Infections and Antibiotic Therapy in Surgical Newborn Infants

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Abstract

Colonisation of the gastro-intestinal tract of newborn infants starts immediately after birth and occurs within a few days. Initially, the type of delivery (passage through the birth canal versus caesarean section) and the type of diet (breast versus formula feeding) might affect the colonisation pattern. Nearly all full-term, formula-fed, vaginally delivered infants were colonised with anaerobic bacteria within 4–6 days. 61% harboured *Bacteroides fragilis*. In contrast, anaerobes were present in 59% and *B. fragilis* in only 9% of infants delivered by caesarean section, suggesting that significant contamination occurred during passage through the birth canal. Both prematurity and breast feeding reduced the likelihood of isolating anaerobic species. Enterococci were isolated from all neonates, *Escherichia coli* from 82.6%, anaerobic cocci from 52.2% and both streptococci and staphylococci from 34.8%. Colonisation of the small bowel occurs perorally. In newborn infants with congenital small bowel obstruction, a faecal-type flora is found immediately proximal to the site of obstruction, and the distal bowel remains sterile.

Keywords

Infection • Newborns • Sepsis • Antibiotics • Selective decontamination of the digestive tract (SDD)

In memory of Shankar, his kindness, dedication and superb professionalism.

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13.1 Pathogenesis of Infections: Gut Overgrowth

13.1.1 Introduction: Flora Development in the Neonate

Colonisation of the gastro-intestinal tract of newborn infants starts immediately after birth and occurs within a few days. Initially, the type of delivery (passage through the birth canal versus caesarean section) and the type of diet (breast versus formula feeding) might affect the colonisation pattern. Nearly all full-term, formula-fed, vaginally delivered infants were colonised with anaerobic bacteria within 4–6 days. 61% harboured *Bacteroides fragilis*. In contrast, anaerobes were present in 59% and *B. fragilis* in only 9% of infants delivered by caesarean section, suggesting that significant contamination occurred during passage through the birth canal. Both prematurity and breast feeding reduced the likelihood of isolating anaerobic species. Enterococci were isolated from all neonates, *Escherichia coli* from 82.6%, anaerobic cocci from 52.2% and both streptococci and staphylococci from 34.8% [1]. Colonisation of the small bowel occurs perorally. In newborn infants with congenital small bowel obstruction, a faecal-type flora is found immediately proximal to the site of obstruction, and the distal bowel remains sterile [2].

Other environmental factors also have a major role since differences exist between infants from different hospital wards. Critical illness predisposes surgical neonates to acquisition and subsequent carriage of abnormal aerobic Gram-negative bacilli (AGNB) and methicillin-resistant *Staphylococcus aureus* (MRSA). These abnormal bacteria are most often transmitted amongst neonates via the hands of health care workers (HCW) [3].

13.1.2 Definition

The fundamental pathophysiological event in the surgical neonate is gut overgrowth. Gut overgrowth can be conveniently defined as abnormal bacteria in abnormal concentrations at an abnormal site. More scientifically, gut overgrowth is defined as $\geq 10^5$ AGNB and/or MRSA per ml of digestive tract (small intestine) secretion [4].

13.1.3 Four Harmful Side-Effects

Gut overgrowth harms the surgical neonate in four main ways:

1. Immunosuppression—overgrowth of abnormal AGNB (and associated endotoxin) has been shown to impair systemic immunity due to generalised inflammation following absorption of AGNB and/or endotoxin [5];
2. Inflammation—overgrowth of abnormal AGNB and/or endotoxin has been shown to lead to cytokinaemia and inflammation of major organ systems [6];
3. Infection—there is a quantitative relationship between surveillance and diagnostic samples. As soon as there is overgrowth in surveillance samples the diagnostic samples become positive which is the first stage in the development of infection [7];
4. Resistance—the abnormal carrier state in overgrowth concentrations guarantees increased spontaneous mutation leading to polyclonality and antibiotic resistance [8].

