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Symposium on 'Nutrition and gut barrier function'

Nutritional implications of gut overgrowth and selective decontamination of the digestive tract

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Patients requiring parenteral nutrition (PN) are at risk of infection. Impaired immunity due to an underlying disease process and/or malnutrition, combined with therapeutic interventions including PN, and the presence of a foreign body, the intravenous catheter, renders them prone to septicaemia (Puri & Reen, 1992). Recent studies suggest that this septicaemia may be primarily due to gut-derived micro-organisms, rather than to external contamination of the intravenous catheter (Kurkchubasche *et al.* 1992; Pierro *et al.* 1996). Previous work has shown that PN has a detrimental effect on mucosal defences (Li *et al.* 1995; Kudsk *et al.* 1996), and impairs gut motility (Vantrappen *et al.* 1977) and biliary flow (Jawaheer *et al.* 1995). This promotes small intestinal bacterial overgrowth, particularly with aerobic Gram-negative bacilli (AGNB), and this overgrowth has been identified as a risk factor for impaired systemic immunity (Marshall *et al.* 1987) via endotoxin-induced liver dysfunction (Billiar *et al.* 1988). Suppression of both mucosal and systemic immunity is required for the development of sepsis and septicaemia (Alverdy & Burke, 1992).

A prospective 5-year study in a large homogeneous population of surgical infants of < 6 months postnatal age was undertaken to determine the importance of gut overgrowth with AGNB in the pathogenesis of PN-related septic complications.

Patients and methods

Patients

Infants (*n* 208) who received PN in Alder Hey Children's Hospital, Liverpool, were enrolled in a prospective observational cohort study from 1 February 1992 to 31 January 1997. The neonates and infants, who were less than 6 months postnatal age at the start of PN, all underwent surgical procedures. The indication for PN was gut dysfunction secondary to the following disorders: gastroschisis (*n* 66), congenital intestinal obstruction (*n* 58); necrotizing enterocolitis (*n* 25); Hirschprung's disease (*n* 20); prolonged postoperative ileus (*n* 20) and miscellaneous (*n* 19). All patients were admitted to the neonatal surgical special care unit.

PN was prepared under strict aseptic conditions which were regularly screened microbiologically. Administration was through a central venous catheter in 187 patients and through a peripheral line in twenty-one patients. Liver function tests were monitored at least weekly and when infection was suspected.

Antibiotic policy

Prophylaxis. Three doses of cefotaxime and metronidazole were given for clean and clean-contaminated procedures. For contaminated or dirty procedures intravenous gentamicin was added and antibiotics given for at least 3 d.

Therapy. Blind therapy with a combination of teicoplanin and gentamicin was started at the onset of sepsis. The aminoglycoside was stopped if a Gram-positive micro-organism was cultured. In cases of Gram-negative bacillary septicaemia the glycopeptide was discontinued and replaced by a second or third generation cephalosporin. For fungaemia, liposomal amphotericin B was administered. If cultures proved negative, antibiotics were discontinued unless the severity of sepsis warranted a full 5 d course of treatment.

Abbreviations: AGNB, aerobic Gram-negative bacilli; CFU, colony-forming units; CNS, coagulase-negative staphylococci; PN, parenteral nutrition; PPM, potentially pathogenic micro-organisms.

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End-points

In this homogeneous population four end-points were evaluated:

(1) the incidence of abnormal gut carriage, sepsis and septicaemia;
(2) sepsis and septicaemia rates in infants who developed AGNB overgrowth compared with those who did not;
(3) the temporal relationship between abnormal gut carriage, sepsis and positive blood cultures;
(4) the pathogenesis of septicaemia and clinical importance of gut-derived endogenous septicaemia.

