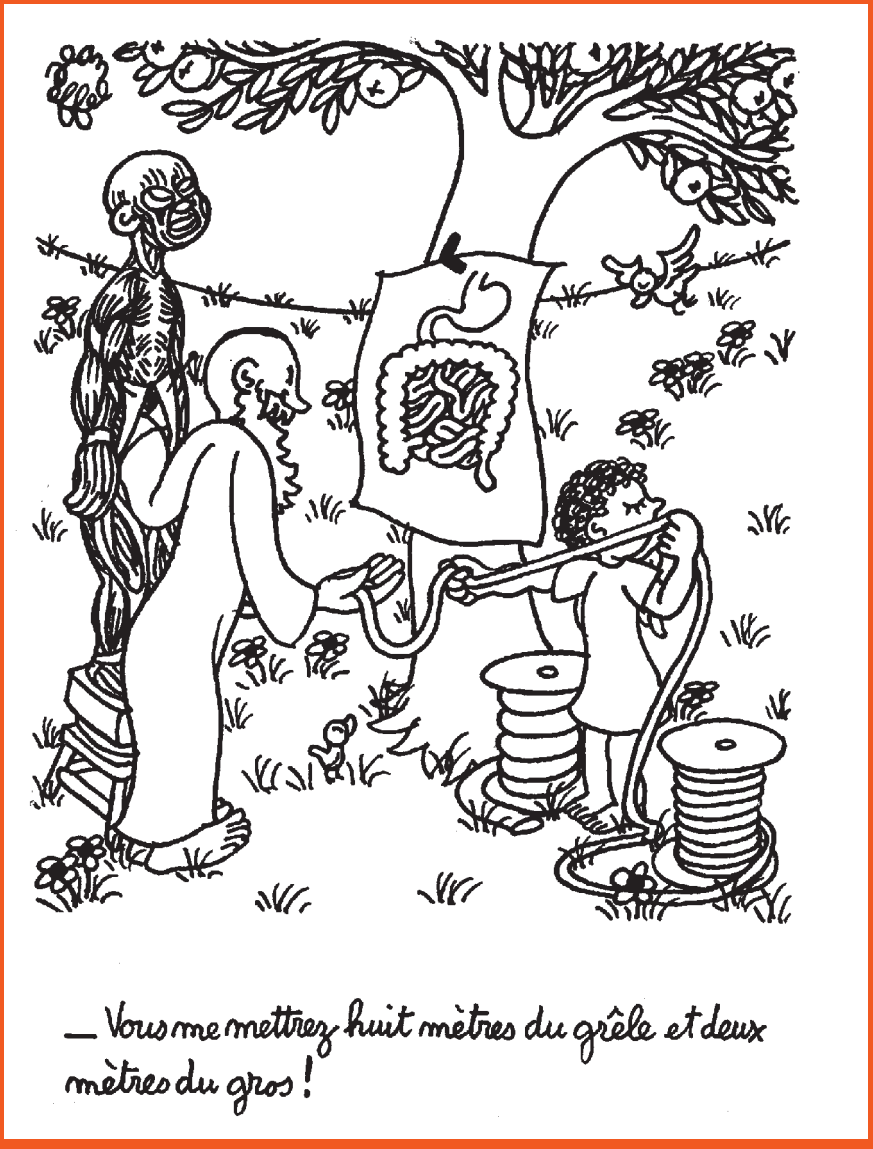
Short small bowel in children




# Short small bowel in children

## Complications and treatment strategies

René Severijnen

René Severijnen

# Short small bowel in children

## Complications and treatment strategies

Financial support for the publication of this thesis was received from:
Nutricia Nederland B.V. and Baxter B.V. Utrecht.

ISBN: 90-808755-1-1
Lay-out: B-Point, ‘s-Hertogenbosch
Printed by: FEBOdruk, Enschede

# Short small bowel in children

## Complications and treatment strategies

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Katholieke Universiteit Nijmegen,
op gezag van de Rector Magnificus Prof. dr. C.W.P.M. Blom,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op woensdag 16 juni 2004
des namiddags om 3.30 uur precies

door

**René Stanislaus Volkwin Maria Severijnen**

geboren op 13 november 1942
te Boekel (Noord-Brabant)

| | |
|---|---|
| PROMOTOR | Prof. dr. J.B.M.J. Jansen |
| CO-PROMOTORES | Dr. C.M.R. Weemaes<br>Dr. G.P.A. Bongaerts |
| MANUSCRIPTCOMMISSIE | Prof. dr. Y.A. Hekster<br>Prof. dr. H.G. Brunner<br>Prof. dr. H.A. Heij, Universiteit van Amsterdam |

Dedicated to:

all the children whom I have accompanied,
or might still accompany,
for some time on their road of life
and to the parents, guardians and grandparents
who entrusted their children to my care.

Professeur Émile Forgue
Au seuil de la chirurgie
Librairie Octave Doin Paris 1927

En chirurgie, comme à la guerre, les qualités de caractère, de décision prompte et judicieuse sont d'importance majeure; ainsi que l'écrivait jadis Bretonneau à Trousseau, "la pièce la plus importante d'un homme, c'est son caractère". Mais, cette force morale, cette fermeté et cette égalité de l'âme peuvent aussi se developer par l'expérience, par l'âge, par la culture volontaire; et, dans son éloge de Nélaton, Gyon définissait, avec justesse, le vrai sang-froid chirurgical, "cette force d'esprit que donnent la prévoyance et le savoir".

In surgery, as in war, qualities of character, of prompt and judicious decision are of extreme importance. Bretonneau at Trousseau Hospital once wrote: "the most important part of a man is his character". This moral force, this firmness and equality of the soul can, however, also be developed by experience, age and self-acquired culture. In his praise of Nélaton, Gyon defined, with accuracy, the real surgical sangfroid: "this moral strength obtained by foresight and knowledge".

In de chirurgie zijn, zoals in de oorlog, karakterkwaliteiten met een directe en oordeelkundige beslissing van levensbelang. Zoals Bretonneau uit het Trousseau ziekenhuis destijds schreef, "het belangrijkste deel van de mens is zijn karakter". Maar deze morele kracht, deze vastberadenheid en deze zielsgelijkheid kunnen ook ontwikkeld worden door ervaring, leeftijd en zelfverworven cultuur. In zijn lofrede op Nélaton, definieerde Gyon zuiver de echte chirurgische koelbloedigheid, "deze geestkracht die voortkomt uit een vooruitziende blik en kennis".

**CONTENTS**

# 1

# Introduction and aim of the thesis

## INTRODUCTION

Short small bowel and short bowel syndrome are terms that are used to describe the same disease process. In this thesis the term "short small bowel" has been chosen since the problems start with the loss of a considerable part of the small intestine. In some children there are sometimes relatively simple remedies to treat the consequences of the intestinal loss. The more commonly used term "short bowel syndrome" describes what happens after the bowel resection.

"Short bowel syndrome is a term used for symptoms and pathophysiologic disorders brought about by the removal of a large portion of the small intestine. Diarrhoea, weight loss and malnutrition are the major features of the syndrome" [1]. It can also be defined as "a state of significant maldigestion and malabsorption requiring a prolonged period of parenteral nutrition to provide for normal growth and development, prevent dehydration, and replace electrolytes, vitamins and trace elements due to extensive loss of the small bowel" [2].

The definition can also be extended to functional lesions: "Short bowel syndrome is a disorder in which malabsorption occurs as a result of massive resection of the small intestine, abnormal gut motility, or mucosal disorders that perturb absorption or digestion" [3].

Other components of the syndrome are the development of end-stage complications such as sepsis from catheter infections, metabolic disorders, the lack of venous access due to thrombosis, cholestasis, cirrhosis and liver failure [4].

The normal length of small bowel is variable and in adults a length of 400 to 800 cm is given. Weaver and co-workers [5], combining eight published reports on small intestinal length from 1010 necropsy measurements, described a mean of 200 cm at 30 weeks of pregnancy, 275 cm at term, 380 cm at one year, 450 cm at five years, 500 cm at 10 years and 575 cm at 20 years. Measured differences in small intestinal length varied between 68 and 386 cm for newborns, 104 to 591 cm (mean 344 cm) from one month to one year and 232-485 cm (mean 396 cm) between one and five years of age [6]. The causes of short small bowel (SSB) in children are many and are mainly due to congenital or perinatal diseases. In premature infants, necrotizing enterocolitis may necessitate an extended resection of small bowel and is the most common cause of short small bowel in the literature. Intestinal atresia and gastroschisis,

which are pro-bably vascular in origin, also account for a large number of children with an SSB (see Table 1). Volvulus of the small bowel with necrosis in children with a malrotation may also necessitate an extended resection. Genetic defects [7] or defects like a near total intestinal aganglionosis are rare causes of a short small bowel [2].

*Table 1. Causes of Short Bowel Syndrome in neonates and children in % [2]*

| | |
|---|---|
| Necrotizing enterocolitis | 36 |
| Intestinal atresia | 21 |
| Volvulus/malrotation | 19 |
| Gastroschisis | 10 |
| Hirschsprung's disease | 7 |
| Trauma | 1 |
| Others | 6 |

The incidence of short bowel syndrome is estimated at 2 to 3 per million population per year in the United Kingdom, half of them being children and 4.8 per million population per year in Canada [8]. In Sweden an estimate of 0.3 to 0.5 per 10,000 births of extreme short bowel in neonates is recorded [9]. The incidence in the Netherlands is not yet known.

Bacterial overgrowth occurs frequently in SSB [10]. It is difficult to diagnose since in normal bowel the amount of bacteria increases from about $10^3$ colony forming units/gram (cfu/g) food mass in the stomach and duodenum to $10^7$ cfu/g food mass in the ileum. Regular courses of enteral antibiotics to eliminate potentially pathogenic gram-negative organisms can help, but may allow non-susceptible strains of bacteria or yeasts to proliferate.

SSB may also predispose to bacterial translocation, defined as the active or passive penetration of viable microorganisms through the epithelial lining into the lamina propria [11]. In the intestinal wall bacteria should be cleared by the host defense system, but sometimes they may invade the mesenteric lymph nodes, the blood and even other organs. This depends on the permeability of the intestinal wall and is influenced by stasis, bacterial overgrowth and parenteral nutrition [12]. While enterobacteria, staphylococci and enterococci are able to translocate, most anaerobes do not appear to have this ability [11,13,14].

## AIM OF THE THESIS

This study is the result of 25 years experience in paediatric surgery. In this period we were regularly confronted with children with a short small bowel. Some of them presented with many serious problems over a long time. This thesis presents an overview of what we have learned during the treatment of these children.

Studies in animals were performed in 1975 to determine which surgery might reduce rapid transit times and improve intestinal absorption (Chapter 2.1). Chapter 2.2 describes the surgery we performed and provides a list of the patients with many of the complications that occurred. Malrotation, an important congenital abnormality that may lead to volvulus and necrosis of the small intestine, was studied to try to identify the patients requiring surgery (Chapter 2.3).

One of the problems of children with an SSB is D-lactic acidosis. A profuse growth of lactobacilli in the remaining bowel was found to be the basic cause of this acidosis. Having found the microbiological and biochemical explanations, the clinical significance for these children was sought and is presented in Chapter 3.

The complications of long-term treatment of SSB are discussed in Chapter 4. Immunological studies were performed to try to explain why children with both an SSB and a parenteral access port are more susceptible to infection than children who have a parenteral access port but a normal bowel (Chapter 4.1). Improvement of bowel function during short-term treatment with growth hormone has been described [15]. The short-term effects and in a later study the long-term effects of growth hormone treatment were therefore investigated to try to decrease the use of parenteral nutrition (Chapter 4.2). The absorption of oral drugs in patients with SSB is unpredictable. The sparse literature on this topic is reviewed (Chapter 4.3). Small intestinal transplantation is nowadays an accepted treatment, but still has a high morbidity and mortality. The results are reviewed in Chapter 4.4.

Ethical problems in treatment, due to the acute loss of all small bowel are discussed in chapter 4.5.

## REFERENCES


1. Shanbhogue LK, Molenaar JC. Short bowel syndrome: metabolic and surgical management. Br J Surg 1994; 81: 486-99.
2. Höllwarth ME. Short bowel syndrome: pathophysiological and clinical aspects. Review article. Pathophysiology 1999; 6: 1-19.
3. Warner BW, Vanderhoof JA, Reyes JD. What is new in the management of short gut syndrome in children. J Am Coll Surg 2000; 190: 725-36.
4. Caniano DA, Kanoti GA New-borns with massive intestinal loss: difficult choices. N Engl J Med 1988; 318: 703-7.
5. Weaver LT, Austin S, Cole JT. Small intestinal length: a factor essential for gut adaptation. Gut 1991; 32: 1321-3.
6. Walker-Smith J and Murch S. Diseases of the small intestine in childhood. 4th ed. 1999 Isis Medical Media Ltd Oxford UK.
7. Erez I, Reish O, Kovalivker M. Lazar L, Raz A, Katz S. Congenital Short-Bowel and Malrotation: Clinical Presentation and Outcome of Six Affected Offspring in Three Related families. Eur J Pediatr Surg 2001; 11: 331-4.
8. Sigalet DL. Short Bowel syndrome in infants and children: an overview. Sem Pediatr Surg 2001; 10: 49-55.
9. Wallander J, Ewald U, Läckgren G, Tufveson G, Wahlberg J, Meurling S. Extreme short bowel Syndrome in Neonates: An Indication for Small Bowel Transplantation? Transplantation Proceedings 1992; 24: 1230-5.
10. Kaufman SS, Loseke CA, Lupo JV, Young RJ, Murray ND, Pinch LW, Vanderhoof JA. Influence of bacterial overgrowth and intestinal inflammation on duration of parenteral nutrition in children with a short bowel syndrome. J Pediatr 1997; 131: 356-61.
11. Lichtman SM. Bacterial translocation in humans. J Pediatr Gastroenterol Nutr 2001; 33: 1-10.
12. Yang H, Finaly R, Teitelbaum DH. Alteration in epithelial permeability and ion transport in a mouse model of total parenteral nutrition. Crit Care Med 2003; 31: 1118-25.
13. Sedman PC, Macfie J, Sagar P, Mitchell CJ, May J, Mancey-Jones B, Johnstone D. The prevalence of gut translocation in humans. Gastroenterology 1994; 107: 643-9.
14. Berg RD. Bacterial translocation from the gastrointestinal tract. Trends Microbiol 1995; 3: 149-54.
15. Byrne TA, Persinger RL, Young LS, Ziegler TR, Wilmore DW. A New Treatment for Patients with Short-Bowel Syndrome. Ann Surg 1995; 222: 243-55.

# 2

# Surgical contribution to a short small bowel

## 2.1 ANIMAL STUDIES ON SHORT SMALL BOWEL

*RSVM Severijnen, JA Grotenhuis*

*Department of Paediatric Surgery, St Radboud Hospital, Nijmegen, The Netherlands*

### INTRODUCTION

In an attempt to resolve the clinical problem of severe diarrhoea and malabsorption in children with a short small bowel, a surgical experiment was performed on dogs. The aim was to select the best surgical method to slow down the accelerated passage through the shortened intestine and to improve absorption by producing a longer contact time. Several authors [1-4] have described the technique of creating antiperistaltic segments in neonates for this. The method has also been recommended to improve the low pH of the intestinal contents, which Flint considered to be one of the causes of rapid transit [5].

In this study, we decided to create antiperistaltic segments and recirculating loops in the canine small intestine after extended resection to see whether we could slow down the intestinal passage and achieve better absorption.

### METHODS

In 1975 we performed a surgical experiment on 10 adult beagle dogs at the Central Animal Laboratory of the Catholic University in Nijmegen. Experiments on rats or mice at that time were not considered to be able to answer our problem of rapid transit and improved absorption.

In a series of different resection percentages, we selected two of the many operation techniques described by Hoffmann von Kapherr in 1972 [6]: resection with a 10 cm antiperistaltic segment or a recirculating circular loop (isoperistaltic or antiperistaltic according to Mackby) [7] in the small intestine (Table 1).

*Table 1. Type of operation and outcome in 10 dogs*

| *Dog* | *Resection in %* | *Residual bowel length (cm)* | | *Additional surgery* | *Outcome* |
|---|---|---|---|---|---|
| | | *Jejunum* | *Ileum* | | |
| 319 | 80 | 30 | 12 | antiperistaltic segment | died |
| 320 | 0 | 130 | 130 | antiperistaltic segment | survived |
| 321 | 50 | 30 | 90 | antiperistaltic segment | survived |
| 350 | 80 | 10 | 40 | none | survived |
| 369 | 80 | 42 | 12 | recirculating loop (Mackby I) | died |
| 371 | 50 | 90 | 30 | antiperistaltic segment | survived |
| 374 | 80 | 10 | 53 | recirculating loop (Mackby II) | survived |
| 381 | 90 | 20 | 10 | recirculating loop (Mackby I) | died |
| 395 | 80 | 90 | 1 | none | died |
| 398 | 80 | 65 | 0 | ileocaecal resection | died |

The D-Xylose test, with pentose-sugar is a marker for carbohydrate absorption. It is mainly absorbed in the proximal jejunum, is not metabolised, but excreted into the urine. Abnormal intestinal flora in a blind loop syndrome may consume the xylose. This test was performed some months postoperatively, after the intestinal adaptive period. Following the oral administration of 0.5 gram xylose/kilogram body weight in a 10% solution, blood samples were taken at 0, 30, 60 and 120 minutes.

A D-Xylose tolerance test and an indicantest were also performed on urine collected during 0-8 hours and 8-24 hours after the duodenal administration of xylose. In four dogs we resected 50 to 90% of the small intestine and created an antiperistaltic ileal segment with an end-to-end one-layer anastomosis, sutured with atraumatic silk. In three dogs, we resected 80 or 90% and created iso- or antiperistaltic circulating loops with an end-to-side anastomosis.

