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Prophylactic non-absorbable antibiotics in leukaemic patients

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SUMMARY

A regimen of oral non-absorbable prophylactic antibiotics (kanamycin–vancomycin–nystatin) was given to nine severely neutropaenic leukaemic patients on cytotoxic therapy (11 courses), in conjunction with isolation procedures. An appreciable decrease in faecal organisms, especially anaerobes, was apparent after 48 h of commencing the course, and most bacteria had disappeared from the stool after five days. There were three episodes of septicaemia, all with enteric organisms, whilst on these antibiotics; one proved fatal. The emergence of resistance to aminoglycosides in faecal flora, notably *Klebsiella*, in 6/11 courses constituted a major problem in the use of such prophylaxis.

INTRODUCTION

Oral antibiotics are used in many centres to reduce the gastrointestinal flora of patients with acute leukaemia (Levine, Robinson & Hauser, 1975). In conjunction with other measures such prophylaxis is said to decrease the incidence of infection with endogenous flora during periods of severe neutropaenia occurring whilst on cytotoxic therapy (Hahn *et al.* 1978). Some authors have stated that up to 92% of routine bacterial stool cultures from patients on these regimens are sterile even when organisms isolated before prophylaxis (notably *Bacteroides* spp.) are insensitive to the antibiotics used (Bodey, Loftis & Bowen, 1968; Preisler, Goldstein & Henderson, 1970). In order to determine whether quantitative stool cultures on a variety of media would yield faecal organisms despite gut prophylaxis, we studied in detail the effect of oral antibiotic prophylaxis on the faecal flora of severely neutropaenic leukaemics and whether such a decrease in gut flora could be correlated with a decreased incidence of septicaemia.

In one report (Hahn *et al.* 1978), 23% (16/70) of patients on gut prophylaxis became colonized with gentamicin-resistant gram-negative bacilli, three of which appeared to have developed resistance during use of oral aminoglycosides. In this study, therefore, sensitivity testing was routinely carried out on all bacteria isolated in order to determine the incidence of resistant strains and whether such resistance had developed during the course of prophylaxis.

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MATERIALS AND METHODS

Eleven courses of oral antibiotic prophylaxis were administered between July 1978 and May 1979 to nine patients, five males and four females, aged from 23 to 72 years. Eight patients had acute myeloid leukaemia; four were undergoing primary induction chemotherapy with cytotoxic agents and four were being re-induced, three after relapse, one after partial remission. The ninth patient had chronic myeloid leukaemia in blastic crisis.

The antibiotics used were kanamycin 250 mg, vancomycin 500 mg, nystatin $0{\cdot}5 \times 10^6$ units and nystatin syrup 5 ml ($0{\cdot}5 \times 10^6$ units), all administered four times a day (range 10–50 days) for a mean of 20 days. Patients used 'pHisohex' for twice daily bathing and were nursed in single rooms with air-conditioning. Before entering the patient's room, all personnel and visitors were required to wash their hands and to put on gowns and masks. All those with infections, for example upper respiratory tract infections and infected skin lesions, were strictly excluded from contact with the patient. Before cytotoxic treatment all patients had neutrophil counts of less than 400×10^9/l. Four patients were totally without neutrophils.

Antileukaemic therapy

Therapy for initial induction or first relapse was usually a combination of daunorubicin, cytosine arabinoside and thioguanine. One patient in relapse refractory to this treatment received 5-azacytidine.

Specimens

A stool specimen was obtained before starting prophylaxis and then at 24, 48 and 72 h after starting the regimen and at five-day intervals from the start. Specimens were received in the laboratory and processed as soon as possible after being passed. Gram-stained films were examined from all stool specimens.

Quantitative technique

Approximately 1 g of faeces was weighed out and added to sterile saline with 20% peptone water (PW20S) to give a dilution of 1/100. This was emulsified in a stomacher (Colworth 80) and a series of dilutions made in PW20S to give a final dilution of $1/10^8$. Volumes of 0·025 ml of each dilution were dropped, using a 40 dropper, onto various media (shown with incubation times at 37 °C in Table 1). Counts were performed following incubation on all colonial types after Gram stain, and the concentration of each organism in the original sample expressed in logarithms to the base 10 ($\log_{10}$) per g faeces.

All organisms were identified by API-20E, API-20A or API-20C (API system, S.A.) or according to the methods of Cowan & Steel (1974) where kit systems were inappropriate.

