ELSEVIER

European Journal of Cancer 41 (2005) 2132–2140

European Journal of Cancer

www.ejconline.com

A prospective study of septicaemia on a paediatric oncology unit: A three-year experience at The Royal Liverpool Children's Hospital, Alder Hey, UK

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Received 13 July 2004; received in revised form 22 March 2005; accepted 5 April 2005
Available online 29 August 2005

Abstract

Septicaemia in neutropaenic patients is predominantly due to gut translocation [endogenous septicaemia] and contamination of the central venous catheter by microorganisms not carried by the patient [exogenous septicaemia]. To control both types of infection, a protocol was implemented based on pre 1990's parenteral and enteral antimicrobials together with strict hygiene. Surveillance cultures of throat/rectum were taken to distinguish exogenous from endogenous septicaemia and enteral non-absorbable antibiotics are administered as part of selective decontamination of the digestive tract (SDD). This protocol was evaluated in a 14-bedded paediatric oncology unit over a period of 3 years. 313 septicaemia episodes were recorded in 131 children. 28.4% of the septicaemias were caused by microorganisms associated with the unit, equivalent to 0.82 episodes per 100 patient days. Low-level pathogens such as coagulase-negative staphylococci caused more than 70% of infections. Amongst the potential pathogens, *Pseudomonas* species (7.8%) and *Staphylococcus aureus* (5.5%) were predominant. Antibiotic resistance was rare with no superinfections or outbreaks. Four patients (3%) died, two due to *Candida* species and two due to *Pseudomonas aeruginosa*. We believe that the addition of enteral non-absorbable antibiotics to systemic antibiotics maintained a low level of resistance and mortality but a randomised controlled trial is indicated to confirm these observations.

Keywords: Infection; Septicaemia; Oncology; Cancer; Child

1. Introduction

Infection is the most important cause of morbidity in children with malignancy and, after the cancer itself, the second major cause of death in this population of patients [1–9]. A variety of factors contribute to the susceptibility to infection including myelosuppression, the presence of indwelling catheters and malnutrition. The most important factor is undoubtedly the repeated episodes of neutropaenia that follows myelosuppressive chemotherapy. Additionally, cancer patients are particularly prone to develop abnormal carriage of potentially pathogenic microorganisms (PPM), including aerobic Gram-negative bacilli (AGNB), in the oropharynx [10] and the gastrointestinal tract [11]. The translocation of such microorganisms through the mucosal lining into the systemic circulation is the major mechanism of AGNB septicaemia [11]. This also applies to the pathogenesis of septicaemia due to staphylococci, both coagulase positive and negative [12,13] although contamination of central venous catheters is also an important factor [14,15].

As universally accepted, our antibiotic policy relies on the immediate use of parenteral antibiotics in febrile neutropaenia to prevent mortality due to potential pathogens, including AGNB and *Staphylococcus aureus*. Our

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doi:10.1016/j.ejca.2005.04.037

policy also aims to preserve the normal indigenous flora [16–18] that is required to control overgrowth of pathogenic microorganisms and to prevent resistance. Thus antimicrobials that leave the flora undisturbed were selected for our policy. In addition, we aimed to limit the emergence of resistant microbes by using antimicrobials with the lowest resistance potential [19,20]. Where resistance to an antimicrobial that occurs during drug development or clinical trials, or within 2 years of general use, then that antibiotic has a high resistance potential. Antimicrobials with a high resistance potential were not incorporated into our policy, and were only available on a restricted basis requiring approval from the infection control team. Finally our policy uses the somewhat controversial practices of routine surveillance cultures of rectum and throat to detect the presence of PPMs and the administration of enteral non-absorbable antibiotics as part of selective decontamination of the digestive tract (SDD) [21–24] to eradicate or reduce carriage of these PPMs at both oropharyngeal and intestinal level.

To examine the effectiveness of our infection control policy a prospective study of septicaemias over a three-year period was undertaken.

