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Selective Gut Decontamination with Nalidixic Acid or Trimethoprim-Sulfamethoxazole for Infection Prophylaxis in Neutropenic Cancer Patients: Relationship of Efficacy to Antimicrobial Spectrum and Timing of Administration

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Eighty-four cancer patients at risk of infection because of neutropenia were randomized to receive nalidixic acid as an alternative to trimethoprim-sulfamethoxazole (TMP-SMX) for infection prophylaxis. Infections were documented significantly earlier and more often among patients who entered the trial with neutrophil counts of $<0.1 \times 10^9$/liter. TMP-SMX recipients experienced fewer microbiologically documented infections and bacteremias and were free of infection for a higher proportion of days with severe neutropenia ($<0.1 \times 10^9$/liter) than nalidixic acid recipients. Gram-negative bacillary and *Staphylococcus aureus* infections accounted for the major differences. Although the majority of aerobic gram-negative bacilli were eliminated from the feces after 1 week of prophylaxis with either agent, TMP-SMX was proved superior to nalidixic acid in this regard and was associated with acquired drug resistance by gram-negative bacilli less frequently. Both agents selected for colonization and subsequent infection by gram-positive cocci. Our data suggest that prophylaxis is most likely to be effective if administered to patients for at least 1 week before they become severely neutropenic. Nalidixic acid used as a single agent in doses of 4 g daily, however, cannot be recommended as an alternative to TMP-SMX for infection prophylaxis in neutropenic cancer patients.

Trimethoprim-sulfamethoxazole (TMP-SMX) has been reported to be a safe, effective, well-tolerated, and inexpensive agent for selective decontamination of the gastrointestinal tract for infection prophylaxis in neutropenic patients with cancer (9, 10, 12, 14, 15, 17, 18, 21–25, 35, 36). More recently, enthusiasm for the use of this agent for infection prophylaxis has been dampened by reports that TMP-SMX may select for antibiotic-resistant aerobic gram-negative bacilli (GNB) (8, 10, 18, 21, 23, 26, 28, 39) and for colonization by fungi (5, 15, 18, 24). Furthermore, myelosuppression associated with the use of this combination (5, 10, 29) is of concern.

Nalidixic acid, a quinolone compound which acts as an inhibitor of bacterial DNA gyrase (3, 4), has been used since the mid-1960s in the therapy of gram-negative urinary tract and intestinal infections (31). Low cost, low frequency of intolerance, absence of myelosuppressive potential, and a wide spectrum of activity against aerobic GNB without harm to the anaerobic intestinal microflora favor the use of nalidixic acid in neutropenic patients. Nalidixic acid has been used for selective decontamination of the gut in this patient population either as a component of a four-drug regimen (19, 20) or as part of a sequential alternating regimen (13, 32). Only one previous comparative report has been published directly evaluating the efficacy of nalidixic acid and TMP-SMX. In that study, TMP-SMX was found to be superior for infection prophylaxis (35). Nalidixic acid was administered in doses of 8 g daily, and TMP-SMX was given in a dose 50% higher than in previously reported studies (5, 9, 10, 18, 21, 23, 25). We report here the results of a randomized, nonblinded clinical trial comparing the microbiological and clinical efficacy of nalidixic acid (4 g daily) to TMP-SMX (320 mg of TMP and 1,600 mg of SMX [expressed as, e.g., 320/1,600 mg hereafter] daily), doses more frequently used in clinical practice (5, 9, 10, 18, 21, 23, 25, 31, 38).

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MATERIALS AND METHODS

Patient population and antimicrobial prophylaxis. Hospitalized patients treated between July 1981 and December 1983 with cytotoxic myelosuppressive theraperies for a variety of malignancies in the wards of two hospitals affiliated with the University of Manitoba were studied. Randomizations were generated from a computer program and assigned from the pharmacies of the participating hospitals. Patients were candidates for inclusion if they were neutropenic (absolute segmented neutrophil count plus the band neutrophil count less than 1.0×10^9/liter) or if they were expected to become neutropenic on the basis of the cytotoxic therapies administered. Patients infected at the time of randomization were not eligible for inclusion in the study. Patients with a known hypersensitivity to the study drugs were also excluded. Informed consent was obtained from all patients.

