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Acquisition of *Staphylococcus aureus* by patients undergoing cytotoxic therapy in an ultra-clean isolation unit

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The purpose of this paper is to report the results of bacteriological studies carried out in a special unit. The unit was designed for the intensive treatment of patients by cytotoxic drugs in a clean environment and a general description of it has been presented elsewhere (Bagshawe, 1964). It is generally accepted that patients receiving these drugs have an increased susceptibility to infection and where repetitive exposure to these drugs is necessary the risks are substantial. The majority of patients with post-gestational choriocarcinoma can be cured by cytotoxic treatment which lasts three to 18 months (Bagshawe, 1963; Ross *et al.* 1965), and it seems desirable that mortality from infection during the treatment of a potentially curable disease of young adults should be avoided. In view of the long period of treatment no attempt was made to achieve bacteriological sterility of the patients under study. The unit provides an opportunity to define and analyse the problems in reducing risk of infection by exclusion of pathogens and by monitoring the endogenous flora under conditions which are acceptable for long periods by both patients and nursing staff. The data presented here relate to nasal carriage, acquisition of and infection by *Staphylococcus aureus* (= coagulase positive staphylococci), in the twenty-five patients admitted to the unit during the year following its opening in March 1964.

THE PATIENTS

Source of patients, diagnoses, age, sex and previous therapy

Six patients were admitted direct to the unit from referring hospitals and nineteen were admitted after a period of investigation and sometimes after cytotoxic treatment in the open medical wards at Fulham Hospital. The patients included one man aged 52 years with an anaplastic carcinoma from an unidentified primary site. The others were women aged 18–35 years with trophoblastic tumours. One patient had an ovarian non-gestational choriocarcinoma and the remaining twenty-three patients had either post-gestational choriocarcinoma or invasive mole (chorioadenoma destruens). Eight patients were known to have received antibiotic therapy shortly before admission to the unit and eighteen had received cytotoxic therapy before admission.

Cytotoxic therapy

All the patients received courses of methotrexate usually in combination with 6-mercaptopurine and some also received actinomycin D and alkylating agents. Courses of treatment generally lasted 3–10 days and produced moderate to severe toxic symptoms with stomatitis, skin eruptions, hair loss, etc. The intervals between courses of treatment were generally 7–14 days. Courses were administered repetitively until there was no clinical or hormonal evidence of residual disease. Eight patients received cytotoxic therapy by continuous infusion into the low aorta. Infusion catheters introduced by the Seldinger technique (Seldinger, 1953) were *in situ* for periods of 4–12 weeks.

The male patient and the patient with ovarian choriocarcinoma died from progressive disease during the period of study.