Selective decontamination of the digestive tract (SDD) is a prophylactic measure using selected antimicrobials to control gut overgrowth thereby reducing the four harmful side effects of it. Immunosuppression was reverted to normality in patients who were successfully decontaminated [9]. Patients free from AGNB overgrowth were able to control generalised inflammation [10]. SDD has been shown to control severe infections of lower airways and blood, to reduce mortality without resistance emerging [11].

13.1.4 Risk Factors

1. Critical illness related carriage in overgrowth concentrations (CIRCO) is common on admission [12]
2. CIRCO often develops during treatment on ICU [13]
   Drugs including opiate analogues [14], H_2 antagonists [15, 16] and antibiotics [17] promote gut overgrowth of potential pathogens following the impairment of gut motility, the

increase in gastric pH of ≥4, and the suppression of the indigenous anaerobic flora required for colonisation resistance, respectively.

13.1.4.1 Diagnosis

The traditional microbiological approach of obtaining and culturing diagnostic samples such as tracheal aspirate, blood and urine can never detect gut overgrowth, as these samples only confirm the clinical diagnosis of infection. Surveillance samples of throat and gut are the only samples that allow the detection of overgrowth [18].

13.2 Prevention

13.2.1 Surgical Prophylaxis

All neonates undergoing operations classified as potentially contaminated, contaminated or 'dirty' were given 48 h of antibiotic prophylaxis in the form of cefotaxime and metronidazole [19]. Infants with suspected central venous line-related blood stream infections were prescribed teicoplanin and gentamicin initially, pending blood culture results [20]. The standards of hygiene recommended by the Centres of Disease Control (CDC) were used [21].

13.2.2 Early Enteral Feeding

A period of starvation ('nil by mouth') is common practice after gastro-intestinal surgery during which an intestinal anastomosis has been formed [22]. The stomach is decompressed with a nasogastric tube and parenteral nutrition is given, with oral feeding being introduced as gastric dysmotility resolves. The rationale of 'nil by mouth' is to prevent post-operative nausea and vomiting and to protect the anastomosis, allowing it time to heal before being stressed by food. It is, however, unclear whether deferral of enteral feeding is beneficial.

Contrary to widespread opinion, evidence from clinical studies directly comparing strategies of early feeding with 'nil by mouth' after elective gastro-intestinal surgery, suggests that initiating feeding early is advantageous. Eleven studies with 837 patients who met the inclusion criteria have been meta-analysed [22]. Early feeding reduced the risk of any type of infection (relative risk 0.72, 95% confidence interval 0.54–0.98, p = 0.036) and the mean length of stay in hospital (number of days reduced by 0.84, 0.36–1.33, p = 0.001). Risk reductions were also seen for anastomotic dehiscence (0.53, 0.26–1.08, p = 0.080), wound infection, pneumonia, intra-abdominal abscess, and mortality, but these failed to reach significance. The risk of vomiting was increased among patients fed early (1.27, 1.01–1.61, p = 0.046). There seems to be no clear advantage to keeping patients nil by mouth after elective gastro-intestinal surgery. Early feeding may be of benefit. The significantly reduced risk of infection following early feeding may be due to the control of overgrowth achieved in patients who received early enteral feeding.

13.2.3 Enteral Antimicrobials: SDD

Recently, four studies with 355 children who met the inclusion criteria for randomisation have been meta-analysed [23]. Pneumonia was diagnosed in 5 of 170 children (2.9%) for SDD and 16 of 165 patients (9.7%) for controls (odds ratio, 0.31; 95% confidence interval, 0.11–0.87; p = 0.027). There was no difference in overall mortality. The significant reduction in infectious morbidity is highly likely due to overgrowth control, and the sample size was too small to impact survival for a paediatric mortality varying between 5 and 10%. A recent French Consensus Conference recommends SDD as pneumonia prophylaxis in critically ill children [24].

