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Four outbreaks of nosocomial systemic candidiasis

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SUMMARY

Candida albicans has recently been described as a cause of nosocomial infection. This paper reports four further outbreaks occurring over a 12-month period in England. There were 13 systemic cases and 6 deaths. The outbreaks were defined by morphotyping and the new technique of immunoblot fingerprinting. Control of the outbreaks was produced by the implementation of strict cross-infection control policies without recourse to systemic chemoprophylaxis.

INTRODUCTION

In 1985 a cluster of 18 cases of systemic candidiasis was reported on the Intensive Care Unit of the London Hospital (Burnie *et al.* 1985*a*, *b*). Isolates from the patients were identical by serotyping (Hasenclever & Mitchell, 1961), morphotyping (Brown-Thomsen, 1968), biotyping (Odds & Abbott, 1980) and immunoblot fingerprinting (Lee, Burnie & Matthews, 1986). This supported the concept that in some circumstances cross-infection with *Candida albicans* resulting in systemic candidiasis could take place. In the original outbreak, control was achieved by the introduction of oral chemoprophylaxis with ketoconazole combined with strict cross-infection control and changes in handwashing reagents (Burnie *et al.* 1985*b*).

Ketoconazole failed to protect six patients and there has been recent controversy over its safety (Hay, 1985). This paper reports four further episodes of *C. albicans* cross-infection demonstrating that the first outbreak was not an idiosyncratic event. Control in each of the four outbreaks was achieved without recourse to oral systemic chemoprophylaxis.

Isolates were typed by morphotyping (Brown-Thomsen, 1968) and immunoblot fingerprinting (Lee, Burnie & Matthews, 1986). Both schemes have the disadvantage that a single type is produced by a substantial percentage of all isolates examined (90% morphotype A1 (Brown-Thomsen, 1968)); 43% immunoblot fingerprint type 1 (Lee, Burnie & Matthews, 1986). However, if a cluster of isolates is found to be different from this type, then this information is of great value. The original London outbreak and the four following episodes illustrate this point.

PATIENTS AND METHODS

The outbreaks

The London Hospital, London, the Intensive Care Unit

In the 20-month period after the first outbreak (July 1983 to March 1984) there was only one case of systemic candidiasis reported on the unit. During December 1985 to January 1986 there was a second outbreak where five patients developed systemic *C. albicans* infections and three urinary tract infections (Table 1). Systemic candidiasis was diagnosed on the basis of isolation of *C. albicans* from a deep biopsy site or multiple blood cultures taken from two separate sites at least 24 h apart.

King's College Hospital, London, the Neonatal Intensive Care Unit

In a 3-week period from 11 November 1985 to 6 December 1985 three babies who had not been colonized at birth became systemically infected with *C. albicans*. Two of them developed skin abscesses and the third a hydrocephalus. All three systemic cases survived after treatment with amphotericin B and 5-flucytosine (Table 2). The blood culture isolates were available for typing. Four other babies required topical antifungals (Table 2) and five other babies were found to be colonized with *C. albicans* during a 6-week period of active surveillance. Unfortunately, none of these isolates was available for typing so their significance is difficult to assess. Prior to this episode there had been no systemic cases on the unit for 12 months.

Queen Elizabeth Hospital, Birmingham, the Intensive Care Unit

Over an 8-day period (27 December 1985 to 3 January 1986) five patients became infected (Table 3). Two patients died of systemic candidiasis despite treatment with amphotericin B and 5-flucytosine. One had multiple blood cultures positive and the other was confirmed at autopsy. *C. albicans* was isolated from numerous microabscesses. Three patients had urinary tract infections as defined by isolating greater than 10^4 colony-forming units of *C. albicans*/ml of urine and were treated with 5-flucytosine. Two further isolates from sputum were available for typing from patients who were admitted to the unit after the critical 8-day period. There had been no cases of systemic candidiasis on this unit in the previous 6 months.

St Helier's Hospital, Carshalton, Dialysis Unit

Within a 4-day period three patients with chronic renal failure on chronic ambulatory peritoneal dialysis (CAPD) developed *C. albicans* peritonitis whilst on the same dialysis unit. Two of the patients were treated with amphotericin B and 5-flucytosine intraperitoneally but recovered only after the Tenchkhoff dialysis catheters were removed. The third patient died despite antifungal chemotherapy. All the isolates were from the CAPD fluid. For comparison five further isolates were examined from the CAPD fluid from patients on the same unit during the following 10 months (Table 4).

