

ORIGINAL COMMUNICATION

Gut overgrowth with abnormal flora: the missing link in parenteral nutrition-related sepsis in surgical neonates

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Background and aims: Patients receiving parenteral nutrition are at risk of septicaemia. Intestinal dysmotility and impaired gut immunity due to parenteral nutrition promote bacterial overgrowth. Gut overgrowth with aerobic Gram-negative bacilli (AGNB) impairs systemic immunity. The aim of this study was to determine the potential role of gut overgrowth with AGNB in the pathogenesis of septicaemia related to parenteral nutrition.

Methods: A prospective 5y study of surgical infants less than 6 months of age was undertaken. Surveillance samples of the oropharynx and gut were obtained at the start of parenteral nutrition and thereafter twice weekly, to detect AGNB carriage. Blood cultures were taken on clinical indication only.

Results: Two-hundred and eight infants received parenteral nutrition for 6271 days (median 13 days, range 1–512 days). The incidence of AGNB carriage was 42%, whilst the septicaemia rate was 15%. Eighty-four percent of septicaemic infants carried AGNB, whilst 16% never carried AGNB ($P < 0.005$). Carriage developed significantly earlier than septicaemia.

Conclusions: The incidence of septicaemia was significantly greater in the subset of abnormal carriers. Although gut overgrowth with abnormal flora reflects illness severity, the fact that it preceded septicaemia implicates AGNB overgrowth, *per se*, as a contributory factor in the development of septicaemia related to parenteral nutrition. Prevention is unlikely to be successful if it ignores the abnormal flora.

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Introduction

Patients receiving parenteral nutrition are at risk of septic morbidity following immunosuppression induced by parenteral nutrition. Previous work has shown that parenteral nutrition causes atrophy of the small intestinal gut-associated lymphoid tissue (GALT) (Li *et al*, 1995), lowers small intestinal immunoglobulin A (IgA) levels (Kudsk *et al*,

1996), and impairs secretory IgA-mediated mucosal immunity (Kudsk *et al*, 1996). Apart from its detrimental effect on mucosal defences, parenteral nutrition impairs gut motility (Vantrappen *et al*, 1977), which is frequently reduced by the underlying disease, and it also impairs biliary flow (Jawaheer *et al*, 1995). The combination promotes small intestinal bacterial overgrowth. Gut overgrowth, particularly with aerobic Gram-negative bacilli (AGNB) has been identified as a risk factor for impaired systemic immunity (Marshall *et al*, 1987). Endotoxin released by these bacteria is thought to induce a depression of systemic immunity via liver dysfunction (Billiar *et al*, 1988). Suppression of both mucosal and systemic immunity is required for the development of sepsis and septicaemia following endotoxin absorption and/or bacterial translocation (Alverdy & Burke, 1992).

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A prospective 5 y study (1 February 1992–31 January 1997) in a large homogeneous population of surgical infants less than 6 months of age was undertaken to determine the importance of gut overgrowth with AGNB in the pathogenesis of septic complications related to parenteral nutrition.

Patients and methods

Patients

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

Of the 208 patients 187 received parenteral nutrition through a central venous line, whilst a peripheral line was used in 21 infants. Central venous lines were inserted by percutaneous venepuncture or by surgical cutdown and the catheter was advanced to a central venous position. All central venous lines were made of silicone. The central venous lines inserted via cutdown were tunnelled under the skin leaving the attached Dacron cuff in the subcutaneous tissue to reduce the risk of dislodgement. The same protocol for central venous line care was applied to all patients. Every 4 days, the dressing on the exit site of the intravenous line was removed, the skin was cleansed with an antiseptic solution, and a new sterile dressing applied. A Pall ELD 96 filter (0.22 μm ; Pall Biomedical, Portsmouth, UK) was placed in-line to remove particulate matter, such as calcium salts or micro-organisms, that may have contaminated the solution. All intravenous tubing and the containers of infusate were changed daily. Chlorhexidine 0.5% in 70% alcohol solution was applied to all joints in the circuit to prevent entry of micro-organisms.