13.3 Treatment

Shankar was the first to classify infections in surgical new born infants, using the carrier state [25]. Out of a total of 167 infants, 21 infants (15%) had 33 episodes of infection. The predominant infecting micro-organism was *Staphylococcus aureus* (n = 11), others were enterococci, coagulase negative staphylococcus, *Candida* spp., AGNB and

anaerobes. A total of 27 out of 33 infective episodes (82%) were caused by micro-organisms carried by the infants on admission (primary endogenous). Only six (18%) infections were caused by micro-organisms acquired in the unit: three secondary endogenous infections (micro-organisms not present in the admission flora, but acquired and carried later on during treatment on the unit) and three exogenous infections (not preceded by previous carriage). The micro-organisms causing infections were mostly low level pathogens such as coagulase-negative staphylococci, enterococci and anaerobes. 'Normal' potential pathogens included *S.aureus* and *Candida* spp. Only two infections were caused by 'abnormal' flora, and the responsible micro-organisms were *Klebsiella* and MRSA causing one secondary and one exogenous infection each. Bloodstream and wound infections were the two main infection types in the surgical newborn infants. Lower airway infections were not diagnosed, highly likely because none of them were mechanically ventilated.

The pathogenesis of practically all infections is endogenous in surgical new born infants [26–29]. The same pathogenesis applies to all types of micro-organisms whether they are low level or potential pathogens both normal and abnormal. If the surgical new born infant was admitted immediately after delivery the pathogens are low level and 'normal' such as *Escherichia coli*, *S.aureus* and *Candida* species. If the patient is admitted from another hospital, or has been treated on the surgical neonatal unit, the abnormal pathogens such as AGNB and MRSA may be carried by the new born infant apart from low level and normal pathogens.

13.4 Septicaemia

Septicaemia [11] is defined as sepsis (i.e. clinical picture caused by generalised inflammation due to micro-organisms and/or their toxic products) combined with a positive blood culture. Once the diagnosis of sepsis has been made and blood cultures taken, immediate antibiotic combination therapy should be started in order to provide an adequate spectrum of antimicrobial therapy. This is a combination of an aminoglycoside with cefotaxime. If an intra-abdominal focus is suspected, metronidazole and amphotericin B are added to this treatment. Initial empirical therapy is adjusted according to diagnostic culture results. The source of sepsis should be identified and eliminated as soon as possible. SDD using enteral polymyxin/tobramycin/amphotericin B should be commenced immediately to eradicate the internal source [11].

13.5 Wound Infection

Clinical signs of wound infection [11] are purulent discharge, redness, swelling, tenderness, and local warmth. The clinical diagnosis is microbiologically confirmed by isolating $\geq$3+ or $\geq 10^5$ micro-organisms from the purulent discharge in which $\geq$2+ leukocytes can be seen. Systemic antimicrobial therapy is seldom indicated, unless symptoms of sepsis occur. Local treatment, drainage, debridement, and removal of plastic devices are essential and generally sufficient. Following treatment, the wounds are rinsed twice daily with a disinfectant, 2% taurolin, for 3 days. Aquaform gel mixed with 2% polymyxin/tobramycin/amphotericin B and/or vancomycin can be applied to colonised/infected wounds [11].

13.6 Control of Antibiotic Resistance

The two potential pathogens that display antimicrobial resistance are AGNB producing extended spectrum beta-lactamase (ESBL) and MRSA.

Available parenteral antimicrobials with good activity against many resistant potential pathogens include the carbapenems and cefepime [30]. The enteral antimicrobials polymyxin/tobramycin need to be added to the parenteral antimicrobials, to eradicate gut overgrowth that promotes polyclonality and resistance [31]. Compounds directed against resistant Gram-positive bacteria include streptogramin combinations such as quinupristin/dalfopristin and linezolid. Similarly, enteral vancomycin needs to be added to the parenteral anti-

microbials active against Gram-positive bacteria to control gut overgrowth.

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