2. Patients and methods

2.1. Setting

The oncology unit at Alder Hey hospital, a 14-bedded unit designated referral centre for half of Northwest England, North Wales and the Isle of Man. Approximately 100 new referrals were made each year.

2.2. Infection control policy

- Antibiotic policy in the treatment of febrile neutropaenia: Piperacillin/netilmicin were administered as first line antibiotics, with the addition of teicoplanin after 48 h in patients still febrile with a central line in situ. If fever was still present after 3 days of treatment, second line antibiotics, ceftazidime and amikacin, were then used. When an organism was isolated from the blood, the antibiotic therapy was adjusted according to the sensitivity pattern. For fever persisting more than 5 days without an organism isolated, amphotericin was added particularly in case of yeast carriage. Coagulase-negative staphylococcal (CNS) infections were treated with teicoplanin, whilst coagulase-positive infections were treated with vancomycin.
- Selective decontamination of the digestive tract (SDD) (Table 1): SDD consisted of non-absorbable antibiotics in order to clear carriage of AGNB by using the combination of polymyxin and tobramycin, and oral amphotericin to eradicate yeasts. The patients were placed on the SDD regimen if they were carrying an AGNB, except *Escherichia coli*, in the gut and were, or were expected to become, neutropaenic (neutrophils $<0.5 \times 10^9$/L). SDD was continued until the patient's neutrophil count rose to $>1.0 \times 10^9$/L. Additionally, in patients at higher risk of septicaemia, namely bone marrow transplant patients and those with acute myeloid leukaemia, SDD was routinely given until recovery of neutropaenia. Carriage of *S. aureus* sensitive to methicillin was treated with oral cephradine. *S. aureus* resistant to methicillin was treated with oral vancomycin.
- Hygiene: Strict hand washing techniques were used throughout the unit. Central lines were accessed using aseptic techniques. Patients were not strictly isolated in febrile neutropaenic episodes.
- Surveillance cultures: Swabs of the throat, rectum and the central venous catheter exit site were performed on all oncology patients on admission and afterwards twice a week if they remained hospitalised.

2.3. Microbiology

Surveillance samples of throat and rectal swabs were processed qualitatively and semi-quantitatively [25]. Three solid media – MacConkey, staphylococcal and yeast agar – were inoculated using the four-quadrant method combined with brain–heart-infusion broth. Each swab was streaked onto the three solid media,

Table 1
SDD regimen

	Total daily dose (mg) divided into four doses/day		
	<5 years	5–12 years	>12 years
Gut			
AGNB: polymyxin E and	100	200	400
tobramycin	80	160	320
Yeasts: amphotericin B	400	1000	2000
MRSA: vancomycin	20–40 mg/kg	20–40 mg/kg	500–2000 mg/kg
Oropharynx			
AGNB/yeasts: polymyxin E, tobramycin and amphotericin B paste	2 g of 2% paste/gel qds		

and then the tip was broken off into 5 ml of enrichment broth. All cultures were incubated aerobically at 37 °C. The MacConkey plate was examined after one night and the staphylococcal and yeast plates after two nights. Additionally, if the enrichment broth was turbid after one night's incubation it was then inoculated onto the three media. A semi-quantitative estimation was made by grading growth density on a scale of 1+ to 5+, as follows: growth in broth only = 1 + [approximately 10 colony forming units (CFU)/ml]; growth in the first quadrant of the solid plate = 2+ [$\geqslant 10^3$ CFU/ml or g of faeces]; growth in the second quadrant of the solid plate = 3 + [$\geqslant 10^5$ CFU/ml or g]; growth in the third quadrant of the solid plate = 4 + [$\geqslant 10^7$ CFU/ml or g]; and growth on the whole plate = 5 + [$\geqslant 10^9$ CFU/ml or g].