In one dog, 80% of the small intestine was resected together with the ileocaecal junction. In two dogs, 80% of the jejunum or ileum was resected, without any additional constructive surgery, except for a primary end-to-end anastomosis.

To judge the results of surgery, we evaluated clinical performance, weight against time, fat and nitrogen excretion into the faeces and we performed D-Xylose tolerance

tests, an indican test as a marker of bacterial overgrowth from pathological flora and a radiological examination.

## RESULTS AND DISCUSSION

The length of the canine small intestine measured at the time of surgery varied between 240 and 450 cm. A major section was resected in all except one dog. In the latter case a 10 cm antiperistaltic segment was constructed in the ileum to study its isolated effect.

In the postoperative period we did not administer parenteral feeding to these dogs; they only received intravenous fluids.

Severe diarrhoea and weight loss in the first six weeks led to the death of four dogs within twelve weeks. One dog was put down after seven months because of his poor condition. All these dogs had twelve cm of ileum, or less. Five dogs survived; all had an ileal segment of more than 30 cm.

The dog that performed best on all the parameters had undergone 80% resection of the jejunum, without any additional constructive surgery. The same resection procedure on the ileum led to intractable cachexia and death within twelve weeks.

The D-Xylose test showed very wide variation in xylose blood levels in 5 control animals, probably due to different rates of gastric emptying. Therefore we performed a D-xylose tolerance test after duodenal administration of xylose: 75 to 95% of the xylose was excreted in the urine in the first 8 hours.

The qualitative test of indican excretion in the urine was very often positive in the second period of urine collection. The negative tests in the first 8 hours may have been caused by the water (250 ml) the dogs drank after the xylose load.

Fat excretion in the faeces should be zero, but it was between 5.1 and 10.2%, with the best result again in the dog that underwent extended jejunal resection alone. Nitrogen excretion was considered normal.

Radiological examination after two to six weeks showed recirculation of the barium meal in the dogs with the Mackby loops. In the dog with an isolated anti-peristaltic segment that did not undergo resection, gastric emptying time was over one hour. In two out of the three dogs with a recirculating loop, gastric emptying was also delayed. The other dogs showed normal gastric emptying. Anti-peristaltic movement was clearly visible in the inverted segment. No serious distension of the small bowel was seen in any of the dogs.

We observed that the dog that performed best was the one with a simple end-to-end anastomosis after extended jejunal resection. Although this operation caused severe diarrhoea, all the additional constructive operations caused new problems, especially stasis of the intestinal contents.

All the dogs that survived had an ileum that was 30 cm or longer. Recirculation of bowel contents in the circular loop did not improve the situation. The dog that survived with the recirculating loop had an ileum of 50 cm long. We assume that this was the reason for survival, not the recirculating loop.

Antiperistaltic segments and recirculating loops had some influence but the effects were unpredictable.

The very good clinical and laboratory performance of the dog that underwent extended resection of the jejunum compared to the one with 80% resection of the ileum surprised us and emphasized the importance of preserving as much of the ileum as possible. Apparently, the ileum is better able to take over the function of the jejunum than vice versa.

## CONCLUSION

On the basis of these studies in 1975, we have performed only end-to-end anastomosis after bowel resection in children. No additional constructive surgery has been performed since antiperistaltic segments and recirculating loops had unpredictable and non-reproducible effects. To date, these conclusions are still valid.

## ACKNOWLEDGEMENTS

The study was designed by Prof. C. Festen, head of the Paediatric Surgery Department at that time, and Dr. J. van Kleef, surgeon. We also thank Theo Arts, head of the animal operating theatre and Ton Peters, animal technician, for their indispensable help with all the operations and examinations.

## REFERENCES

1. Trinkle JK and Bryant LR. Reversed colon segment in an infant with massive small bowel resection: a case report. J. Kentucky Med Ass 1967; 65: 1090-2.
2. Cywes S. The surgical management of massive small bowel resection. J Ped Surg 1968; 3: 740-8.
3. Sauer H. Über intestinale Zirkulationsstörungen bei chirurgischen Erkrankungen im Säuglings- und Kindesalter. Langenbeck's Arch Klin Chir 1969; 323: 203-45.
4. Gdanietz K, Biewald W. Umkehrung eines Darmsegments bei Malabsorptions-syndrom nach ausgedehnter Dünndarmresektion bei einem Säugling. Zbl Chir 1973; 98: 251-5.
5. Flint JM. The effect of extensive resection of the small intestine. Bull John Hopkins Hosp 1912; 23: 127.
6. Hoffmann S. Experimentelle Studien an gegengeschalteten Dünndarmsegmenten zur Therapie des ´Short Bowel Syndrome´. Bruns´ Beitr Klin Chir 1972; 219: 8.
7. Mackby MJ, Richards V, Gilfillan RS, Floridia R. Methods of increasing the efficiency of residual small bowel segments: a preliminary study. Am J Surg 1965; 109: 32-8.

## 2.2 OVERVIEW OF PATIENTS AND SURGERY

*RSVM Severijnen*

*University Medical Centre St Radboud, Nijmegen, The Netherlands*

### DEFINITION OF SHORT SMALL BOWEL

The length of the normal small bowel is variable. In adults, a length between 400 and 800 cm is given. Weaver and co-workers [1] combined data from eight studies based on 1010 necropsies. They reported a mean small bowel length of 200 cm at 30 weeks of pregnancy, a mean length of 275 cm at term, 380 cm at one year, 450 cm at five years, 500 cm at 10 years, and 575 cm at 20 years of age.

Normal small intestinal length varies between 68 and 386 cm for newborns, between 104 and 591 cm in children from one month to one year and between 232 and 485 cm between one and five years of age [2]. This makes a definition of a short small bowel and the short bowel syndrome difficult. In addition, there are large differences in intestinal adaptation in children. Even 20 cm of remaining small bowel in some newborns may be sufficient to gain nutritional autonomy after an adaptation period, whereas in others 100 cm of remaining small bowel is hardly enough to keep intestinal nutritional autonomy.

The American Gastroenterological Association states that a short bowel syndrome is present when less than 200 cm of functional small bowel remains [3]. Touloukian and Walker-Smith state that a short bowel syndrome is present when less than 30% of functional small bowel remains [4]. In accordance with them, we consider 50 cm for premature babies between 28 and 35 weeks, 75 cm for newborns and 100 cm of remaining small bowel after 1 year sufficient to prevent the short bowel syndrome, since we were seldom confronted with problems in neonates and young children when more small intestine remained [5]. We use the term short small bowel if less than 50, 75 or 100 cm for prematures, newborns or older children respectively, remains and acknowledge that even some of these children, have few problems.

## SURGICAL THERAPY

### Primary operation

After resection of a diseased small bowel and careful assessment of the situation, the paediatric surgeon will preferentially perform an end-to-end anastomosis. If an end-to-end anastomosis is not possible, stomata have to be created. Care has to be taken to preserve every piece of non-diseased tissue. Leaving non-functioning sclerotic tissue behind, however, causes problems of stasis and/or diarrhoea. Stomata have to be closed as soon as the condition of the child permits, usually after 3 to 4 weeks [6].

### Secondary operations

Despite the paediatric surgeon's best efforts and judgement a stenosis of the remaining intestines can occur. This will necessitate a second operation. Antiperistaltic or valve operations have, in our opinion, no place in the surgical management of these children. Dilated intestine with an acceptable transit time should be left alone. When dilatation and delayed transit without an anatomical stenosis is present, it is sometimes possible to perform tapering or infolding of part of the intestine [7]. Stasis without transit obviously requires corrective surgery. In such cases, we prefer longitudinal bowel splitting and lengthening according to the technique described by Bianchi [8]. Obstructive ileus that requires adhesiolysis is not unusual in children with a short small bowel [9].

### Vascular approach

In order to deliver nutrients parenterally, we initially prefer polyurethane catheters put into a subclavian vein via the percutaneous route. Later, we use cuffed silicone central venous catheters via the same route. We avoid, if possible, open placement by venesection of these catheters, since the available sites for this technique are restricted. In our opinion, there is no indication for subcutaneously implantable systems at an early age, since these systems are more difficult to remove in case of infection or occlusion.

If access to the circulation is or becomes problematic, direct arterio-venous shunts or shunts with artificial material can help, but in small children it is difficult to accomplish a usable shunt. Later, reoperation of such arterio-venous anastomoses is sometimes necessary because of "steal-syndromes". Trombotic occlusion of the great vessels, that scatters embolic particles, requires operative removal of the thrombus.

**Adjuvant intestinal operations**
When administration of nutrients via the enteral route is possible, we often perform a Stamm gastrostomy for continous or nocturnal administration in order to prevent the long-term use of nasogastric tubes. Where there is delayed gastric emptying with gastro-oesophageal reflux a Witzel's jejunostomy is created for continous administration of nutrients. Although parenteral administration of nutrients is associated with gallbladder hypomobility and sludge formation, we have never had to remove a gallbladder for gallstone disease in our children.

## PATIENTS

In this chapter, the code numbers of patients with extensive problems described in the different chapters of this thesis are presented. Patients IN 5, 6 and 7 are from former articles and are changed into CH 5, 6 and 7. No higher IN numbers are used. The older child from Chapter 4.5 where treatment was refused, evoking an ethical dilemma, is not included here.

*CH 1* is a girl, born at term in 1987. She was admitted on the first day post-partum because of bilious vomiting and a distended abdomen, caused by malrotation and acute volvulus. She underwent surgery and a large part of necrotic intestine was resected, leaving 15 cm of proximal small bowel measured from the pylorus and 35 cm of the distal ileum, with the ileo-caecal valve in situ. Only the last 5 cm of the ileum looked healthy. Since a primary anastomosis was not thought to be a good option, stomata were created. These stomata were closed after 3 weeks. During closure of the stomata, only the last 15 cm of the ileum were left in situ. One month later, however, the child again required surgery since another 7 cm of the ileum were stenotic. In the end she had only 22 cm of small bowel. Central venous catheter complications occurred frequently and she developed thrombosis of the superior caval vein. After seven months in hospital while on parenteral nutrition (PN) she developed a meningo-encephalitis with a low-pressure hydrocephalus, probably related to catheter infection. We therefore decided to construct an arterio-venous anastomosis in the upper leg using a human venous graft. Unfortunately, this graft did not function well enough to be used. At the age of nine months she was finally discharged from hospital on home PN. One month later, after another septic episode, an MRI was performed and showed an occluded superior caval vein with flow via the azygos

system. We then decided to keep her only on enteral feeding, initially through a gastrostomy and later orally. For many years she experienced abdominal pain, which was assumed to be due to abdominal angina. Presently, she is doing fine, discharged from paediatric surgical check-ups, but still under control of the paediatric gastroenterologist. Her height and weight are on the 50th percentile.

*CH 2* is a girl, born at term in 1984. She was admitted because of bilious vomiting shortly after birth. Acute volvulus with malrotation had caused gastrointestinal obstruction with blood loss resulting in anaemia. On the second day of life, she underwent an extensive resection of necrotic small bowel, leaving 15 cm of proximal small bowel measured from the pylorus in place as well as 50 cm of the distal small bowel, of which only 20 cm looked healthy. Stomata were constructed. At the age of one month, an end-to-end anastomosis was constructed between the proximal 15 cm of small intestine and 30 cm of the distal part. Two months later she was re-operated because of ileus. Two cm of stenotic ileum was resected. For the same reason, another 15 cm of fibrotic ileum had to be resected at the age of four months. She ended up with 28 cm of remaining small bowel. For one year she was totally dependent of PN and it took another year to provide all nutrition enterally. At the age of 21 months an infected thrombotic mass in the heart was surgically removed. During that procedure, a small part of the tricuspid valve was removed. At the age of two years parenteral nutrition could be stopped. She remained short in stature and we tried to increase her height using growth hormone. Unfortunately, she died at the age of six years during a second cardiac operation for valvuloplasty after decompensation due to tricuspid valve insufficiency.

*CH 3* is a girl born in Austria in 1989. At the age of nine months, she developed an ileo-colic intussusception necessitating resection of 15 cm ileum. Six months later a strangulation ileus caused necrosis, necessitating resection of 220 cm small bowel, including the ileo-caecal valve. Fifty cm of small intestine remained as well as the colon. One year later, a third laparotomy was necessary to resolve an adhesion ileus. Removal of small intestine was not necessary during this operation. Enteral feeding was possible, but complete oral feeding could only be reached at the age of six years. She suffered frequently from metabolic acidosis. Growth developed along the 25th percentile.

*CH 4* is a girl born in 1990. She was healthy until the age of four years when she was admitted with abdominal pain and fever caused by an acute intestinal ischaemic accident. After resection of the necrotic bowel, she was left with 60 cm of small intestine. She had repeated surgery for abdominal abscesses and anastomosis leakages. Eventually, 45 cm of small bowel remained, including the ileo-caecal valve. After a hospital stay of six months, complicated by eight episodes of catheter related problems, she was discharged while on PN. She received home PN for three years.

She participated in both the short- and long-term study on the effect of growth hormone on bowel adaptation. In 1998 PN had to be stopped because of vascular access problems. After this she failed to thrive. In 1999 PN was reinstituted initially via central venous catheters, but this again caused frequent occlusion and infections. An arteriovenous shunt was constructed in 2001 and several revision procedures were necessary. Eventually, a second shunt had to be constructed and later the first one had to be closed a steal-syndrome. In 2001 her last central venous catheter caused a *Candida guilliermondi* infection with thrombosis in the heart. This problem was solved by long-term antimycotic therapy. Gastrostomy feeding caused too many abdominal complaints and so the gastrostomy was closed during a shunt revision in 2003. She is at present on home PN. She can manage to keep her weight constant for several days without PN using Neocate®.

*CH 5* (IN 5) is a boy born in 1996. We assume that he had an omphalocèle that closed before birth. This resulted in the loss of most of the small bowel with a jejunal atresia and both closed loops ending at the umbilicus. After surgery on the first day of life the remaining small bowel tissue was 25 cm in length. He was re-operated five times because of stasis of bowel contents in a non-functioning distended bowel and the ileo-caecal valve was resected. In 1997, he underwent an intestinal lengthening procedure according to Bianchi performed by professor Waag in Mannheim. During this procedure his estimated bowel length was 43 cm of which 30 cm could be doubled. The operation improved the passage of enteral feeding. He participated in both the short and long term study on the effect of growth hormone on intestinal adaptation. However, it was only after initiation of selective bowel decontamination that PN could be diminished from daily to two times a week. At present PN is administered for one or two nights a week at home. He was proposed for small bowel transplantation because of venous access problems but was not accepted because of the ultimate prospect of reaching intestinal autonomy.

*CH 6* (IN 6) is a boy born in 1996 with a gestational age of 31 weeks. At birth he weighted 1185 grams. In the first week post-partum he suffered from bloody stools. At week seven he became septic and necrotizing enterocolitis (NEC) was suspected but at laparotomy no necrosis was detected. A second laparotomy at week 11 revealed torsion of the intestine with necrosis of 70 cm of small intestine. After resection, 35 cm of jejunum distal to the ligament of Treitz and 5 cm of the distal ileum remained. Stomata were created. After three additional laparotomies for abscess and fistula formation, the stomata were closed at week 18 of life but had to be reconstructed two days later. At week 23 during his 8th laparotomy the stomata were closed again over a trans-anastomotic drain via a caecostomy. A gastrostomy for continuous feeding was also performed. During this period a total of five central venous catheters had to be inserted; complications were infections and trombosis of the subclavian vein. He was treated with growth hormone and glutamine for nine weeks. After this treatment period, PN could be stopped. He was discharged after 10 months in hospital. Since this he is doing well despite an almost continuously distended abdomen.

*CH 7* (IN 7) is a boy born in 1996 after a pregnancy of 33 weeks. At birth he weighted 1510 grams. Perinatally, he was asphyctic leading to periventricular leucomalacia. Six days after discharge from the neonatal intensive care unit he was readmitted with NEC. After a difficult haemodynamic stabilisation period, a laparotomy was necessary. At surgery 20 cm of necrotic ileum had to be resected. Subsequently, a jejunostomy and a colostomy had to be constructed. Several weeks later reconstructive surgery was performed leaving 50 cm of small bowel and 10 cm of colon. Although he is mentally retarded, blind and suffers from hearing loss, he can manage pretty well. He participated for 18 weeks in the short- and for one year and a half in the long-term study on the effect of growth hormone on bowel adaptation.

*CH 8* is a boy born at term in 2001. At birth his body weight was in the normal range. Only two vessels were seen in the umbilical cord. Cryptorchidism was also found. In the first weeks of his life he was treated for neonatal convulsions. Three weeks postpartum he was admitted to hospital acutely because of a swollen abdomen and sepsis due to malrotation and volvulus. A laparotomy was necessary and a necrotic part of the small intestine had to be removed. Stomata were created. Three weeks later these stomata were closed. During this period he developed cholestatic icterus while on PN.

Two weeks after closure of the stomata, a further resection of 30 cm of fibrotic small bowel was necessary with an end-to-end anastomosis. Finally, 40 cm of duodenum and jejunum and 10 cm of ileum were left. He is nearly completely dependent of PN, which is administered at home. Presently he has distended bowel loops but no signs of relevant stasis. A colonoscopy, performed at the age of 16 months for anal blood loss demonstrated a vulnerable atrophic mucosa with eosinophilic colitis at biopsy. Central lines have had to be replaced several times because of occlusion and/or infectious complications.

