J. Hyg., Camb, (1980), **84**, 457
Printed in Great Britain

Infection prevention in patients with cancer: microbiological evaluation of portable laminar air flow isolation, topical chlorhexidine, and oral non-absorbable antibiotics

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(*Received* 31 *October* 1979)

SUMMARY

The increasing use of intensive cytotoxic chemotherapy for patients with solid tumours enhances the risk of opportunistic infection to levels formerly seen only in patients with acute leukaemia, and prevention of infection is a major concern. A relatively simple regimen of isolation, topical antisepsis, and orally administered non-absorbable antibiotics was studied in 18 patients. Sixteen of 21 studies were performed using portable laminar air flow apparatus and five with isolation only. All patients became severely neutropenic but there were no major infections. Microbiological results showed effective decontamination of the skin, which was maintained without recolonization or acquisition of new organisms. The ears, nose and throat were effectively decontaminated only when the regimen was intensified. Colonization with *Pseudomonas aeruginosa*, a major pathogen in compromised hosts, did not occur. The protective regimen is less expensive than regimens previously described, is acceptable to patients, and requires no modification of existing hospital rooms. It merits further evaluation in patients with common cancers who receive intensive cytotoxic drug therapy.

INTRODUCTION

In clinical oncology, studies of infection prevention have been mainly in patients with acute leukaemia, in whom infection is the major cause of death (Hersh *et al.* 1965). Improved antimicrobial therapy has not altered this (Chang *et al.* 1976), and new, intensive regimens of cytotoxic therapy and the practice of bone marrow transplantation have enhanced the risks of severe infection. Numerous studies have used isolation rooms (Jameson *et al.* 1971), laminar airflow (LAF) rooms (Schimpff *et al.* 1975) and plastic film isolators (Trexler, Spiers & Gaya, 1975) to protect leukaemia patients from infection. Most studies have combined protective isolation with decontamination of the gastrointestinal tract by orally administered, non-absorbable antibiotics, and application to the skin of antiseptic solutions. Results from several studies indicate that the incidence of bacterial infections, the number of days with fever, and the number of deaths with infection, can all be reduced in patients with leukaemia.

0022–1724/80/0097–1979 $01.00

Table 1. *Diagnoses and nursing environment of* 18 *patients entered into the study of isolation and decontamination*

Diagnosis	Environment		Total
	LAF*	RP†	
Acute leukaemia	4	3	7
Breast cancer	2	0	2
Lung cancer	10	2	12
	16	5	21‡

* Laminar-air-flow.
† Reverse precautions.
‡ 21 studies were performed on 18 patients.

There is a need to apply these lessons in the numerically far more important solid tumours, since modest progress in the chemotherapy of metastatic cancers has led to much interest in developing more intensive chemotherapy. Use of intensive cytotoxic drug therapy places patients with solid tumours at higher risk of infection than in the past, and if the gains secured by better drug therapy are not to be offset by an increased number of fatal infections, means for patient protection similar to those shown to be effective in leukaemia should be considered. Elaborate and costly isolation systems could not be provided for the large number of patients with solid tumours; we therefore have investigated a relatively simple and less expensive system, using a structurally unmodified hospital room, and studying principally patients with common cancers. This pilot study was not randomized, and concentrated chiefly upon the microbiological results obtainable and the incidence of infection, rather than the results of the cytotoxic drug therapy, which are part of a more extended study.

METHODS AND MATERIAL

Patients

We performed 21 studies on 18 patients with malignant disease who could benefit from intensive chemotherapy and who consented to the study. Sixteen studies were performed in single rooms equipped with LAF apparatus and five were done in single rooms with reverse precautions (RP) but without LAF. Reverse precautions in our hospital correspond to 'reverse isolation' in British hospitals and include a single room with restricted entry of staff and visitors, who wear protective clothing as described below while attending the patient. The intention is to prevent, by restricted traffic and physical barriers, transfer of organisms from attendants to the patient, or by the attendants from one patient to another. Apart from use of the LAF apparatus, the management of patients in the two groups was identical. Details of the patients are given in Table 1. The cytotoxic chemotherapy administered varied with the diagnosis but was always intensive and produced significant neutropenia, which was monitored by blood counts three times each week.