Microbiological methods

Surveillance samples. Samples comprising throat and rectal swabs were taken at the start of PN, and twice weekly thereafter. They were processed using a semi-quantitative method, i.e. the four-quadrant technique combined with enrichment broth (van Saene HKF *et al.* 1996). Both swabs were inoculated onto four solid media (staphylococcal agar, yeast agar, MacConkey agar and aesculine azide agar), and placed into 5 ml brain-heart infusion broth (Oxoid, Basingstoke, Hants, UK). The target micro-organisms were staphylococci (both coagulase-positive and coagulase-negative; CNS), yeasts, AGNB and enterococci. Growth density was classified as very low (equivalent to < 10 colony-forming units (CFU)/ml) where only the enrichment broth was positive, low (equivalent to $< 10^3$ CFU/ml), medium (equivalent to $< 10^5$ CFU/ml), high (equivalent to $< 10^7$ CFU/ml), and very high (equivalent to $> 10^7$ CFU/ml) where the plate had grown completely.

Diagnostic samples. Samples of blood for culture were taken from the central venous line and/or from a peripheral vein when signs of generalized inflammation were observed. Blood was processed using BACTEC 9240 (Becton and Dickinson, Diagnostic Instrument Systems, Sparks, MD, USA). Identification was performed using the Automatic Test in Bacteriology system (Biomerieux, Lyon, France), and sensitivity patterns were determined using the breakpoint method (Working Party on Antibiotic Sensitivity Testing of the British Society for Antimicrobial Chemotherapy, 1991).

Definitions

Microbial carriage. This existed when the same strain of a micro-organism, in any concentration, was isolated from a minimum of two consecutive surveillance samples over a period of at least 1 week (van Saene HKF *et al.* 1996). Whilst the presence of *Escherichia coli* in the rectum is considered normal, persistence in the throat constitutes abnormal carriage.

Microbial overgrowth. This was defined as $\geq 10^5$ micro-organisms/ml, i.e. very high or high growth density in the throat and/or rectal swabs (van Saene HKF *et al.* 1996).

Sepsis. This was defined as the clinical signs of generalized inflammation caused by micro-organisms and/or their products. At least three of the following had to be present: pyrexia, tachycardia, hypotension, poor peripheral perfusion, lethargy and respiratory distress (Goldmann, 1990).

Septicaemia. This was defined as sepsis accompanied by a positive blood culture drawn through the catheter and/or from a peripheral vein (Pierro *et al.* 1996).

Microbial translocation. This was diagnosed if the micro-organisms isolated from the blood culture were identical to those carried in the throat and/or rectum within the 2 weeks preceding the episode of septicaemia (Pierro *et al.* 1996).

Identity of micro-organisms. This was based on antibiotyping using extended sensitivity patterns (CNS and enterobacteria), phage (*Staphylococcus aureus*), sero (*Streptococcus pneumoniae*) and pyocine (*Pseudomonas aeruginosa*) typing.

Endogenous and exogenous septicaemia. A septicaemia was defined in the present study to be of endogenous development if the micro-organism isolated from the blood culture was previously carried in throat and/or gut (van Saene HKF *et al.* 1996) due to microbial translocation. If the micro-organism causing septicaemia was not present in the patient's flora, the septicaemia was of exogenous pathogenesis, i.e. due to external catheter contamination.

Pathogenicity of micro-organisms. Micro-organisms causing septicaemia were classified by their intrinsic pathogenicity (van Saene HKF *et al.* 1996). CNS and enterococci are considered to be low-level pathogens because they cause morbidity only, whilst potentially pathogenic micro-organisms (PPM) also cause mortality. PPM can be conveniently divided into those carried by otherwise healthy individuals, i.e. 'community' PPM (*S. pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, E. coli, S. aureus* and *Candida albicans*) and those carried by individuals with underlying disease, i.e. 'hospital' PPM (*Klebsiella, Proteus, Morganella, Enterobacter, Citrobacter, Serratia, Acinetobacter* and *Pseudomonas* spp.). AGNB are the 'hospital' PPM and *E. coli* (abnormal only when persistent in the throat).

Liver impairment. This was indicated by an increased total bilirubin level of > 15 μmol/l (the upper limit of the normal reference range), after physiological unconjugated hyperbilirubinaemia had resolved.