*CH 9* is a girl born in 2001 after a pregnancy of 31 weeks. At birth her body weight was 1740 grams. She was delivered because her intra-uterine condition deteriorated caused by antenatal volvulus due to malrotation. Surgery was performed immediately at birth. Part of the small bowel was removed and stomata were constructed. At the age of two and a half weeks she suffered from candida sepsis. At week five the stomata were closed, leaving 45 cm of small bowel, including the ileo-caecal valve. After this operation, she became septic and developed a complete wound dehiscence. During this period she was continuously on artificial ventilation. It was not possible to eradicate *Morganella Morganii*, causing the sepsis, probably because of an infected thrombus in the pulmonary vein. She also suffered from intrahepatic cholestasis. She died at the age of two months.

*IN 4* is an at term born girl (1994). At the age of two months she was admitted to hospital because of vomiting and bloody stools. Volvulus and malrotation were diagnosed at laparotomy and a necrotic part of small intestine was removed. After resection with end-to-end anastomosis, 100 cm of small intestine remained. At four months she was readmitted because of bilious vomiting. This was caused by stenosis of the anastomosis. The stenotic part, including the ileo-caecal valve, was removed leaving 80 cm of proximal small intestine. She suffered from a short bowel syndrome and was admitted for nine months until complete enteral feeding became possible.

## REFERENCES

1. Weaver LT, Austin S, Cole JT. Small intestinal length: a factor essential for gut adaptation. Gut 1991; 32: 1321-1323.
2. Walker-Smith J and Murch S. Diseases of the small intestine in childhood. 4th ed. 1999 Isis Medical Media Ltd Oxford UK.
3. American Gastroenterological Association. Medical position statement: Short bowel syndrome and intestinal transplantation. Gastroenterol 2003; 124: 1105-1110.
4. Touloukian RJ, Walker Smith GJ. Normal intestinal length in preterm infants. J Pediatr Surg 1983; 18: 720-723.
5. Bongaerts G, Bakkeren J, Severijnen R, Sperl W, Willems H, Naber T, Wevers R, van Meurs A, Tolboom J. *Lactobacilli* and acidosis in children with short small bowel. J Pediatr Gastroenterol Nutr 2000; 30: 288-93.
6. Festen C, Severijnen RSVM, van der Staak FHJM. Early closure of enterostomy after exteriorization of the small intestine for abdominal catastrophies. J Pediatr Surg 1987; 22: 144-145.
7. Vernon AH, Georgeson KE. Surgical options for short bowel syndrome. Sem Pediatr Surg 2001; 10: 91-98.
8. Bianchi A. Longitudinal intestinal lengthening and tailoring: Results in 20 children. J R Soc Med 1997; 90: 429-432.
9. Wilkins BM, Spitz L. Incidence of postoperative adhesion obstruction following neonatal laparotomy. Br J Surg 1986; 73: 762-764.

## 2.3 MALROTATION IN 33 CHILDREN IN ONE YEAR

*RSVM Severijnen[1], FHJM van der Staak[1], JJM Tolboom[2], BCJ Hamel[3], CMR Weemaes[2]*

*Departments of [1]Paediatric Surgery, [2]Paediatrics and [3]Human Genetics, University Medical Centre Nijmegen, Nijmegen, The Netherlands*

*Submitted for publication*

### ABSTRACT

*Background*: Volvulus of the small bowel is a life-threatening event and in most cases malrotation is the cause. Recognition of malrotation is difficult for general or gastro-enterological surgeons and infrequently diagnosed in adults. As children with congenital anomalies become adult, the possibility of malrotation should be considered if they present with abdominal problems.
*Methods*: Thirty-three children, diagnosed with a malrotation in 2001 were examined as regards diagnosis, treatment and results. Thirty-two of them were operated.
*Results*: The diagnosis was missed in two older children at the first operation. Surgery cured 24 of the 32 operated children of their abdominal problem. In two children resection resulted in a short small bowel. Two children died, one infant with a short small bowel and intractable sepsis, and one from severe untreatable congenital heart disease. In five children with constipation or motility problems, intestinal passage did not improve after surgery.
*Conclusion*: The indications for surgery in the neonatal period and in the case of an acute abdomen are undisputed. In other cases once the diagnosis is confirmed, surgery should be performed to prevent a life-threatening volvulus. A wait-and-see policy is only acceptable if there are severe contraindications to surgery and the parents warned of the possible dangers of an acute volvulus.

## INTRODUCTION

Volvulus of the small intestine is a life-threatening event as it may lead to a short small bowel (SSB). In most cases it is due to an abnormal rotation and fixation of the small bowel. For many gastrointestinal surgeons who operate mainly on adults, malrotation is an uncommon finding occurring in 1:6000 patients [1]. It is also difficult to recognise [2]. In paediatric surgery it is seen more often and a figure of 1:500 live births has been reported [3].

The intestines grow so fast in the first weeks of pregnancy, that they are temporarily located outside the abdomen. This physiological omphalocèle disappears in the 10th week when the intestines take their proper place, i.e. the first jejunal coil lies behind the mesenteric vessels at the ligament of Treitz, and the caecum becomes fixed in the right lower part of the abdomen [4]. The mesentery is broadly attached from the ligament of Treitz to the ileo-caecal valve of Bauhin, making a volvulus of the complete small bowel unusual. If there is an abnormal re-entry of the intestines in the abdomen, the normal fixation of the mesentery may be absent. The narrow stalk of the attachment of the entire intestine may constitute the basis for a volvulus from the duodenum to the middle of the transverse colon - the part of the bowel supplied by the upper mesenteric artery. Volvulus may occur in children and adults and may even present antenatally.

A clear and extensive description by NM Dott about the anomalies of intestinal rotation was written in 1923 [5]. He considered the abnormally situated appendix, the problems of recognition of the malrotation during laparotomy and cases of secondary volvulus in the newborn. He suggested fixation of the caecum in the right lower abdomen, but left the possibility open of putting the intestine back in a position of non-rotation.

Waugh in 1928 described "indigestion" with attacks of pain in childhood, diagnosed as "chronic appendicitis" caused by a congenital malformation of the mesentery. He noted a high-positioned caecum on an X-ray enema and suggested a barium meal would be better for diagnosis [6].

Since then few publications have been written outside the paediatric surgical literature and few cases have been described in adults [2]. Von Flüe and co-workers in 1994 found 40 adult patients in German and English literature and added nine cases [7].

*Table 1. Some syndromes with malrotation as a feature.*

| *Syndrome* | *Some features* | *Inheritance* | *Locus/Gene* |
|---|---|---|---|
| Beckwith-Wiedemann | Omphalocèle, macroglossia, gigantism, hypoglycaemia | AD/imprinting | p15.5 |
| Cornelia de Lange | Pre- and postnatal growth deficiency, facial dysmorphisms, mental retardation | Sporadic | -- |
| Fraser cryptophthalmus | Cryptophthalmus, genital anomaly, ear anomalies | AR | FRAS1 |
| Fryns | Diaphragmatic defects, coarse facies, distal digital hypoplasia | AR | -- |
| Focal dermal hypoplasia (Goltz) | Poikiloderma with focal hypoplasia, syndactyly, dental anomalies | XLD | Xp |
| Ivemark | Situs inversus, a/polysplenia, heart defect | AR/multifactorial | -- |
| McKusick-Kaufman | Polydactyly, hydrometrocolpos, heart defect | AR | MKKS |
| Marfan | Ectopia lentis, aortic dilatation, long stature, pectus excavatum/carinatum | AD | FBN-1 |
| OEIS | Omphalocèle, Exstrophy, Imperforate anus, Spinal deformities | Sporadic | -- |
| Simpson-Golabi-Behmel | Macrocephaly, coarse facies, overgrowth, poly/syndactyly | XLR | GPC3 |
| Smith-Lemli-Opitz | Facial dysmorphisms, syndactyly, hypospadias, mental retardation | AR | DHCR7 |
| Total colonic aganglionosis | Aganglionosis of the entire colon | Multifactorial | -- |
| VACTERL | Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal defects, Limb anomalies | Multifactorial | -- |
| X-linked heterotaxia | Situs inversus | XLR | ZIC3 |

*Legend: AD: autosomal dominant; AR: autosomal recessive; XLD: X-linked dominant; XLR: X-linked recessive.*

Malrotation commonly accompanies other congenital abnormalities, like duodenal atresia, abdominal wall defects or diaphragmatic hernia. Its presence is described in nearly 100 different combinations and syndromes [8]. Some of the more common are listed in Table 1. We studied the symptoms at diagnosis and the outcome of surgery in children with a malrotation referred to us in one year, both typical and atypical cases in neonates and older children.

## METHODS AND PATIENTS

### Diagnosis

Since it is difficult even for experienced paediatric surgeons to discern all the different forms of malrotation, nonrotation or fixation disorders, we prefer to speak of a malrotation, when the first jejunal loop does not cross behind the superior mesenteric artery and vein.

Clinically, green vomiting with cramping abdominal pain is the cornerstone of the diagnosis of malrotation in neonates. In older children a story of intermittent or recurrent abdominal pain and vomiting may suggest the diagnosis. In patients with failure to thrive or even chronic constipation, a malrotation may also be considered. In cases of bilious vomiting in an older child, malrotation must be excluded. Acute volvulus presents as an acute abdomen and this is the indication for surgery.

Upper gastrointestinal X-rays may show the typical corkscrew appearance of the first part of the jejunum with no crossing of the spine of the duodeno-jejunal junction at the Treitz ligament [9]. It can be difficult for a radiologist, who is not familiar with this picture, to recognise it. Barium enema may show the caecum to be localised in the upper right part of the abdomen. However a normal position of the caecum does not rule out an abnormal position of the small bowel and on the other hand, a mobile caecum may exist without malrotation.

Echography as a diagnostic method is described [10], but may not be reliable enough to indicate the need for surgical intervention in cases of malrotation. Most surgeons will ask for an upper gastrointestinal X-ray to confirm the suspected diagnosis.

CT-scanning for unclear abdominal complaints may suggest an abnormal course of the mesenteric vessels and a "whirl like" arrangement [11]. Chronic volvulus with superior mesenteric vein thrombosis diagnosed by CT or MR angiography is also described [12].

Antenatal diagnosis of malrotation is mostly impossible. In cases of duodenal atresia, omphalocèle, gastroschisis and diaphragmatic hernia concomitant malrotation can be expected. Volvulus in utero may lead to intestinal atresia with congenital short bowel.

### Operation

Operative diagnosis is based on the typical absence of the ligament of Treitz and the jejunum not crossing behind the mesenteric vessels. Ladd's bands between the lateral abdominal wall and the caecum may be present in neonates and compress

the duodenum but are not always present in older patients. In the case of an abnormal position in the abdomen of the caecum or appendix at emergency appendectomy a mobile caecum must be distinguished from a typical malrotation.

If the ascending colon is fixed on the right lateral side it should be cut loose from the right abdominal wall and the first jejunal loop must be completely freed. This can be quite difficult at the deepest point at the duodeno-jejunal flexure. If there are Ladd's bands between the right upper abdominal wall and the caecum, compressing the duodenum [13], usually in neonates, they should be divided to free the duodenum completely. The mesentery stalk, thickened in cases of chronic volvulus, can be broadened by cutting the overlying peritoneum to prevent a volvulus. The intestine is placed back in a non-rotated position in the abdomen, i.e. the small intestine to the right, to assure a free passage from the duodenum to the jejunum and the colon to the left side of the abdomen. The appendix is removed in most cases as it lies somewhere in the middle or the left upper abdomen. We never fix both parts of the colon as described by some authors [2], and neither place nor fix the caecum in its "proper" place.

## PATIENTS

In 2001, thirty-three cases of malrotation were diagnosed, aged from one day to fifteen years. Thirty-two of them were operated and are listed and numbered according to age at surgery in Table 2.

Nine children underwent surgery in the first week of life, six were male. Of the 23 children operated in the first year, 16 were male. Of the nine children operated after the first year three were male.

Malrotation was the only diagnosis (besides prematurity or a single umbilical artery), in 7 of 13 neonates, 4 of 9 infants and 2 of 9 children above one year.

The only child not operated was a boy with Down's syndrome and Hirschsprung's disease. The malrotation was diagnosed on X-ray at two years of age, when he was investigated for vomiting. However, no operation for the malrotation was performed as his passage problems disappeared on laxative treatment. As the malrotation was not diagnosed at three previous laparotomies to correct his Hirschsprung's disease, (a colostomy, a low anterior resection and closure of the colostomy), we concluded that the chance of developing a volvulus was low.

In one neonate - not included in Table 2 - the diagnosis was made on a typical X-ray appearance, but could not be confirmed at operation.

*Table 2. Thirty two children with malrotation, operated in 2001*

| *No* | *Malrotation operation* | *Gender* | *Presentation* | *Concomitant diagnosis* | *Abdominal problem solved?* |
|---|---|---|---|---|---|
| 1 | 1 day | F | Antenatal volvulus | Premature, 31 weeks 1780 g. | Short small bowel, died at 2 months |
| 2 | 2 days | M | Pulmonary problems | Diaphragmatic hernia | Cured |
| 3 | 2 days | M | Antenatally | Duodenal atresia, Down's Syndrome | Cured |
| 4 | 2 days | F | Gastric bleeding | Duodenal atresia | Cured |
| 5 | 3 days | M | Bilious vomiting, acute volvulus | - | Cured |
| 6 | 4 days | M | Bilious vomiting | - | Cured |
| 7 | 6 days | M | Bilious vomiting | Convulsions, colonic perforation (NEC?), Meckel | Cured |
| 8 | 6 days | F | Vomiting | Duodenal stenosis | Cured |
| 9 | 6 days | M | Bilious vomiting | Pseudo-obstruction syndrome | Motility problems |
| 10 | 12 days | F | Bilious vomiting | - | Chyloperitoneum Cured |
| 11 | 13 days | M | Bilious vomiting | - | Cured |
| 12 | 15 days | M | Bilious vomiting | - | Cured |
| 13 | 24 days | M | Bilious retentions acute volvulus | Single umbilical artery | Short small bowel, home PN |
| 14 | 1 month | M | Abdominal distension | Hypoplastic left heart | Cured |
| 15 | 1 month | M | Vomiting | - | Cured |
| 16 | 1 month | F | Bilious vomiting | Premature 31 weeks, 1120 g | Cured |
| 17 | 2 months | F | Ileus after heart operation | Hypoplastic left heart, duodenal stenosis | Died after 1 day, multiorgan failure, and septic shock |
| 18 | 2 months | M | Abdominal pain, vomiting, gastro-oesophageal reflux | Oesophageal and anal atresia, left radius aplasia, floating thumbs, pylorus hypertrophia | Cured, Fundoplication later |
| 19 | 2 months | M | Strangulation ileus with volvulus | Diaphragmatic hernia | Cured |
| 20 | 4 months | M | Oesophageal stenosis | Oesophageal atresia | Chyloperitoneum Cured |
| 21 | 5 months | M | Feeding problems | | Cured |
| 22 | 5 months | M | Feeding problems and Gastro-Oesophageal Reflux | | Motility problems solved after 6 months |
| 23 | 6 months | F | Abdominal pain | Hypoplastic left heart, cholelithiasis | Cured |
| 24 | 1 year | M | Vomiting | Urethral valves, hydronephrosis, renal insufficiency | Cured |
| 25 | 1 year | F | Adhesion ileus | Diaphragmatic hernia | Cured |
| 26 | 2 years | F | Vomiting and Gastro-Oesophageal Reflux | Sliding gastric hernia | Fundoplication later |
| 27 | 2 years | F | Failure to thrive, constipation | | Motility problems |
| 28 | 5 years | M | Ileus, acute abdomen | Diaphragmatic hernia + recidive, Meckel | Cured |
| 29 | 7 years | F | Failure to thrive | Pseudo-obstruction syndrome | Motility problems |
| 30 | 8 years | F | Constipation | Situs inversus solitus | Motility problems |
| 31 | 9 years | M | Bilious vomiting acute volvulus | - | Cured |
| 32 | 15 years | F | Acute volvulus | - | Cured, adhesion ileus |

## RESULTS

Table 2 shows the heterogeneity of the patients with isolated malrotation, other congenital abnormalities and motility problems.

Acute volvulus was observed in six children. Resection of necrotic bowel in two of the infants resulted in SSB. The two older children were operated in another hospital where the malrotation was not recognised. A nine-year-old boy was transferred after surgery after untwisting of a volvulus to our paediatric intensive care unit. Repeat laparotomy was performed with treatment of the malrotation by us the next day.

A fifteen-year-old girl first underwent an untwisting of a volvulus, but her malrotation was unrecognised because of the normal fixation of the ascending colon. A second laparotomy showed improvement of the colour of the intestine. At her third laparotomy, because of intestinal transit problems, the malrotation was recognised and treated. The girl recovered without intestinal resection, but had to be operated for a strangulation ileus two years later.

Bilious vomiting or green gastric retentions were seen in nearly all neonates, but only twice in the group of infants and older children.

Duodenal stenosis or atresia was diagnosed in four children, one had also a heart problem and another Down's syndrome.

Oesophageal atresia was seen twice, anal atresia in one of these two with a VACTERL association (Table 1).

One child presented with acute gastric bleeding, for which no satisfying explanation could be found, as there was no acute volvulus combined with her duodenal atresia.

Five children presenting with feeding problems, failure to thrive or severe constipation, were diagnosed and referred by the paediatric gastroenterologist. One of them also had an abdominal situs inversus. One boy and a girl showed a pseudo-obstruction syndrome.

Diaphragmatic hernia was the primary diagnosis in four children. The malrotation was corrected in one at the first operation and in the other three at a secondary operation. Two of these children had an acute ileus, and one presented with a recurrent hernia.