For specimens taken later in the course of prophylaxis when lower counts were expected, 1 g of faeces was diluted 1/10 with PW20S and a series of further dilutions made to give a final dilution of $1/10^6$. Volumes of 0·025 ml of each dilution were dropped, using a 40 dropper, onto media as in Table 1. The 1/10 and 1/100

Table 1. *Media used and mode of incubation*

Agar medium	Culture	Incubation time
Layered horse blood*	Aerobic	18 h
Layered horse blood*	Anaerobic	5 days
Cysteine (10 μg/ml), horse blood†	Anaerobic	5 days
Kanamycin (75 μg/ml), cysteine (10 μg/ml), horse blood†	Anaerobic	5 days
MacConkey (Oxoid)	Aerobic	18 h
Sabouraud‡	Aerobic	48 h
Mannitol salt‡	Aerobic	48 h

* Base layer of Columbia agar (Oxoid) and top layer of tryptone soy agar (Oxoid) with 8% defibrinated horse blood.
† As for blood agar but with addition of cysteine or kanamycin and cysteine to top layer.
‡ Prepared according to Oxoid manual.

dilution fluids were separately added in 1 ml volumes to 20 ml tryptone soy broth (to dilute the antibiotic effect) and after incubation at 37 °C aerobically for 24 h and anaerobically for five days, aliquots of fluid were subcultured to the media in Table 1 for a qualitative assessment of viable faecal bacteria.

Antibacterial activity

Antibacterial activity was assayed in all stool specimens using 0·025 ml volumes of 1/10 and 1/100 dilutions against lawns of a standard *Escherichia coli* and the Oxford staphylococcus on Sensitest agar (Oxoid).

Sensitivity testing

Antimicrobial sensitivity testing was carried out on all bacterial strains isolated, by the calibrated dichotomous disk sensitivity method of Bell (1975).

Minimum inhibitory concentrations of cultures were determined by a method conforming with that recommended by Ericsson & Sherris (1971).

RESULTS

Effects of oral prophylaxis on faecal flora

The number of strains of aerobic and anaerobic faecal bacteria present at various times after starting gut prophylaxis is shown in Tables 2 and 3. Some inhibitory effect on aerobic organisms is apparent even after 24 h and becomes maximal for both aerobes and anaerobes between three and five days after starting the non-absorbable antibiotic combination. After five days, anaerobic organisms are virtually absent from the stool, and aerobes appreciably diminished. The initial decrease in bacterial counts precedes the presence of increasing faecal antibacterial activity as measured against the Oxford staphylococcus and a standard *E. coli* (Table 4), although most patients had substantial amounts of antibacterial activity present by five days, when organisms are largely absent from the stool.

Table 2. *Faecal aerobic organisms in leukaemics on gut prophylaxis*

Organisms	No. of strains	Pre-trial strains	No. of strains present on day of trial: 1	2	3	5	7–13	14+
Enterobacteria	44	33	19	5	1	4	1	5
Staphylococci	77	40	16	22	6	11	6	5
Streptococci	16	12	5	2	1	0	1	1
Gram-positive bacilli	11	4	1	2	0	0	0	5
Fungi	2	2	2	0	0	0	1	1
Candidaceae	7	3	0	1	0	0	2	4
Lactobacilli	1	0	0	0	0	0	0	1
Totals	158	94	43	32	8	15	11	22

Table 3. *Faecal anaerobic organisms in leukaemics on gut prophylaxis*

Organisms	No. of strains	Pre-trial strains	No. of strains present on day of trial: 1	2	3	5	7–13	14+
Bacteroides	33	32	16	15	4	5	1	0
Peptococci/ peptostreptococci	4	3	3	1	0	0	0	0
Clostridia	22	17	11	9	4	3	0	2
Bifidobacteria	2	2	1	0	0	0	0	0
Lactobacilli	5	4	3	1	1	0	0	0
Totals	66	58	34	26	9	8	1	2

Table 4. *Antibacterial activity in stools of leukaemics on gut prophylaxis*

Activity against*	No. of patients† with faecal antibacterial activity on day: 1	2	3	5	7–13	14+
Oxford staphylococcus (1/10)	1/11	4/11	2/11	7/11	6/11	8/8
Oxford staphylococcus (1/100)	1/11	4/11	2/11	5/11	6/11	6/8
E. coli 1/10)	0/11	2/11	2/11	7/11	5/11	8/8
E. coli (1/100)	0/11	2/11	2/11	1/11	5/11	3/8
Total patients with global activity	0/11	2/11	2/11	7/11	5/11	8/8

* Faecal dilution in parentheses.