Statistical analysis

Data were analysed using the Shapiro-Wilks test and found not to be normally distributed. They are expressed, therefore, as medians and ranges. Between-group differences were analysed using the Mann-Whitney U and Fisher's exact tests. Statistical significance was considered when $P < 0{\cdot}05$.

Results

Patients

Table 1 shows the demographics of the study population. PN was administered for a total of 6271 patient days, a mean of 1254 PN days per year.

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Incidence of carriage, sepsis and septicaemia in the total study population

Of the 208 infants, abnormal carriage of AGNB occurred in eighty-eight (42 %) and, of these, overgrowth was detected in sixty-eight (77 %). A total of 198 blood cultures were taken from fifty-two patients (25 %) with clinical evidence of sepsis, and seventy-nine were positive in thirty-two patients (15 %), giving a septicaemia rate of 12·6 episodes/1000 PN days.

Comparison between normal and abnormal flora carriers

When the normal and abnormal flora groups were compared there were no significant differences in birth weight, gestational age, age at starting PN, gender or usage of central venous catheters (Table 2). However, the duration of PN was different, with carriers of AGNB receiving a median of 25 d, whilst non-carriers received only 9 d. The incidence of both sepsis, 39 % (thirty-four of eighty-eight patients) *v.* 15 % (eighteen of 120 patients), and septicaemia 31 % (twenty-seven of eighty-eight patients) *v.* 4 % (five of 120 patients) were significantly higher in the group with abnormal flora, as indeed were the concomitant rates (Table 3).

Time relationship between onset of carriage, sepsis and septicaemia

Of the thirty-two infants with positive blood cultures, twenty-seven (84 %) belonged to the group with abnormal carriage (Table 3). Of the eighteen who had more than one septicaemic episode, 90 % had abnormal flora. In this group, carriage with AGNB developed at a median of 14 (range 1–113) d, signs of clinical sepsis at a median of 19 (range 1–104) d, and bacteriologically-proven septicaemia at a median of 23 (range 1–118) d. The intervals between the onset of carriage and of septicaemia, and of onset of sepsis and of septicaemia were significantly different. In contrast, AGNB-free infants developed positive blood cultures at a median of 7 (range 3–13) d.

Micro-organisms causing septicaemia

A single micro-organism was isolated in seventy-four episodes, whilst blood cultures from five episodes yielded two micro-organisms. All but four of the thirty-two patients had a blood culture positive for CNS (Table 4). More than half all septicaemic episodes were due to CNS. Nine patients developed nineteen episodes of infection due to enterococci. 'Community' PPM were responsible for a total of ten episodes in eight patients, and six septicaemias in six children were due to 'hospital' PPM (Table 4).

Patients with normal flora developed septicaemia with CNS (six episodes in four patients) and *C. albicans* (two episodes in the same infant).

Table 5 shows the AGNB carried by the eighty-eight abnormal carriers and the AGNB isolated from ten blood cultures. Notably, only seven patients (3 %) were found to be septicaemic with those target micro-organisms.

Table 1. Demographics of infants who had undergone surgical procedures and were receiving parenteral nutrition (PN)

(Values are medians and ranges for 208 patients, 123 male and eighty-five female)

	Median	Range
Gestational age (weeks)	37	25–45
Birth weight (kg)	2·6	0·73–4·28
Postnatal age at start of PN (d)	5	1–176
Duration of PN (d)	13	1–512

Table 3. Comparison of sepsis and septicaemia and duration of parenteral nutrition (PN) between groups of infants with normal and abnormal flora who had undergone surgical procedures*

	Normal flora (*n* 120)	Abnormal flora (*n* 88)	Statistical significance of difference: *P*
Total period of PN (d)	1376	4895	
Sepsis:			
No. of patients	18	34	0·005
No. of episodes	29	169	
Rate of septic episodes (episodes/1000 PN days)	21	35	0·025
Septicaemia:			
No. of patients	5	27	0·005
No. of episodes	8	71	
Rate of septicaemic episodes (episodes/1000 PN days)	6	14	0·045

*For details of patients and procedures, see pp. 381–382 and Table 1.

