rather than dissemination of fluoroquinolone resistant strains in the general population. Data on resistance in the trials included in this review were difficult to interpret, and not all trials reported on resistance, therefore no conclusion can be drawn on development of resistant organisms from these data.

The fear of developing resistant organisms raises the question of whether it is wise to stratify the use of oral prophylaxis to certain high-risk groups of patients. A benefit was shown for the use of oral prophylaxis in patients who undergo both conventional chemotherapy and BMT procedure. Both groups may have benefited due to the intensity of conventional chemotherapy that is comparable to BMT procedure.

Quinolones provide poor coverage for streptococci and coagulase-negative staphylococci, therefore there is a higher risk of colonisation of these organisms and increased chance for infection [43,44]. In our meta-analysis we found that the incidence of Gram-positive bacteraemia did not increase with the use of oral prophylactic antibiotics.

In conclusion, our study provides evidence that prophylactic oral antibiotics should be considered clinically effective treatment for decreasing both mortality and morbidity in a heterogeneous population of oncology patients. Whether quinolones or TMP/SMZ confers benefit in selected populations of patients requires further study. According to current state of knowledge, factors that may influence the choice of oral prophylactic antibiotics include the individual clinician's preference, the tolerability of the treatment, its potential to induce bacterial resistance and finally cost.

Conflict of interest statement

All authors declare that there is no financial or personal relationship with other people or organizations that can inappropriately influence the work.

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