† Not all patients continued on prophylaxis for same time.

If the highest $\log_{10}$ count at various intervals after starting prophylaxis is tabulated for each anaerobic species isolated from stool (Table 5), it can be seen that after three days most anaerobes are either present in only a ten-millionth of their original numbers or altogether absent. Anaerobic species persisting after five days of the antibiotic course invariably yielded only one species where earlier several had been isolated.

Table 6 shows the highest $\log_{10}$ counts at various times after starting prophylaxis for aerobic species in faeces, the steady decrease shown by aerobic species being

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Table 5. *Highest faecal anaerobic counts of leukaemics on gut prophylaxis*

Anaerobe	Highest log $_{10}$ count at day				
	Pre-trial	1	2	3	5
Bacteriodes fragilis	8·82	8·91	2·51	1·59	1·10
B. thetaiotaomicron	9·17	9·07	3·97	1·99	0
B. vulgatus	8·21	0	0	0	0
*B. ovatus**	9·05	8·33	2·37	1·74	5·52
B. distasonis	9·11	8·63	4·64	0	2·64
B. melaninogenicus ssp. *melaninogenicus*	8·83	8·73	4·34	0	0
B. asaccharolyticus	9·05	6·33	0	0	2·28
B. melaninogenicus ssp. *intermedius*	8·10	0	0	0	0
B. oralis	9·05	9·03	7·11	0	0
B. ruminicola ssp. *ruminicola*	8·03	0	0	0	0
B. ruminicola ssp. *brevis*	9·23	8·87	4·04	0	2·34
B. uniformis	6·81	6·29	2·58	0	0
Bacteroides spp.	9·14	8·77	3·97	2·29	0
Peptostreptococcus asaccharolyticus	0	9·03	0	0	0
Anaerobic streptococci	8·74	8·61	2·48	0	0
Clostridium welchii	9·05	0	7·11	0	2·68
Cl. bifermentans	8·24	0	0	0	0
Cl. sporogenes	8·41	8·98	4·51	0	2·28
Cl. inocuum	0	1·98	0	0	0
Cl. ramosum	8·66	8·69	3·97	1·99	0
Cl. sphenoides	0	9·03	5·11	0	0
Cl. tertium†	0	0	0	0	0
Cl. spp.‡	9·05	9·03	7·11	1·99	1·95
Bifidobacterium adolescentis	8·26	7·99	0	0	0
Bifido. brevis	7·94	0	0	0	0
Lactobacillus spp.	8·82	8·69	4·68	1·06	0

* One strain at 2·58 at 10 days. † One strain at 1·95 at 46 days.
‡ One strain at 3·93 at 25 days.

similar to that observed with the anaerobes. After an initial decrease, *Candidaceae* start to appear again in faeces at five days. The yeast count rises with the length of time the patient continues on prophylaxis. The re-appearance of *Klebsiella aerogenes* counts at five days reflects the emergence of several aminoglycoside-resistant strains. Other resistant strains isolated at 14 days or more included an *Enterobacter agglomerans* and a *Pseudomonas maltophilia*. Both coagulase-positive and negative staphylococci (sensitive to kanamycin or to vancomycin or to both) were present in faeces almost throughout prophylaxis, although the number of strains diminished later in the course. Very few specimens were completely sterile on culture (Table 7). Of the 3/49 that were, none yielded growth even when diluted 1/200 and 1/2000 to overcome the antibacterial effect.