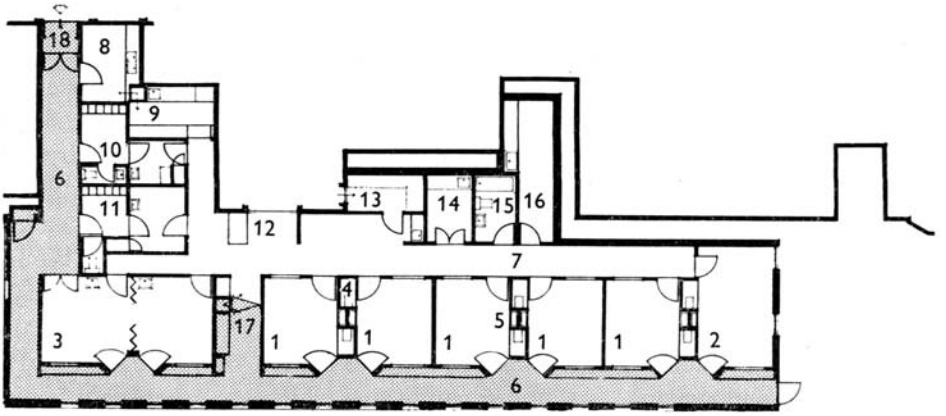

Fig. 1. Reproduced by kind permission of the *British Medical Journal*. Layout of unit. (1) Standard room. (2) Patient's room or sitting room. (3) Special procedure room or two separate rooms. (4) Lavatory. (5) Recessed wash-bowl. Television above. (6) Service and visitors' corridor. (7) Nursing area. (8) Wash-up kitchen. (9) Food-preparation kitchen. (10) Men's changing rooms. (11) Women's changing rooms. (12) Sister's desk. (13) Delivery hatch into linen store. (14) Sterilizing room. (15) Bathroom. (16) Store room fitted with washing and drying machine. (17) Sluice fitted with bed-pan washer and sterilizer accessible both from dirty and clean sides. (18) Entrance from main hospital corridor. (Architects: Gore, Gibberd, and Saunders; Consulting Engineers: Donald, Smith, Seymour, and Rooley; Main Contractors: Marshall Andrew and Co. Ltd.)

THE UNIT

Layout of the unit

The unit consists of eight patient rooms and during the period of the present study six of these were in use in the manner described here (Fig. 1).

One room was used for two patients throughout. Access to the patients' room is from the clean corridor side only and the clean corridor can be entered only through the changing rooms. Visitors can see and talk to patients through a transparent panel, but do not enter the unit. The only persons admitted to the unit are patients, ward staff and personnel required to service equipment within the unit. The unit was designed to reduce the need to admit non-medical staff to a minimum.

Air conditioning

Two-stage microcell filters remove particles larger than 0·5 μ. The air temperature is $25 \pm 1{\cdot}5°$ C., humidity 65 %, with eight changes of air per hour in the patients' rooms, supplied by inlet ports in the ceilings. Fifty per cent of the input is extracted at floor level in the patients' rooms and at ceiling level in the lavatory; the other 50 % maintains the gradient and leaks away. The patients' rooms are positive with respect to the nursing area and the nursing area is positive with respect to the exterior. Recirculation of the air is not employed.

ROUTINE PROCEDURES

General

One per cent Tego (an ampholytic quaternary ammonium compound) is used to wash the floors, walls and all hardware daily, and also for washable foodstuffs which are subsequently rinsed in tap water. Cooked foods obtained from the hospital diet kitchen are reheated in a microwave oven, (Lacey *et al.* 1965).

Letters, magazines, papers and other things not damaged by heat were sterilized in the hot air oven at 65° C. for 1½ hr. Goods from the Central Sterile Supply were double wrapped and the outer wrappings were removed at the entry port. Mattresses, pillows and blankets (cotton) were sterilized periodically by gamma irradiation. Other bed linen and laundry were autoclaved. Patients' and staff underwear were washed in a Bendix washer-dryer unit located inside the unit. Bedpans, crockery and all goods used in the patients' rooms were removed through two-way cupboards to the service corridor. Bedpans were washed in a standard washer, passed into a Dishlex bedpan sterilizer from the service corridor side and removed from the clean corridor side. Crockery was returned to the outer kitchen, and passed into a Westinghouse dishwasher (drying temperature 96° C.). Ophthalmoscopes, etc., were wiped with 1 % Tego after use.

Staff

Staff stripped completely on each admission to the ward, washed hands and face with Cidal soap (Hexachlorophane 1 %), and put on clean uniform (this includes nylon tights for the nursing staff). Cidal soap was provided for use on duty and at home. Hexachlorophane coal tar shampoo was supplied for use weekly. Nose, throat and hand swabs were cultured weekly on blood agar. Selective media were not used. Sensitivity testing was done with an Oxoid multodisk containing penicillin 5 units, tetracycline 50 μg., streptomycin 25 μg., erythromycin 50 μg.; chloramphenicol 50 μg. Naseptin nasal cream (chlorhexidine hydrochloride 0·1 %, neomycin sulphate 0·5 %) was applied to the anterior nares for 1 week after a positive nasal swab, or until the next negative weekly swab. In addition to medical and nursing staff in the unit the study includes orderlies and cleaners employed in the wash-up room and service corridor.

Patients

All patients were bathed on admission, in the bathroom if mobile, blanket-bathed if not. Hair was washed on admission and at least once weekly with hexachlorophane-coal tar shampoo. Hands were washed with Cidal soap only. Patients were graded according to total WBC count, done three or more times weekly.

