Diagnosis and pharmacological management of small intestinal bacterial overgrowth in children with intestinal failure

Le diagnostic et la prise en charge pharmacologique de la prolifération bactérienne dans l’intestin grêle chez des enfants une insuffisance intestinale


Le présent article donne un aperçu général des techniques diagnostiques possibles pour prendre en charge la prolifération bactérienne dans l’intestin grêle chez des patients pédiatriques ayant une insuffisance intestinale. Les auteurs s’intéressent aux outils diagnostiques courants et à comprendre leurs avantages et désavantages d’après une analyse bibliographique. Ils abordent la culture des aspirats de l’intestin grêle, les épreuves respiratoires non effectives et l’intérêt émergent pour l’empreinte génétique quantitative des bactéries. Une prise en charge convenable est essentielle pour prévenir la récurrence de prolifération bactérienne dans l’intestin grêle et ses complications connexes. La prophylaxie antibiotique fait partie des interventions thérapeutiques de la prolifération bactérienne chez les personnes ayant une insuffisance intestinale. Même si les essais thérapeutiques peuvent être difficiles à exécuter auprès d’une population si vulnérable, il faut tenir plus d’essais cliniques explorateurs sur le diagnostic précoce, assurer un contrôle plus efficace des récurrences et prévenir les complications connexes.

Key Words: Antibiotics; Hydrogen breath test; Intestinal failure; Pediatrics; Small bowel culture; Small intestinal bacterial overgrowth

Small intestinal (bowel) bacterial overgrowth (SIBO) is a clinical problem associated with abnormally high bacterial counts in the small intestine that are associated with clinical features. The presence of more than $10^5$ colony-forming units/mL of colonic-type (eg, Gram-negative strains, strict anaerobes and enterococci) counts from intestinal aspirate is considered to be diagnostic of bacterial overgrowth (1). This increase is believed to be the result of excess numbers of Gram-negative aerobes and, especially anaerobes, migrating from the lumen of the large bowel to the small bowel. Abnormal concentrations of bacteria in the small bowel often leads to malabsorption due to inadequate micellar formation and exacerbation of mucosal injury resulting in increased intestinal permeability (2).

Little has been published on SIBO in children with intestinal failure (IF). For the present review, a comprehensive literature search from 1966 to present was performed using PubMed, and from 1990 to present using ‘Google Scholar’. The following search phrases were used: “paediatric small bowel bacterial overgrowth”, “paediatric intestinal failure”, “intestinal bacterial overgrowth”, “diagnosis for bacterial overgrowth”, “hydrogen breath test for bacterial overgrowth” and “antibiotics for bacterial overgrowth”. The reference lists of the selected articles were also searched for additional references. An evaluation of 97 potential articles (and their abstracts) yielded only 52 full articles that met the inclusion criteria for the present review. Although articles focusing on pediatric care were favoured, papers reporting on adult subjects were also reviewed.

Children with IF are at high risk for developing SIBO because of impaired intestinal motility (due to stasis) and/or short bowel syndrome. Additional factors and predisposing conditions for SIBO in IF patients are outlined in Table 1. Children may appear malnourished, show symptoms of vomiting, diarrhea, abdominal distension and, in some cases, may develop metabolic acidosis from the accumulation of D-lactate, a byproduct of bacterial fermentation of carbohydrates (3). However, SIBO symptoms may be masked by manifestations of underlying gastrointestinal tract diseases in these patients. SIBO may also increase the risk of catheter-related sepsis and exacerbate IF-associated liver disease in this parenteral nutrition-dependent population (4-6) because 40% to 60% of cases involving infants on long-term parenteral nutrition develop liver disease secondary to IF (3). SIBO and its complications may delay or prevent weaning these patients off total parenteral nutrition, thus contributing to the progression of their liver disease (7).

Increased intestinal permeability and impaired host immune defence are believed to be the primary mechanisms promoting the translocation of bacteria and their byproducts across the epithelial tract (7). This, in turn, increases the risk of sepsis,
which is an important cause of morbidity and mortality in children with IF (8). Experimentally induced SIBO in rats leads to the appearance of gut bacteria in the mesenteric lymph nodes (MLNs) and visceral organs (9,10). Using DNA fingerprinting, Reddy et al (11) confirmed that Escherichia coli isolates from the MLNs of surgical patients were identical to the fecal samples obtained from within the lumen of resected colostomy specimens immediately after removal, thus confirming the gut origin of translocated bacteria.

The limitations of currently available tests and, consequently, the lack of an established criterion for accurate diagnosis of SIBO, continue to challenge physicians managing children with IF. Therefore, empirical antibiotics are often used to treat presumed SIBO in this population to reduce bacterial counts. To date, large, controlled, clinical trials aimed at establishing diagnostic techniques and ascertaining the efficacy of antibiotics against SIBO in pediatric IF patients have not been reported. The present article provides an overview of the current understanding in detection and proposes potential management strategies for SIBO in pediatric IF.