Table 1. *Details of infected patients on the Intensive Care Unit of the London Hospital*

Patient	Age	Underlying diagnosis	Date of admission	Date of first candida isolation (and interval in days)	Sites of isolation of *C. albicans*	Other microorganisms			Outcome
						MRSA*	*P. aeruginosa* (res.)	*P. aeruginosa* (sens.)	
A	59	CABG, renal failure	24.xii.85	28.xi.85 (4)	Sputum, CAPD fluid, IV catheter	+	+	−	Recovered after Amp B and 5 FC
B	71	Diverticular disease	5.i.86	14.i.86 (9)	Bile, peritoneum at laparotomy	−	−	−	Died despite Amp B
C	54	Post cholecystectomy	7.i.86	13.i.86 (6)	Blood, IV catheters	−	−	−	Recovered after Amp B and 5 FC
D	18	Road traffic accident	13.i.86	18.i.86 (5)	Urine	+	−	+	5 FC, recovered
E	42	Crohn's disease	11.i.86	15.i.86 (4)	Urine	−	+	+	5-FC, died Gram-negative septicaemia
F	48	Post gastrectomy	10.i.86	18.i.86 (8)	Subphrenic abscess	−	−	−	Amp B and 5-FC, recovered
G	76	Pyloric sterosis	10.i.86	21.i.86 (11)	Urine, intra-abdominal pus	−	−	+	Amp B, died
H	65	Intestinal obstruction	15.i.86	18.i.86 (3)	Urine				5-FC, recovered

* MRSA, Methicillin-resistant *Staphyloccus aureus* also (Rifampicin-resistant); *P. aeruginosa* (res.): *P. aeruginosa* resistant to antibiotics; *P. aeruginosa* (sens.): *P. aeruginosa* sensitive to antibiotics (see results section); Amp B: amphotericin B; 5-FC: 5-flucytosine. Patients A, B, C, F, and G had systemic candidiasis as defined by isolation of *C. albicans* from multiple blood cultures (taken at least 24 h apart from two separate sites) or a deep biopsy site. All isolates were morphotype A1.

Table 2. *Details of infected patients on the Neonatal Intensive Care Unit of King's College Hospital*

Patient	Gestational age at birth (weeks)	Date of birth and of admission	Date of first candida isolation (and interval in days)	Sites of isolation of *C. albicans*	Outcome
A	26	18.x.85	11.xi.85 (24)	Blood, groin	Survived
B	26	30.x.85	28.xi.85 (29)	Blood, groin	Survived
C	26	18.x.85	6.xii.85 (49)	Blood, urine	Survived
D	28	18.xi.85	13.xii.85 (25)	Groin, urine	Survived
E	34	21.xii.85	3.i.85 (13)	Urine	Survived
F	34	28.i.86	11.ii.86 (14)	Perineum	Survived
G	29	5.iii.86	10.iii.86 (5)	Perineum	Survived

Patients A, B and C and systemic candidiasis, multiple blood cultures being positive when taken 24 h apart from two different sites. Isolates from patients A, B and C were morphotype A3.

Table 3. *Details of cross-infected patients on the Intensive Care Unit of Queen Elizabeth Hospital*

Patient	Age	Underlying diagnosis	Date of admission	Date of first candida isolation (and interval in days)	Sites of isolation	Morphotype	Outcome
A	65	Aortic aneurysm repair	30.xi.85	27.xii.85 (27)	Sputum, Blood cultures	A4	Died despite Amp B and 5-FC
B	28	Liver transplant	16.xii.85	27xii.85 (11)	Blood cultures, post mortem	A4	Died despite Amp B and 5-FC
C	23	Chronic granulocytic leukaemia	22.xii.85	31.xii.85 (8)	Urine, sputum	A4	5-FC, Died respiratory failure
D	31	Road traffic accident	28.xii.85	3.i.86 (6)	Sputum, urine	A4	5-FC, recovered
E	50	Coronary artery by-pass graft	1.i.86	7.i.86 (7)	Throat swab,	A4	5-Fc, recovered
F	48	Aneurysm repair	13.i.86	17.i.86 (4)	Sputum	A1	—
G	32	Post-partum haemorrhage	20.i.86	27.i.86 (7)	Sputum, high vaginal swab	A4	—

All isolates fingerprinted identically with the exception of G.