Diagnostic samples of blood for culture were taken from the central venous line or from a peripheral vein if the patient had no central venous access. Blood was processed using the BACTEC 9240 (Becton and Dickinson, Diagnostic Instrument Systems, Sparks, MD, USA) method.

Identification was performed using the ATB system. To differentiate CNS from coagulase-positive staphylococci, i.e., *S. aureus*, the production of DNAase by a DNA agar plate method, and a slide-agglutination test (Staphaurex, Wellcome Diagnostics) to detect clumping factor and protein A were used. *S. aureus* was identified by a positive DNAase and slide-agglutination test. When results were inconclusive, a tube-coagulase test with NCTC 6571 strain as a positive control was performed, and read at 4 and 24 h. CNS was identified by a negative tube-coagulase test.

Susceptibility patterns: Antibiotic susceptibility testing of all isolates was performed using the Vitek system (Bio Merieux Inc., Hazelwood, MO), using commercially available panels provided by the manufacturer. Interpretations for susceptible and resistant tests were performed according to the National Committee for Clinical Laboratory Standards guidelines [26].

2.4. Study design

All oncology patients who developed one or more episodes of septicaemia during their entire course of treatment were included over the period from 1st April 1999 to 31st of March 2002. These patients were identified at the weekly clinical microbiological meeting where the antimicrobial management was discussed. The infection control team registered all patients and episodes of septicaemia, the causative microorganisms and sensitivity patterns. Blood cultures yielding the same microorganism with the same sensitivity pattern within a seven day period were considered to be the same septicaemic episode; in contrast, when the sensitivity pattern was different it was considered to be a different episode.

Episodes of septicaemia due to microorganisms present in the patients' flora were recorded as endogenous, whilst the episodes were considered exogenous if the microorganism was not present in the patient's surveillance cultures of throat and rectum. Primary endogenous episodes due to microorganisms present in the admission flora were distinguished from secondary endogenous episodes due to microorganisms acquired on the oncology unit. All microbiological data were available on the MEDITECH™ system. Deaths associated with infection were analysed separately.

2.5. Endpoints

1. The incidence of septicaemia and of episodes of infections due to micro-organisms acquired on the unit, i.e., secondary endogenous and exogenous episodes of septicaemia.
2. The microorganisms causing septicaemia.
3. The pathogenesis of septicaemia with classification into primary endogenous, secondary endogenous or exogenous infections.
4. Antimicrobial resistance.
5. Mortality due to septicaemia.

2.6. Definitions

Low-level pathogens, e.g., coagulase-negative staphylococci (CNS) were defined as microorganisms that in general caused infectious morbidity only.

Potential pathogens, e.g., *P. aeruginosa* and *S. aureus* were defined as pathogens that cause both morbidity and mortality. About 15 potentially pathogenic microorganisms were recognised. These consisted of the six 'community' PPMs *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *E. coli*, *S. aureus* and *Candida albicans* present in previously healthy individuals and nine 'hospital' bacteria carried by patients with an underlying condition either chronic or acute: *Klebsiella*, *Proteus*, *Morganella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Pseudomonas*, *Acinetobacter* species and methicillin-resistant *S. aureus* (MRSA).

High-level pathogens, e.g., *Neisseria meningitidis* were defined as microorganisms that caused infection and death even in an individual with normal defence capacity. Primary endogenous infection was defined as an infection caused by pathogens carried by the patient on admission to the unit. Secondary endogenous infection was defined as an infection caused by pathogens not carried on admission to the unit, but acquired in the unit, initially in the gut. Exogenous infection was defined as an infection caused by pathogens without previous carriage. Infections due to organisms acquired on the unit only included exogenous and secondary endogenous

infections. The difference between these two types of infection is that there is an initial phase of throat and/or gut carriage required for the subsequent development of a secondary endogenous infection. Patient days were defined as the sum of the length of stay for each patient admitted to the oncology unit for a period of one month. Only patients who were admitted for more than one day were considered.