DIAGNOSTIC TOOLS FOR PEDIATRIC SIBO

Culture of direct aspirates of small bowel contents, and hydrogen breath testing (HBT) are techniques used in the diagnosis of SIBO. These techniques vary in sensitivity and specificity, and are susceptible to false-positive or false-negative interpretations. Although there is evidence supporting the utility of breath tests for SIBO diagnosis in adults and older children, they are not reliable in young IF patients due to inadequate breath collection and rapid gut transit, especially in patients with short bowel syndrome, thus giving rise to false-positive results (12). Serum levels of folate and vitamin B12 may be used in conjunction with the aforementioned techniques to support evidence of bacterial overgrowth. The rationale for this test is that exogenous sources such as diet are relied on for maintaining adequate folate levels; however, synthesis of folate by intestinal microflora also contributes to the host’s folate level (13). Therefore, serum folate levels may increase while vitamin B12 levels decrease as a result of SIBO; however, measuring vitamin B12 and folate levels were found to have a poor diagnostic yield (14).

Due to the difficulty in diagnosing SIBO, emerging molecular techniques in bacterial ‘fingerprinting’ such as the use of polymerase chain reaction denaturing gradient gel electrophoresis (PCR-DGGE) and bacterial 16S-ribosomal DNA sequencing may offer a more reliable way to define microbial populations in intestinal samples.

Direct aspiration and culture of small bowel contents

Upper small bowel aspirate is collected during gastrointestinal endoscopy or via nasojejunal tube insertion with a sterile catheter. The collection of upper small bowel aspirate is rarely performed in pediatric patients because it is time consuming and often requires the use of general anesthetic (15). For culture and isolation, the samples are diluted and plated on aerobic- and anaerobic-specific enriched agar plate media, with the actual numbers of bacteria determined by serial dilutions and counting CFUs (16). Box 1 describes the major concerns with direct aspirate culture: intubation is a high-risk invasive
dominant bacterial population in the sample is identified using specific detection of a wide range of bacterial species (28). The bacterial 16S ribosomal RNA primers enables rapid, comprehensive fingerprinting is one example of these advanced molecular techniques that can be used as novel strategies for the detection of microbes in the gastrointestinal tract of IF patients with suspected SIBO. It is a versatile technique that can be applied to different samples obtained noninvasively (eg, fecal mass) or through invasive methods (eg, small intestinal aspirate, MLN or tissue samples obtained from biopsy). PCR using universal bacterial 16S ribosomal RNA primers enables rapid, comprehensive qualitative and quantitative information, as well as specific detection of a wide range of bacterial species (28). The dominant bacterial population in the sample is identified using molecular 'fingerprinting' of bacterial populations

Molecular ‘fingerprinting’ of bacterial populations

Introduced in the early 1980s, DNA fingerprinting remains a developing area of interest for clinical use. PCR-DGGE fingerprinting is one example of these advanced molecular techniques that can be used as novel strategies for the detection of microbes in the gastrointestinal tract of IF patients with suspected SIBO. It is a versatile technique that can be applied to different samples obtained noninvasively (eg, fecal mass) or through invasive methods (eg, small intestinal aspirate, MLN or tissue samples obtained from biopsy). PCR using universal bacterial 16S ribosomal RNA primers enables rapid, comprehensive qualitative and quantitative information, as well as specific detection of a wide range of bacterial species (28). The dominant bacterial population in the sample is identified using densitometry. Knowing the bacterial profile of the identified SIBO patient can direct the use of target-specific antibiotic therapy. The PCR-DGGE method has been evaluated (11,28-30). PCR is regarded to be a superior technique over standard culture because it can detect unculturable or dead bacterial cells in situ (25).

Management

Bacterial overgrowth often recurs, and requires prolonged treatment including sporadic or periodic antibiotic therapy. During treatment of IF patients, the risks of long-term antibiotic therapy, intolerance, extent of systemic absorption and bacterial resistance must also be considered (8). Proton pump inhibitors, H₂-receptor antagonists and antidiarrheals should be used with caution because decreased gastric acidity and motility may promote SIBO. Effective medical management and the correction of nutritional deficiencies reduce severity, and could prevent recurrent bacterial overgrowth. The bacterial species involved in inducing SIBO are diverse; preference is given to antibiotics effective against Gram-negative and anaerobic bacteria. Table 2 lists the antibiotics commonly used for treating SIBO described in the literature including controlled clinical trials, comparison studies and clinical reviews (8,31-41). At our institution, empirical treatment for moderate-risk patients (defined as those with no radiological or clinical evidence of dysmotility) comprises a seven-day treatment of rotating oral gentamicin and metronidazole, followed by no antibiotics for seven days and then restarting the cycle again (Figure 1A). Antibiotic cycling for high-risk patients (defined as radiological evidence of dysmotility, such as dilated bowel and/or clinical evidence of dysmotility such as gastrochosis) is comprised of cycling oral gentamicin and metronidazole for seven days each (Figure 1B). If high-risk patients experience recurrent sepsis, line infection or worsening cholestasis, antibiotic cycling of oral gentamicin and metronidazole followed by amoxicillin-clavulanic acid is recommended for seven days each (Figure 1C). In cases for which a duodenal aspiration is possible, a tailored antibiotic regimen according to sensitivity is considered. The efficacy of the three antibiotic cycling regimens has yet to be clinically validated and is, therefore, offered herein as an expert opinion only. Gentamicin is an aminoglycoside associated with very poor enteral absorption and minimal side effects, and is administered to pediatric IF patients harbouring an overgrowth of