Parenteral nutrition was prepared under strict aseptic conditions which were regularly checked for sterility. Intravenous fluid intake varied from 100 to 180 ml/kg/day according to patient requirement. A standardized protocol for intravenous nutrition was used in all patients. The intravenous diet included amino acids, lipids, carbohydrate, electrolytes, vitamins and trace elements. Intravenous energy intake was progressively increased over a 4 day period. Intravenous amino acid intake was increased from 1.25 g/kg/day on the first day of parenteral nutrition to a maximum of 2.5 g/kg/day on day 2. Vamin 9[®] solution (Pharmacia & Upjohn, Milton Keynes, Bucks, UK) or Primene[®] 10% (Clintec Nutrition Ltd, Slough, UK) were the sources of intravenous amino acids. Lipid was increased from 1 g/kg/day on the first day of parenteral nutrition to a

maximum of 4 g/kg/day by day 4. Intralipid[®] 20% (Pharmacia & Upjohn, Milton Keynes, Bucks, UK) and Lipofundin[®] MCT/LCT 20% (B Braun Medical Ltd, Aylesbury, UK) were the sources of intravenous lipid. A minimum of 10 g/kg/day and a maximum of 15 g/kg/day of intravenous carbohydrate was prescribed. Non-protein intravenous energy intake, after achieving stabilization, varied from 75 to 90 kcal/kg/day according to weight gain and individual needs. Infants initially received all nutrients intravenously. Enteral feeds were introduced gradually when the gut motility recovered (ie substantial reduction in gastric aspirate and/or passage of faeces). The observational period ended once parenteral nutrition was discontinued.

Antibiotic policy

Prophylaxis. Cefotaxime and metronidazole were given for clean and clean-contaminated procedures (such as fundoplication and repair of oesophageal atresia). Three doses were given intravenously, the first at induction of anaesthesia to be followed by two more doses 8 h apart. For contaminated or dirty procedures (such as gastroschisis and necrotising enterocolitis) intravenous gentamicin was added and the antibiotics given for at least 3 days. None of the patients received selective decontamination of the digestive tract.

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 isolated. 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 day course of treatment.

Endpoints

In this homogeneous population three endpoints were evaluated:

- (i) the incidence of abnormal gut carriage, sepsis and septicaemia;
- (ii) sepsis and septicaemia rates in infants who developed AGNB overgrowth compared with infants who remained free of AGNB; and
- (iii) the temporal relationship between abnormal gut carriage, sepsis and positive blood cultures, in infants developing septicaemia.

Microbiological methods

Surveillance samples comprising throat and rectal swabs were taken at the start of parenteral nutrition, and twice weekly thereafter to detect the carrier state. They were processed using a semi-quantitative method, ie, the four

quadrant technique combined with enrichment broth. Both swabs were inoculated onto a solid medium, MacConkey agar, and also placed into 5 ml of brain–heart infusion broth. The target micro-organisms were AGNB. 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 of blood for culture were taken from the central venous line and/or from a peripheral vein when sepsis was suspected. Blood was processed using BACTEC 9240 (Becton and Dickinson, Diagnostic Instrument Systems, Sparks, MD, USA). Identification was performed using the ATB system, and sensitivity patterns were determined using the break-point method.

Definitions

(1) The abnormal carrier state or carriage existed when the same AGNB strain, in any concentration, was isolated from at least two consecutive surveillance samples over a period of at least one week. Whilst rectal carriage of *Escherichia coli* was considered as normal, persistence of *E. coli* in the throat constituted an abnormal carrier state (Sarginson *et al*, 2001).

(2) Sepsis was defined as the clinical signs of generalised inflammation caused by micro-organisms and/or their products. At least three of the following signs had to be present: pyrexia, tachycardia, hypotension, poor peripheral perfusion, lethargy and respiratory distress (Saez-Llorens & McCracken, 1993).

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

(4) Overgrowth was defined as a concentration of AGNB in the throat and/or rectal swabs of $\geq 10^5$ bacteria/ml, ie high or very high growth density (Husebye, 1995).