Table 6. *Highest faecal aerobic counts of leukaemics on gut prophylaxis*

Aerobe	Pre-trial	Highest $\log_{10}$ count at day 1	2	3	5	7–13	14+
Escherichia coli	8·34	8·29	4·48	0	0·98	0	0
Klebsiella aerogenes	6·53	6·03	0	0	5·95	6·05	7·67
Proteus mirabilis	6·66	6·47	0	1·99	0	0	0
Enterobacter cloacae	5·93	6·03	0	0	0	0	0
E. agglomerans	0	0	0	0	0	0	4·23
Citrobacter freundii	7·05	7·03	0	0	0	0	0
C. diversus	6·10	0	0	0	0	0	0
Pseudomonas maltophilia	3·94	0	4·20	0	1·98	0	0
Ps. fluorescens gp.G	0	0	0	0	0	0	3·93
Ps. cepacia	3·97	2·28	0	0	0	0	0
Acinetobacter calcoaceticus var. *anitratus*	0	0	0	0	0	0	3·91
Staphylococcus aureus	8·04	3·98	5·11	0	6·04	5·91	6·23
Coag −ve staphylococci	8·04	7·47	6·00	2·00	6·04	6·17	6·27
Streptococcus faecalis	6·73	5·91	5·11	4·10	0	3·93	2·43
Strept. viridans	7·93	8·63	5·11	0	0	0	0
Gp. B streptococci	4·67	0	0	0	0	0	0
Bacillus coagulans	1·96	0	0	0	0	0	1·95
B. licheniformis	0	0	4·30	0	0	0	1·95
B. laterosporus	0	2·33	0	0	0	0	0
B. macerans	3·05	0	0	0	0	0	0
B. sphaericus	3·94	0	0	0	0	0	0
Listeria monocytogenes	0	0	4·91	0	0	0	0
Corynebacterium hofmanni	3·94	0	0	0	0	0	0
Lactobacillus brevis	0	0	0	0	0	0	3·75
Candida albicans	4·03	0	0	0	3·11	4·01	2·41
C. krusei	0	0	1·95	0	0	1·99	0
Saccharomyces cerevisiae	2·26	0	0	0	0	0	0
Aspergillus niger	3·05	3·03	0	0	0	2·03	1·93
Fungus	1·97	1·98	0	0	0	0	0

Table 7. *Suppression of faecal flora of leukaemics on gut prophylaxis*

Patient (course)	No. of specimens received	Specimens with no growth: Aerobes	Anaerobes	Yeasts/Fungi	Specimens with no growth
1 (*a*)	6	1	2	5	0
(*b*)	6	2	2	4	1
2	5	2	1	3	1
3 (*a*)	6	3	0	6	0
(*b*)	6	3	2	4	1
4	5	0	1	0	0
5	2	0	1	1	0
6	7	0	3	7	0
7	1	0	1	1	0
8	3	0	1	0	0
9	2	0	1	2	0
Totals	49	11 (22%)	15 (31%)	33 (67%)	3 (6%)

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Correlation between diminishing faecal population and septicaemia

Three patients developed a septicaemia whilst on gut prophylaxis.

Case 1 occurred five days after starting gut prophylaxis in a 25-year-old woman in acute blastic crisis from chronic myeloid leukaemia, who had absolute neutropaenia (0%). Her stools were free of aerobic organisms when she became hypotensive and pyrexial (39·5 °C). Blood culture yielded an *E. coli* and an *E. coli* (*alkalescens – dispar* group). The former had been isolated only from her pre-trial stool specimen but not from subsequent specimens. The latter had not previously been isolated. Both organisms were sensitive to kanamycin. She was treated with gentamicin and ampicillin and recovered.

Case 2 was a 62-year-old man who had presented with acute myeloid leukaemia (0% neutrophils) and was septicaemic with a *Ps. fluorescens* biotype II (B) at the time of starting gut prophylaxis. He was treated with gentamicin and carbenicillin and improved. Unfortunately, no pre-trial faecal specimen was obtained, but stool culture five days later yielded *E. coli*, *K. aerogenes* and *Ps. maltophilia*, all resistant to gentamicin. The *Ps. fluorescens* was, however, not recovered. He developed a bronchopneumonia, followed six days later by septicaemia with the gentamicin-reistant *E. coli* which was sensitive only to amikacin. He died after having received only two doses of this antibiotic.

Case 3 was a 68-year-old woman with partially treated acute myeloid leukaemia and 250×10^9/l neutrophils at the time she simultaneously commenced prophylaxis and cytotoxic treatment. One month after starting gut prophylaxis, she developed widespread necrotic skin lesions from which *Ps. aeruginosa* was grown. This organism was also subsequently isolated from blood culture. At no time was the *Ps. aeruginosa* present in her stools. She received gentamicin and carbenicillin and recovered.

Incidence of development of aminoglycoside resistance

In 6/11 courses, after periods of time varying from five to twenty-five days, patients grew faecal strains of *K. aerogenes* resistant to kanamycin. Some of these strains were resistant to gentamicin on disk testing. These results were borne out by quantitative estimation of the minimum inhibitory concentrations of both aminoglycosides for these strains (Table 8).