The patients were randomly assigned to receive nalidixic acid (1 g orally every 6 h) or TMP-SMX (160/800 mg orally every 12 h). Oral antifungal agents were not used prophylactically since the impact of the study agents on fungal colonization was an endpoint of the study. Oral antifungal agents were used to treat oral fungal mucositis (defined by culture and by microscopy as consistent with fungal infec-

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TABLE 1. Patient characteristics[a]

Characteristic	Nalidixic acid	TMP-SMX
No. entered	48	42
No. excluded (never became neutropenic)	4	2
No. eligible	44	40
Male/female (no.)	23/21	22/18
Age (mean yr ± SD)	56.7 ± 15.3	52.4 ± 15.5
Underlying illness (no. of patients)		
Acute nonlymphocytic leukemia	15 (13)	16 (11)
Acute lymphoblastic leukemia	1 (1)	4 (3)
Chronic myeloid leukemia—blast crisis	3 (2)	2 (1)
Lymphoreticular malignancy	13 (5)	5 (2)
Solid tumor	12 (7)	13 (5)
Status of underlying illness at entry (no. of patients)		
At initial diagnosis	14 (11)	12 (10)
Progressive illness despite therapy	28 (16)	25 (11)
Remission	2 (1)	3 (1)
Neutrophil count (10^9/liter) at entry (no. of patients)		
<0.1	12 (10)	6 (5)
0.1–0.499	12 (6)	18 (10)
0.5–0.999	7 (3)	9 (4)
>1.0	13 (9)	7 (3)
Duration (mean days ± SD) neutropenia on study with neutrophil count (10^9/liter) of:		
<0.1	1.6 ± 1.7	2.9 ± 3.8
0.1–0.499	2.7 ± 2.9	3.2 ± 3.2
0.5–0.999	1.8 ± 2.3	2.3 ± 2.7

[a] The number of patients developing infection during the trial is shown in parentheses.

tion). Patients continued the antibacterial prophylaxis until they had recovered from the neutropenic episode, developed evidence of infection, or died. The patients were managed in simple protective isolation consisting of single rooms and strict handwashing before and after patient contact. They ate cooked-food diets prepared in the hospital kitchens.

Infection was suspected and documented as described previously (5) and used as one of the endpoints for evaluation of prophylaxis efficacy. Febrile patients with suspected infection were candidates to receive empiric intravenous antibiotic therapy (16, 27). Oral antibacterial prophylaxis was discontinued at the onset of the febrile episode, because concurrent therapy with parenteral and oral antibacterial agents was expected to compromise the evaluation of the efficacy of antibacterial therapy. Accordingly, potential differences in myelosuppression attributable to the study drugs could not be assessed.

Surveillance cultures. Serial surveillance cultures of samples from the nasal passages, oropharynx, and feces were done twice weekly and processed as described previously (5). Colonization profiles were derived for a variety of microorganisms from these cultures. Colonization in this study was defined as recovery of the same species or biotype of microorganism in two or more serial cultures for a given sample site. The elimination rate was the proportion of microorganisms recovered in initial cultures that were eliminated from subsequent cultures. Persistence was defined as microorganisms recovered in all surveillance cultures from a given site while on study. The acquisition rate was the number of new strains of microorganisms colonizing a patient at a given site divided by the total number of evaluable patients. Transient flora were microorganisms recovered in only one surveillance culture for any given site.

Analysis. The endpoints of the study were to determine the incidence and types of infection encountered in each group; the relative protective effect (measured as the proportion of afebrile days at various degrees of neutropenia); and the impact of each study drug on the microbial colonization profiles for each surveillance sampling site. Patients were eligible for microbiologic analysis if two or more positive serial surveillance samples were obtained from any site.