Table 2. Comparison of normal and abnormal carriers among infants who had undergone surgical procedures and were receiving parenteral nutrition (PN)*

(Values are means and ranges)

	Normal flora (*n* 120)		Abnormal flora (*n* 88)		Statistical significance of difference: *P*
	Median	Range	Median	Range	
Duration of PN (d)	9	1–58	25	1–512	< 0·0001
Birth weight (kg)	2·7	1·7–4·1	2·5	0·8–4·3	0·4
Gestational age (weeks)	37	25–45	37	25–42	0·5
Age at PN start (d)	5	1–156	6	1–176	0·76
Male	72		51		0·8
Female	48		37		
Central venous catheters	102		85		0·14

*For details of patients, see p. 381 and Table 1.

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Parental nutrition duration and liver dysfunction at onset of septicaemia

CNS septicaemia occurred significantly earlier than the septicaemias due to enterococci or PPM (Table 6). Median PN days at onset of septicaemia in these three groups were 34, 74 and 108 respectively. The difference between the onset of septicaemia due to PPM and enterococci was not significant ($P = 0{\cdot}3$).

In seventy-one episodes (90 %) the total serum bilirubin at the time of septicaemia was abnormal, i.e. > 15 μmol/l. In all but two episodes, physiological unconjugated hyperbilirubinaemia had resolved. These two episodes were excluded from the analysis of liver dysfunction. The level of total bilirubin was significantly higher when septicaemia was due to PPM or enterococci, compared with CNS. Median total bilirubin levels were 127 and 155 μmol/l for PPM and enterococci respectively, compared with 78 μmol/l for CNS (Table 6). Again the difference between enterococci and PPM was not significant ($P = 0{\cdot}43$).

The total bilirubin level was less than 15 μmol/l in five patients who had eight septicaemic episodes, of which five were due to CNS and one each to *Enterococcus faecalis*, *C. albicans* and *Klebsiella pneumoniae*.

The two patients with physiological unconjugated hyperbilirubinaemia at the time of septicaemia had infections with CNS and *P. aeruginosa*.

Table 4. Micro-organisms isolated from seventy-nine septicaemic episodes yielding eighty-four micro-organisms in thirty-two infants who had undergone surgical procedures* (five episodes yielded two micro-organisms)

Micro-organisms	No. of patients	No. of episodes	% Episodes
Coagulase-negative staphylococci	28	49	62
Enterococci	9	19	24
Potentially pathogenic micro-organisms	14	16	20
'Community'†	8	10	12·5
'Hospital'‡	6	6	7·5

*For details of patients and procedures, see pp. 381–382 and Table 1.
†Those carried by otherwise healthy individuals.
‡Those carried by individuals with underlying disease.

Table 5. Aerobic Gram-negative bacilli (AGNB) isolated from abnormal carriers among infants who had undergone surgical procedures (*n* 88, 42 % of study infants) and blood cultures (*n* 10, 12·5 % of septicaemias)*

AGNB	Abnormal carriers†	Septicaemia
Escherichia coli in throat	9	4
Klebsiella spp.	22	3
Proteus spp.	3	
Morganella spp.	1	
Enterobacter spp.	30	1
Citrobacter spp.	7	1
Serratia spp.	2	
Acinetobacter spp.	5	
Pseudomonas aeruginosa	35	1

*For details of patients and procedures, see pp. 381–382 and Table 1.
†Nine infants carried more than one AGNB.

Microbial translocation

Of the total of seventy-nine septicaemic episodes, sixty-eight were evaluable for seventy-three micro-organisms (Tables 7 and 8). Throat and rectal swabs were not processed for CNS at the start of the study and, therefore, eleven episodes of CNS septicaemia in ten patients could not be evaluated for microbial translocation. However, seven of these patients had other evaluable episodes, leaving twenty-nine patients for evaluation of translocation.

Of the thirty-eight evaluable CNS episodes in nineteen patients, the CNS strains were identical in blood and surveillance samples in twenty-eight cases involving thirteen patients. Microbial translocation most probably occurred in 74 % of episodes and 68 % of patients. CNS overgrowth was detected in eighteen episodes and in twelve patients. A total of ten blood cultures in six patients were positive for CNS, but surveillance cultures were negative or yielded a different strain of CNS, suggesting exogenous infection due to catheter contamination.