Components of the protective regimen

Environment

Patients were nursed in precleaned single rooms with private baths. The doors were kept closed and staff entering the rooms wore caps, masks, boots, disposable gowns, and sterile gloves. In 16 studies, sterile filtered air was supplied by the 'Med-Assist' portable LAF apparatus (Young *et al.* 1975). Wheeled LAF cabinets at the head and foot of the bed each contain a pump, coarse filters, and a High Efficiency Particulate Absolute (HEPA) filter which removes particles larger than 0·3 microns in diameter. The cabinet at the head of the bed provides an outflow of sterile air and the cabinet at the bed's foot an intake: patients thus are enclosed in a laminar flow of sterile air moving from head to feet. When the cabinets are switched on and the room door is closed, the organism count in the room air progressively falls. Draught and noise from the apparatus are minimal and do not interfere with conversation or sleep.

Topical antisepsis

The antiseptic used was chlorhexidine gluconate, as a 4% solution with detergent ('Hibiclens', 'Hibiscrub') and in 0·02% aqueous solution. The regimen used comprised: (*a*) a daily bath or bed bath using 'Hibiclens', with a shower afterward; (*b*) twice-weekly washing of hair and beard with 'Hibiclens'; (*c*) spraying of the nostrils, ears, and throat four times daily with 0·02% chlorhexidine from a atomizer; (*d*) a mouth rinse four times daily with 20 ml of the same solution; (*e*) teeth were brushed daily with 0·02% chlorhexidine and dentures were stored in the same solution; (*f*) vaginal douching twice daily with 0·02% chlorhexidine solution. Numerous reports attest both the safety and efficacy of chlorhexidine (Lowbury & Lilly, 1973; Trexler *et al.* 1975).

Gastrointestinal decontamination

We used a modification of a regimen which we previously had shown to be effective in leukemia patients (Storring *et al.* 1977): nystatin suspension 1 000 000 units by mouth 6-hourly; neomycin 500 mg tablets, one 6-hourly; colistin sulphate 75 mg capsules, one 6-hourly. Neomycin and colistin were begun 48 h after the nystatin and all medications were continued throughout isolation. Diarrhoea is common but is either self-limited or readily controlled with diphenoxylate with atropine ('Lomotil'). Characteristically the stools are soft and odourless.

Nutrition

Most patients received a freshly-cooked diet low in bacteria but not sterile, with sterile drinking water and ice cubes. Patients with severe anorexia received total parenteral nutrition via a subclavian venous catheter.

Surveillance

In addition to routine observation of vital signs, the following surveillance was carried out by the nurse oncologist: (*a*) daily inspection of skin, mouth and

perianal area for infection or dermatitis from antiseptic; (*b*) weekly cultures of the nostrils, ears, throat, axillae, umbilicus, groins, perianal area, vagina, and any skin lesions; (*c*) twice-weekly cultures of stool and urine. In the event of pyrexia, cultures were repeated and blood cultures were taken also. Skin cultures were obtained before antiseptic treatment and weekly thereafter, using sterile swabs moistened with sterile distilled water without preservative. These were taken direct to the microbiology laboratory for processing.

Nursing

The nurses were responsible for instructing the patients in the use and purpose of the topical antiseptics, non-absorbable antibiotics, and special diet. Patients were encouraged to carry out the topical antiseptic regimen themselves. The nurses wiped all horizontal surfaces in the LAF or RP room with 70% isopropyl alcohol, and mopped the floors with antiseptic and a sterilized mop, three times each week. Particularly important was the nurses' role in providing psychological support and encouragement for these seriously ill patients.

Assessment of microbiological results

Skin swabs were plated out by the conventional 'streak plate' technique and scored as 0 to 4+, where 0 represents no bacterial growth and 4+ represents growth extending into the fourth set of streaks on the medium. *Contamination scores* for individual sites were made by pooling the numerical scores for each site sampled and dividing by the total number of samples. The percentage change in contamination score over a given time interval was then calculated for each site. *Recovery of specific pathogens* at specified intervals was expressed as the number of sites positive for each organism and also as the percentage of all sites sampled which proved to harbour the organism. These unsophisticated assessments can be carried out by the routine microbiological services of the hospital.

RESULTS

Neutropenia and infection

All patients became neutropenic following the high-dose chemotherapy. They were at enhanced risk of infection (neutrophil count less than 1000/mm^3) for a total of 264 days. The mean duration of neutropenia was 12 days for the whole group. In the solid tumour patients, recovery from neutropenia was predictable, occurring about Day 18 after chemotherapy. Leukaemia patients had longer periods of neutropenia and recovery was unpredictable because it depended upon their attaining a remission of their disease. For the seven studies carried out in leukaemia patients, the mean duration of severe neutropenia (neutrophil count less than 500/mm^3) was 32 days. In our 21 studies there were four documented infections: one leukaemia patient developed oral candidiasis which was cured and two leukaemia patients died of disseminated aspergillosis. A solid tumour patient developed a *Proteus* urinary tract infection which may have been present before the study. There were several unexplained fevers for which antibiotics were