The significance of differences between the means was determined by Student's t test. The significance of differences observed between proportions was determined by Fisher's exact probability test or the chi square test with Yate's correction when appropriate. Associations were deemed significant for $P \leq 0.05$.

RESULTS

Patients. A total of 90 patients who were neutropenic or expected to become neutropenic were entered into the trial. Table 1 shows the demographic characteristics of 84 patients who were considered evaluable for assessment of prophylactic drug efficacy. Six patients who never became neutropenic were excluded from the analysis. No significant differences were observed between study arm with respect to age, sex, underlying disease, status of underlying disease at trial entry, degree of myelosuppression at trial entry, or duration of prophylaxis. No patients had evidence of infection at study entry. Both regimens appeared to be well tolerated, and compliance among the 84 clinically evaluable patients was excellent, as patients received more than 95% of scheduled doses under the supervision of the nursing staff. Gastrointestinal upset resulted in discontinuing the allocated study drug in four nalidixic acid recipients and in three TMP-SMX recipients. One TMP-SMX recipient developed a drug-related macular erythematous skin rash. The excessive myelosuppression attributable to TMP-SMX in some studies (5, 10, 29, 35) was not observed in this study because the study design precluded such analysis by requiring that the study agents be discontinued with the institution of empiric systemic antimicrobial agents for suspected infection.

Over half (57%) of the patients entered the trial with severe neutropenia (neutrophil count less than 0.5×10^9/li-

ter). Patients entering the trial with neutrophil counts of $<0.1 \times 10^9$/liter were significantly more likely to develop infection (15 of 18 [83%] versus 35 of 66 [53%]; $\chi^2 = 4.206$, $P = 0.04$). Of those who developed infection during the trial, all but one had neutrophil counts of $<0.5 \times 10^9$/liter at the time infection was documented. The median time until infection was documented was 2.0 days for the 15 patients entering with neutrophil counts of $<0.1 \times 10^9$/liter, 6.5 days for the 16 patients entering with neutrophil counts of 0.1×10^9 to 0.499×10^9/liter, and 11.0 days for the 19 patients entering with neutrophil counts of 0.5×10^9/liter or more ($\chi^2 = 14.989$, $P = 0.0006$) (Fig. 1). No GNB infections were observed after day 5 of prophylaxis ($\chi^2 = 5.852$, $P = 0.016$). Bacterial infections due to *Staphylococcus epidermidis* were more common among patients who received more than 7 days of prophylaxis ($P = 0.04$, Fisher exact test). Overall, more than two-thirds of the infected patients had neutrophil counts of $<0.1 \times 10^9$/liter at the time infection was documented.

Comparison of clinical efficacy. Febrile episodes requiring empiric antibiotic therapy developed in over half of the patients in each group (28 of 44) [64%] in the nalidixic acid group and 22 of 40 [55%] in the TMP-SMX group) (Table 2). Among patients entering the trial with neutrophil counts of $<0.1 \times 10^9$/liter, nalidixic acid recipients had three times as many infections documented before 7 days of prophylaxis as TMP-SMX recipients. There were significantly more microbiologically documented bacterial infections (19 versus 7, $P = 0.02$) and bacteremias (13 versus 3, $P = 0.02$) in the nalidixic acid group than in the TMP-SMX group, respectively. This difference in infections was accounted for by an increased number of both gram-positive infections (14 versus 6) and aerobic GNB infections (5 versus 0) in nalidixic acid recipients. None of the infecting pathogens recovered from nalidixic acid recipients were susceptible to this agent. All five aerobic GNB infections occurred after a mean of 3.0 ± 1.3 (standard deviation) days of prophylaxis in patients who entered the trial with neutrophil counts of $<0.1 \times 10^9$/liter. No gram-negative infections occurred in patients who received at least 5 to 7 days of prophylaxis.