(A) WBC > 2000/mm.^{3}	Patient could use bathroom, i.e. leave own room, but could not enter any other patient's room. They could talk to one another in the corridor
(B) WBC 2000–1000/mm.^{3}	Patient confined to room. Staff wear masks and wash hands immediately before entering
(C) WBC < 1000/mm.^{3}	As B but staff put on sterile gown before entering

Swabs from the nose, throat and rectum (if stool not available), and mid-stream urine specimens were collected weekly. Patients with arterial catheters had weekly swabs taken from the entry site. Patients with *Staph. aureus* on nose swabs were treated as described above for staff.

When febrile reactions developed in these patients, during or after a course of cytotoxic therapy, it was rarely possible to identify a causal organism. Nevertheless, when the patients were leucopenic, systemic antibiotics were usually given even though it was recognized that the reactions were not necessarily bacterial in origin. The sensitivities of the organisms recovered on the routine swabs determined the choice of antibiotics used.

RESULTS

One of six patients admitted to the unit directly from other hospitals carried a multiple resistant *Staph. aureus*. Eight of nineteen patients admitted from the general medical wards at Fulham Hospital had *Staph. aureus* on initial nasal culture and four of these were multiple resistant. All nineteen had received cytotoxic therapy in the general wards, whereas those admitted directly from other hospitals had not.

Table 1 shows the nasal carrier rate of *Staph. aureus* of patients in the unit. The initial swabs were collected during the week preceding admission (from patients transferred from the medical wards) or within 24 hr. after admission to the unit. The number of initial swabs is small, but there does appear to be a reduction of nasal carriage of *Staph. aureus* after admission to the unit. The figures for nasal carriage by the staff of the unit are shown in Table 2. Comparison with an obstetric ward in the same hospital group (Table 3) demonstrates a lower total nasal carriage by the unit staff (15·6 % against 24·3 % by the obstetrics staff) accounted for mainly by the differences in carriage of the *Staph. aureus* resistant to penicillin only. The patients of both wards show a similar total nasal carriage rate, but whereas three quarters of the unit patients' *Staph. aureus* were multiple resistant, only one-sixth of those of the obstetrics patients were multiple resistant.

Antibiotic treated unit patients carried a higher proportion of multiple resistant *Staph. aureus* and a smaller proportion resistant to penicillin only, although the total carriage rates were similar (Table 4). The number of patients who did not

receive any antibiotic is small and the difference between the treated and untreated groups is not significant.

The rate of total and of multiple resistant *Staph. aureus* nasal carriage by patients was four times as high in those who had several WBC counts of less than 1000/mm.^{3} than in those who had not more than one count of less than 1000/mm.^{3} This difference was highly significant ($\chi^2 = 12{\cdot}2$, $P = < 0{\cdot}01$) (Table 5).

Table 1. *Nasal carriage of* Staph. aureus *by patients on admission to the unit compared with the results of subsequent weekly nose swabs*

	Initial		Weekly	
Total swabs cultured ...	25		367	
Staph. aureus	No.	%	No.	%
Sens.	1	4	4	1·1
R/P	3	12	9	2·5
R/T	—	—	1	0·3
R/M	5	20	53	14·5
Not known	—	—	2	0·5
Total	9	36	69	18·8

Notes:
Sens. = sensitive to penicillin, tetracycline, streptomycin, erythromycin and chloromycetin.
R/P = resistant only to penicillin.
R/T = resistant only to tetracycline.
R/M = resistant to two or more antibiotics, usually penicillin and tetracycline.

Table 2. *Nasal carriage of* Staph. aureus *by isolation unit staff*

	April 1964–March 1965–	
Total swabs cultured ...	786	
Staph. aureus	No.	%
Sens.	54	6·9
R/P	24	3·0
R/T	4	0·5
R/M	40	5·1
Total	122	15·6

Notes as for Table 1.

Table 3. *Nasal carriage of* Staph. aureus *by staff and patients on an obstetric ward in the same group*

	Patients		Staff	
Total swabs cultured ...	465		542	
Staph. aureus	No.	%	No.	%
Sens.	26	5·6	18	3·3
R/P	45	9·7	88	16·2
R/T	—	—	2	0·4
R/M	14	3·0	24	4·4
Total	85	18·3	132	24·3

Notes as for Table 1.