There were three children with a hypoplastic left heart syndrome. In two, with a low flow state after Norwood surgery, an acute abdomen led to an acute abdominal operation. The girl who died also had a duodenal stenosis and an absent gallbladder. The third child had severe abdominal complaints after major heart surgery. She

underwent cholecystectomy for proven cholecystolithiasis at the age of three months but the severe abdominal complaints continued. After suspecting a gastric volvulus and diagnosing the abnormal intestinal fixation, a malrotation operation was performed with a side-to-side duodeno-jejunostomy. This cured her cramping abdominal pain as proven by ending her inconsolable crying. A combination with a renal problem was seen once.

**Outcome**

In 24 of the 32 operated patients surgery was successful in relieving the abdominal complaints. Two children died, a girl from untreatable abdominal infection after an extensive bowel resection, the other girl from complications of her hypoplastic left heart syndrome. The boy with SSB who survived is still on home parenteral nutrition. Three children experienced continuing motility problems, two of them showed high passage problems after three to six weeks, requiring a reoperation with a duodeno-jejunostomy, as the fixation to the rear wall at that point could not be completely freed. In fact surgery caused more problems after the malrotation correction as passage before surgery was not completely obstructed. The third one is a boy with an intestinal pseudoobstruction syndrome.

Two of the three children with gastro-oesophageal reflux underwent at first a malrotation correction, but this did not solve the reflux and later a fundoplication operation was necessary.

Chyloperitoneum as a complication of the operation was seen twice, requiring one month of total parenteral nutrition and two months of a medium chain triglyceride diet afterwards in one and six months of this diet in the other child.

## DISCUSSION

The diagnosis of malrotation was missed in several children especially the older ones. Surgeons who treat non-neonatal cases or older children should be aware of the possibility of a malrotation and how to recognise the failing crossing of the jejunum behind the mesenteric vessels. Recognition is especially difficult in cases of a normal fixation of the ascending colon and caecum, because the surgeon may not realise the possibility of a malrotation. The observation of a first jejunal loop not passing behind the superior mesenteric vessels is proof of the abnormality. If there is a chronic incomplete volvulus, there are many thickened glands in the mesentery. To prevent a

chyloperitoneum we consider the necessity of broadening of the mesenterial stalk. This should be restricted to the peritoneum only.

Fortunately many neonates with a malrotation have Ladd's bands obstructing the second part of the duodenum and this allows fast recognition of the condition. In older children, adolescents or adults volvulus as a result of the malrotation may be the first sign. There may exist a long history of abdominal complaints, resulting in unsuccessful psychological or psychiatric consultation and treatment.

In cases of an acute abdomen or adhesion ileus after previous paediatric surgery like diaphragmatic hernia, oesophageal atresia, anal atresia or Hirschsprung's disease, the surgeon should consider the possibility of a malrotation contributing to the complaints instead of only operating on adhesions from fibrous bands.

We re-operated three children (9%). This is a higher figure than described by Festen as a number of 2.2% postoperative small bowel obstructions in 1476 laparotomies [14], but more resembling the 15% Wilkins gives for re-operation in cases of malrotation in neonates, compared to 8.3% for all neonatal abdominal operations [15]. Conservative treatment in cases of mechanical obstruction causes unnecessary delay and should be avoided.

For surgeons experienced in laparoscopy, who are familiar with the clinical and operative picture, the malrotation operation can be performed completely by laparoscope [16]. Maziotti suggests in unclear cases of malrotation to decide after laparoscopy if a correction to prevent volvulus is necessary, depending on the width of the mesenterial stalk [17].

Malrotation is associated with a large variety of other congenital malformations, in particular of the gastro-intestinal tract, e.g. oesophageal [18], pyloric, duodenal, applepeel small bowel and anal atresia [19], congenital short bowel, Hirschsprung's disease [20] and biliary atresia. It is seen in congenital hernia diaphragmatica, situs inversus, omphalocèle and gastroschisis and also in congenital heart disease and urogenital tract anomalies [8]. The recurrence risk in a family in case of an isolated, non-syndromal malrotation is 1% or less for a sibling and for offspring.

A special problem nowadays are the children with complicated heart disease like a hypoplastic left heart syndrome. When, between the necessary cardiac corrections, can surgery for the malrotation be planned? This also is dependent on the haemodynamic situation at the time.

We do not correct malrotation in children while on ECMO (Extra Corporal Membrane Oxygenation) at the time of repairing the diaphragmal defect, which we do during ECMO treatment, because we fear the possibility of bleeding. Later two of these children were operated on their malrotation when another procedure like fundoplication or a laparotomy for a strangulation ileus was needed. In motility disorders like pseudo-obstruction cases or children with severe constipation where a malrotation is found on work-up, the paediatric surgeon should warn the parents that operation only prevents a volvulus, and may not improve intestinal passage and constipation.

In cases of documented gastro-oesophageal reflux we perform the malrotation correction and antireflux procedure simultaneously [21].

When at an emergency appendectomy with abnormal presentation of the caecum, a malrotation correction is contraindicated at that time because of the appendicitis, a corrective operation should be performed later.

As operation results are good in general, surgery should not be dependent upon the age of the patient, every patient with a malrotation merits surgery to prevent a life-threatening volvulus [22]. With nearly 50.000 births in our region a number between 8, when the number of 1:6000 is correct [1] and 100 cases with malrotation, when 1:500 is used [3], may be expected each year. Thirty-three cases were referred in 2001, 6 of them presented with an acute volvulus. This supports our recommendation for surgery in asymptomatic cases.

## CONCLUSION

Emergency operation is indicated in all infants and in cases of acute volvulus and non-acute operation in symptomatic children without signs of a vascular intestinal problem [23,24]. In completely asymptomatic cases in older children also an operation should be performed. If after extensive consultation with the patient and parents a wait-and-see policy is adopted for acceptable reasons, they should be warned of the possible dangers of an acute volvulus.

## ACKNOWLEDGEMENT

The authors thank Dr. E. Robertson, anaesthesiologist, for the English language editing.

## REFERENCES


1. Rescorla FJ, Shedd FK, Grosfeld JL. Anomalies of intestinal rotation in childhood: analysis of 447 cases. Surg 1990; 108:710-715: discussion 715-716.
2. Dietz DW, Walsh RM, Grundfest-Broniatowski S, Lavery IC, Fazio VW, Vogt DP. Intestinal malrotation: a rare but important cause of bowel obstruction in adults. Dis Colon Rectum 2002; 45: 1381-1386.
3. eMedicine: http://www.emedicine.com/ped/byname/intestinal- malrotation.htm [18 Oct 2002].
4. Larsen WJ. Human embryology (2nd edition). Churchill Livingstone New York 1997.
5. Dott, N.M. Anomalies of intestinal rotation: Their embryology and surgical aspects: with report of 5 cases. Brit J Surg 1923; 11: 251-286.
6. Waugh, G.E. Congenital malformations of the mesentery: A clinical entity. Brit J Surg 1928 ; 15: 438-449.
7. Von Flüe M, Herzog U, Ackermann C, Tondelli P, Harder F. Acute and chronic presentation of intestinal non-rotation in adults. Dis Colon Rectum 1994; 37:192-198.
8. Passage E, Stevenson RE. Small and large intestines. In: Human malformations and related anomalies. Stevenson RE, Hall JG, Goodman RM. Vol II, Oxford university Press, New York, 1993, 475-492.
9. Mehall JR, Chandler JC, Mehall RL, Jackson RJ, Wagner CW, Smith DW. Management of typical and atypical intestinal malrotation. J Pediatr Surg 2002; 37: 1169-1172.
10. Chao HC, Kong MS, Chen JY, Lin SJ, Lin JN. Sonographic features related to volvulus in neonatal intestinal malrotation. J Ultrasound Med 2000; 19: 371-376.
11. Fukuya T,Brown BP, Lu CC. Midgut volvulus as a complication of intestinal malrotation in adults. Dig Dis Sci 1993; 38: 438-444.
12. Walsh DS, Crombleholme TM. Superior Mesenteric Venous Thrombosis in Malrotation with Chronic Volvulus. J Pediatr Surg 2000; 35: 753-755.
13. Ladd, W.E. Congenital obstruction of the duodenum in children. N Engl J Med 1932; 206: 277-283.
14. Festen C. Postoperative small bowel obstruction in infants and children. Ann Surg 1982; 196: 580-583.
15. Wilkins BM, Spitz L. Incidence of postoperative adhesion obstruction following neonatal laparotomy. Br J Surg 1986; 73: 762-764.
16. Bax NM, van der Zee DC. Laparoscopic treatment of intestinal malrotation in children. Surg Endosc 1998; 12: 1314-1316.
17. Mazziotti MV, Strasberg SM, Langer JC. Intestinal rotation abnormalities without volvulus: the role of laparoscopy. J Am Coll Surg 1997; 185: 172-176.

18. Cieri MV, Arnold GL, Torfs CP: Malrotation in conjunction with esophageal atresia/tracheo-esophageal fistula. Teratology 1999; 60: 114-116.
19. Agarwala S, Goswami JK, Mitra DK. Pyloric atresia associated with epidermolysis bullosa, malrotation, and high anorectal malformation with recto-urethral fistula: a report of successful management. Pediatr Surg Int 1999; 15: 264-265.
20. Poenaru D, Uroz-Tristan J, Leclerc S,Murphy S, Bensoussan AL. Imperforate anus, malrotation and Hirschsprung's disease: a rare association. Eur J Pediatr Surg 1995; 5: 187-189.
21. Kumar D, Brereton RJ, Spitz L, Hall CM. Gastrooesophageal reflux and intestinal malrotation in children. Br J Surg 1988; 75: 533-535.
22. Prasil P, Flageole H, Shaw KS, Nguyen LT, Youssef S, Laberge JM. Should malrotation in children be treated differently according to age? J Pediatr Surg 2000; 35: 756-758.
23. Powell DM, Othersen HB, Smith CD. Malrotation of the intestines in children: the effect of age on presentation and therapy. J Pediatr Surg 1989; 24: 777-780.
24. Maxson RT, Franklin PA, Wagner CW. Malrotation in the older child: Surgical management, treatment and outcome. Am Surg 1995; 61: 135-138.

# 3

# Microbial activity and a short small bowel

## 3.1 INTESTINAL MICROBIAL ACTIVITY

*RSVM Severijnen[1], GPA Bongaerts[2]*

*Department of [1]Paediatric Surgery and [2]Medical Microbiology,*
*University Medical Centre St Radboud, Nijmegen, The Netherlands*

### INTESTINAL MICROBIAL ACTIVITY

Development of a stable microflora ecosystem in the gut is a slow process that takes several years from birth. Once formed, it remains remarkably constant throughout life. Gut flora is an important factor in certain pathological disorders, but bacteria and other bowel inhabitants may also contribute to human health [1].

After vaginal birth, the first micro-organisms in the bowel are facultative anaerobic bacteria, mainly streptococci, enterobacteria and to a minor extent staphylococci, depending on the mother's vaginal and rectal flora. After 48 hours, the number reaches $10^4$-$10^6$ colony-forming units (cfu) per gram faeces. Caesarean section may alter the flora for up to 6 months.

Premature babies in an incubator have a much lower developmental rate of anaerobic flora, possibly due to antibiotics and nursing care. This may lead to an increase in harmful bacteria such as clostridia or *Klebsiella*, *Citrobacter* and *Enterobacter* spp, and nosocomial infections [2].

On day 10, bifidobacteria and lactobacilli reach stable concentrations of $10^9$ cfu/g faeces. This colonisation is associated with increases in *Escherichia coli*, *Bacteroides* spp and clostridia and decreases in staphylococci.

In breast-fed children, nearly all faecal microbes are bifidobacteria, whereas in bottle-fed children, they form only 30-40% of all bacteria. The growth of these bifidobacteria is enhanced by the low protein and low phosphorus content combined with high lactose concentration in human milk, and is not due to bifidogenic growth factors alone, such as glycoproteins and mono- or oligosaccharides [3].

With dietary supplementation, differences between bottle-fed and breast-fed children disappear. Enterobacteria, streptococci and clostridia increase and diverse anaerobic flora with fusobacteria and eubacteria develop.

## NORMAL ADULT INTESTINAL MICROFLORA IN THE INTESTINAL TRACT

In the human adult, the intestinal microflora is a complex system that contains about 400 different species. Anaerobes are 100 to 1000 times more prevalent than aerobic or facultative aerobic bacteria, but nearly all are restricted to the colon [2].

The gastric pH of below 3.5 is normally too low to permit the growth of human bacteria. Most bacteria present in the food are killed in the stomach. Only a few acid-tolerant micro-organisms survive the stomach and will enter the small bowel.

In the duodenum, the first bacteria encountered are lactobacilli. Later in the small bowel at a pH of 4.5 to 5.5, the enterococci emerge and at a pH of 5.5 to 7, especially the enterobacteria, such as *E. coli*. At the end of the small bowel, the food mass has become completely anaerobic. In the colon the food mass is infused with many kinds of strictly anaerobic bacteria, such as pepto(strepto)cocci, eubacteria, propionibacteria, fusobacteria and *Bacteroides* spp.

In the proximal part of the small bowel, the resident flora concentration amounts to about $10^3$ cfu/g food mass, while distally it may rise to $10^7$ cfu/g [1]. In the colon the bacterial count increases to $10^{11}$- $10^{12}$ cfu/g faeces [4].

### Microbial intestinal activity

The activity of microbes in the intestinal tract depends on the food consumed, intestinal location and type and amount of bacteria. There is only limited microbial activity in the small bowel due to the relatively small number of bacteria. In the colon different bacteria and different biochemical reactions give rise to short chain fatty acids (SCFA), such as acetic acid, butyric acid and propionic acid [5]. They are reabsorbed, used as fuel to produce energy for the colonocytes, and excreted in the faeces [6]. They also have important effects on gastrointestinal motility via the peptide YY pathway [7].

$H_2$ and $CO_2$ are also products of colonic bacterial fermentation of glucose, in contrast to $CH_4$, which is a waste product of intestinal methanogenous bacteria, that arises from the anaerobic oxidation of $H_2$ in the presence of $CO_2$; all are released as flatus. The bad smell is related to butyric acid (produced from indigestible carbohydrates), amines, $H_2S$ and indol. The latter three compounds are produced from aminoacids and proteins.

The most important advantage of intestinal $CH_4$ production is that it reduces the intestinal gas volume. As the molar gas volume is identical for all gases, a volume of 1 mol gaseous $CO_2$ and 4 mol gaseous $H_2$ are reduced, in the presence of the necessary bacteria, to a volume of 1 mol gaseous $CH_4$ and a negligible volume (2 mol) of liquid $H_2O$. This means reduction in intestinal gas volume up to maximally 80%.
The intestinal microflora also plays a role in the gut immune system, including the development of oral tolerance to harmless antigens, such as food proteins.

We studied the microbiological and biochemical consequences of the overwhelmingly high concentration of lactobacilli we discovered in the faeces of children and adults with a short small bowel. In the following parts of this chapter we present some of our results.

## REFERENCES

1. Guarner F, Malagelada JR. Gut flora in health and disease. Lancet 2003; 361: 512-519.
2. Adlerberth I. Establishment of a Normal Intestinal Microflora in the Newborn Infant. In: Hanson LA, Yolken RH. Probiotics, other nutritional factors, and intestinal microflora. Lippincott Raven Philadelphia, 1999.
3. Orrhage K, Nord CE. Factors controlling the bacterial colonization of the intestine in breastfed infants. Acta Paediatr Suppl. 1999; 88: 47-57.
4. Bongaerts GP, Tolboom JJ, Naber AH, Sperl WJ, Severijnen RS, Bakkeren JA, Willems JL. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathog 1997; 22: 285-93.
5. Tannock GW. Normal microflora: an introduction to the microbes inhabitating the human body. Chapman and Hall, London, 1995.
6. Olesen M, Gudmand-Høyer E, Holst JJ, Jørgensen S. Importance of colonic bacterial fermentation in short bowel patients. Small intestinal malabsorption of easily digestible carbohydrate. Dig Dis Sci 1999; 44: 1914-1923.
7. Cherbut C. Motor effects of short chain fatty acids and lactate in the gastrointestinal tract. Proc Nutrit Soc 2003; 62: 95-99.

## 3.2 LACTOBACILLI AND ACIDOSIS IN CHILDREN WITH SHORT SMALL BOWEL

*Ger Bongaerts[1], Jan Bakkeren[2], René Severijnen[3], Wolfgang Sperl[4], Hans Willems[5], Ton Naber[6], Ron Wevers[2], Alfred van Meurs[7], Jules Tolboom[8].*

*Departments of [1]Medical Microbiology, [3]Pediatric Surgery, [5]Clinical Chemistry, [6]Gastroenterology and Hepatology, and [8]Pediatrics and [2]Laboratory of Pediatrics and Neurology, University Hospital Nijmegen St Radboud, Nijmegen, The Netherlands; [7]Juliana Children's Hospital, The Hague, The Netherlands; [4]Kinderspital Landeskrankenanstalten Salzburg, Salzburg Austria*

*Journal of Pediatric Gastroentrology and Nutrition 2000; 30: 288-293*



*Presented in part at the 6th Southeast European Symposium of Pediatric Surgery on Short Bowel Syndrome, May 22-23 1998 in Graz, Austria*

### ABSTRACT

*Background*: In patients with a short small bowel, D-lactic acidemia and D-lactic aciduria are caused by intestinal lactobacilli. The purpose of this study was to obtain a detailed picture of the metabolic acidosis in young children with short small bowel.
*Methods*: Feces, blood, and urine of children with short small bowel and acidosis were studied microbiologically and/or biochemically.
*Results*: Previous findings were confirmed that more than 60% of the fecal flora of patients with short small bowel, who are not receiving antibiotics, consists of lactic acid-producing lactobacilli. In blood, D-lactic acid was the most prominent metabolite: the highest serum D-lactate (15.5 mmol/l) was observed in a sample taken immediately after the onset of hyperventilation. The highest D-lactate excretion was in urine collected some hours after the onset of hyperventilation, and amounted to 59 mol/mol

creatinine. Acidosis in the patients with short small bowel was related to strongly increased serum D-lactate and anion gap, and to strongly decreased serum bicarbonate and pH.
*Conclusion*: In children with short small bowel and acidosis, the common intestinal flora of mainly lactobacilli abundantly produces D-lactic acid from easily fermentable carbohydrates. Thus, these bacteria directly cause shifts of bicarbonate, pH, and base excess, and indirectly cause shifts of the anion gap, as well as hyperventilation. These kinetic parameters are strongly associated.