The nineteen enterococcal episodes were all evaluable. Identical strains were carried by all nine affected patients, at the time of each episode of septicaemia, meeting our definition of microbial translocation. Enterococcal overgrowth was diagnosed in all nine infants and fifteen episodes.

All sixteen episodes of PPM septicaemia were evaluable. In fourteen episodes in twelve patients, identical PPM were carried in throat and/or rectum in the 2 weeks preceding the septicaemia, i.e. the infections were endogenous. In all but one case, there was overgrowth. In this case, due to *S. pneumoniae*, the micro-organism was only isolated in low concentration. The two septicaemias caused by *S. aureus* and *P. aeruginosa* were both exogenous, i.e. the micro-organisms were not carried at all by the patients.

Table 6. Time of onset and total bilirubin at the time of septicaemic episodes in infants who had undergone surgical procedures†, with causative micro-organisms classified into coagulase-negative staphylococci (CNS), enterococci and potentially pathogenic micro-organisms (PPM)‡

(Values are medians and ranges for no. of episodes shown)

	CNS (*n* 49)		Enterococci (*n* 19)		PPM (*n* 16)	
	Median	Range	Median	Range	Median	Range
Time of onset (PN days)	34*	1–513	74	1–264	108	1–486
Total bilirubin (μmol/l)	78*	1–368	155	3–232	127	6–667

Median values were significantly different from those for both enterococci and PPM (Mann-Whitney U test): *$P < 0{\cdot}05$.
†For details of patients and procedures, see pp. 381–382 and Table 1.
‡CNS and enterococci are considered to be low-level pathogens, whilst PPM include the 'community' and 'hospital' micro-organisms (for details, see p.382).

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In summary, septicaemia due to translocation occurred in 84 % of episodes and in twenty-two (76 %) of the twenty-nine evaluable patients.

Discussion

Several findings emerged from the present study:

(1) the incidence of AGNB carriage was 42 %, whilst the sepsis and septicaemia rates were 25 and 15 % respectively. However, only 3 % of the patients had a septicaemia due to AGNB;
(2) sepsis and septicaemia rates were significantly higher in the subset of abnormal carriers. Of the infants who had septicaemia, 84 % belonged to the subset of AGNB carriers;
(3) carriage of AGNB developed significantly 'earlier' than sepsis and septicaemia;
(4) of the infectious episodes, 80 % were caused by low-level pathogens, whilst PPM caused only 20 %, and AGNB only 12·5 %;
(5) PPM caused septicaemia significantly later than CNS at a time when liver function was also significantly more impaired;
(6) translocating micro-organisms caused septicaemia in 76 % of the infected patients and in 84 % of the infective episodes when these were evaluable.

Our finding that 84 % of infants (twenty-seven of thirty-two) with a positive blood culture belonged to the subset who carried an abnormal gut flora suggests that the AGNB carrier state is a marker of the severity of underlying disease. This observation is consistent with earlier and recent work in both adults and infants. Johanson *et al.* (1969) showed that the frequency of oropharyngeal carriage of AGNB is proportional to the severity of illness. In critically-ill neonates, Harris *et al.* (1976) found that systemic infection occurred only in those who initially and subsequently carried abnormal flora. Sprunt (1985) demonstrated in infants requiring intensive care an infection rate of only 0·5 % as long as they did not carry abnormal flora, but the rate increased to 15 % in abnormal carriers. These researchers were convinced that surveillance cultures identified at-risk patients.