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Table 4. *Nasal carriage of* Staph. aureus *by patients—effect of antibiotic therapy*

	Patients who received no antibiotics (6 patients)		Patients treated with antibiotics (19 patients)	
Total swabs ...	40		327	
Staph. aureus	No.	%	No.	%
Sens.	0	—	4	1·2
R/P	4	10·0	5	1·5
R/T	—	—	1	0·3
R/M	3	7·5	50	15·3
Not known	—	—	2	0·6
Total	7	17·5	62	18·9

Notes as for Table 1.

Table 5. *Nasal carriage of* staph. aureus *by patients whose WBC count fell below* 1000/mm.^{3} *only once or less compared with those in whom the WBC were below* 1000/mm.^{3} *on three or more occasions*

	Patients with total WBC < 1000/mm.^{3} once or less		Patients with total WBC < 1000/mm.^{3} three or more times	
Total swabs cultured ...	87		280	
Staph. aureus	No.	%	No.	%
Sens.	1	1·1	3	1·1
R/P	0	—	9	3·2
R/T	0	—	1	0·3
R/M	4	4·6	49	17·5
Not known	—	—	2	0·7
Total	5	5·7	64	22·8

$\chi^2 = 12{\cdot}2$, $P = < 0{\cdot}01$.
Notes as for Table 1.

Table 6. *Rate of nasal acquisition of new strains of* Staph. aureus. *by patients showing the fall in rate of apparent acquisition of new strains with increasing time after admission*

	Overall	Excluding 1st 2/52	Excluding 1st 4/52	Excluding 1st 6/52
Total new strains/ patient weeks at risk	23/366	17/317	14/270	11/233
New strains/100 patient weeks	6·3	5·4	5·2	4·7
R/M new strains/ patient weeks	18/366	15/317	12/270	9/233
R/M new strains/ 100 patient weeks	4·9	4·7	4·4	3·9

Notes as for Table 1.

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Following Parker, John, Emond & Machacek (1965) we considered as members of a single strain those organisms which had phage-typing patterns differing by one strong lytic reaction or less, and with the same sensitivity to penicillin and tetracycline. The rate of acquisition of strains of staphylococci new to the patient decreased progressively during the first 6 weeks in the unit (Table 6).

Table 7. *Source of apparent acquisition of new strains of nasal* Staph. aureus *by patients*

Staph. aureus	Total	Staff	Other patients	Not known
Sens.	4	2	0	2
R/P	2	0	1	1
R/M	17	7	4	6
Total	23	9	5	9

Notes as for Table 1.

Table 8. *The effect of antibiotic therapy on the patients' rate of apparent nasal acquisition of new strains of* Staph. aureus

	No antibiotics		Antibiotics	
Staph. aureus	Total	R/M	Total	R/M
Acquisitions	3	2	20	16
Weeks at risk	40		327	
Aquisitions/100 patient weeks	7·5	5·0	6·1	4·9

Notes as for Table 1.

Table 9. *The relation between leucopenia and the rate of patients' nasal acquisition of new strains of* Staph. aureus: *the rate for patients whose WBC fell below* 1000/mm.^{3} *once or less is compared with those whose WBC fell below* 1000/*mm.*^{3} *three or more times*

	Patients with leucopenia < 1000/mm.^{3} once or less		Patients with leucopenia < 1000/mm.^{3} three or more times	
Staph. aureus	Total	R/M	Total	R/M
Acquisitions	4	3	19	15
Weeks at risk	87		280	
Acquisitions/100 patient weeks	4·6	3·5	6·7	5·3

Notes as for Table 1.

The source of these apparent acquisitions was sought among the results of all swabs from staff and patients during the 6 weeks preceding acquisition (Table 7). No likely source was discovered for nine of the twenty-three acquisitions, a further nine were isolated from staff, and five from other patients. There was no difference in the number of acquisitions/100 patient weeks between patients treated or not with antibiotics, but only six patients received no antibiotics, remaining in the unit for a total of 40 weeks (Table 8).