## INTRODUCTION

In patients with a short small bowel (SSB), intestinal uptake capacity is strongly reduced, and therefore these patients have malabsorption. Absorption of food components is too slow, and because of the prolonged presence of nutrients in the acidic proximal bowel lumen, an overgrowth of lactobacilli emerges within a very short time. These bacteria produce massive amounts of D- and L-lactic acid, and thus prevent other bacteria from increasing [1]. Both D- and L-lactic acid are intestinally absorbed.

Consequently, D-lactic acidemia and aciduria will arise daily, but D-lactic acidosis also may be seen, and less frequently, D-lactic acidosis-associated encephalopathy. Often, these patients have a complex of symptoms and metabolic alterations, that all may be part of the short small bowel syndrome (SSBS) [2-7]. This report demonstrates both the causal factors and the time-related consequences of the abundant lactic acid production in the SSB. With data collected from a large number of samples of mostly feces and urine, and occasionally blood, we constructed a detailed picture of the pathogenesis of D-lactic acidosis.

## MATERIALS AND METHODS

### Definition.

In this study a short small bowel (SSB) was defined as either a small bowel from which more than 70% has been resected, or, as in neonates, one with a length of less than 50 cm.

**Patients**

This study included seven patients with SBB, three children (CH) and four infants (IN); their clinical data are listed in Table 1. CH 1, CH 2 and IN 4 have been described previously [1]. All patients were consuming a lactose-free diet. At the time of study IN 4 and CH 3 had a full oral diet, whereas IN 5, -6, -7 were partially dependent on parenteral nutrition. All children with SSB received dextrin-maltose-based food as their main carbohydrate source. During enteral nutrition by gastrostoma or by nasogastric drip feeding, and also during oral nutrition, the infants and children had daily D-lactic acidemia and had regular occurrence of metabolic acidosis. This study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983. It was approved by the Ethics Committee of the University Hospital Nijmegen.

*Table 1. Clinical data of study patients with short small bowel*

| *Patient/ (yr of birth)* | *Sex* | *Cause of small short bowel*[b] | *Year of resection* | *Length of small intestine*[c] | *Ileocaecal valve present*[a] | *Colon present*[a] |
|---|---|---|---|---|---|---|
| CH 1 ('87) | F | V | 1987 | 22 | + | + |
| CH 2 ('84) | F | V | 1984 | 28 | + | + |
| CH 3 ('89) | F | ICI | 1990 | 50 | - | + |
| IN 4 ('94) | F | V | 1995 | 80 | - | + |
| IN 5 ('96) | M | CSB | -- | 25 | - | + |
| IN 6 ('96) | M | V | 1996 | 40 | + | + |
| IN 7 ('96) | M | NEC | 1996 | 50 | - | 10 cm |

a +. present; -. absent.
b V, resection due to volvulus of small intestine; ICI, ileocolic invagination; NEC, necrotizing enterocolitis; CSB, congenital short bowel (without resection).
c Length of small intestine (immediately after intestinal surgery) in cm.

*Methods*

Bacteriological analysis was performed as previously described [1]. Capacity of fecal samples to produce lactic acid was measured after a 3-hour anaerobic incubation of one part feces to nine parts 3.7% brain heart infusion-0.6% yeast extract broth with

10 mg vitamin $K_3$/l, 1% (filter-sterilized) glucose, 5 mg hemin/l (comprising BHI/YE-glucose broth) with initial pH of 5.0. The D- and L-lactic acid were quantified by enzymatic assay [8]. Serum and urine were studied qualitatively and quantitatively by use of both capillary gas chromatography-mass spectrometry; (GC-MS), especially for determining organic acids [8,9], and nuclear magnetic resonance spectroscopy according to Wevers et al [10]. Minerals (sodium, chloride, bicarbonate) were determined with a fully automated analyzer for measurements of clinical chemical parameters (Hitachi 747; Roche Diagnostics, Almere, The Netherlands) using standard procedures. The pH and base excess were determined and calculated, respectively, with a fully automated blood gas analyzer (Corning 288; Bayer Diagnostics Division, Mijdrecht, The Netherlands). The anion gap was defined as $[Na^+]-\{[HCO_3^-]+[Cl^-]\}$ in serum.

## RESULTS

### Fecal Short Small Bowel Syndrome flora

During a 10-year period, we examined about 200 SSB fecal samples. In the past 5 years we confirmed in all fecal samples of new, orally fed patients with SSB, who were receiving no antibiotic therapy, the previously reported rather constant and characteristic flora with more than 60% gram-positive rods, mainly lactobacilli [1]. After inoculation in BHI/YE-glucose broth (pH 5.0), fresh fecal samples had a marked capacity to ferment glucose completely in a rather short time, with D- and L-lactic acid as main fermentation products. Nevertheless, we found that in fecal samples of patients without acidosis, who had SSB the D- and L-lactic acid concentrations were low (i.e., not higher than in healthy control subjects without SSB). The pH of most samples usually ranged between 5.0 and 5.5, but the lowest pH observed was 3.9. A relation between the fecal content of gram-positive rods and the presence of the ileocaecal valve was not observed.

### Serum D-Lactic Acid During Short Small Bowel Syndrome Acidosis

D-lactic acid is usually unmeasurable in healthy persons; the reference value for serum L- and thus also for total lactic acid is 2.0 mmol/l or less. Serum D-lactate values of acidosis in children with SSBS generally were less than 6.8 mmol/l [8]. However, in the blood of CH 3 in the hospital, sampled during critical phases of seven acidotic episodes, total lactic acid ranged between 3.1 and 14.9 mmol/l (median

value, 10.5 mmol/l). During the next episode of acidosis of this patient, we specifically measured serum D- and L-lactic acid to be 15.5 mmol/l and 1.55 mmol/l, respectively. Blood sampling of the various patients mostly occurred several hours after the onset of hyperventilation. However, in the case of CH 3, who was in the hospital, blood was immediately, sampled as soon as hyperventilation began.

In serum of infants and children with SSB acidosis, lactic acid was always present in clearly elevated concentrations. Sometimes, increased concentrations of other organic acids (mainly 3-OH-propionic acid, p-OH-phenyl-acetic acid, p-OH-phenyl-lactic acid, phenyl-lactic acid, oxalic acid, glycolic acid and glutaric acid) were observed in blood and urine of our patients [11].

**Urinary D-Lactic Acid During Short Small Bowel Syndrome Acidosis**

Urinary D-lactic acid excretion is usually not detected in healthy persons; the reference value of L-lactic acid and thus also for total lactic acid, is 60 mmol/mol creatinine or less. In a urine sample of CH 1 collected at night, after an emergency admission to the hospital, the D-lactic acid excretion was measured at 40 mol/mol creatinine; in a sample of IN 4 it was as high as 59 mol/mol creatinine (concomitant L-lactic acid excretion was 95 mmol/mol creatinine); and in two samples of CH 3, collected during two acidotic episodes, it was 34 and 19 mol/mol creatinine, respectively. The mentioned urine sample of CH 3 (with D-lactic acid at 34 mol/mol creatinine) was also studied for organic acids both by GC-MS and by nuclear magnetic resonance spectroscopy. Lactic acid was the most important metabolite excreted, as detected by both techniques. Several other organic acids (e.g. formic acid) were detected, but only in extremely small amounts.

**Relation Between Lactic Acid and Other Acid-Base Parameters During Untreated Acidosis**

In spite of the long period of 10 years, available data concerning serum D-lactic acid, L-lactic acid, total lactic acid, bicarbonate, pH and/or anion gap, in untreated patients with SSBS acidosis, were limited. Still, the data collected from our patients made clear that the acidosis was always related to decreased serum bicarbonate (reduced to 4 mmol/l; reference range in healthy control subjects, 22-26 mmol/l) and pH (reduced to 7.05; reference range, 7.38-7.43) and to increased total serum lactic acid (increased to 17 mmol/l) and anion gap (increased to 26 mmol/l; reference range: 4-12 mmol/l). Of the anion gap parameters (defined in Materials and Methods) serum sodium was

constant, whereas serum bicarbonate (as mentioned) and chloride were much more variable.

## DISCUSSION

Just as in the previously described patients with a SSB, the new entries in our study had acquired a characteristic intestinal flora mainly consisting of lactobacilli. Because these bacteria are regarded as benign, the standard arsenal of media used in clinical diagnostic bacteriological laboratories for the isolation of bacteria is not adequate for convenient isolation and quantification of these bacteria. Especially, the tomatojuice- and the Man-Rogosa-Sharp-media facilitate these assays. Also, microscopy according to Gram's technique conveniently reveals the abundant presence of gram-positive rods, which have been shown in these patients to be mainly lactobacilli [1].

Lactobacilli can be divided in two major groups: homolactic and heterolactic. The homolactic ones produce lactic acid(s) only from fermentable sugars (not lactulose), and the heterolactic ones produce lactic acid(s), ethanol and $CO_2$. Because sugar hydrogen breath tests are based on bacterial fermentative production of molecular hydrogen from the sugar, whereas this type of bacteria cannot do so, it is useless to examine overgrowth of lactobacilli or malabsorption of sugars by means of a sugar breath test. During a glucose loading experiment in an adult with SSB, we confirmed that molecular hydrogen was not detectable in a breath test (unpublished data).

In our studies, all patients with SSB had abundant lactobacilli in the intestinal flora, and all had episodes of hyperventilation and, simultaneously, of acidosis. In general, the shorter the small bowel, the more the patient is affected by malabsorption, the more and the longer any food is available in an acidic environment for acidophilic bacteria (especially the lactobacilli), and the sooner the overgrowth of lactobacilli emerges.

The massive amounts of lactobacilli ($10^{10}$-$10^{12}$ colony-forming units/g wet feces) affect the intestinal environment and subsequently also the patient. Because of their fermentative activity in all orally or enterally fed, symptom-free patients with SSB, who are not receiving antibiotic therapy (1), D- and L-lactic acid clearly emerge daily, first in the intestinal lumen, next in serum and finally in urine [8,11]. Production of D-lactic acid may be so massive, that acute SSB-associated metabolic acidosis, also called D-lactic acidosis, may arise [2-5].

Lactic acidosis is generally defined as metabolic acidosis, in which serum lactic acid is a major factor in the decrease of serum bicarbonate. Often, in patients with lactic acidosis, serum lactic acid may transiently reach concentrations as high as 20-25 mmol/l, with systemic pH declining to 6.80 [12]. The literature on SSB contains many reports on D-lactic acidosis with hyperventilation, and the presence of serum D-lactic acid, but at concentrations of only 2 to 6 mmol/l, with near normal pH [12]. In the current study, we report that during D-lactic acidosis, serum total lactic acid transiently reached high concentrations (17.5 mmol/l) and that, consequently, systemic pH may fall to low values (e.g., 7.05) as in general (L-)lactic acidosis.

D-lactic acid was demonstrated to be the most prominent acid in serum and urine in the presence of SSB. Serum D-lactic acid was highest (up to 15.5 mmol/l) in samples that had been obtained very soon after the onset of hyperventilation. Strongly elevated D-lactic acid excretion (up to 59 mol/mol creatinine) was measured in urine that had been collected several hours after the onset of hyperventilation. It is hypothesized that in patients with SSB-induced hyperventilation who come to the hospital, a major part of the serum D-lactate has already been cleared from blood into urine by the time they reach the hospital.

Acidosis associated with SSB was mostly acute, unpredictable, and short-lasting. The onset of acidosis was especially signalled by hyperventilation. Although organic acids other than (D-)lactic acid may be increased, it is mainly the D-lactic acid load in blood and tissues that strongly affects serum pH and thus contributes to SSBS acidosis.

An increase of serum lactic acid means merely an increase of serum organic anions. The emergence of SSBS acidosis is strongly related to decrease of bicarbonate and increase of the anion gap. This may imply that during the emergence of acidosis, the serum mineral concentrations and blood gases also may change, as well as the related base excess. Anion gaps of more than 12 mmol/l have only been observed early in the acidosis.

As soon as lactic acid enters serum, the total organic anion concentration increases, whereas the protons are spread over the buffering substances: serum proteins, phosphate and bicarbonate. Thus, bicarbonate neutralizes the protons, and consequently the bicarbonate concentration decreases, and the (undissociated) carbonic acid increases. As intestinal organic acid supply continues, the buffering capacity decreases, causing neutralization to fail and, consequently, the pH to decrease [13].

As might be expected, our data confirm the compensatory mechanisms based on the chloride shift. If the increase of D-lactic acid is extremely high, the influx of its anion

is increasingly compensated by the neutralization-mediated disappearance of bicarbonate and an efflux of chloride, sometimes leading to hypochloremia [14]. Both the organic anions and equimolar amounts of protons (as bound to buffering substances) are cleared by the kidneys. The result may be an abundant excretion of a mixture of organic anions (especially D-lactate), proton-bearing phosphate and sodium and a decrease in urine pH down to 4.0. If the body is not able to restore sufficiently the efflux of organic anions by adequate production of new bicarbonate, chloride will replace these anions. This may often lead to hyperchloremia [2,4,5,15-20]. Hyperchloremia does not mask (through a lower anion gap) the serum D-lactate whatsoever [15]. Rather, it indicates that the maximal D-lactic anion level in serum has passed and that these anions are increasingly be found in urine. At sufficient supply of bicarbonate by the human metabolism, chloride decreases to normal.
The frequent neutralization in acidotic SSBS-patients by use of sodium bicarbonate solutions is meant to restore the serum pH. In these patients $H_2CO_3$ arises massively from the bicarbonate-mediated neutralization of organic acids in serum and tissues and is decomposed in the lungs. An increased amount of $CO_2$ is expired, and activates the respiratory center to ventilate at a higher rate (hyperventilation). This process stops as soon as the $CO_2$ release is reduced to normal. Consequently, hyperventilation is a marker of both the increase of organic anions in blood and simultaneous neutralization. As continuous organic acid supply goes on with a simultaneous, too slow release of $CO_2$ (due to strongly decreased bicarbonate concentration), hyperventilation stops, and a dangerous condition may result, because the progressive acidification of the body cannot be recognized anymore.

We wonder whether some of the mentioned parameters other than organic acids might be useful in monitoring and managing patients with SSBS. For example, the base excess together with the pH seem best to represent the state of the neutralisation. As long as one or both are below the lower reference value, the acidosis has not yet completely disappeared.

For a better understanding of the D-lactic acidosis in pediatric patients with SSB the essential microbiological and physiological aspects are illustrated in the following description [1,8]. Overgrowth of lactobacilli gradually emerges within 2 to 3 weeks after the introduction of oral feeding that contains fermentable carbohydrates. Just after the stomach in the resected small bowel, the pH is rather low due to the not yet neutralized gastric acid, and thus it creates an optimal environment for the lactobacilli. In contrast to controls, in these patients (because of the malabsorption), more

food is available for the lactobacilli, thus permitting them to increase. Soon, the resultant massive bacterial production of lactic acid overwhelms the buffering capacity of the pancreatic juice, transforms the whole intestine into an optimal environment, and inhibits the increase of other bacteria, thus warranting a massive production of merely lactic acid.

In all orally fed children with SSB who receive normal amounts of dietary carbohydrates, without antibiotic therapy and with normal gastric acid production, the same characteristic flora develops, comprising more than 50% (up to nearly 100%) lactobacilli. During acidosis and hyperventilation the bacterial composition of stool samples is the same as before, but the lactic acid concentration increases and the pH decreases, sometimes from approximately 6 to 7 to approximately 4.0. The differences in the colonic pH are merely temporarily fermentative effects of lactobacilli on a large amount of fermentable sugars. After the lactic acid has been resorbed from the bowel, the pH increases again, but the lactobacilli remain present. Because of the characteristic acidogenic SSB flora, which often contains an abundance of D-lactic acid-producing lactobacilli, all young pediatric SSB-patients are at high risk for excessive levels of total serum lactic acid, and thus the occurrence of acidosis may be predicted. Determination of serum pH and base excess is therefore useful in the managing of the neutralization process. In these patients, abundant amounts of lactobacilli are continuously present, even in the absence of acidosis. In the total absence of oral feeding, the lactobacilli starve, and soon die. In orally fed patients D-lactic acidemia occurs daily soon after consumption of carbohydrates, whereas D-lactic acidosis with hyperventilation occurs only as the amount of D-lactic acid in serum and tissues becomes too high. Subclinical (D-)-lactic acidosis (without hyperventilation) occurs only as the amount of serum and tissue bicarbonate becomes too low. To reach the subclinical stage, patient must pass the clinical stage, during which lactic acid is normally neutralized with bicarbonate, and oral feeding is stopped. Consequently, the subclinical stage seldom emerges.

Lactobacilli produce lactic acid, as long as suitable substrate is present. They begin as soon as the first substrate of the day enters the bowel (after breakfast) and stop in the evening after the last substrate has disappeared. Most of the bacterial L-lactic acid is catabolized for energy generation, whereas most D-lactic acid is accumulated during the day. The consequent peak concentrations in blood and urine are found early in the evening. During the whole day, D-lactic acid is renally cleared, but the

effect is most obvious during the night when no D-lactic acid is produced. Every day, the serum D-lactic acid is minimal at the first meal, increases again until peak concentration is reached after the last meal, and decreases again during the night (circadian rhythm). If the nightly clearing is prevented by nightly tube feeding, instead of decreasing, the acid and the risk of acidosis increases.