Statistical analysis

Data were not normally distributed and were therefore expressed as medians. The Mann–Whitney and the Wilcoxon matched-pairs signed-rank non-parametric tests and Fisher's exact test were used for tests of the significance of differences between the abnormal and normal flora groups. A probability of less than 0.05 was considered significant.

Results

Patients

The total population of 208 patients comprised 123 male and 85 female infants. Their median gestational age was 37 weeks (range 25–45 weeks), median birth weight was 2.6 kg (range

0.73–4.28 kg), median age at the start of parenteral nutrition was 5 days (range 1–176 days) and median duration of parenteral nutrition was 13 days (range 2–512 days). Parenteral nutrition was administered for a total of 6271 patient days (a mean of 1254 parenteral nutrition days per year).

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

Out of 208 infants abnormal carriage with AGNB occurred in 88 patients (42%). Overgrowth was detected in 68 of these (77%). A total of 198 blood cultures were taken from 52 patients (25%) with clinical evidence of sepsis, but only 79 were positive in 32 patients (15%).

Table 1 shows the AGNB carried by the 88 infants who developed the abnormal carrier state, and the AGNB isolated from the blood cultures of seven patients found to be septicaemic with those target micro-organisms.

Abnormal carriage predisposed to blood stream infection with coagulase-negative staphylococci (CNS) in 16 neonates of whom three had septicaemia with dual micro-organisms, CNS and enterococci. Four abnormal carriers developed blood cultures positive for *S. pneumoniae* (2), *S. aureus* (1) and *Candida albicans* (1). The remaining five neonates who developed septicaemia with CNS (4) and *Candida albicans* (1) were AGNB free.

Comparison between abnormal and normal flora carriers

When the abnormal and normal flora groups were compared there were no significant differences in gender, birth weight, gestational age, age at starting parenteral nutrition or usage of central venous catheters (Table 2). The infants who became carriers of AGNB received a median of 25 days of parenteral nutrition (1–512), whilst the patients who remained free of these abnormal bacteria received only 9

Table 1 Aerobic Gram-negative bacilli (AGNB) isolated from 88 abnormal carriers (42%) and from seven septicaemic children (3%)

AGNB	Carriage ^a	Septicaemia ^b
<i>E. coli</i> ^c	9	4
<i>Klebsiella</i> spp.	22	3
<i>Proteus</i> spp.	3	
<i>Morganella</i> spp.	1	
<i>Enterobacter</i> spp.	30	1
<i>Citrobacter</i> spp.	7	1
<i>Serratia</i> spp.	2	
<i>Acinetobacter</i> spp.	5	
<i>P. aeruginosa</i>	35	1

^aNine infants carried more than one AGNB.

^bTwo infants suffered more than one episode of AGNB septicaemia.

^c*Escherichia coli* isolated from the oropharynx in a concentration of $\geq 3+$ or $\geq 10^5$ colony forming units/ml reflected an abnormal carrier state.

Table 2 Patient demographics in both normal and abnormal carriers

	Abnormal flora (n = 88)	Normal flora (n = 120)	P
Male/female	51/37	72/48	
Birth weight (kg)	2.5 (0.8–4.28)	2.68 (1.73–4.1)	0.4
Gestational age (weeks)	37 (25–42)	37 (25–45)	0.5
Postnatal age at start of PN ^a (days)	6 (1–176)	5 (1–156)	0.76
Central venous catheters	85/88 (96%)	102/120 (85%)	0.14

^aPN denotes parenteral nutrition.

days of parenteral nutrition (1–58; $P < 0.0001$). The total number of days at risk was 4895 in the abnormal flora group and 1376 in the group who carried normal flora. Both the incidence and rate of sepsis and of septicaemia were significantly higher in the group of infants with abnormal flora (Table 3).

Time relationship between onset of carriage, sepsis and septicaemia

Of the 32 infants with positive blood cultures, 27 (84%) belonged to the group with abnormal carriage. Only five patients (16%) developed septicaemia whilst remaining free of AGNB ($P < 0.005$). In this subset of 32 infants, abnormal carriage with AGNB developed at a median of 14 days (range 1–113 days), signs of clinical sepsis at 19 days (1–104), and bacteriologically proven septicaemia at 23 days (1–118). The intervals between the onset of carriage, sepsis and septicaemia were significantly different; the P -value for the differences between onset of carriage and sepsis and between onset of carriage and septicaemia were < 0.05 and < 0.0003 , respectively. Unlike the 27 abnormal carriers who developed 'late' septicaemia, at a median of 23 days, the five

AGNB-free infants developed positive blood cultures 'early', at a median of 7 days.