The occurrence of several episodes of leucopenia increased the rate of apparent acquisition of new strains of nasal staphylococci, but the patients whose WBC fell below 1000/mm.^{3} once or less only totalled 87 weeks in the unit and the results are not significant at the 5% level (Table 9). Further data are being collected.

During the year under review staphylococci were recovered on twelve occasions from sites of minor infection. Seven of these positive swabs were obtained from superficial skin lesions; one from the mouth, two from conjunctivae and on two occasions from the entry points of arterial catheters in the groin. This gave an overall infection rate of 3·3/100 patient weeks.

Table 10. *Probable source of* Staph. aureus *causing patients' lesions*

Staph. aureus	Total	Staff	Other patients	Not known	Patient herself
Sens.	3	1	0	1	1
R/P	1	0	0	0	1
R/M	8	1	2	1	4
Total	12	2	2	2	6

Notes as for Table 1.

Table 11. *The effect of leucopenia on the occurrence of staphylococcal lesions: patients whose WBC fell below* 1000/*mm.*^{3} *once or less are compared with those whose WBC fell below* 1000/*mm.*^{3} 3 *or more times*

	Patients with leucopenia < 1000/mm.^{3} once or less	Patients with leucopenia < 1000/mm.^{3} three or more times
Staphylococcal lesions	1	11
Weeks at risk	87	280
Lesions/100 patient weeks	1·1	4·1

It was found that in six instances the source of the *Staph. aureus* was staff or another patient or was unknown (Table 10) and in six instances the patient's nose had been colonized before the lesion occurred. Where the patient was the direct source of the organisms in a lesion the organisms had apparently been acquired from staff and from other patients in equal numbers.

Patients who had several leucopenic episodes had nearly four times as many staphylococcal lesions/100 patient weeks as those with one leucopenic episode or less (Table 11).

Two strains of *Staph. aureus* caused more than one lesion. Five lesions in three patients were caused by type 52/52A/80/81 multiple resistant *Staph. aureus* over a period of 45 weeks. Two patients shared the double room and the third patient was in the adjacent room. Two lesions in two patients were caused by an untypable strain, which was sensitive to antibiotics tested. The patients were in adjacent rooms but the second lesion occurred 13 weeks after the first. During this interval the organism was recovered in sequence from a staff throat swab, a staff hand swab, the patient's nose, and another patient's nose swab.

DISCUSSION

Various factors are known to influence the staphylococcal carriage rate. Females aged 20–40 years were found to be least susceptible in the P.H.L.S. Report (1965). It is well known that in hospital there is a steady increase in the general carrier rate of *Staph. aureus* and in the carrier rate of resistant strains. Williams *et al.* (1959) found that the general carrier rate rose from 38% in the first week to 70% after 8 weeks, and the penicillin resistant carrier rate from 13 to 50%. The P.H.L.S. Report (1965) showed that the incidence of staphylococcal infection in patients with malignant disease was twice the overall rate for hospital patients. The incidence is also increased by corticosteroids and by antibiotics (P.H.L.S. Report, 1965). The apparent acquisition rate of new multiple resistant strains was higher in antibiotic treated patients than in those receiving no antibiotics (Parker *et al.* 1965; Knight & Holzer, 1954).

On the grounds of age and sex the patients in the present report might have been expected to have a low incidence of staphylococcal infection. Despite this and the extensive precautionary measures taken, staphylococcal acquisition occurred within the unit and there were minor instances of infection. It is clear that the underlying malignant disease may be a predisposing factor as is the use of antibiotics for febrile reactions of uncertain aetiology. Corticosteroids could not be incriminated since only one patient received these during the period under study. Surgical procedures on patients in the unit included hysterectomy (two cases), oversewing of vaginal mucosa on account of haemorrhage (four cases), and venous (approx. 140) and arterial cannulation (8 cases), but no great responsibility could be attached to these as a source of infection although *Staph. aureus* was grown from routine swabs taken from the entry point of arterial catheters in the groin in two of eight cases. These arterial catheters were however *in situ* for periods of up to 3 months and were not comparable to the cannulation reported in the P.H.L.S. survey (P.H.L.S. Report, 1965), where a sepsis rate of 2·7% was found.