The fact that AGNB carriage preceded sepsis and septicaemia may implicate gut overgrowth with abnormal AGNB as an aggravating or contributing role in septic morbidity. More than 40 % of study infants were so ill that they were unable to clear the AGNB acquired on the neonatal surgical unit, whilst the others did not become carriers despite exposure to the same micro-organisms. The hands of staff caring for neighbouring patients with AGNB are the main vehicle for transmission. The subset of patients with AGNB overgrowth received PN for a median of 25 d, significantly longer than the non-carriers. Duration of PN reflects the severity of underlying disease and suggests that non-use of the gut is an important factor in PN-related septic morbidity. Some may argue that the time of exposure to the unit micro-organisms determines acquisition and subsequent carriage. However, healthy carers rarely develop gut carriage of the unit's AGNB, despite being exposed to these bacteria day and night for decades (Chambers *et al.* 1987). Moreover, in almost all infants who acquired AGNB the carrier state occurred 'early', exonerating duration of stay on the unit, *per se*, as a risk factor.

Table 7. Endogenous pathogenesis of septicaemic episodes (*n* 68) suggesting microbial translocation in infants who had undergone surgical procedures and were receiving parenteral nutrition*

	Episodes	Carriage	Overgrowth	% Endogenous
CNS	38	28	18	74
Enterococci	19	19	15	100
PPM	16	14	13	88
Total	73†	61	46	84

CNS, coagulase-negative staphylococci; PPM, potentially pathogenic micro-organisms.
*For details of patients and procedures, see pp. 381–382 and Table 1.
†Five episodes were polymicrobial.

Table 8. Endogenous pathogenesis of septicaemia in infants who had undergone surgical procedures and were receiving parenteral nutrition (*n* 29)*

	No. of patients	No. of patients with: Microbial carriage	Microbial overgrowth	% Endogenous
CNS	19	13	12	68
Enterococci	9	9	9	100
PPM	14	12	11	86
Total†	29	22	20	76

CNS, coagulase-negative staphylococci; PPM, potentially pathogenic micro-organisms.
*For details of patients and procedures, see pp. 381–382 and Table 1.
†Eleven patients had several episodes of septicaemia due to different micro-organisms, and four patients developed five polymicrobial septicaemia.

The predominating micro-organisms causing septicaemia were CNS and enterococci. In total, they were responsible for 80 % of all septicaemic episodes (Table 4). However, these micro-organisms may be regarded as low-level pathogens; for example, they rarely cause pneumonia and, even when infecting blood, they are an infrequent cause of mortality. Conversely, 'community' and 'hospital' PPM were involved in only ten and six blood infections respectively. This ranking among causative micro-organisms is in line with previous reports (Kurkchubasche *et al.* 1992; Pierro *et al.* 1996).

Recent prospective work (Damjanovic & van Saene, 1995; Eastick *et al.* 1996) in premature neonates requiring intensive care and/or surgery has shown that CNS is often the first micro-organism that these patients acquire in throat and gut (as well as on the skin). Underlying disease has been shown to promote persistence of CNS, leading to oropharyngeal and gastrointestinal carriage (Damjanovic *et al.* 1993). Only in individuals who enjoy a reasonably good or improving standard of health, does CNS become transient in the alimentary canal (Bloomfield, 1920), whilst skin carriage is physiologically established. This may explain our finding that more than half all septicaemic episodes were due to CNS, whilst only 7·5 % were caused by hospital PPM, the bacteria considered to be 'markers' of illness severity (Table 4).

The new theory that the gut is a major source of micro-organisms which may cause systemic illness, including septicaemia, is supported by three observations from this present

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study. First, in 84 % of episodes, carriage in the digestive tract preceded systemic blood infection with identical micro-organisms of the same biotype and/or sensitivity pattern (Table 7). Second, microbial overgrowth was observed in 90 % (twenty of twenty-two) of the patients in whom endogenous septicaemia developed (Table 8), and third, microbial translocation almost always (90 %) occurred where there was evidence of liver dysfunction as measured by an elevated bilirubin level. Additionally, septicaemias due to PPM have been found to occur significantly later, and at a time when liver function has been significantly more impaired than those due to CNS (Table 6).