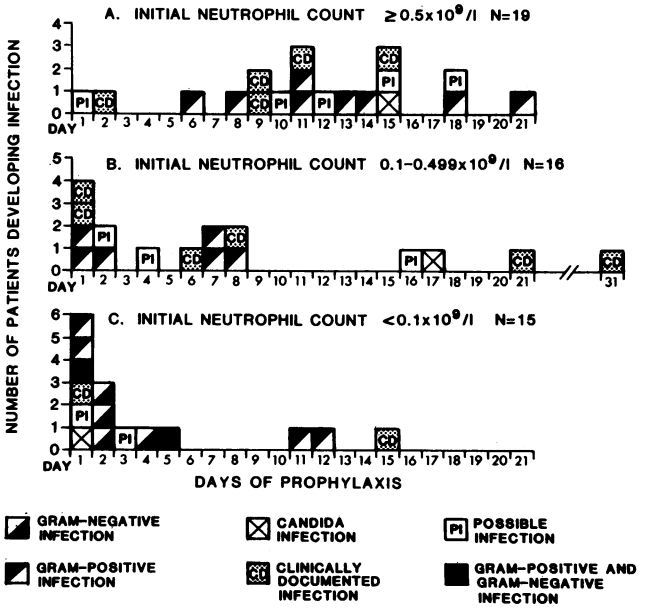

FIG. 1. Relationship of neutrophil count at study entry, when antimicrobial prophylaxis was initiated, to the incidence of infection, time of infection from study entry, and classification of infection for all patients developing infection during the study.

TABLE 2. Infections observed during the study

Infection	Nalidixic acid[a]	TMP-SMX[b]
Microbiologically documented		
Bacteremia	14	5
GNB	4[c]	0
Gram-positive cocci	9[d]	2[e]
Polymicrobic	0	1[f]
Candida SP.	1[g]	2[h]
Nonbacteremia	6	4
GNB	1[i]	0
Gram-positive cocci	5[j]	4[k]
Clinically documented		
Lung	4	7
Soft tissue	1	2
Oropharynx	0	1
Perirectal	1	2
Possible infection	5	5

[a] Total of 31 infections in 28 patients.
[b] Total of 26 infections in 22 patients.
[c] Two *P. aeruginosa*, *Klebsiella pneumoniae*, *K. pneumoniae* plus *Pseudomonas maltophila*.
[d] Four *S. aureus*, 4 *S. epidermidis*, 1 viridans group streptococcus.
[e] Two *S. epidermidis*.
[f] *S. epidermidis* plus *Fusobacterium nucleatum*.
[g] *C. tropicalis*.
[h] One *C. albicans*, 1 *C. pseudotropicalis*.
[i] *Enterobacter cloacae* pneumonia.
[j] *S. aureus*: 1 pneumonia, 1 urinary infection, 1 cellulitis; viridans group streptococcal pneumonia; *S. epidermidis* cellulitis.
[k] *S. aureus* cellulitis; viridans group streptococcal plus *S. aureus* pleuropulmonary infection, diphtheroid, injection site infection; *S. epidermidis* urinary tact infection.

There were seven *Staphylococcus aureus* infections in the nalidixic acid recipients (four bacteremias, one urinary tract infection, one cellulitis, and one pneumonia associated with *Pseudomonas aeruginosa* bacteremia), compared with only two in TMP-SMX recipients (both organisms were susceptible to TMP-SMX). One of these patients, who had an advanced lymphoma, entered the trial with an absolute neutrophil count of $<0.1 \times 10^9$/liter and developed a pleuropulmonary infection due to *S. aureus* and a viridans group streptococcus within 72 h of entry. The other patient, with acute leukemia, developed cellulitis due to *S. aureus* at the site of an axillary lymph node biopsy on day 8 of prophylaxis, when the absolute neutrophil count was $<0.1 \times 10^9$/liter. The higher incidence of *S. aureus* infections in nalidixic acid recipients correlated with its lack of activity against this organism.