The results obtained here suggest that cytotoxic chemotherapy increases susceptibility to the acquisition and nasal carriage of *Staph. aureus*. Patients admitted to the unit from other hospitals, who had not received cytotoxic drugs, had an average rate of nasal carriage for hospital patients (1/6), whereas those admitted via the medical wards at Fulham Hospital where they received cytotoxic chemotherapy had a higher carriage rate (8/19). Similarly, it was found that the nasal carriage rate was significantly higher for those patients whose treatment was more vigorous as reflected in the number of leucopenic episodes which they incurred. The acquisition of new strains by the patients with more leucopenic episodes was also higher but the difference was not statistically significant. The population studied here thus has heightened susceptibility to infection with *Staph. aureus*, and remains infected longer.

The way in which cytotoxic agents increase susceptibility to acquisition is not known but possible mechanisms can be suggested. The agents used here have gross effects on the integrity of mucosal surfaces. They are known to exert immunosuppressive effects in the dosages used, and to cause profound leucopenia.

In a study of experimental staphylococcal nasal colonization Ehrenkrantz (1966) found that 'resistance to intra nasal implantation was characterized by induction, anamnestic response and specificity—the cardinal signs of an immune reaction'.

Nasal secretions do contain immunoglobulins in the γ_1A and γ_2-globulin fractions (Remington, Vosti, Lietze & Zimmerman, 1964; Bellanti, Artenstein & Buescher, 1965) but a clear relationship between serum antibodies and rejection of nasal staphylococci has not been established.

It seems likely that some acquisitions of *Staph. aureus* are apparent rather than real as suggested by Parker *et al.* (1965). That is, the organisms were present on admission but were only revealed by repeated swabbing during the first weeks after admission. The 'acquisition' rate measured in this unit fell progressively during the six weeks after admission.

Contact between patients in the unit leads to some cross-transmission of organisms. However desirable it might be to prevent this, compromise has to be made in the interests of the patients' acceptance of prolonged and often unpleasant treatment. Also, by permitting contact during periods of well-being strict isolation is more acceptable when necessary.

It is also clear from our results that the ward staff are responsible for introducing organisms which are acquired by and infect the patients. 'Nasal carriers' cannot be usefully defined since most of the staff had positive swabs at some time. Clearly, it is not practical to exclude staff carrying *Staph. aureus* from the ward. In trying to determine the effectiveness of topical anti-bacterial agents it is necessary to distinguish between the efficiency of the agent as applied according to the instruction given and the disciplinary aspect which determines whether the instructions are carried out. The carrier rate for the unit staff was lower (15·6 %) than that on the obstetric ward studied (24 %). Nevertheless, it is clear that there is room for improvement. In practice it is relatively easy to ensure that medical and nursing staff follow the instructions given but more difficult in the case of untrained personnel. Included in the present ward staff were domestics employed in the wash-up kitchen and service corridor and who assisted with ward cleaning, and these showed a particularly high carriage rate. This emphasizes the need for a high standard of discipline.

It is hoped that by defining the routes and factors involved in the access of pathogens to these patients, control measures can be progressively improved without producing less acceptable conditions. Alternative topical agents are now being used on a regular routine basis, whether or not the previous nasal swab was positive.

SUMMARY

The twenty-four young women and one man treated in an ultra-clean isolation ward should have had a low incidence of staphylococcal infection on grounds of age, sex and clean environment alone. However, they apparently acquired new strains of *Staph. aureus* at the rate of 4·7/100 patient weeks (3·9 multiple resistant strains/100 patient weeks) from the sixth week after admission onwards.

Environmental factors contributing to infection included introduction of re-

sistant strains by the patients on admission, contact between patients in the unit, and failure to eliminate nasal carriage in staff and patients.

Host susceptibility was increased by malignancy, and by antibiotic and cytotoxic therapy. The nasal carriage rate of *Staph. aureus* was significantly greater for patients with repeated episodes of leucopenia induced by cytotoxic drugs.

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