The endurance of an acidosis episode depends on the level of lactic acid accumulation in blood and tissues. At a low level of accumulation the episode lasts only a few hours, but at a high level it may last several days. Often the acidosis is neutralized with bicarbonate, and thus the episode may substantially be shortened. Normally, the moment at which the accumulation of D-lactic acid reaches the level at which pH decreases causing the onset of hyperventilation is unpredictable. Many factors may affect this process, but the most important factor is the oral consumption of low molecular weight, easily fermentable carbohydrates (as in sweets). In many cases, high serum lactate seems to represent a high-carbohydrate food, but in some cases it seems to represent a quite different phenomenon (in study). Patients who have acidosis should alter their diet to consume less easily fermentable, long-chain carbohydrates; should have a higher meal frequency, perhaps with smaller quantities, to prevent high lactate peaks, and thus lactic acidosis; and should permit nightly D-lactic acid clearing.

The primary prerequisite to the development of acidosis is the absence of a major part of the small bowel. The overproduction of lactate is merely the massive response of the lactobacilli to excessive consumption of fermentable sugars. The secondary prerequisite is an insufficient D-2-OH acid dehydrogenase activity [2,21] in neonates, infants and young children (until approximately 5-7 years). This enzymes oxidizes the D-2-OH acids, D-lactic acid included, and thus converts a major part of D-lactic acid to the easily metabolizable pyruvic acid. The low serum D-lactate and the low urinary D-lactate excretion in the bodies of older children and adults are fully explained by sufficient activity of this enzyme.

The short chain fatty acids in the human intestines are mainly produced (with lactate as the intermediate) in the colon by anaerobic bacteria other than the lactobacilli. Because the SSB flora contains up to 100% lactobacilli, short-chain fatty acids are produced in only small or even negligible amounts in stool.

In patients with SSB, lactic acidosis is primarily related to massive resection of the small bowel. Nevertheless, all other factors (e.g. sepsis and thiamine insufficiency due to the continuous malabsorption) that per se may cause lactic acid production,

may also contribute to the accumulation of total lactic acid, and thus may help induce lactic acidosis in patients with SSB.

## CONCLUSION

Because of (iatrogenic) malabsorption, strong predomination of lactobacilli in the intestinal flora is inherent in all pediatric patients, and consequently acidification may occur, depending on the amount of available fermentable carbohydrates. Many symptoms and aberrant parameters may be seen during the acidification, but the fundamental ones, which have been mentioned above (e.g. serum pH and base excess), always show the same characteristic pattern.

## ACKNOWLEDGEMENTS

The authors thank Jacqueline Corstiaensen and Jacintha Barten-Van den Elzen, Laboratory of Pediatrics, for technical support in conducting the gas chromatographic analyses; the Special Chemistry group of the Department of Clinical Chemistry for assistance with the D- and L-lactate measurements; the Department of Clinical Chemistry for analysis of serum minerals; Udo Engelke, Laboratory of Pediatrics and Neurology, for assistance with nuclear magnetic resonance measurements; and Coby Arts of the Department of Clinical Chemistry for collecting chemistry data.

## REFERENCES

1. Bongaerts GPA, Tolboom JJM, Naber AHJ, Sperl W, Severijnen RSVM, Bakkeren JAJM, Willems JL. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathogen 1997; 22: 285-93.
2. Oh MS, Phelps KR, Traube M, Barbosa-Saldivar JL, Boxhill C, Carroll HJ. D-lactic acidosis in a man with the short-bowel syndrome. N Engl J Med 1979; 301: 249-52.
3. Satoh T, Narisawa K, Konno T, Katoh T, Fujiyama J, Tomoe A, et al. D-lactic acidosis in two patients with short bowel syndrome: Bacteriological analyses of the fecal flora. Eur J Pediatr 1982; 138: 324-6.
4. Perlmutter DH, Boyle JT, Campos JM, Egler JM, Watkins JM. D-lactic acidosis in children: An unusual metabolic complication of small bowel resection. J Pediatr 1983; 102: 234-8.
5. Haan E, Brown G, Bankier A, Mitchell D, Hunt S, Blakey J, Barnes G. Severe illness caused by the products of bacterial metabolism in a child with a short gut. Eur J Pediatr 1985; 144: 63-5.

6. Vanderhoof JA, Langnas AN, Pinch LW, Thompson JS, Kaufman SS. Short bowel syndrome. J Pediatr Gastroenterol Nutr 1992; 14: 359-70.
7. Schoorel EP, Giesberts MAH, Blom W, Van Gelderen HH. D-lactic acidosis in a boy with a short bowel syndrome. Arch Dis Child 1980; 55: 810-2.
8. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems H. D-lactic acidemia and aciduria in pediatric and adult patients with short bowel syndrome. Clin Chem 1995; 41: 107-10.
9. Bakkeren JAJM, De Abreu RA, Sengers RCA, Gabreëls FJM, Maas JM, Renier WO. Elevated urine, blood and cerebrospinal fluid levels of uracil and thymine in a child with dihydrothymine dehydrogenase deficiency. Clin Chim Acta 1984; 140: 247-56.
10. Wevers RA, Engelke U, Heerschap A. High-resolution 1H-NMR-spectroscopy of blood plasma for metabolic studies. Clin Chem 1994; 40: 1245-50.
11. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems H. [(Response on) Letter to the Editor] D-lactic acidosis in patients with short bowel syndrome. Clin Chem 1995; 41: 768-9.
12. Foster DW. Lactic acidosis. In: Braunwald E, Isselbacher KJ, Petersdorf RG, Wilson JD, Martin JB, Martin AS, eds. Harrison's principles of internal medicine, 11th ed. New York: McGraw-Hill Book Company, 1987: 1797-1800.
13. Rose BD. Metabolic acidosis. In: Clinical physiology of acid-base and electrolyte disorders, 4th ed. New York: McGraw-Hill Inc., 1994: 540-603.
14. Coronado BE, Opal SM, Yoburn DC. Antibiotic-induced D-lactic acidosis. Ann Intern Med 1995; 122: 839-42.
15. Cross SA, Callaway CW. [Editorial] D-lactic acidosis and selected cerebellar ataxias. Mayo Clin Proc 1984; 59: 202-5.
16. Flourié B, Messing B, Bismuth E, Étanchaud F, Thuillier F, Rambaud JC. Acidose D-lactique et encéphalopathie au cours d'un syndrome du grêle court à l'occasion d'un traitement antibiotique. Gastroenterol Clin Biol 1990; 14: 596-8.
17. Stolberg L, Rolfe R, Gitlin N, Merritt J, Mann L, Linder J, Finegold S. D-lactic acidosis due to abnormal flora. N Engl J Med 1982; 306: 1344-8.
18. Karton M, Rettmer R, Lipkin E. Effect of parenteral nutrition and enteral feeding on D-lactic acidosis in a patient with short bowel. J Par Ent Nutr 1987; 11: 586-9.
19. Mayne AJ, Handy DJ, Preece MA, George RH, Booth IW. Dietary management of D-lactic acidosis in short bowel syndrome. Arch Dis Child 1990; 65: 229-31.
20. Ramakrishnan T, Stokes P. Beneficial effects of fasting and low carbohydrate diet in D-lactic acidosis associated with short-bowel syndrome. J Par Ent Nutr 1985; 9: 361-3.
21. Yasuda T, Ozawa S, Shiba C, Maeba T, Kanazawa T, Sugiyama M, Owada S, Ishida M. D-lactate metabolism in patients with chronic renal failure undergoing CAPD. Nephron 1993; 63: 416-22.

## 3.3 BILE ACID DECONJUGATION BY LACTOBACILLI AND ITS EFFECTS IN PATIENTS WITH A SHORT SMALL BOWEL

*Ger P.A. Bongaerts[1], René S.V.M. Severijnen[2], Albert Tangerman[3], Aad Verrips[4], Jules J.M. Tolboom[4]*

*Department of [1]Medical Microbiology, [2]Pediatric Surgery,[3]Gastroenterology and [4]Pediatrics, University Hospital Nijmegen, Nijmegen, The Netherlands*

*Journal of Gastroenterology 2000; 35: 801-804*


### INTRODUCTION

As early as 1986 Ohkohchi et al. [1] reported on the nutritional condition and the absorptive capacity of infants with a short small bowel (SSB), especially with respect to severe steatorrhea, disrupted absorption of bile acids, and subnormal concentrations of serum vitamin D and of total cholesterol, with the intake of normal meals. In 1997 the same group [2] specifically reported on the disturbed bile acid metabolism in children with SSB. In children without diarrhea, no severe fat malabsorption was recognized, and the content of total bile acids in the feces was normal to slightly increased [2]. In patients with intractable diarrhea, fat malabsorption was observed, and the fecal content of total bile acids in these patients exceeded by more than tenfold that of controls [2]. In healthy persons the primary bile acids, cholic acid and chenodeoxycholic acid, account for 60%-70% of the total serum bile acids, but in SSB-children with intractable diarrhea, they account for more than 95%. In these children the (taurine- and glycine-) conjugated bile acids accounted for only 10% of the total serum bile acids. Some children with and without diarrhea had hyperbile acidemia [2].

In the same year, 1997, we published our findings on the intestinal flora in patients with a SSB[3]. Most remarkable was the intestinal predominance of lactobacilli (up to 95%) in the fecal flora of orally fed SSB patients without antibiotic therapy [3]. Ohkohchi et al.[2] assumed that unconjugated bile acids from an indistinct origin

affected the growth of intestinal bacteria such as lactobacilli. It is clear now that the contrary is true: the intestinal lactobacilli are bile acid-resistant, and they deconjugate the bile acids [4,5], thus strongly disturbing bile acid and lipid metabolism. An essential factor in the reporteddisorder of patients with SSB is bacterial bile salt hydrolase (BSH) activity [6,7], a specific property of many *Lactobacillus* spp, especially the intestinal ones.

## INTESTINAL BACTERIA AND BILE ACIDS

In the liver, the primary bile acids, cholic acid and chenodeoxycholic acid, are produced from cholesterol, and are next conjugated with glycine or taurine. As bile constituents, the conjugated bile acids enter the gastrointestinal tract in the duodenum (see Fig. 1a.), and are important in the emulsification, digestion, and absorption of dietary lipid that occurs in the small bowel. More than 95% of the conjugated bile acids are reabsorbed in the small intestine, mostly in the terminal ileum (enterohepatic cycle [8]). The bile acids that escape absorption in the ileum (2-3% per cycle), are metabolized by colonic bacteria (mainly bacteroids [9]). Deconjugation and subsequent dehydroxylation of the conjugated primary bile acids results in the formation of the secondary bile acids, deoxycholic acid and lithocholic acid. Part of these secundary bile acids (about 30%) is absorbed in the proximal colon and enters the enterohepatic circulation, and part (about 70%) is excreted in feces. The latter loss of secondary bile acids is compensated by the liver-controlled synthesis of primary bile acids from cholesterol. Increased concentrations of unconjugated bile acids in serum are thought to arise from intestinal bacterial activity, and are therefore markers for small-intestinal bacterial overgrowth [10].

### Lactobacilli in the (short) small bowel

During some parts of the day the proximal part of the intact small bowel, i.e. the duodenum and the proximal part of the jejunum, presents an optimal "ecosystem" for intestinal lactobacilli with, on one hand, a low pH, absence of oxygen and abundance of sugars, and on the other, the bile resistance of the lactobacilli [4,5]. However, this combination of optimal conditions is limited in time. The intestinal concentrations of sugars, especially glucose, sucrose and lactose, i.e. the energy-rich substrates for lactobacilli, and of aminoacids strongly decrease due to the luminal uptake, whereas pancreatic juice effects intestinal neutralization. Therefore, the optimal "ecosystem"

exists only during a rather short time after food intake. Consequently, after this optimal "ecosystem" period the growth rate of lactobacilli strongly decreases, and for this reason, (i) the final ileal concentration of lactobacilli will not exceed $10^7$ cfu/g wet intestinal mass, and (ii) the effects of lactobacilli are limited.

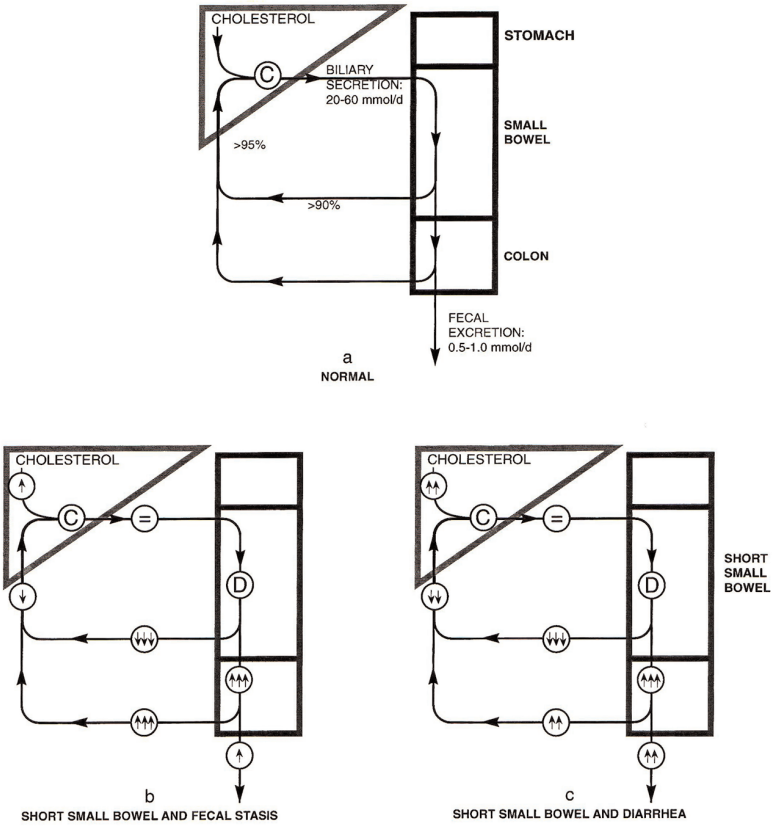
In SSB patients, however, the extensive resection has strongly reduced the uptake capacity regarding sugars and other nutrients by the luminal wall. Consequently, soon after the onset of oral feeding these patients will suffer from malabsorption. Therefore, appreciably more suitable mono- and disaccharides are available for the lactobacilli [3], which fermentatively produce lactic acid and, thus, acidify the bowel lumen [11]. In this way the initial acidity is strongly extended, and, consequently, the pancreatic juice-mediated neutralization of the acidic food mass in the duodenum and jejunum is slowed down. The prolonged acidity stimulates growth of lactobacilli, and simultaneously inhibits growth of most other bacteria [3]. Thus, a considerable portion of the fermentable sugars is consumed by lactobacilli. Consequently, an abundant characteristic flora emerges, which consists mainly of lactobacilli ($10^{10}$-$10^{12}$ cfu/g feces) and *Escherichia coli* ($10^8$-$10^{10}$ cfu/g feces [3]).

**Effect of lactobacilli in SBB patients**

Previously it has been shown that the lactobacilli, but not the coliforms, are able to deconjugate bile acids [4,5], probably in order to resist the solubilizing effect of conjugated bile acids on bacterial membranes, and thus to resist the bactericidal and cytotoxic effect of the conjugated bile acids [12,13]. Because of the massive amount of lactobacilli in the intestines of SSB-patients, the conjugated bile acids present will be rapidly deconjugated [2,14]. The fate of the bile acid molecules depends on the length of the non-resected part of both the small bowel and the colon, as well as on the intestinal passage time. With decreasing length of the ileal part of the SSB, the ileal resorption of conjugated bile acid will decrease, and the flow of deconjugated bile acid to the colon will increase, due to the increased lactobacilli-mediated deconjugation. The longer the colonic part that has additionally been resected, the less the deconjugated bile acid molecules will be resorbed from the colon.

The changes expected in the case of either a long or a short fecal passage time are presented in Fig. 1b and 1c, respectively. In both cases, the flow of deconjugated bile acid to the colon will be strongly increased. During fecal stasis, with a long passage time, colonic resorption of (deconjugated) bile acid will be strongly increased, whereas fecal excretion will fully disappear.

*Figure 1. Causes of Short Bowel Syndrome in neonates and children in %*




Representation of the enterohepatic circulation of bile acids in **a** healthy adults and **b** and **c** in extreme situations in patients with a short small bowel (SSB-) with either a very long fecal passage time (**b**), a situation which is nearly comparable with fecal stasis, or a very short fecal passage time (**c**), as in intractable diarrhea. The effect of both the lactobacilli-mediated deconjugation and massive short bowel resection on the total flow of all (i.e. conjugated plus de/unconjugated, and primary plus secondary) bile acids is compared with the identical flow in healthy controls. The effects are presented relatively as: *equal sign*, No change; *upward arrows*, increasing levels; *downward arrows*, decreasing levels. Hepatic neosynthesis of primary bile acids from cholesterol precedes the conjugation, and is suggested to equal the fecal loss of the various bile acids together. The site of conjugation (in the liver) is marked C, and of lactobacilli-mediated deconjugation (in the SSB) is marked D. For SSB-patients without fecal stasis or intractable diarrhea, intermediate bile acid flows may be derived. For a more detailed explanation, also see text.

During intractable diarrhea with a continuous short passage time, colonic resorption will be less, and fecal excretion will be strongly increased [2]. The deconjugative activity of the intestinal lactobacilli in SSB-patients, especially those with intractable diarrhea, also suggests that steatorrhoeal loss of nutritional energy may strongly contribute to the growth failure of these children.