Table 4. *Details of the CAPD-infected patients on the renal unit at St Helier's Hospital.*

Patient	Age	Date of isolation from CAPD fluid	Morphotype
A	36	3.iii.86	A1
B	53	3.iii.86	A1
C	73	28.ii.86	A1
D	53	13.vi.86	A3
E	33	14.vi.86	A5
F	52	31.viii.86	A1
G	65	18.ix.86	A3
H	72	10.xii.86	A7

Isolates from patients A, B, C and E were identical on the immunoblot fingerprinting.

Samples and screening

Blood cultures were taken from systemically ill patients. At King's College Hospital and Queen Elizabeth Hospital all patients on the unit were screened with weekly groin, perineum and mouth swabs, urine samples and endotracheal tube aspirates as appropriate. These were cultured on Sabourauds glucose agar at 37 °C overnight and confirmed as *C. albicans* by the germ-tube test and the API 20C system (API Laboratories).

In the King's College outbreak settle plates of Sabouraud's agar were left on all parts of the neonatal unit and surrounding service areas. Fluid was sampled from hand basins, incubators and moistened swabs were taken from the hands of 13 nurses and 6 medical staff caring for infected and colonized babies. The outbreak strain of *C. albicans* was isolated from none of these swabs.

Typing of candida

(*a*) *Immunoblot fingerprinting*

Isolates identified as *C. albicans* were fingerprinted by the immunoblot method previously described (Lee, Burnie & Matthews, 1986). Briefly, each isolate was fragmented by treatment with alpha-mannosidase followed by sonication: the extracts were then immunoblotted against a rabbit hyperimmune antiserum raised against a pressate of *C. albicans* National Collection Tissue Culture number 3153. Isolates were considered to be distinguishable if they were different in at least three antigenic bands. The presence or absence of bands at 74, 69, 67, 63, 61, 58, 55, 53, 47 and 33 kDa had previously been shown to be most significant (Lee, Burnie & Matthews, 1986).

(*b*) *Morphotyping*

Malt extract agar was prepared according to the method of Brown-Thomsen, 1968. Each isolate was streaked onto one plate as a single central line inoculated three times. The plates were incubated at room temperature for 21 days. The different morphotypes were compared to the original morphotypes of Brown-Thomsen (1968). All the outbreak isolates were examined as well as a reference collection of 401 isolates of *C. albicans*. This included 283 isolates collected from the London Hospital from patients not involved in either outbreak.