Discussion

Three findings emerged from this study:

- (i) the incidence of AGNB carriage was 42%, whilst the sepsis and septicaemia rates were 25 and 15%, respectively. However, only 3% of the patients (7/208) had a septicaemia due to AGNB;
- (ii) sepsis and septicaemia rates were significantly higher in the subset of abnormal carriers, 84% of infants who had septicaemia belonged to the subset of AGNB carriers;
- (iii) carriage of AGNB developed significantly 'earlier' than sepsis and septicaemia.

Recently, scoring systems including the simplified acute physiology score (SAPS), the acute physiology and chronic health evaluation score (APACHE II), and paediatric risk and mortality score (PRISM) have become routine methods for estimating the disease severity in ill patients. Emergence of resistance amongst AGNB has prompted investigators to establish a link between the carriage of these micro-organisms and illness severity as measured by such scoring systems (Garrouste-Orgeas *et al*, 1996; Lortholary *et al*, 1995; Toltzis *et al*, 1997). A study in adult ICU patients reported that one third of patients with a mean SAPS score of 13 ± 4.6 carried *Acinetobacter baumannii* and *Klebsiella pneumoniae* in the oropharynx and/or gut (Garrouste-Orgeas *et al*, 1996). In another study, high SAPS (12.3 ± 5.3) and APACHE II (20.6 ± 9.1) scores were identified as independent risk factors for rectal carriage of multi-resistant *A. baumannii* (Lortholary *et al*, 1995). A PRISM score of 6.45 ± 4.85 predicted carriage of ceftazidime-resistant micro-organisms in a paediatric ICU (Toltzis *et al*, 1997). Additionally, the second study showed that patients who developed an infection with the multi-resistant *A. baumannii* were more ill than those who only became carriers (APACHE II 26.7 ± 9.1 vs 17.7 ± 9.2). In keeping with these observations, our finding that 84% of infants with a positive blood culture belonged to the subset of patients who carried abnormal flora suggests that the AGNB carrier state is a marker of severity of underlying disease, and hence of infection risk. Indeed, this observation is not new. As early as 1969, Johanson showed that the rate of oropharyngeal carriage of AGNB is proportionate to the severity of illness (Johanson *et al*, 1969). In critically ill neonates Harris found that systemic infection occurred only in these infants who initially and subsequently carried abnormal flora (Harris *et al*, 1976). In infants requiring intensive care Sprunt demonstrated an infection rate of only 0.5% with normal flora but 15% with abnormal carriage (Sprunt, 1985). These researchers believed surveillance cultures useful in identifying infants at risk.

Over 40% of our infants were so ill that they were unable to clear the AGNB acquired on the neonatal surgical unit,

Table 3 Sepsis and septicaemia during parenteral nutrition

	Abnormal flora (n = 88)	Normal flora (n = 120)	P
Total days of risk ^a	4895	1376	
Sepsis			
patients	34 (39%)	18 (15%)	0.005
episodes	169	29	
rate of septic episodes (episodes/1000 days) ^b	35	21	0.025
Septicaemia			
patients	27 (31%)	5 (4%)	0.005
episodes	71	8	
rate of septicaemic episodes (episodes/1000 days) ^b	14	6	0.045

^aDays at risk of sepsis and septicaemia = number of days on parenteral nutrition.

^bRate of septic or septicaemic episodes = number of episodes divided by the number of days at risk.

whilst the less ill 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 (Larson, 1981). Some may argue that the duration of exposure to the unit micro-organisms determines acquisition and subsequent carriage, but healthy carers infrequently develop gut carriage of the unit's AGNB despite exposure to them for decades (Chambers *et al*, 1987). Moreover, in almost all infants who acquired AGNB the carrier state occurred 'early' (median 14 days) denying duration of stay on the unit, *per se*, as a risk factor (Garrouste-Orgeas *et al*, 1996).