Normally, the primary bile acids are enzymatically transformed (by chemical reduction) to secondary bile acids during intestinal bacterial fermentation of sugars. In patients with diarrhea, this process is limited, because of the limited contact time between the primary bile acids and bacteria, resulting in an extremely high percentage of unconjugated primary bile acids (95% of all bile acids) in the feces of these patients. SSB-patients without diarrhea have a rather high percentage of secundary bile acids in their feces [2].

**Significance of bile acid deconjugation in SSB patients**

The significance of the rapid lactobacilli-mediated deconjugation is that, in SSB-patients, only a very small amount of conjugated bile acids is available to facilitate the intestinal micellar uptake of triglycerides, fatty acids, cholesterol and lipophilic vitamins. This corresponds with our finding that, in SSB sera, the concentrations of cholesterol, triglycerides and lipophilic compounds, e.g., the vitamins A, D and E, were often low to low-normal: e.g., cholesterol concentration was 1.4 mM (normal range [NR]: 2.6-5.2 mM), the concentration of triglycerides was 0.8 mM (NR, 0.8-2.0 mM), the concentration of vitamin A was 0.5 μM (NR, 0.7-3.0 μM), the concentration of vitamin D was 11 nM (NR, 10-40 nM) and the concentration of vitamin E was 7.7 μM (NR, 7-33 μM). Thus, it is clear that a rather large amount of the lipophilic nutrients will not be resorbed, and will be present in the feces (sometimes observed as steatorrhea). Additional factors which contribute to fat malabsorption, steatorrhea and insufficient serum concentrations of lipophilic vitamins are: the length of the resected SSB (and colon), the absence of the ileocecal valve, and diarrhea. The larger the resected ileum, i.e., the smaller the intestinal site for conjugated bile acid-facilitated lipid uptake, the less the intact conjugated bile acid molecules will be resorbed in the enterohepatic cycle, and the more (deconjugated) bile acid molecules will arrive in the colon (Fig. 1b,c). Absence of the ileocecal valve will speed up the flow to the colon, decrease the resorption from the ileal part of the SSB, and contribute to diarrhea. In particular, because of the short contact with the bowel wall, a considerable portion of the bile acids may be lost from the enterohepatic cycle (see

Fig. 1c) during periods of frequent diarrhea. To compensate for this loss, it is suggested that, in agreement with the observed low serum cholesterol, high-density lipoprotein (HDL)-cholesterol, and low density lipoprotein (LDL)-cholesterol (unpublished data, [13]), the systemic pool of cholesterol is depleted [6,7,15,16]. Thus, the mechanism presented by De Smet et al. [7] to explain the lowering of serum cholesterol in mice intestinally treated with *Lactobacillus plantarum*, seems to be confirmed now in human SSB-patients. Theoretically speaking, probiotic lactobacilli may indeed lower the cholesterol pool in healthy people to some extent, but for a significant effect, other supporting conditions seem to be necessary.

In bile of an antibiotic therapy-free SSB patient we observed that the unconjugated bile acid had increased up to 25% of the total bile acid content, whereas in plasma of similar patients the percentage of unconjugated bile acids increased up to 73%. The hyperbile acidemia in SSB-children with and without diarrhea refects an aspect closely associated with the enterohepatic cycle: the extraction of bile acids from portal blood is much higher for conjugated than for unconjugated bile acids [17,18]. The hyperbile acidemia is explained by a higher than normal load of unconjugated bile acids to the liver, resulting in elevated levels of unconjugated bile acids in the systemic circulation.

**Management of bile acid deconjugation in SSB patients**

How to manage the lactobacilli-mediated deconjugation of bile acids? Every attempt must be made in coherence with the therapeutic management of D-lactic acidosis [3,19-21]. In spite of the mentioned deconjugation effects, lactobacilli remain rather innocent bacteria; antibiotic-mediated replacement of lactobacilli by other more pathogenic bacteria will probably create greater, especially infectious, problems.

Bicarbonate meant to neutralize a too low intestinal pH will stop the overgrowth of lactobacilli, but will also stimulate the overgrowth of other bacteria. Theoretically, replacement of the lactobacilli in SSB intestines by probiotic, L-lactic acid-producing and facultatively heterolactic lactobacilli, such as *Lactobacillus casei*, may be suitable for combating D-lactic acidosis [22], and for reducing diarrhea, but not for stopping deconjugation. A disadvantage of probiotic, non-acidophilic yeasts, e.g., *Saccharomyces boulardii*, is the production of 2 mol carbondioxide from 1 mol glucose during simultaneous production of 2 mol ethanol from the same glucose molecule. Because of its gaseous character, carbon dioxide may increase diarrhea and thus contribute to loss of nutritional fat and bile acids. We hypothesize that parenteral feeding

(to prevent fecal loss) enriched with essential lipophilic compounds and with mevalonic acid, a well-known precursor of cholesterol and thus of bile acids, would be a suitable therapy to restore both the level of essential lipophilic compounds and the depleted cholesterol pool, preferrably combined with oral feeding enriched with probiotic *L. casei*.

## CONCLUSIONS

Whereas lactobacilli are rather innocent bacteria, it is clear now that their permanent massive presence in the bowel of orally fed SSB-patients has important effects on the physiology and the metabolism of lipophilic substrates. These effects may, additionally, contribute to the very vulnerable condition of the SSB-patient.

## REFERENCES

1. Ohkohchi N, Igarashi Y, Tazawa Y, Abe H, Kobayashi Y, Ohi R, Kasai M. Evaluation of the nutritional condition and absorptive capacity of nine infants with short bowel syndrome. J Pediatr Gastroenterol Nutr 1986; 5: 198-206.
2. Ohkohchi N, Andoh T, Izumi U, Igarashi Y, Ohi R. Disorder of bile acid metabolism in children with short bowel syndrome. J Gastroenterol 1997; 32: 472-479.
3. Bongaerts GPA, Tolboom JJM, Naber AHJ, Sperl WJK, Severijnen RSVM, Bakkeren JAJM, Willems JL. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathogen 1997; 22: 285-293.
4. Tannock GW. Effect of dietary and environmental stress on the gastrointestinal microbiota. In : Hentges DJ (ed). Human intestinal microflora in health and disease. Academic Press, New York 1983, pp 517-539.
5. Tannock GW, Tangerman A, Van Schaik A, McConnell MA. Deconjugation of bile acids by *lactobacilli* in the mouse small bowel. Appl Environ Microbiol 1994; 60: 3419-3420.
6. Klaver FAM, Van der Meer R. The assumed assimilation of cholesterol by *lactobacilli* and Bifidobacterium bifidum is due to their bile salt-deconjugating activity. Appl Environ Microbiol 1993; 59: 1120-1124.
7. De Smet I, Van Hoorde L, De Saeyer N, Vande Woestyne M, Verstraete W. In vitro study of bile salt hydrolase (BSH) activity of BSH isogenic *Lactobacillus* plantarum 80 strains and estimation of cholesterol lowering through enhanced BSH activity. Microb Ecol Health Dis 1994; 7: 315-329.
8. Carey MC. The enterohepatic circulation. In: Arias I, Propper H, Schachter D, Shafritz DA (eds). The liver: biology and pathobiology. Raven Press, New York 1982, pp 429-465.

9. Drasar BS, Hill MJ, Shiner M. The deconjugation of bile salts by human intestinal bacteria. Lancet 1966; 1966: 1237-1238.
10. Masclee A, Tangerman A, Van Schaik A, Van der Hoek EW, Van Tongeren JHM. Unconjugated serum bile acid as a marker of small intestinal bacterial overgrowth. Eur J Clin Invest 1989; 19: 384-389.
11. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems H. D-lactic acidemia and aciduria in pediatric and adult patients with short bowel syndrome. Clin Chem 1995; 41: 107-110.
12. Kobayashi A, Kawai S, Ohbe Y, Benno Y. Fecal flora of infants with biliary atresia: effects of the abscence of bile on fecal flora. Am J Clin Nutr 1988; 48: 1211-1213.
13. Van der Meer R, Termont DSML, De Vries HT. Differential effects of calcium ions and calcium phosphate on cytotoxicity of bile acids. Am J Physiol 1991; 260: G142-147.
14. Bolt MJG, Stellard F, Sitrin MD, Paumgartner G. Serum unconjugated bile acids in patients with small bowel bacterial overgrowth. Clin Chim Acta 1989; 181: 87-102.
15. Grunewald KK. Serum cholesterol levels in rats fed skim milk fermented by *Lactobacillus acidophilus*. J Food Sci 1982; 47: 2078-2079.
16. Gilliland SE, Nelson CR, Maxwell. Assimilation of cholesterol by *Lactobacillus acidophilus*. Appl Environ Microbiol 1985; 49: 377-381.
17. Gilmore IT, Thompson RPH. Plasma clearance of oral and intravenous cholic acid in subjects with and without chronic liver disease. Gut 1980; 21: 123-127.
18. Aldini R, Roda A, Morselli Labate AM, Cappelleri G, Roda E, Barbara L. Hepatic bile acid uptake: effect of conjugation, hydroxyl and keto groups, and albumin binding. J Lipid Res 1982; 23: 1167-1173.
19. Ramakrishnan T, Stokes P. Beneficial effects of fasting and low carbohydrate diet in D-lactic acidosis associated with short-bowel syndrome. J Par Ent Nutr 1985; 9: 361-363.
20. Mayne AJ, Handy DJ, Preece MA, George RH, Both IW. Dietary management of D-lactic acidosis in short bowel syndrome. Arch Dis Child 1990; 65: 229-231.
21. Bongaerts G, Bakkeren J, Severijnen R, Sperl W, Willems H, Naber T, Wevers R, Van Meurs A, Tolboom J. *Lactobacilli* and acidosis in children with short small bowel. J Pediatr Gastroenterol Nutr 2000; 30: 288-293.
22. Bongaerts GPA, Tolboom JJM, Naber AHJ, Bakkeren JAJM, Severijnen RSVM, Willems JL, Sperl WJK. *Lactobacillus* flora in short bowel syndrome. Dig Dis Sci 1997; 42: 1611-1612.

## 3.4 $CO_2$ PRODUCED BY LACTOBACILLI AS CAUSE OF ABDOMINAL COMPLAINTS IN SHORT SMALL BOWEL SYNDROME

*RSVM Severijnen[1], GPA Bongaerts[2], AT Naber[3], JJM Tolboom[4].*

*Department of [1]Paediatric Surgery, [2]Medical Microbiology, [3]Gastroenterology and [4]Paediatrics, University Medical Centre Nijmegen, Nijmegen, The Netherlands*

*Submitted for publication*

### ABSTRACT

Stool analysis in patients with a short small bowel showed an intestinal flora with 90% lactobacilli. Sugar fermentation by $CO_2$-producing lactobacilli may be the cause of abdominal pain, diarrhoea and flatulence.

In the faeces of a child the heterolactic $CO_2$-producing *Lactobacillus fermentum* was dominant. The only gas the bubbling faeces and *L. fermentum* produced was $CO_2$. With oral feeding, a parenterally fed girl suffered from a distended abdomen, flatulence, diarrhoea and abdominal pain, and without oral feeding she did not. After glucose loading in an adult woman, D-lactic acidaemia developed as well as massive intestinal $CO_2$ production; there was no hydrogen gas present in the expelled air. The patient became increasingly flatulent and ill. After passing flatus and diarrhoea all symptoms disappeared.

*Conclusion*: Oral consumption of easily fermentable carbohydrates in short small bowel patients, will give rise to production of $CO_2$ from lactobacilli, causing flatulence, diarrhoea and abdominal pain.

### INTRODUCTION

The American Gastroenterological Assocation in its publication "Short bowel syndrome and intestinal transplantation" states that less than 200 cm. of functional small intestine is its definition of short bowel syndrome [1]. We count 75 cm remaining

jejuno-ileal segment for an infant born at term, and 50 cm for infants born between 28 and 35 weeks gestational age as our limits for a short small bowel (SSB) in accordance with 30% remaining intestinal length according to the measurements of Touloukian and Walker Smith [2]. For children above one year we keep 100 cm as the limit of an SSB.

Common characteristics of the most SSB-patients are: diarrhoea, increased flatulence and abdominal pain. The diarrhoea is caused by a combination of factors as rapid intestinal transit time and loss of absorptive capacity, but abnormal bacterial growth may also occur. Steatorrhoea from inadequate fat absorption is often present [3]. Because of nutrient malabsorption in the small intestine these patients develop a characteristic intestinal flora consisting mainly of lactobacilli [4,5]. With massive lactic acid production and subsequent low pH, the lactobacilli inhibit the growth of other bacteria in the intestine [6]. This particular flora causes daily D-lactic acidaemia and aciduria in many patients [5,6], less frequent acute D-lactic acidosis [6] and probably also sporadic D-lactic acidosis-associated encephalopathy [4].

Over the years we have studied SSB-patients, and some characteristic diarrhoea-related features are seen. Most SSB-patients suffer frequently from audible intestinal bubbling, visibly distended abdomen, flatulence, painful abdominal cramps and diarrhoea. Abdominal cramps are decreased by flatulence and diarrhoea. These symptoms are strongly related to food consumption. Apple juice and lactose-containing dairy products are diarrhoeagenic and cause abdominal complaints in our patients and have to be avoided. The frequency of bowel movements in SSB-patients varies markedly (up to 20 times/day), but normally ranges between 4 and 10 times per day.

The total bacterial concentration in the faeces of SSB-patients ($10^{10}$-$10^{12}$ cfu/g wet faeces) is the same or slightly higher than that of healthy people ($10^{10}$-$10^{11}$ cfu/g wet faeces). However 85-90% of the faecal flora of the SSB-patients studied, are Gram-positive and mainly *lactobacilli* [4]. Homolactic lactobacilli species (e.g. *Lactobacillus acidophilus*) produce only 2 mol lactate from fermentable monosaccharides (such as glucose or galactose) and no gas, whereas heterolactic species (e.g. *Lactobacillus fermentum*) produce 1 mol lactate, 1 mol ethanol, and 1 mol of the gaseous $CO_2$. Since lactobacilli are predominantly present in the intestine of SSB-patients, we postulate that the occurrence of diarrhoea in SSB-patients is mainly determined by the fermentative activity of the present heterolactic lactobacilli on fermentable sugars such as glucose, fructose, sucrose and lactose.

We collected data to confirm that $CO_2$ gas in particular may be the main cause of the abdominal complaints in SSB-patients.

## METHODS

### Patients

The clinical data of three SSB-patients, CH 2, CH 4 and AD 7, have been studied in more detail. They have been previously described by us [4] and are listed in Table 1. The small bowel of the girl CH 2 had been resected on the second day after her birth. Presented observations and experimental data were obtained, when she was between 4 and 6 years old.

*Table 1. Clinical data of the patients with a short small bowel*

| *Patients* | *CH 2* | *CH 4* | *AD 7* |
|---|---|---|---|
| Year of birth | 1984 | 1990 | 1950 |
| Cause of resection | volvulus | ischaemic incident | mesenteric thrombosis |
| Length of small bowel (cm) | 28 | 45 | 50 |
| Ileocoecal valve present | + | + | - |
| Colon present | + | + | 85% |

The length of the remaining small bowel of the girl CH 4 was 45 cm after a second resection. Parenteral feeding was gradually replaced by enteral feeding, consisting of both oral nutrition and enteral drip-feeding by a gastrostomy. The presented observations and experimental data were obtained when she was 7 years of age.

The SSB-children, CH 2 and CH 4, were on an essentially lactose-free oral diet, with soy milk replacing dairy products, and with micronutrient supplementation; they received dextrin-maltose-based food as the main carbohydrate source. With oral feeding the patients suffered daily from D-lactic acidaemia and aciduria, and very often from flatulence, abdominal pain and diarrhoea. Other common features were a characteristic Gram-positive faecal flora consisting mainly of lactobacilli [4] and an excessively distended abdomen especially after meals.

The small bowel of the adult female patient AD 7 was resected in 1991. The reported glucose loading tests were performed five years after resection. The patient was on an essentially lactose-free, but otherwise normal caloric diet enriched with carbohydrates and proteins. She also received additional parenteral nutrition. With normal oral feeding she suffered daily not only from slight D-lactic acidaemia and aciduria, but also from diarrhoea. Other common features were a characteristic Gram-positive faecal flora with mainly lactobacilli [4] and an excessively distended abdomen, especially after each meal. The mean defecation frequency of AD 7 was about 16 times a day, and sometimes this increased up to 20 times a day. She used loperamide as antidiarrhoea medication.

This study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983, and approved by the Ethics Committee of the University Hospital Nijmegen.

**Bacteriological analysis**

Bacteriological analysis was performed as previously described [4]. For microscopy, smears of faecal samples were studied after Gram-staining. For total counts of non-acidophilics, faecal samples were plated on both aerobic blood agar and anaerobic Brucella blood agar. To count the total number of the acidophilic lactobacilli the same samples were cultured anaerobically on De Man-Rogosa-Sharpe agar (Oxoid CM-361) and on Tomato Juice agar (Oxoid CM-113). The capacity of either faeces or lactobacilli to produce gas was tested in a test tube equipped with a reversed Durham test tube in filter-sterilised 5% glucose solution.

**Biochemical analysis**

The only gas accumulated under the reversed Durham test tube that is fully absorbed by the growth medium after the addition of NaOH pellets, is $CO_2$ (chemical conversion to non-gaseous soluble bicarbonate). For quantification of L-lactate in blood and urine, an enzymatic assay with L-LDH was performed, and for quantification of D-lactate L-LDH was replaced by D-LDH [4]. Quantitative analysis of organic acids was performed by capillary gas chromatography-mass spectrometry [7]. Urine was also studied by nuclear magnetic resonance (1H-NMR) spectroscopy according to Wevers et al [8].