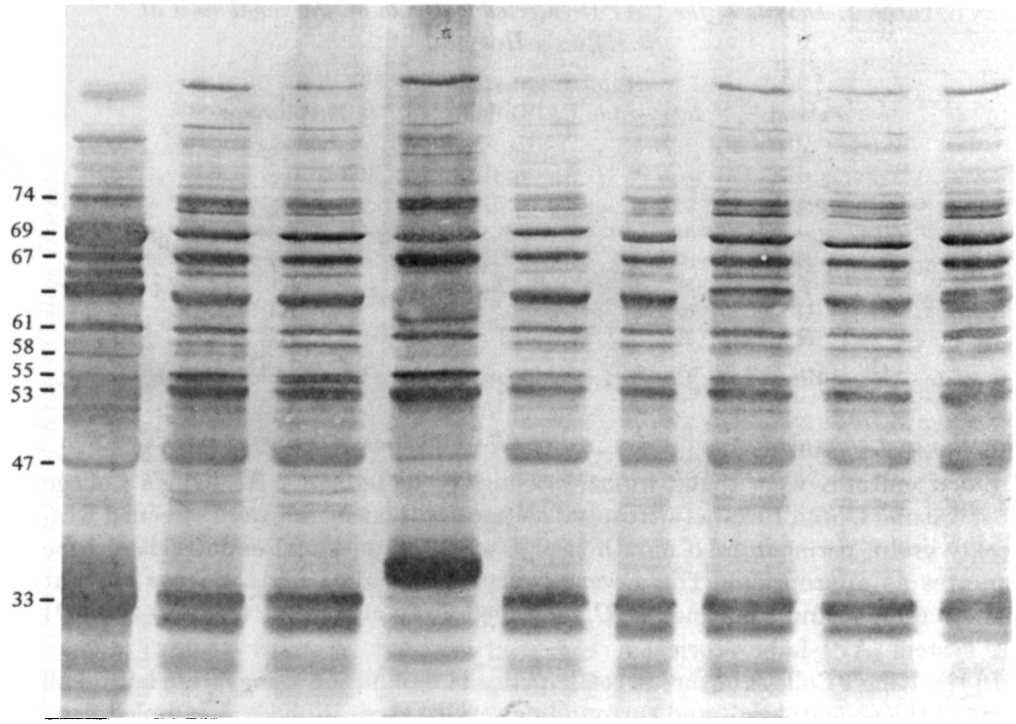

Fig. 1. Immunoblot analysis of the isolates from the Queen Elizabeth Hospital outbreak (tracks 2–6 and 8), the first London outbreak (tract 1), the second London outbreak (tract 9) and the St Helier's outbreak (tract 7).

RESULTS

Typing

(*a*) *Immunoblot fingerprinting*

All isolates from the eight patients involved in the second outbreak at The London Hospital were indistinguishable on immunoblot typing. When this strain (tract 9, Fig. 1) is compared with the strain causing the first outbreak on the unit (tract 1, Fig. 1) the two are clearly distinguishable, the second outbreak having double antigenic bands at 74, 63 and 33 kDa and distinct antigenic bands at 55 and 53 kDa.

The three isolates from patients from St Helier's (represented by tract 7) involved in the outbreak were indistinguishable from each other and from the second London Hospital outbreak strain (tract 9, Fig. 1). Isolates from four out of the five subsequent cases of CAPD peritonitis over the next 10 months at St Helier's Hospital were different by immunoblot fingerprinting. Six of the seven patients at Queen Elizabeth Hospital were harbouring indistinguishable isolates (tracts 2–6 and 8, Fig. 1), and this outbreak strain was only slightly different from the St Helier's and the second London Hospital outbreak strain. It had a single rather than double band at 63 kDa. The isolate from a mouth swab from a seventh patient in Queen Elizabeth Hospital (tract 4, Fig. 1) clearly differed from the outbreak strain, there being differences in bands at 63, 58 and 33 kDa as well as an extra band at 62 kDa.

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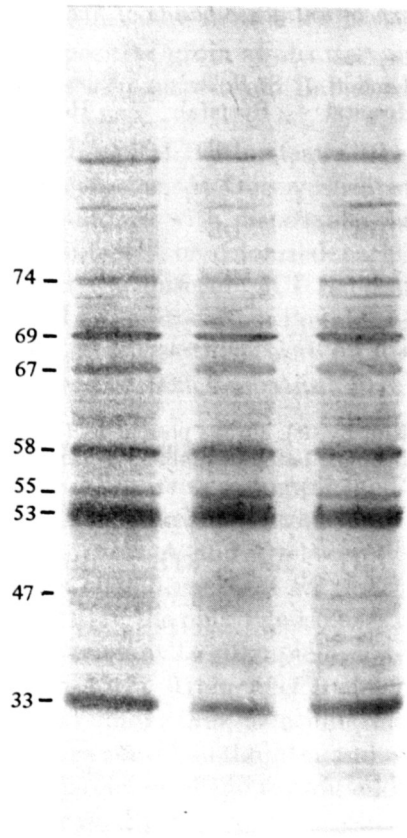

Fig. 2. Immunoblot analysis of the three isolates from the King's College outbreak.

All isolates from the three systemically ill babies at King's College Hospital were indistinguishable, as illustrated in Fig. 2. They differ from the second London Hospital strains, St Helier's and Queen Elizabeth Hospital strains. There are single antigenic bands at 74, and 33 kDa and faint/absent bands at 63 and 61 kDa. They also differ from the first London Hospital outbreak strain in the presence of distinct antigenic bands at 55 and 53 kDa and the faintness/absence of bands in the 63 and 61 kDa region. These differences are summarized in Table 5.