In 5/6 cases an indole-negative *K. aerogenes* sensitive to kanamycin had been isolated from the pre-trial specimen (one pre-trial specimen was not received) and a kanamycin-resistant *K. aerogenes* with an API number differing by only one digit (indole-positive) isolated from subsequent specimens. Only 1/9 patients (1/11 courses) did not receive systemic gentamicin during the non-absorbable antibiotic course. Five of the patients who received systemic gentamicin did not have positive blood cultures at any time.

In addition to a gentamicin-resistant *K. aerogenes*, one patient had a gentamicin-resistant *E. coli* and a *Ps. maltophilia* in his faeces after five days of prophylaxis (table 8), and one patient had a gentamicin-resistant *K. aerogenes* with a genta-

Table 8. *Minimum inhibitory concentrations of resistant faecal strains to aminoglycosides*

Patient	Isolate		Kanamycin (μg/ml)	Gentamicin (μg/ml)
4	*K. aerogenes*	Pre-trial	2	0·5
		On prophylaxis	32	2
5	*K. aerogenes*	Pre-trial	2	1
		On prophylaxis	128	1
6	*K. aerogenes*	Pre-trial	2	0·5
		On prophylaxis	> 128	4
7	*K. aerogenes*	On prophylaxis	> 128	2
	E. coli	On prophylaxis	> 128	4
	P. maltophilia	On prophylaxis	32	8
8	*K. aerogenes*	Pre-trial	1	0·25
		On prophylaxis	> 128	2
9	*K. aerogenes*	Pre-trial	2	0·5
		On prophylaxis	64	2

micin-resistant *E. agglomerans* and a kanamycin-resistant (vancomycin-sensitive) *Staphylococcus aureus* after one month on prophylaxis.

DISCUSSION

Gentamicin–vancomycin–nystatin (Preisler *et al.* 1970) and framycetin (or neomycin)–colistin–nystatin (Storring *et al.* 1977; Watson & Jameson, 1979) are the principal non-absorbable antibiotic regimens which have been described for prophylaxis against infection in compromised patients. Supplies of framycetin and colistin were for various reasons unavailable in Sydney and, in view of the possible development of aminoglycoside resistance by faecal organisms, it seemed desirable to reserve gentamicin for treatment of infections. We therefore elected to use kanamycin, which is rarely used in this hospital (and to which nearly all of the enteric bacteria and staphylococci isolated from pre-trial specimens proved to be sensitive), in combination with vancomycin and nystatin.

Decrease in faecal bacterial numbers was evident about 48 h after starting prophylaxis and was maximal at five days. This is of great importance when administering cytotoxics, as gut prophylaxis should consequently be started some days before cytotoxic therapy to achieve maximum benefit through suppression of endogenous flora. Cytotoxic agents may, however, also have some action on bacteria (Goldschmidt & Bodey, 1972), although this is now in doubt (Moody *et al.* 1978).

Despite the use of non-absorbable antibiotics with no anti-anaerobic activity except that of vancomycin on *Clostridia* spp., anaerobes proved virtually impossible to culture from the stools of patients on such antibiotics for several days, while some aerobes, notably staphylococci, antibiotic-resistant organisms and yeasts, were nearly always isolated. Occasionally, enterobacteria which were sensitive to the antibiotics used could be isolated from faeces. It would seem that an inter-

action occurs between aerobes and anaerobes in the gut, and that diminution in the numbers of aerobes leads to dramatic diminution in the numbers of anaerobes. This may be related to the greater sensitivity of anaerobes to local changes in pO_2 and E_h (Gorbach *et al.* 1971). These changes particularly occur in diarrhoea, and all patients experienced mild to severe diarrhoea on the regimen, with cytotoxics probably also having a contributory effect. It is probable that some organisms can survive in colonic mucosal crypts, where antibiotics may fail to penetrate in bactericidal concentrations, but cannot be cultured from faeces where antibacterial activity is high. Routine Gram stains on faecal specimens often showed low numbers of Gram-positive and -negative bacilli which could not be isolated on culture, and one of our patients did become septicaemic with an organism present pre-trial in her stool which presumably had survived in an intestinal crypt as it was not cultured from other faecal specimens.