2.7. Descriptive statistics

Fractions of the total population, median and interquartile range were used to describe the demographics. The incidence of septicaemia was calculated per 100 patient days for each calendar month. The incidence of episodes of septicaemia classified by pathogenesis, i.e., primary endogenous, secondary endogenous and exogenous infections was defined as the number of episodes diagnosed per 100 patient days, again for each calendar month.

3. Results

3.1. Demographics

131 children were included in the study (Table 2). The median age was 7.94 years (IQR 4.06–13.14). There were 78 (60%) boys and 53 (40%) girls. The leading causes of malignancies were acute lymphoblastic leukaemia (51%), brain tumours (9%), acute myeloid leukaemia (7%), non-Hodgkin's lymphoma (7%) and Hodgkin's lymphoma (6%).

3.2. Activity of the unit

Between 1st April 1999 and 31st March 2002, there were a total of 10,080 patient days on the unit for patients staying at least one day on the unit. The number of patient days per calendar month has remained stable over the study period and ranged from 181 in June 2000 to 390 in March 2001, with a mean of 280 patient days per month.

Table 2
Demographics

Number of patients	131
Age	
Median (years)	7.94
Range (IQR)	4.06–13.14
Sex	
Male/female (%)	60/40
Number of diagnoses	
ALL	67
AML	9
Brain tumour	13
Non-Hodgkin's lymphoma	9
Hodgkin's lymphoma	8
Other	25

3.3. Septicaemia episodes

313 Septicaemic episodes were recorded in 131 children over the three-year period, with a total of 345 isolates being identified. The septicaemia rate, as expressed by the number of septicaemia episodes per 100 patient days remained stable over the duration of this study with no evidence of an outbreak. The monthly incidence of septicaemia per 100 patient days varied between 0.8 and 5.0, with a mean of 3.1 septicaemia episodes per 100 patient days.

There were a total of 246 (71%) primary endogenous infections, due to microorganisms present in the patient's flora on admission. Ninety-eight episodes of septicaemia due to microorganisms not present in the admission flora were recorded: one secondary endogenous and 97 exogenous infections. The overall incidence of septicaemia due to organisms acquired on the unit was 0.82 episodes per 100 patient days.

3.4. Microorganisms causing septicaemia (Table 3)

Salmonella dublin, *Campylobacter jejuni* and *Neisseria meningitis* were the only three high level pathogens isolated from one child. They all had a primary endogenous pathogenesis.

100 PPMs were isolated over three years. This represents almost 30% of all isolates. *Pseudomonas* species, isolated from 27 blood cultures (7.8%), was the most commonly identified PPM. *P. aeruginosa* was present in 15 blood samples (4.3%). *S. aureus* was isolated on 19 occasions (5.5%). The other predominant potential pathogens were *Klebsiella* species and *E. coli*, with 11 isolates each and *Candida* species, with 9 isolates. PPMs were involved in 20% of the primary endogenous infections, and caused more than half (51.5%) of the exogenous infections.

70% of all microorganisms causing septicaemia belonged to the category of low level pathogens: 242 isolates over the 3 year period. The most common microorganism was CNS, which was isolated from 164 blood cultures. This represents almost half of all identified organisms (47.5%). Viridans streptococci were present in 34 samples (9.8%). The remaining organisms were enterococci (8 isolates) and anaerobes (9 isolates). About 79% of all primary endogenous septicaemias were due to low-level pathogens.