The efficacy of TMP-SMX appeared to be independent of underlying illness and disease status. Among acute leukemias, 8 of 19 (42%) nalidixic acid recipients and 4 of 22 (18%) TMP-SMX recipients developed bacterial infections. Among those with lymphoreticular malignancy or solid tumors, 9 of 25 (36%) nalidixic acid recipients and 3 of 18 (17%) TMP-SMX recipients developed bacterial infections.

Fungemia developed in two TMP-SMX recipients with acute nonlymphocytic leukemia (*Candida albicans* and *Candida pseudotropicalis*, the former of which was fatal). A fatal fungemia due to *C. tropicalis* developed in one nalidixic acid recipient with acute nonlymphocytic leukemia.

For each 100 neutropenic days when the neutrophil count was $<0.1 \times 10^9$/liter, nalidixic acid recipients had a total of

TABLE 3. Colonization profile for organisms recovered from afebrile neutropenic patients receiving antimicrobial prophylaxis

Sample and organism	No. of positive cultures					
	Nalidixic acid			TMP-SMX		
	Elimination	Persistence	Acquisition	Elimination	Persistence	Acquisition
Nasal passages						
GNB	0	0	1	1	0	0
Yeasts	0	0	0	0	0	0
S. aureus	4	5	2	3	1	0
S. epidermidis	11	12	5	11	18	7
Enterococci	0	0	0	0	0	0
Viridans group streptococci	1	0	0	0	0	0
Diphtheroids	2	0	3	0	0	0
Aspergillus sp.	0	0	0	0	0	0
Oropharynx						
GNB	4	0	2	5	0	1
Yeasts	0	0	2	2	1	1
S. aureus	3	1	1	1	0	1
S. epidermidis	6[a]	1	2	0[a]	4	7
Enterococci	1	0	2	0	0	0
Viridans group streptococci	8	5	3	6	7	1
Diphtheroids	2	1	3	4	4	0
Feces						
GNB	33[b]	9	0	42[b]	2	1
Yeasts	2	0	6	1	0	5
S. aureus	1	0	1	0	0	0
S. epidermidis	6	7	8	2	11	12
Enterococci	4	5	9	4	3	9
Viridans group streptococci	6	2	5	4	2	1
Diphtheroids	13	6	5	8	9	3

[a] $\chi^2 = 4.482$, $P = 0.03$. Elimination rates for *S. epidermidis*, nalidixic acid versus TMP-SMX.
[b] $\chi^2 = 4.082$, $P = 0.04$. Elimination rates for GNB, nalidixic acid versus TMP-SMX.

15.7 microbiologically documented infections and 12.8 bacteremias, versus 3.4 microbiologically documented infections and 1.7 bacteremias for TMP-SMX recipients. The differences between the groups for these microbiologically documented infections and bacteremias were significant ($P < 0.01$ for both).

Eleven patients died while on study. The only fatality among TMP-SMX recipients had acute nonlymphocytic leukemia and developed a *C. albicans* fungemia with disseminated candidiasis on day 15 of prophylaxis. Of the 10 fatalities among nalidixic acid recipients, 2 were associated with refractory underlying disease without evidence of infection. The eight remaining fatalities were infection related. Overall, no deaths were attributable to failure of antibacterial prophylaxis in TMP-SMX recipients, compared with seven prophylaxis failure-related deaths among nalidixic acid recipients ($\chi^2 = 5.016$, $P = 0.025$). Of these, six were associated with progressive underlying disease.

Protective effect. The protective effect of each study drug was measured in terms of the number of afebrile days at different degrees of neutropenia. The proportion of afebrile days was significantly greater in TMP-SMX recipients (35% of 336 days) than in nalidixic acid recipients (26% of 267 days) ($\chi^2 = 5.087$, $P = 0.024$) when the neutrophil counts were $<0.1 \times 10^9$/liter. This difference was not observed at lesser degrees of neutropenia. The mean time to first fever was greater for TMP-SMX recipients (9.7 days) than for nalidixic acid recipients (7.2 days); however, the difference was not statistically significant ($P = 0.067$).