(*b*) *Morphotyping*

The results of the morphotyping are summarized in Table 6. The predominant morphotype was A1 which accounted for 57% of all isolates. Both the London Hospital outbreaks and the outbreak at St Helier's Hospital were due to isolates of this morphotype. The Queen Elizabeth Hospital outbreak was of morphotype A4 which accounted for 3% of all isolates. The King's College episode was due to isolates which morphotyped as A3 which was produced by 7% of all isolates. Morphotyping confirmed the similarity between the St Helier's isolate and the second London Hospital outbreak strain. It was most useful for differentiating the Queen Elizabeth Hospital strain from the St Helier's and the second London Hospital outbreak strain. The combination of immunoblot fingerprinting and

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Table 5. *Detail of the pattern of antigenic bands of five candidal outbreak isolates*

Band molecular weight (kDa)	First London Hospital	Second London Hospital	St Helier's Hospital	King's College Hospital	Queen Elizabeth Hospital
74	+	DB	DB	+	DB
69	+	+	+	+	+
67	+	+	+	+	+
63	+	DB	DB	−	+
61	+	+	+	−	+
58	ft	+	+	+	+
55	ft	+	+	+	+
53	ft	+	+	+	+
47	+	+	+	+	+
33	+	DB	DB	+	DB

Absent is indicated by (−), faint by (ft), always present by (+) and double bands by (DB). All isolates were typed against a single batch of rabbit hyperimmune serum.

Table 6. *Details of morphotyping the* 401 *isolates*

Morphotype	LH*	LH1	LH2	STH	BH	KC	Other hospitals
A1	200	62	9	4	1	—	13
A2	11	—	—	—	—	—	
A3	13	—	—	2	—	3	10
A4	6	—	—	—	6	—	
A5	1	—	—	1	—	—	1
A6	6	—	—	—	—	—	
A7	10	—	—	1	—	—	1
A8	—	—	—	—	—	—	—
A9	13	—	—	—	—	—	
A10	6	—	—	—	—	—	1
A11	—	—	—	—	—	—	—
A12	—	—	—	—	—	—	—
A13	1	—	—	—	—	—	—
A14	—	—	—	—	—	—	—
A15	—	—	—	—	—	—	—
Non-typable isolates	16	—	—	—	—	—	3

* LH, London Hospital, non-outbreak; LH1, London Hospital, first outbreak; LH2, London Hospital, second outbreak; STH, St Helier's Hospital, Carshalton; BH, Birmingham Hospital; KC, King's College Hospital.

morphotyping in both the Queen Elizabeth Hospital outbreak and the St Helier's Hospital allowed a clear demarcation between outbreak and non-outbreak isolates.

Control of infection

Queen Elizabeth Hospital, Intensive Care and King's College Hospital, Neonatal Intensive Care Unit

At King's College Hospital a second neonatal intensive therapy unit was opened and new babies requiring intensive care were admitted to this room. The main intensive care unit was then used for babies colonized or infected with *C. albicans*. New babies were only admitted to the main unit after all the colonized or infected

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babies had been treated with antifungal agents for at least 48 h. Babies with blood cultures positive for *C. albicans* were treated with systemic amphotericin B and 5-flucytosine. Infants with positive groin swabs were commenced on topical miconazole cream and oral nystatin suspension. Babies with no evidence of infection were not treated.

At Queen Elizabeth's Hospital, systemically ill patients were treated with amphotericin B and 5-flucytosine. At Queen Elizabeth and King's College Hospital, barrier nursing techniques with disposable plastic aprons and disposable gloves were used for all infected or colonized patients. Hand disinfection was changed from chlorhexidine (Hibiscrub, ICI Laboratories) or soap to alcoholic chlorhexidine (Hibisol, ICI Laboratories) or Povidone Iodine (Napp Laboratories). After institution of these measures there were no further cases of systemic candidiasis on either unit over the next 6 months.

The London Hospital, Intensive Care Unit

The outbreaks due to *C. albicans* were complicated by independent evidence of a general breakdown in cross-infection control.

Two patients (Table 1, cases A and D) became colonized and developed a septicaemia due to the methicillin-resistant *Staphylococcus aureus*. These isolates were unusual in that they were the only two isolates of this microorganism in the hospital which were also resistant to rifampicin. Two patients (Table 1, cases A and E) became colonized by a strain of *Pseudomonas aeruginosa* which was resistant on disk testing to amoxicillin, azlocillin, mezlocillin, cefuroxime, ceftazidime, gentamicin, tobramycin, trimethoprim and chloramphenicol. It was sensitive to amikacin, not typable on phage testing and serology type 5d. In one of these patients (Table 1, case E) it caused a septicaemia. Three other patients became colonized by isolates of *P. aeruginosa* which were fully sensitive to all the antibiotics previously mentioned (Table 1, cases D, E and G). The unit was closed to new admissions for 14 days until the patients on it could be discharged to another ward. It was then re-opened after thorough cleaning. This effectively brought all three outbreaks to an end. No patient received systemic oral antifungal chemoprophylaxis.