3.5. Antimicrobial resistance (Table 4)

There was no resistance to the appropriate antimicrobials amongst the high level pathogens. These three

Table 3
Pathogenesis of 313 episodes of septicaemia

	Primary endogenous	Secondary endogenous	Exogenous	Not evaluable	Total
High level pathogens	3				3
Neisseria meningitidis	1				1
Campylobacter jejoni	1				1
Salmonella dublin	1				1
Potential pathogens	49	1	50		100
• 'Community' PPM					
Streptococcus pneumoniae	6				6
Haemophilus para-influenzae	4				4
Escherichia coli	9		2		11
Staphylococcu aureus	3		16		19
Candida species	7		2		9
• 'Hospital' PPM (AGNB)	4		7		11
Klebsiella species	1		4		5
Enterobacter species	1		1		2
Citrobacter species			1		1
Serratia species			5		5
Acinetobacter species					
Pseudomonas species					
• *aeruginosa*	6	1	8		15
• non-*aeruginosa*	8		4		12
Low level pathogens	194		47	1	242
Coagulase-negative staphylococci					
S. epidermidis	74		15	1	90
S. hominis	20		8		28
S. warneri	9		2		11
S. capitis	4		2		6
S. auricularis	1		3		4
S. haemolyticus	4		1		4
CNS unspecified	17		4		21
Viridans streptococci	34				34
Enterococci	8				8
Bacillus species	3		4		7
Micrococcus species	7		4		11
Corynebacterium species	1		1		2
Acinobacillus jumii			1		1
Leclercia carboxy			1		1
Abiotrophia			1		1
Anaerobes	9				9
Miscellaneous	3				3
A total of 345 microbes obtained from 313 septicaemia episodes	246	1	97	1	345

isolates were also sensitive to the first line antibiotics, piperacillin and netilmicin.

Amongst the PPMs, there was no MRSA causing septicaemia over three years. All fungi were sensitive to amphotericin B. All AGNB were sensitive to both first and second line antibiotics except *E. coli*, *Klebsiella* and *Pseudomonas* species. Of the 11 *E. coli* isolates obtained from blood cultures, five were resistant to piperacillin but sensitive to netilmicin, ceftazidime and amikacin. *Klebsiella* caused 11 infections: five isolates were resistant to piperacillin, two to netilmicin, and one isolate to both ceftazidime and amikacin. All but two *Pseudomonas* isolates were sensitive to the antipseudomonal agents, netilmicin, ceftazidime and amikacin, used on our unit. The two resistant isolates, one *P. aeruginosa* and one *Stenotrophomonas maltophilia*, were still sensitive to ciprofloxacin.

All CNS were sensitive to vancomycin. Three isolates were resistant to teicoplanin. Resistance to piperacillin was tested in 34 viridans streptococci and all were sensitive. Vancomycin-resistant enterococci did not occur throughout the study.

3.6. Mortality due to septicaemia (Table 5)

Over the three-year study period, 4 patients (3%) died following septicaemia. Two patients died of *Candida*, and two succumbed during *Pseudomonas aeruginosa* sepsis. One isolate was resistant to ceftazidime but sensitive to the other antipseudomonal agents.

Table 4
Antimicrobial resistance

Microorganism	Number	Teicoplanin	Vancomycin	Methicillin		
Coagulase-negative staphyloccoci	164	3	0			
S. aureus	19	0	0	0		
		Piperacillin	Netilmicin	Ceftazidime	Amikacin	Multi-resistant
P. aeruginosa	15	2	3	3	2	1
P. non-aeruginosa	12	3	3	2	3	1
E. coli	11	5	0	0	0	0
Klebsiella species	11	5	2	1	1	0
		Amphotericin				
Yeasts	9	0				

Table 5
Mortality

Patient	Age	Primary disease	Causative microorganism	Note
1	7	Relapsed ALL	*Candida lusitaniae*	Disseminated disease
2	13	Relapsed ALL	*Pseudomonas aeruginosa*	Secondary to typhilitis
3	4	Non-Hodgkin's lymphoma	*Pseudomonas aeruginosa*	ARDS
4	5	ALL	*Candida albicans*	Disseminated disease Brain hemorrhage

ALL, acute lymphoblastic leukaemia; ARDS, adult respiratory distress syndrome.