Colonization profiles. Complete surveillance culture data for the nasal passages and oropharynx were available for 25 nalidixic acid recipients and 27 TMP-SMX recipients (Table 3). Complete fecal surveillance data were available for one additional nalidixic acid recipient. The remaining patients did not have sufficient numbers of surveillance culture samples because of early prophylaxis failure.

The elimination rates were similar between the study

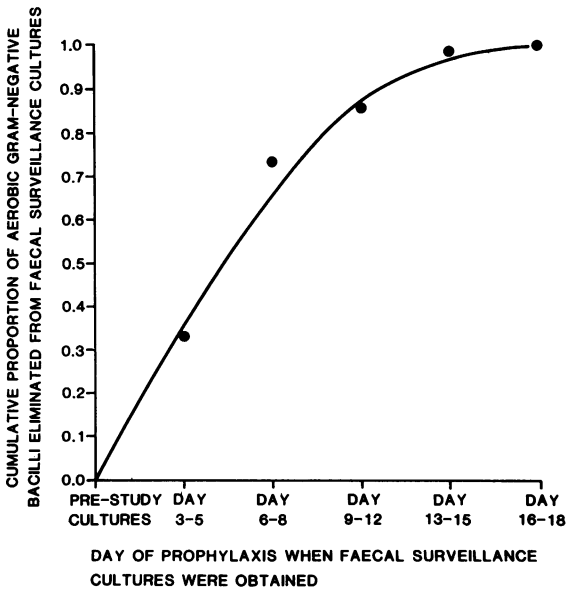

FIG. 2. Relationship of duration of antimicrobial prophylaxis to elimination of potentially pathogenic aerobic GNB from fecal surveillance cultures.

groups in each of the three surveillance sites for yeasts, *S. aureus*, enterococci, viridans group streptococci, and diphtheroids. GNB were more effectively eliminated from the feces of TMP-SMX recipients (42 of 44, 95%) than nalidixic acid recipients (33 of 42, 79%) ($\chi^2 = 4.08$, $P = 0.04$). The majority (74%) of the GNB were eliminated by week 1 of prophylaxis (Fig. 2).

The acquisition rates were similar between the study groups for all organisms for all three surveillance sites. Gram-positive cocci were acquired significantly more often than GNB at all surveillance sites (nasal samples, 0.27 versus 0.02, respectively, $P < 0.001$; oropharyngeal samples, 0.33 versus 0.06, respectively, $P = 0.001$; fecal samples, 0.84 versus 0.02, respectively, $P < 0.001$). Four TMP-SMX recipients acquired an *Aspergillus* sp. transiently, as determined by nasal sample cultures, compared with only one nalidixic acid recipient (not significant).

Fecal GNB acquired resistance to the study drug more often in nalidixic acid recipients than in TMP-SMX recipients (6 of 41 and 1 of 47 strains in nalidixic acid and TMP-SMX recipients, respectively; $P = 0.04$, Fisher exact test).

DISCUSSION

In this randomized clinical trial, we evaluated the clinical and microbiologic efficacy of nalidixic acid as an alternative to TMP-SMX for selective decontamination of the gastrointestinal tract and infection prevention in hospitalized neutropenic patients with cancer. Nalidixic acid was selected for comparison because of its wide spectrum of activity against aerobic GNB, lack of activity against anaerobic faecal flora which may confer colonization resistance (33), lack of myelotoxicity, ease of administration, patient tolerance, and low cost.