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
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<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>2–10 mg/kg/dose bid</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>10 mg/kg/dose bid</td>
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<tr>
<td>Broad-spectrum antibiotics</td>
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<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>15 mg/kg/dose bid</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>10–15 mg/kg/dose bid</td>
</tr>
<tr>
<td>*Tetracycline</td>
<td>10–15 mg/kg/dose tid</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
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</tr>
<tr>
<td>Ciprofloxacin</td>
<td>10–20 mg/kg/dose bid</td>
</tr>
<tr>
<td>Aminoglycoside antibiotics</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5 mg/kg/dose bid</td>
</tr>
<tr>
<td>Neomycin</td>
<td>2.5 mg/kg/dose qid</td>
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*Recommended for children older than eight years of age. bid Twice per day; qid Four times per day; tid Three times per day. Data from reference 52

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Gram-negative organisms (12,42). Bartlett et al (43) conducted a randomized, double-blind, placebo-controlled clinical trial of oral gentamicin (10 mg/kg body weight/day for five days) in 45 children with persistent diarrhea (placebo n=47). A significant difference between treatment groups was not identified and serum trough gentamicin levels were not measurable (43). We commonly prescribe an oral dose of 10 mg/kg/day and believe this is effective and safe. In our clinical practice, serum trough gentamicin levels have always been either undetectable or less than the therapeutic range in routine monitoring. In animal models (44), gentamicin was found to improve small intestinal motility and transit rate in rats with SIBO. The study also reported that oral treatment with gentamicin lowered serum alanine aminotransferase, aspartate aminotransferase and tumour necrosis factor-alpha levels, indicating a reduction in the severity of nonalcoholic steatohepatitis in rats. Nitromidazoles are active against anaerobic bacteria, with limited activity against aerobes (45). Human and animal models (46) demonstrated the prevention of and protection against hepatic injury following metronidazole treatment for SIBO. Boukhnik et al (47) reported that amoxicillin-clavulanic acid is a suitable candidate for treating SIBO. Amoxicillin-clavulanic acid was effective against more than 90% of bacterial strains, thus supporting its use as first-line therapy (47). In a randomized crossover study, Attar et al (31) compared the efficacy of antibiotics (norfloxacin, 800 mg/day; amoxicillin-clavulanic acid, 1500 mg/day) and probiotic (Saccharomyces boulardii 1500 mg/day) in 10 adults with bacterial overgrowth-related diarrhea. Each patient underwent five seven-day treatment periods; amoxicillin-clavulanic acid and norfloxacin reduced the number of stools and improved HBT results. Antibiotics for SIBO management are summarized in Table 2. Most of these antibiotic studies were performed in adults; unfortunately, there are very few published interventional studies that assessed the effectiveness of prophylaxis and therapy in pediatric SIBO patients with IF. Probiotic use for SIBO in children with IF has been reported; however, the safety and efficacy of this treatment in this particular population needs further study, especially for the risk of probiotic bacteremia and catheter-related sepsis (8,48).

CONCLUSION

With substantial improvements in the surgical and medical approaches to the management of pediatric gastrointestinal pathologies, the frequency of children diagnosed with IF is increasing. Reduced antegrade peristalsis combined with impaired mucosal immunity creates an optimal environment for bacterial colonization and subsequent overgrowth (49). Bacterial translocation is a potential complication of SIBO; therefore, early diagnosis and management, and prevention of recurrent SIBO is extremely important. Although many diagnostic techniques have been introduced over the years, each test has limitations in identifying patients with SIBO. Establishing a gold standard diagnostic test for SIBO in children requires further investigation. The application of emerging molecular techniques in profiling bacterial populations in the gastrointestinal tract is promising in the study of SIBO. Monitoring and managing SIBO in IF patients is crucial and challenging. For cases in which a firm diagnosis cannot be made, but clinical symptoms favour SIBO, empirical antibiotic use may be a more cautious approach to prevent delay of treatment and to prevent increases in symptom severity. The efficacy of antibiotic cycling in SIBO must be clinically investigated in the pediatric IF population. Close monitoring and early detection of infection, and aggressive prevention of bacterial overgrowth, will likely improve prognosis.

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