St Helier's Hospital

This outbreak appeared to be self-limiting as there were no further cases over the next 3 months. All subsequent isolates from CAPD fluid had either a different morphotype or immunoblot fingerprint.

DISCUSSION

This paper describes three intensive care units and a dialysis unit in which systemic candidiasis occurred secondary to cross-infection. A total of 13 patients required treatment with amphotericin B and 6 patients died. Immunoblot fingerprinting and morphotyping showed that a single strain was responsible for the outbreak of peritonitis at St Helier's dialysis unit and an indistinguishable strain was identified from the second London Hospital outbreak. These strains had a different morphotype but a similar immunoblot fingerprint to the outbreak strain

at Queen Elizabeth Hospital. A single strain was also responsible for the outbreak on the neonatal unit at King's College Hospital, but on immunoblot fingerprinting and morphotyping this strain differed considerably from the other three outbreak strains. None of these outbreak isolates produced the same immunoblot pattern as the first outbreak strain from The London Hospital.

The King's College Hospital outbreak isolates were indistinguishable on immunoblot fingerprinting to the Type 1 isolates described by Lee, Burnie & Matthews (1986). This type accounted for 43% of the original 190 isolates at the London Hospital where it was not associated with serious infection. Perhaps the immunoblot fingerprint Type 1 isolates are less virulent in that there were no deaths in the King's College outbreak. The majority (71%) of non-outbreak London Hospital isolates were morphotype A1 whereas the King's College isolate was A3. The combination of fingerprinting and morphotyping produced a better differentiation between isolates.

The mode of transmission of *C. albicans* in these four outbreaks is not entirely clear. King's College Hospital were unable to isolate *C. albicans* from the hands of staff or the environment. In the first outbreak at the London Hospital the cycle of infection was shown to be between patients and staff with hands acting as the conduit (Burnie *et al.* 1985*a*, *b*). In another neonatal outbreak described by Phelps, Ayliffe & Babb (1986) *C. albicans* was isolated from 11 of the 42 hand samples taken from staff. In the second outbreak at The London Hospital there was evidence of cross-infection due to *P. aeruginosa*, another microorganism spread by hands (Knittle, Eitzman & Baer, 1975). The original outbreak strain of *C. albicans* was found to survive better on hands than control strains of *C. albicans*, but no longer than the controls on formica blocks (Burnie *et al.* 1985*b*). Kashbur, Ayliffe & George (1980) examining the *C. albicans* from the outbreak of Phelps, Ayliffe & Babb (1986) found it survived poorly on dry surfaces. Only two fomite isolates were found during the outbreak from 155 environmental samples and these were a dummy and a dropper, both of which were moist at the time of sampling. Other small episodes of cross-infection due to *C. albicans* have been reported by Cremer & de Groot (1967), Malamatinis, Mattmiller & Westfall (1968) and Marples *et al.* (1985).

Early awareness that cross-infection might be occurring was aided by the use of immunoblot fingerprinting which demonstrated that these patients were indeed being infected by the same strain of *C. albicans*. The results from this technique were available in 48 h whereas morphotyping required 3 weeks. The initiation of cross-infection policies and the alteration of hand disinfection reagents to Povidone-Iodine or alcoholic chlorhexidine brought the outbreaks at King's College, the London Hospital and Queen Elizabeth Hospital under control. It was unnecessary to use systemic oral chemoprophylaxis.

The episode at St Helier's Hospital was self-limiting which emphasizes the element of host predisposition which must exist before an outbreak of systemic candidiasis can occur. In King's College Hospital the patients were preterm infants on broad spectrum antibiotics requiring intensive care. In the London Hospital and Queen Elizabeth Hospital the patients were on antibiotics and many of them had undergone major bowel surgery. The patients at St Helier's Hospital were on

renal dialysis and the subsequent five sporadic cases of candidal peritonitis on the unit all followed broad spectrum antibiotics for bacterial peritonitis.

In summary, this paper reports four outbreaks of systemic candidiasis where control was achieved without recourse to systemic chemoprophylaxis. The outbreaks were identified by immunoblot fingerprinting and confirmed by morphotyping. Hospital units that see frequent candida colonization and infection need to consider the possibility of cross-infection and may need to introduce measures to control it.

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