Our hypothesis is that the sicker and more-physiologically-stressed infants do not establish normal gut function as quickly as the less-sick infants. The need for and duration of PN is a reflection of a poorer clinical response. Gut-associated lymphoid tissue atrophy (Li *et al.* 1995), impairment of secretory immunoglobulin A-mediated mucosal immunity (Kudsk *et al.* 1996) and cholestasis (Jawaheer *et al.* 1995) in infants and neonates may be due to long-term PN alone. Impaired mucosal defences (Hadfield *et al.* 1995) and cholestasis (Deitch *et al.* 1990) have been identified as risk factors for translocation of gut micro-organisms that are present in high concentration in the small intestine. Our study suggests that these conditions related to PN alone are unlikely to make an infant septicaemic. Over a period of 5 years, only five patients, i.e. one patient per year, suffered early septicaemia whilst being free from AGNB. This observation suggests the exclusion of PN as the only cause of developing positive blood cultures. An additional and abnormal condition of small intestinal overgrowth with AGNB has been shown in the present study to be required for the systemic immunosuppression that allows translocating bacteria to spill over into the blood.

Gut overgrowth with AGNB is associated with an abnormally high gut endotoxin pool (van Saene *et al.* 1992), unlikely to be controlled by the gut-associated lymphoid tissue impaired by long-term PN. AGNB overgrowth alone has been shown to cause liver dysfunction (Marshall *et al.* 1987; Billiar *et al.* 1988), and systemic immunity is impaired in proportion to the degree of that liver dysfunction (Alverdy & Burke, 1992).

When translocation promoted by PN is combined with gut endotoxin-induced systemic immunosuppression, micro-organisms present in the gut, particularly in high concentrations, may traverse through the impaired gut-associated lymphoid tissue, including the liver, into the circulation. While systemic immunodysfunction remains moderate, the patient develops Gram-positive septicaemias, mainly CNS (Y Okada, NJ Klein, HKF van Saene and A Pierro, unpublished results). Recently, it has been reported in adults that low-level pathogens, including CNS, are able to translocate from the gut to the mesenteric lymph nodes (Ferri *et al.* 1997), and recent work in infants receiving long-term PN has shown that the bactericidal activity of the blood is initially impaired for CNS, whilst PPM are still successfully eliminated (Y Okada, NJ Klein, HKF van Saene and A Pierro, unpublished results). Only at a later stage, when liver dysfunction and systemic immunosuppression are more severe, do AGNB (apart from their systemic immunosuppressive role) survive translocation and host defences to make blood cultures positive.

What can be done to bolster the local and systemic defences, impaired by PN and gut-derived endotoxin, to control septic morbidity?

Refeeding is the most important single factor in restoring both lines of defence. There is good evidence that enteral feeding is associated with better gut function, including return of peristalsis (Hadfield *et al.* 1995) and gall bladder contractility (Jawaheer *et al.* 1995). Return of gut motility is required to clear overgrowth of AGNB (Vantrappen *et al.* 1977). There appears to be good evidence that enteral nutrition significantly reduces the incidence of infection (Minard & Kudsk, 1994) following the reversal of gut leakage (Mainous *et al.* 1991) and of defective macrophage function (Shou *et al.* 1994; Y Okada, NJ Klein, HFK van Saene and A Pierro, unpublished results).

Until the patient is able to tolerate enteral feeds, protection should be directed towards both the gut and its flora. Glutamine, an essential nutrient for the small intestinal enterocyte, reduces gut permeability and atrophy (van der Hulst *et al.* 1996), epidermal growth factor has a trophic effect on the small intestine (Fürst & Rombeau, 1996), and cholecystokinin has been shown to reduce cholestasis (Rintala *et al.* 1995). Our finding that small intestinal overgrowth with AGNB is usually associated with septic morbidity suggests that AGNB carriers may benefit from selective decontamination of the digestive tract (Baxby *et al.* 1996). Oral polymyxin and tobramycin have been shown to be effective in eradicating AGNB overgrowth and in neutralizing gut endotoxin (van Saene JJM *et al.* 1996) and may reverse the PN-related immunosuppression (Houdijk *et al.* 1997; Yao *et al.* 1997).

The answer is unlikely to be one single manoeuvre, but a combination of interventions (Deitch, 1990).

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