Our hypothesis is that the sicker the infant, the longer it takes to re-establish normal gut function. Lack of gut peristalsis in an abnormal carrier leads to overgrowth. The subset of patients with AGNB received parenteral nutrition for a median of 25 days, significantly longer than the median of 9 days for non-carriers. The need for and duration of parenteral nutrition is a reflection of a poorer clinical response and suggests that non-use of the gut is an important factor in septic morbidity related to parenteral nutrition. GALT atrophy (Li *et al*, 1995), impairment of secretory IgA mediated mucosal immunity (Kudsk *et al*, 1996) and cholestasis (Jawaheer *et al*, 1995) may be due to long term parenteral nutrition alone. Impaired mucosal defences and cholestasis predispose to the translocation of micro-organisms that are present in high concentration in the small intestine (Hadfield *et al*, 1995). Nonetheless, our study suggests that these conditions related to parenteral nutrition, on their own, are unlikely to result in septicaemia. Over a period of 5 y, only five patients, or one patient per year, suffered septicaemia whilst being free from AGNB. Gut overgrowth with AGNB is associated with an abnormally high gut endotoxin pool (van Saene *et al*, 1992), unlikely to be controlled by the GALT impaired by long term parenteral nutrition. 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). We suggest that it is small intestinal overgrowth with AGNB that is required for systemic immunosuppression (Marshall *et al*, 1987) that then allows viable translocating bacteria to 'spill over' into the blood.

Thus, when translocation promoted by parenteral nutrition is combined with gut endotoxin-induced systemic immunosuppression (Meyer *et al*, 1988), micro-organisms present in the gut, particularly in high concentrations, may traverse through the impaired GALT, including the liver, into the circulation. Recently, it has been reported 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 parenteral nutrition has shown that the bactericidal activity of the blood is initially impaired for CNS, whilst PPM including AGNB are still successfully eliminated (Okada *et al*, 2000). While systemic immunodysfunction remains moderate the patient

develops Gram-positive septicaemias, mainly CNS, and it is only when liver dysfunction and systemic immunosuppression have become more pronounced, that AGNB—apart from their systemic immunosuppressive role—can survive translocation and host defences to make blood cultures positive. The potential pathogens including AGNB caused septicaemia significantly later than CNS, at a time when liver function was also significantly more impaired (Donnell *et al*, 2002). The fact that AGNB carriage precedes sepsis and septicaemia increases the evidence that gut overgrowth with abnormal AGNB contributes to septic morbidity.

The obvious question is what can be done to bolster the local and systemic defences impaired by parenteral nutrition and gut-derived endotoxin respectively to control septic morbidity? Feeding 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; Okada *et al*, 1998). Until the patient is able to tolerate enteral feeds, protection can be directed towards both gut and flora. Glutamine which is an essential nutrient for the small intestinal enterocyte has several benefits including reduction of gut permeability and atrophy (van der Hulst *et al*, 1996). More recently, epidermal growth factor has been shown to have a trophic effect on the small intestine (Fürst & Rombeau, 1996). Cholecystokinin may reverse cholestasis (Rintala *et al*, 1995), but experience suggests it is only effective once enteral feeding is significant. Our findings suggest that patients who receive parenteral nutrition and who become AGNB carriers might benefit from selective decontamination of the digestive tract (Baxby *et al*, 1996; Nathens & Marshall, 1999). Oral polymyxin and tobramycin have been shown to be effective in eradicating AGNB overgrowth and in neutralizing gut endotoxin (van Saene *et al*, 1996) and may reverse the immunosuppression related to parenteral nutrition (Houdijk *et al*, 1997; Yao *et al*, 1997). The answer to the question is unlikely to be one single manoeuvre but a combination of interventions (Deitch, 1990).

Finally, the criterion of AGNB carriage increases the homogeneity of a study population and we suggest that it should therefore be a prerequisite for the enrolment of infants into prospective trials aimed at reducing septicaemia related to parenteral nutrition. Patients with normal flora who do not become abnormal carriers are at low risk of infection.

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