Our observations clearly demonstrate the superiority of TMP-SMX over nalidixic acid. Among TMP-SMX recipients there were significantly fewer infections due to aerobic GNB and gram-positive cocci such as *S. aureus*. No TMP-SMX recipients died of bacterial infections acquired during the study, compared with seven deaths among nalidixic acid recipients. There were more documented infections among nalidixic acid recipients despite lesser degrees of neutropenia (Table 1). Furthermore, TMP-SMX was more protective at neutrophil counts of $<0.1 \times 10^9$/liter and appeared to delay the onset of infection longer than did nalidixic acid. We feel that the observed differences in microbiologically documented infections and infection-related mortality reflect the wider antibacterial spectrum (1, 7), wider volume of distribution, and superior tissue penetration of TMP-SMX (2, 11) than of nalidixic acid.

The colonization profiles were developed to demonstrate the impact of each study agent on the aerobic host microflora. Both agents were effective for eliminating most of the aerobic gram-negative pathogens from the gut after an average of 1 week of prophylaxis; however, TMP-SMX was superior. A greater degree of inactivation of nalidixic acid by intestinal contents, as observed by others (34), could account for this difference. Acquired drug resistance by aerobic GNB was observed more often among nalidixic acid recipients.

Antifungal prophylaxis was not routinely used in this trial because the relationship of antibacterial prophylaxis to fungal colonization was an endpoint of the study and because a previous study at this institution (6) had suggested that no significant benefit was obtained from the use of standard prophylaxis with nystatin. In contrast to other reports (5, 15, 18, 24), we did not observe a high incidence of fungal colonization and infection. We have speculated that this may represent the resistance to fungal colonization that may be afforded by maintaining the anaerobic gut microflora.

The elimination of aerobic GNB and *S. aureus* represents a desirable microbiologic endpoint for infection prophylaxis. In this study, the use of either agent was associated with selection for and colonization by gram-positive organisms (mainly *S. epidermidis*, viridans group streptococci, and diphtheroids) in the surveillance cultures. This was associated with 21 gram-positive infections in 20 patients in our series. Overall, the incidence of gram-positive infections appeared to be independent of the duration of prophylaxis or the initial neutrophil count; however, the incidence of infection due to *S. epidermidis* was higher among patients receiving a week or more of prophylaxis. This parallels the colonization profile and is related to the lack of activity of the study agents against this organism. The elimination of morbidity and mortality due to GNB infections among patients receiving at least 7 days of prophylaxis (Fig. 1) was associated with elimination of the majority of those microorganisms from serial surveillance cultures (Fig. 2). These observations are in keeping with those of others (30). Furthermore, in our center, gram-positive infection represents a major consequence of the suppression of the more virulent gram-negative infections. This has been observed elsewhere (35, 37) and implies that the antimicrobial spectrum of the empiric regimen selected to treat fever in neutropenic patients who have received at least a week of selective gut decontamination should include agents effective against *S. epidermidis*. Although we observed no gram-negative infections after a week of prophylaxis, previous experience in our center (5) and elsewhere (10, 39) has shown that acquired gram-negative pathogens resistant to the prophylactic agent are also an important cause of fever in neutropenic patients. The spectrum of the empiric regimen must therefore include these microorganisms regardless of the duration of prophylaxis.

This study supports the view that in addition to compliance (29) the efficacy of antimicrobial prophylaxis in neutropenic patients is related to the antimicrobial spectrum of the prophylactic agent, to the severity of neutropenia at the time the prophylactic regimen is begun, and to the duration of the regimen. The longer duration of administration increases the likelihood that adequate tissue levels will be achieved for an optimum systemic effect and that there will be more complete suppression or elimination of the pool of potential pathogens in the gut. It seems reasonable, therefore, to recommend that prophylaxis be used as a strategy to reduce excess morbidity and mortality due to GNB infection (30) and be prescribed at least 1 week prior to the onset of expected severe neutropenia. Our experience is similar to that of others (35) and demonstrates that nalidixic acid, a first-generation bacterial DNA gyrase inhibitor, administered as a single agent has serious deficiencies in its antimicrobial spectrum which make it suboptimal for use as prophylaxis in neutropenic cancer patients. TMP-SMX remains the agent of choice for infection prophylaxis in this patient population in our institutions.

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