In contrast to other authors (Bodey *et al.* 1968; Preisler *et al.* 1970) who reported that up to 92% of stool cultures in leukaemic patients on non-absorbable antibiotics were free of aerobic and anaerobic bacteria, in our study only 22% of faecal cultures were free of such bacteria. This finding would however agree with the observation of Preisler *et al.* (1970) that suppression of yeasts and fungi varies inversely with the degree of bacterial suppression, as 67% of faecal cultures in our patients, in comparison with 20% of cultures in theirs, were found to be free of yeasts or fungi.

Bodey *et al.* (1968) have suggested that to achieve maximum effectiveness antibiotics must be administered every four hours. However, besides experiencing variable degrees of diarrhoea, several patients complained of the taste of the vancomycin even when mixed with syrup to make it more palatable and one refused to take it. Increasing the frequency of dosage would certainly have resulted in an increased rejection rate. Indeed, Bender *et al.* (1979) have suggested that the omission of vancomycin from the regimen may improve patient compliance and decrease cost without significantly increasing aerobic faecal counts.

On reviewing 42 patients with acute granulocytic leukaemia over a 30-month period in a previous study in this hospital (King, 1979), it was found that 23 episodes of septicaemia occurred in 16 patients during remission – induction or relapse – re-induction and 2/15 patients with chronic granulocytic leukaemia, both in blastic crisis, developed a septicaemia. Thus we were able to predict that in a group of nine patients with acute granulocytic leukaemia at remission – induction or in relapse, or with chronic granulocytic leukaemia in blastic crisis, five episodes of septicaemia could be expected. In practice there were three septicaemic episodes whilst on gut prophylaxis. In one case a *Ps. aeruginosa*, not isolated pre-trial, was involved against which the prophylactic regimen is ineffective. These numbers are too small to draw any conclusion about the efficacy of gut prophylaxis in preventing septicaemia, but may indicate a trend.

The emergence of aminoglycoside resistance in persistent faecal strains, notably klebsiellas, was a possible infection problem in 6/9 patients (6/11 courses). Nevertheless, discontinuation of treatment due to rapidly rising faecal counts of the resistant strain was necessary in only one patient. In the other patients

cessation of prophylactic therapy occurred either on recovery of the neutrophil count (5/9) or at death (3/9). One of the patients who died (Case 2) was already septicaemic at presentation with a *Ps. fluorescens* and eventually died of a septicaemia with a gentamicin-resistant *E. coli*. Regrettably, since a pre-trial stool specimen was not taken, we are unable to determine whether this organism was present in faeces before prophylaxis or whether its emergence occurred after the prophylaxis but *Ps. maltophilia* and *K. aerogenes*, both also gentamicin resistant, were isolated concurrently from this man's stool.

Bodey & Rosenbaum (1974) reported that the majority of resistant strains occurring during treatment were not potential pathogens. Hahn *et al.* (1978) found that only 1% of acquired potential pathogens had gentamicin resistance emerge while patients were on gentamicin–vancomycin–nystatin. Unlike these authors we have found the emergence of aminoglycoside-resistant faecal flora during similar prophylaxis to be a major problem, the potential for acquiring resistant flora being present in every patient with klebsiellas in the stool pre-trial. Of the eleven pre-trial isolates of *K. aerogenes*, five disappeared on prophylaxis and six acquired aminoglycoside resistance. Most neutropaenic patients received systemic, in addition to non-absorbable, aminoglycosides and this may well have contributed to selection pressures. Other authors (Greene *et al.* 1973; Klastersky *et al.* 1974) have reported increasing resistance to gentamicin in *Ps. aeruginosa* isolated from patients receiving oral gentamicin, but such resistance had not been detected in klebsiellas. However, *Ps. aeruginosa* was not detected in faecal specimens from our patients.

In view of the infection danger, the difficulties in treatment that these resistant organisms present to neutropaenic patients, and the additional hazard of introducing new resistant organisms to the hospital environment, prophylactic use, particularly of aminoglycoside antibiotics should be very guarded, even in units with special facilities such as laminar flow isolators (Penland & Perry, 1970) proved to reduce the incidence of infection in conjunction with prophylactic antibiotics (Levine, 1976; Rodriguez *et al.* 1978). In any case such prophylaxis must be carefully monitored by faecal cultures.

Oral co-trimoxazole has recently been advocated as a relatively inexpensive, readily acceptable and surprisingly effective prophylactic antibiotic (Gurwith, 1978). The selection of trimethoprim-resistant enterobacteria and patient allergy to the combination may be disadvantagous. We are, therefore, carrying out a limited trial of co-trimoxazole in suitable haematologically compromised patients along similar lines to this study.

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