Table 2. *The incidence of neutropenia and the occurrence of fatal infection in patients nursed in LAF or RP rooms*

Room	No. of studies	Days with under 1000 neutrophils			Fatal aspergillosis
		Total	Mean/study	Range	
LAF	16	194	12·1	2–36	1
RP	5	70	14·0	4–28	1
Combined	21	264	12·6	2–36	2

Table 3. *The reduction in organisms (all types) at various sites, comparing day* 1 *(before treatment) with day* 15 *of the decontamination regimen: results are percentage reductions*

Site	Patient environment		
	LAF	RP	Combined
Ears	48·2	31·7	48·1
Nostrils	35·8	72·0	32·5
Throat	32·1	39·7	32·9
Axillae	69·3	100·0	76·3
Umbilicus	47·4	100·0	58·8
Groins	55·3	97·0	61·8
Vagina	88·6	*	*
Anal margin	82·0	*	*

* Data insufficient.

given; all blood cultures were negative and no infection was identified. The only deaths during the study were the two patients with aspergillosis. The distribution of neutropenia and infection was similar in LAF and RP patients (Table 2).

Reduction in topical flora

The reduction in surface flora achieved by the first two weeks of the regimen is shown in Table 3. Because there were few RP patients, it is uncertain whether the results differ between LAF and RP patients: the RP group appears not to have fared worse, and we have pooled the other results. It is apparent from Table 3 that decontamination of the upper respiratory tract is less efficient than that of the skin and vagina. Bacteria-free throat swabs were obtained in two patients only. One had acute leukaemia, severe neutropenia, and severe drug-induced stomatitis. She received local applications of 0·02 % chlorhexidine gluconate every 2–3 hours and no bacteria or yeasts were recovered from throat swabs during a 21-day period. This suggests that intensification of the topical antiseptic regimen might achieve better decontamination in other patients. The patients with solid tumours all recovered from neutropenia before Day 22 and were therefore off-study. In the 7 studies in leukaemia patients, day 22 and day 29 cultures showed a percentage reduction in flora remarkably similar to that seen on day 15. Evidently decontamination could be maintained, without recolonization by new organisms, but was not much improved by prolonged exposure to the regimen. Absence of a sterile diet

https://doi.org/10.1017/S0022172400026991 Published online by Cambridge University Press

Table 4. *Recovery of pathogenic organisms from all sites in 21 case studies, before treatment and after 1 and 2 weeks of the decontamination regimen*

Pathogen	Day 1: 232 sites		Day 8: 237 sites		Day 15: 169 sites	
	No. positive	% positive	No. positive	% positive	No. positive	% positive
β-hem. Strep	1	0·4	3	1·3	1	0·6
Staph. aureus	16	6·9	6	2·5	7	4·1
E. coli	*3*	*1·3*	*0*	*0*	*0*	*0*
Ps. aeruginosa	0	0	0	0	1	0·6
Klebsiella spp.	0	0	1	0·4	3	1 8
Prot. mirabilis	1	0·4	1	0·4	2	1·2
Gram negative rods*	4	1·7	1	0·4	1	0·6
Candida spp.	1	0·4	2	0·8	1	0·6
Total pathogens	26	11·2	14	5·9	16	9·5

* Speciation undefined.

Table 5. *The location of pathogenic organisms before and during the decontamination regimen*

Pathogen	Site		
	Day 1	Day 8	Day 15
β-hem. Strep.	1 groin	3 vagina	1 vagina
Staph. aureus	11 nose	5 nose	5 nose
	3 throat	1 ear	1 ear
	1 axilla	—	1 groin
	1 ear	—	—
E. coli	2 anal	—	—
	1 vagina	—	—
Ps. aeruginosa	—	—	1 throat
Klebsiella spp.	—	1 vagina	2 groin
			1 throat
Prot. mirabilis	1 axilla	1 axilla	2 axilla
Gram −ve. rods	4 anal	1 throat	1 umbilicus
Candida spp.	1 throat	2 groin	1 throat

might account in part for this lack of progressive attrition of the flora. In this initial assessment of decontamination, we scored all organisms isolated, since in patients with cancer and neutropenia, it is uncertain that any organism is definitely nonpathogenic.