4. Discussion

Septicaemia is a major infection problem in paediatric oncology. The pathogenesis is generally endogenous, i.e., gut bacteria carried by the patient migrate through the mucosal lining of the gut into the blood stream [11]. This process is termed translocation. Three criteria need to be fulfilled in order for microorganisms to cause septicaemia due to translocation:

1. gut overgrowth, defined as $\geqslant 10^5$ micro-organisms per g of faeces [11,27];
2. increased permeability of the intestinal wall;
3. immunosuppression.

Chemotherapy causes mucositis that promotes adherence and overgrowth of gut microorganisms, increases gut permeability and impairs systemic immunity following neutropaenia. High-level, potential and low-level pathogens have been shown to translocate and cause septicaemia. In oncology, children with long-term invasive devices, such as long lines, all types of microorganisms can be introduced into the blood stream, without previous carriage, but following contamination of the line. This exogenous origin of infection accounts for the majority of acquired infections, which in turn reflect breaches in hygiene practices.

Our study has evaluated a subset of neutropaenic patients at high risk of infection, and describes 131 children with 313 septicaemias over three years. Comparison with the literature is difficult as most reports use different denominators. For example, a recent English study reports on 66 patients with 72 septicaemias over a 9-month period at a mortality rate of 6% [14]. The denominator was central venous catheter days totalling 22,934 days over this less than one-year study. The rate of catheter related septicaemia was 1.7 episodes per 1000 catheter days.

Our infection control policy comprises of four main aspects: (i) the immediate administration of adequate parenteral antimicrobials to prevent mortality associated with septicaemia; (ii) surveillance of throat and gut to monitor the ecology of micro-organisms on our unit, to detect potential pathogens and to monitor resistance patterns; (iii) SDD using enteral non-absorbable antibiotics to eradicate, if already present, and in some circumstances to prevent carriage of pathogens and to prevent resistance; and (iv) a high standard of hygiene.

The immediate administration of adequate antimicrobials is crucial to prevent mortality due to septicaemia caused by AGNB, in particular *P. aeruginosa*, and *S. aureus* [28]. In contrast, low-level pathogens including coagulase-negative staphylococci, enterococci and viridans streptococci generally cause morbidity but rarely mortality. On our unit as in others, glycopeptides are used to cover these low level pathogens. At present we are considering abandoning our practice of the empirical use of teicoplanin, as studies have suggested no benefit from this approach in terms of reducing morbidity of preventing infection [29,30].

A major component of our infection control policy is regular surveillance samples of throat and gut [31]. The aim of surveillance cultures is the detection of the microbial carrier state. Although popular in the 80s, surveillance samples are nowadays abandoned by most units in the UK. Based on the knowledge of the carrier state we were able to show that more than 70% of all septicaemias were primary endogenous, i.e., due to

microorganisms present in the admission flora of the immunocompromised child. This observation, original in paediatric oncology, is in line with recent epidemiological surveillance for infection in the critically ill child requiring intensive care [32].

It is obvious that the traditional infection control measures, in particular, hand hygiene, does not impact on primary endogenous infections, as rigid implementation of hand disinfection does not eradicate oropharyngeal and gastro-intestinal carriage present on admission to the unit. On the other hand, a high level of hygiene is required to prevent exogenous infections. In our study, 89 exogenous infections caused by 97 microorganisms were diagnosed over three years. The magnitude of the exogenous infection problem can only be appreciated by using surveillance samples. This enables the early identification of outbreaks of infection and reinforcement of a high standard of hygiene including appropriate isolation measures. In our centre, surveillance sampling is also used to direct the administration of SDD as discussed below.

We thus recommend that the practice of surveillance sampling should be widely adopted and that the infection control team should continuously monitor the pathogenesis of infections using our classification scheme [33].