Recovery of pathogens

The recovery of pathogenic organisms from all sites is summarized in Table 4. Our patients were relatively free of pathogens before decontamination: the most common organism, *Staphylococcus aureus*, occurred in only 6·9% of samples. The absence of *Pseudomonas aeruginosa* contrasts with the findings of Bodey (1970) who reported a high carriage rate for this organism in new patients with leukaemia. The majority of our patients had neither leukaemia nor neutropenia before admission. Our results show a modest reduction in the rate of staphylococcal carriage

https://doi.org/10.1017/S0022172400026991 Published online by Cambridge University Press

Table 6. *Nasal carriage of* Staphylococcus aureus *before and during decontamination with topical* 0·02 % *chlorhexidine gluconate*

Day	No. sites sampled	No. sites positive	% sites positive
1	38	11	29·0
8	37	5	13·5
15	23	5	21·7

by day 15. There was no evidence of acquisition of pathogens during this period, which is encouraging, since the patients became neutropenic and developed areas of traumatized skin (from invasive procedures) and denuded mucous membrane (from cytotoxic drug therapy).

The location of pathogens is shown in Table 5. The upper respiratory tract most frequently harbours organisms, accounting for 16/26, 7/14, and 9/16 isolates on Days 1, 8 and 15 respectively. More effective decontamination of the upper airways is needed. Examining the incidence of *Staphylococcus aureus*, the most frequent pathogen, at its most common site, the nostrils (Table 6), it is seen that decontamination is poor and may even become less effective with time. Nasal insufflation of chlorhexidine solution does not effectively reach the paranasal sinuses or the hair follicles within the nares, and these may serve as reservoirs of staphylococci.

In contrast to the imperfect decontamination of the upper respiratory tract, serial stool cultures regularly showed suppression of flora with many apparently sterile specimens on routine aerobic and anaerobic cultures. These results agree with those we have previously reported with a similar regimen of oral nonabsorbable antibiotics (Gompertz *et al.* 1973).

DISCUSSION

We have shown that patients can be isolated in a LAF or RP environment, with restricted diet, topical antiseptics, and oral nonsorbable antibiotics without major physical or psychological harm, despite intensive cytotoxic therapy. No patient withdrew from the study, many expressed willingness to undergo a similar regimen again, and three patients actually did so. Excellent nursing is a major factor in acceptance of this regimen. We found that chlorhexidine preparations can be applied to the skin and mucosae intensively and for prolonged periods without toxicity: the only side-effect noted was mild drying or defatting of the skin, probably attributable to the detergent, and in no case requiring cessation of treatment. We have observed much worse reactions when providone-iodine prepartions were used in a similar manner.

The microbiological results indicate that the skin can be effectively decontaminated, but a more intensive regimen is necessary for the ears, nose, and throat. Although skin flora were not progressively reduced to complete sterility, we found no evidence of recolonization or acquisition of new organisms, despite the predisposing factors of continued stay in hospital, neurotropenia, and trauma to the skin. The recovery of pathogens from various sites decreased or remained stable

despite significant iatrogenic suppression of body defences. The absence of colonization by *Pseudomonas aeruginosa* was particularly pleasing, since acquisition of this organism is common in hospital patients (Bodey 1970, Shooter *et al.* 1969). Since *Pseudomonas* species probably are transmitted from patient to patient and also by food and medications (Shooter *et al.* 1969), the isolation, clean diet, and gastrointestinal decontamination might all contribute to the protection seen in our patients.

We found no definite difference between LAF and RP nursing in respect of microbiological findings or occurrence of infections, but the RP patient group was small. The failure to eliminate nasal staphylococci is a weakness of the regimen, and other local measures – for example nasal application of chlorhexidine cream – should be evaluated. The persistent nasal staphylococci did not, however, colonize the remainder of the body, which may be attributable to the antiseptic treatment. Regimens like ours have been shown to confer significant protection from infection upon patients with leukaemia during intensive chemotherapy. Our study shows that effective, though incomplete, decontamination can be achieved in patients with solid tumours and that useful protection may be conferred: no solid tumour patient developed systemic infection despite cytotoxic chemotheraphy given at twice the conventional doses. The wider use of simple and relatively inexpensive protective regimens may make it possible for more patients with cancer to receive the benefits of intensive cytotoxic therapy without a corresponding increase in the morbidity and complications of such treatment.

We wish to pay tribute to our late colleague, A. Alice Jacobs, Ph.D., microbiologist at University Hospital, who contributed to the planning of this study, and whose untimely death prevented her from seeing its completion.

Thanks are owed to the Pharmacy, Dietary, and Housekeeping staff, and especially to the nursing staff of Ward F-4 at University Hospital, whose skill, loyalty, and enthusiasm made this work possible.

This work was supported by I.C.I. Americas Inc., who supplied all the chlorhexidine preparations used in the study.

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