Our oncology unit has, since 1987, used SDD prophylaxis using enteral non-absorbable antimicrobials initially neomycin, colistin or polymyxin E and nystatin (NEOCON) [2] and later polymyxin E, tobramycin and amphotericin B (PTA). We appreciate that compliance with the intake of SDD can be problematic in some patients. An audit on our unit has shown that around 70% of patients take all the elements of the SDD. The benefit of SDD in preventing infectious mortality in the Intensive Care Unit (ICU) setting has been clearly shown in several randomised controlled trials, including four trials in children, and from a number of meta-analyses [34]. There have, however, to date been no RCTs examining SDD in patients treated for cancer. The aim of SDD in the ICU setting is to prevent endogenous septicaemia (principally secondary) due to microorganisms that escaped hand hygiene and led to secondary carriage. In this study only one episode of secondary endogenous septicaemia was recorded over three years.

Due to a lack of comparative data, this observational study is obviously not able to answer the question of whether the use of SDD can reduce morbidity or mortality from infection and in this respect we feel that a carefully conducted RCT is indicated.

We also believe that SDD has a potential benefit in helping to prevent antibiotic resistance, which is only rarely seen in this study. There was no MRSA causing septicaemia over the three years. Two pseudomonal isolates were resistant to the antipseudomonals used in the unit but still sensitive to ciprofloxacin. Prospectively and systematically collected data on antimicrobial resistance on paediatric oncology units are scarce [1,2,6–8,35]. These studies generally report outbreaks with MRSA [7], multi-resistant *Acinetobacter* [8] and *Pseudomonas* [35] species and AGNB resistant to ciprofloxacin [7]. One German study reports the necessity of changing antimicrobials every three years due to development of AGNB resistant to their first line antibiotics [6]. The emergence of resistant microorganisms was uncommon using our infection control policy of adding enteral non-absorbable to parenteral antimicrobials. It is reassuring that using this approach, older antimicrobials from the 80s remained active despite continued use. We believe that their activity is maintained by the addition of oral polymyxin E and tobramycin. When just systemic antibiotics are used, newer more potent antibiotics are needed within a few years [6,19]. As an example, in an adult oncology unit ciprofloxacin replaced ceftazidime following the emergence of extended spectrum beta-lactamases (ESBL). Within a few years of ciprofloxacin use, resistant AGNB and MRSA emerged following the selection of resistant mutants in the gut flora [7]. Although there the case for SDD in preventing antibiotic resistance in cancer patients is yet to be proven, this benefit has been clearly shown in the ICU setting. For example, a recent Dutch RCT reports that the addition of enteral polymyxin/tobramycin to the parenteral antimicrobials reduces resistance compared with the parenteral antibiotics only [36]. This is in line with a previous RCT demonstrating that enteral antimicrobials control extended spectrum beta-lactamase producing *Klebsiella* [37]. Antimicrobial resistance, being a long-term issue, has also been evaluated in eight other SDD studies [33,38–44] monitoring antimicrobial resistance between two and seven years, and bacterial resistance associated with SDD has never been a clinical problem in respect of superinfection and outbreaks. Therefore a comparative study in the oncology setting is also suggested to address the issue of the benefit of SDD in preventing resistance.

Recent studies show mortality rates varying between 1% and 31% in children with cancer and septicaemia [4,5,7,14,45]. This may be due to the different proportions of low-level pathogens that generally cause only morbidity versus high level and potential pathogens that are responsible for death. The mortality was 31% in a subset of children who developed septicaemia due to the potential pathogen *P. aeruginosa* [45]. In an Italian study reporting 15% mortality, 60% of septicaemias were due to PPM including *S. aureus*, AGNB and fungi. In contrast, 30% of infections were caused by PPM in our study with a 3% mortality rate.

In conclusion, our infection-control policy, which has been unaltered over 14 years, employs older cheaper, effective and relatively narrow spectrum antibiotics

combined with a policy of microbiological surveillance and the administration of SDD. This policy has been successful in respect of low mortality and low antimicrobial resistance. A RCT is indicated to examine further the benefit of SDD.

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