## RESULTS

The diarrhoeal stools of CH 2 were often bubbling. In her faeces the resident *L. fermentum* ($10^{11}$-$10^{12}$ cfu/g wet faeces) predominated. This is almost 100 fold more than the resident *L. acidophilus* and the other, transient intestinal bacteria [4]. The capacity of the isolated *L. fermentum* to produce merely $CO_2$ was confirmed. The bubbling faeces (with 90% Gram-positive rods identified as lactobacilli; $10^{12}$ cfu/g wet faeces and 10% Gram-negative rods) have also been found to produce massively $CO_2$; production of hydrogen or methane gas could not be demonstrated.

Patient CH 4 suffered from a distended abdomen and intense abdominal pain with increasing frequency. At the age of seven years her body weight fell from 19.5 kg to 17.5 kg in three months. From the moment she was hospitalised, she received both parenteral and oral feeding. At this point her faecal flora contained 85% Gram-positive rods (identified as lactobacilli; $10^{12}$ cfu/g wet faeces), 10% Gram-negative rods and 5% yeast. During incubation of her faeces with glucose, $CO_2$ was produced. After four days of parenteral feeding in combination with some oral feeding the composition of the faecal flora had not changed, and she still had severe abdominal pain and a distended abdomen. In the next three days of merely parenteral feeding, abdominal pain and distension disappeared completely and so did the lactobacilli in the faeces.

In patient AD 7 the diarrhoeagenic effect of glucose in SSB was studied twice with an interval of four months during 3 hours after loading with 50 g glucose dissolved in 200 ml water. Her faecal flora consisted of 90% Gram-positive rods (among others $CO_2$-producing lactobacilli), 5% Gram-positive cocci, 5% Gram-negative rods, les than 1% Gram-negative cocci and sporadically yeast. The glucose intake lasted five minutes. Immediately after ingestion, intestinal fermentation started and a bubbling sound was heard. During the test large amounts of intestinal gas were produced. The patient felt bloated, first in the upper, later in the lower abdomen, and the whole abdomen became visibly distended. After 15 minutes nausea started, and after 20 minutes abdominal pain and cramps started. At 30 minutes she became flatulent, and slowly felt the urge to defecate. After 45 min she felt ill and had to lie down. After 75 minutes she suffered from severe diarrhoea for about 15 minutes. After 90 minutes all the symptoms mentioned above had gone. During the whole experiment $H_2$ in expired air was constantly 3 parts per million. Serum glucose increased from 4.5 to a maximum of 8.0 mM, D-lactate from 150 µM to a maximum of 400 µM, and L-lactate from 1000 µM to a maximum of 1600 µM. In addition, by NMR investigation a

slight increase of serum acetate was observed, but not of other organic compounds. Serum pH was continuously 7.33. Urinary excretions of total lactic acid just before and after the experiment were low: 30 mmol/mol creatinine. The gas produced after incubation of a small sample of faeces in a glucose solution, was confirmed to be $CO_2$.

## DISCUSSION

Flatulence is a common event in most people and is generally ascribed to intestinal production of gas, mainly $H_2$, but in many people also $CH_4$. Strict anaerobes are normally absent in SSB-patients, and therefore bacterial methane production is not expected to occur. The collected data concerning patients $CH_2$ and $CH_4$ indicate that in SSB-patients without antimicrobial therapy or neutralization of gastric acid and with a normal gastric acid production, flatulence, abdominal pain and diarrhoea are strongly associated with the lactobacilli-mediated production of $CO_2$ gas. As far as we know this is the first time that an intestinal flora is reported to produce up to about 100% $CO_2$ as gaseous metabolic product.

In order to elucidate in more detail the relation between flatulence, diarrhoea and abdominal pain, the intestinal flora of AD 7 was manipulated by use of glucose loading. The data of this study confirmed that after glucose loading in the breath test the $H_2$-production is negligible, and after incubation of the faeces with glucose the only gas produced was $CO_2$. If in the loading experiment only 5 g (10% of the load) of the glucose (Molecular Weight = 180) is not absorbed but fermented by heterolactic lactobacilli, then 600 ml $CO_2$ gas should be produced (molar gas volume: about 22.4 L). With increasing $CO_2$ production intra-intestinal gas-pressure and volume increase and this is seen as abdominal distension. In turn, the intra-intestinal pressure may be diminished by deflation. If the intestines become too distended, and deflating activity is not in relation to the production, abdominal pain is thought to arise.

Four related factors are causative for the massive $CO_2$ production: the diet, malabsorption as a consequence of massive resection, heterolactic bacterial activity and the subsequent low intestinal pH due to fermentative lactic acid production [5]. During intestinal heterolactic bacterial fermentation in acidic watery solution gaseous $CO_2$ will increase massively because of its limited solubility. Consequently, the intestinal lumen will be filled with gas and become distended. The diarrhoeagenic character of apple juice (containing mainly glucose and fructose) and of dairy produce (containing

lactose) in these patients is thought based on the suitability of these sugars for intestinal lactobacilli-mediated fermentation.

Polymeric carbohydrates from ingested food are mixed in the intestine with fermentative SSB-flora, and fermented after depolymerisation by human amylase. Just as of fermenting dough the volume of the intestinal, fermenting food mass increases markedly due to the gaseous $CO_2$ inside. As this gas-pressure passes a threshold, it is thought to create a rather strong neurophysiological stimulus that forces the lumen muscles to contract and the anal sphincter to relax and expel the intestinal contents [9], before all normal digestive processes have been completed, resulting in diarrhoea. If peristalsis is reduced, as in stasis of intestinal contents, bacterial metabolites, e.g., D-lactic acid, can accumulate and contribute to acidosis and/or encephalopathy. Antimicrobial therapy, neutralization of gastric acid or therapeutically reduced gastric acid production may favour uncontrolled intestinal overgrowth of various fermentative micro-organisms [4] and the final effect is unpredictable. Since yeasts produce nearly 2 mol $CO_2$ per mol glucose, they may also increase flatulence, pain and diarrhoea. Heterofermentative microorganisms, like *Escherichia coli*, produce both $CO_2$ and $H_2$. If in SSB-patients $H_2$ is produced, it is done only by *E. coli* and some transient facultative or strict anaerobes, and not by either lactobacilli or yeast. Since obligatory homolactic lactobacilli do not produce $CO_2$ or any other gas, we postulate that they not only prevent diarrhoea, but also may even contribute to intestinal stasis in the absence of heterolactic lactobacilli or yeasts. The presence of the facultative heterolactic *Lactobacillus casei* as probiotic with limited $CO_2$ production theoretically seems to be preferable above the naturally present *lactobacilli*, such as the obligatory heterolactic *L. fermentum* and the obligatory homolactic *L. acidophilus*.

The mentioned data indicate that after the glucose loading intestinally a massive bacterial fermentation with concomitant gaseous $CO_2$-production had occurred, which caused a short transit time, and resulted in diarrhoea, flatulence and pain. To avoid such a massive intestinal gas production one may choose for sugar-free polymeric carbohydrate diet or probiotic L.casei as food supplement, but this study makes clear that for SSB-patients especially high fat, low fermentable carbohydrate diets are very interesting [10]. The absence of fermentable carbohydrates inhibits outgrowth of lactobacilli, and thus massive intestinal gas production will be limited. This agrees with our finding that in the absence of oral feeding, i.e., in the absence of intestinal carbohydrates the faecal lactobacilli of $CH_4$ completely disappeared. This study may also explain the fact that others have not found the uniform overwhelming predomi-

nance of lactobacilli in intestinal overgrowth [11]: the intestinal presence of dietary, fermentable carbohydrates strongly affects the outgrowth of lactobacilli and their consecutive effects in patients with a short small bowel and in the study of Bouhnik [11] only two of the 63 patients had a short small bowel.

An important consequence may be that a smaller percentage of primary cholic acids will be deconjugated, and thus fat and lipophilic vitamins will be taken up more efficiently [3].

## CONCLUSION

Due to malabsorption in SSB patients, a part of the ingested carbohydrates is available for heterolactic fermentation. This leads to massive $CO_2$ production, which is mainly responsible for the flatulence, abdominal discomfort and diarrhoea. Not only the use of probiotic *L. casei* in the diet is thought to reduce the massive $CO_2$ production, but also the use of high fat, low fermentable carbohydrate diet.

## ACKNOWLEDGEMENTS

For technical support for the bacteriological analyses we thank Ilse Breuker (Department of Medical Microbiology), for the gas chromatographic analyses we thank Jacqueline Corstiaensen and Jacintha Barten-van den Elzen (Laboratory of Paediatrics and Neurology), for the D- and L-lactate measurements the Special Chemistry group of the Department of Clinical Chemistry and for the NMR measurements Udo Engelke (Laboratory of Paediatrics and Neurology). Dr E.N. Robertson, Department of Anaesthesia is thanked for the English text corrections.

## REFERENCES

1. American Gastroenterological Association. Medical position statement: Short bowel syndrome and intestinal transplantation. Gastroenterol 2003; 124: 1105-1110.
2. Touloukian RJ, Walker Smith GJ. Normal intestinal length in preterm infants. J Pediatr Surg 1983; 18: 720-723.
3. Bongaerts GPA, Severijnen RSVM, Tangerman A, Verrips A, Tolboom JJT. Bile acid deconjugation by *Lactobacilli* and its effects in patients with a short small bowel. J Gastroenterol 2000; 35: 801-804.

4. Bongaerts GPA, Tolboom JJM, Naber AHJ, Sperl W, Severijnen RSVM, Bakkeren JAJM, Willems JL. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathogen 1997; 22: 285-93.
5. Caldarini MI, Pons S, D'Agostino D, De Paula JA, Greco G, Negri G, Bustos D. Abnormal fecal flora in a patient with short bowel syndrome. An in vitro study of pH on D-lactic acid production. Dig Dis Sci 1996; 41: 1649-1652.
6. Bongaerts G, Bakkeren J, Sperl W, Naber T, Wevers R, Willems H, Severijnen R, Van Meurs A, Tolboom J. Metabolic acidosis in children with a short small bowel. J Pediatr Gastroenterol Nutr 2000; 30: 288-293.
7. Bakkeren JAJM, De Abreu RA, Sengers RCA, Gabreëls FJM, Maas JM, Renier WO. Elevated urine, blood and cerebrospinal fluid levels of uracil and thymine in a child with dihydrothymine dehydrogenase deficiency. Clin Chim Acta 1984; 140: 247-256.
8. Wevers RA, Engelke U, Heerschap A. High-resolution 1H-NMR-spectroscopy of blood plasma for metabolic studies. Clin Chem 1994; 40: 1245-1250.
9. Roth HP, Fein SB, Sturman MF. The mechanisms responsible for the urge to defecate. Gastroenterology 1957; 32: 717-726.
10. Vanderhoof JA, Young RJ. Enteral nutrition in Short Bowel Syndrome. Sem Pediatr Surg 2001; 10: 65-71.
11. Bouhnik Y, Alain S, Attar A, Flourié B, Raskine L, Sanson-Le Pors MJ, Rambaud J-C. Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome. Am J Gastroenterol 1999; 94: 1327-1331.

## 3.5 LACTIC ACIDOSIS CORRECTION BY INTESTINAL YEAST OVERGROWTH. RESULT OF ANTIBIOTIC COCKTAIL TREATMENT IN SHORT SMALL BOWEL

*Ger Bongaerts[1], René Severijnen[2], Daniela Skladal[3], Jan Bakkeren[4], Wolfgang Sperl[5]*

*Department of [1]Medical Microbiology, [2]Paediatric Surgery and [4]Laboratory of Paediatrics and Neurology, University Medical Centre Nijmegen, Nijmegen, The Netherlands ; [3]University Children's Hospital Innsbruck, Innsbruck, Austria, and [5]Kinderspital Landeskrankenanstalten Salzburg, Salzburg Austria*

*Submitted for publication*

### ABSTRACT

During acidotic periods in a girl with a short small bowel very high D-lactate concentrations were measured in blood and urine. Initially the characteristic faecal flora contained many lactobacilli. After treatment with antibiotic cocktails had started, also many yeasts were cultured. Antibiotic cocktail therapy soon reduced both the acidosis-assisted symptoms and the lactobacilli-mediated D-lactate production, but it increased strongly the percentage of yeast in the faecal flora. In 4-6 weeks after each antibiotic cocktail course the percentage of yeast decreased, whereas the percentage of intestinal lactobacilli increased; simultaneously also D-lactate increased in blood and urine. Patient felt very well with high percentages of intestinal yeast, but with high percentages of lactobacilli she suffered from acidosis. The yeast was identified as the potentially pathogenic *Candida glabrata*. The mentioned data together with data from literature were explained as follows: during several weeks the selected yeast acted as a metabolic and microbiological buffer. In an ecological competition for glucose the intestinal yeast cells prevented both abundant bacterial D-lactic acid production and thus D-lactid acid-associated acidosis, and besides they permitted sufficient bile acid-mediated uptake of fats and especially lipophilic vitamins.

## INTRODUCTION

In Short Small Bowel (SSB) patients an extensive part of the small bowel has been resected, and therefore they may have malabsorption [1]. The microbiological consequence in our patients was a change from the normal intestinal flora to one of mainly lactobacilli. Several species abundantly produce D-lactic acid from easily fermentable carbohydrates [2]. Consequently, D-lactic acidemia and aciduria may arise daily [3]; at times D-lactic acidosis can be seen, and less frequently, D-lactic acidosis-associated encephalopathy [1]. SSB-patients may be severely diseased by lactobacilli, which are generally known to be beneficial [2,3,4]. We report the fascinating consequence of antibiotic therapy, which was applied to stop acidification of the body due to lactobacilli.

## PATIENT

Our patient is a girl born in 1989. Her ileum and ileocaecal valve were resected at the age of 9 and 15 months because of an ileocolic invagination and later an ileus; most of the colon remained present. The final length of the jejunum was 50 cm after the second resection. Initially, she was on a combination of parenteral and enteral drip-feeding, next on continuous nasogastric drip-feeding and finally on a lactose-free oral diet at the age of four years. She got dextrin-maltose mixtures as main carbohydrate source. During enteral and later oral nutrition, she had D-lactic acidemia and suffered frequently from acidosis.

## METHODS

Microbiological analysis was performed as previously described [3]. Percentages of bacteria and yeasts in faecal samples were determined by microscopy after Gram-staining. In spite of the about 10-fold difference between the bacterial and yeast size, the percentages concern the numbers of the Gram-stained rod-shaped or spherical (small) bacteria, or of the Gram-positively stained (large) yeasts seen under the microscope. Total lactate in serum and urine was studied by use of capillary gas chromatography-mass spectrometry, and D- and L-lactate in serum and urine by enzymatic assay [3,5].

**Acidotic characteristics**

In January 1992 and May 1993, while short periods of acidosis with somnolence occurred, we measured total serum lactate values of 10 and 15 mM (N: 0-2 mM), respectively. During similar periods in November 1992 and in November 1993 base excess values were -12.9 mM and -20 mM (N: -3 mM to +3 mM). In November 1993 we found the faecal microbial flora not only characteristic for SSB-patients, but even rather extreme, since it contained 97% Gram-positive rods, which appeared to be mainly lactobacilli, and further 1% Gram-positive cocci, 1% Gram-negative rods, and 1% yeasts. In February 1995 during an acidotic period, in a small urine sample a very high D-lactate excretion of 34 mol/ mol creatinine was measured (concomitant L-lactate excretion was 0.1 mol/ mol creatinine). In 1995 the range of measured D-lactate concentrations in various serum samples in non-acidotic periods was 2-5 mM (N: <0.1 mM). In May 1995, as she was acidotic again, we observed a very high serum D-lactate concentration of 15.5 mM (concomitant serum L-lactate was 1.5 mM).

**Management of antibiotic treatment**

In SSB-patients with enteral feeding and antibiotic mono-therapy (e.g. vancomycin or neomycin) susceptible lactobacilli have been found to be replaced by other, resistant, lactobacilli [2]. Therefore, from summer of 1992 till now her bowel flora was regularly treated according to Vanderhoof et al. [1] with an oral antibiotic cocktail containing metronidazole, gentamicin, and initially colistin (till summer of 1994), which was later replaced by vancomycin, for a course of 5-7 days, every 4 to 6 weeks to decontaminate the bowel. In episodes of severe acidosis, feeding was stopped, bicarbonate given, and antibiotic therapy started [4]. Antibiotic therapy soon reduced the acidosis-associated symptoms.

**Effects of antibiotic therapy**

In August 1995 faecal samples, produced during and after antibiotic therapy, revealed strongly increased yeast percentages (up to 40%). Because of these preliminary results, in April 1996 we started a study on the beneficial effect of the antibiotic cocktail in this patient. Because of the great distance between the patient (in Austria) and our laboratories (Nijmegen, The Netherlands) the study was limited to the faecal microbial composition and the urinary excretion of lactic acid (at about 16.00 h) during acidotic periods. During this study patient's faecal flora remained characteristic (45-70% Gram-positive rods, which have been proved mainly to be lactobacilli, 0-5%

Gram-positive cocci, and 0-10% Gram-negative rods), but had still changed, since it contained also 25-50% yeasts. This high concentration was probably selected by the regular antibiotic therapy courses.

The percentage of yeasts during two successive antibiotic courses increased from 25 to 50%, and the percentage of Gram-positive rods decreased from 70% to 45%. Within the next 2-3 weeks the reverse process took place. These data have been paralleled by remarkable lactate excretions in small urine samples (15-50 ml). During the mentioned two successive antibiotic courses D-lactate excretion decreased from 3.5 and 19.0 mol D-lactate/ mol creatinine, respectively, to <0.1 mol D-lactate/ mol creatinine. After the antibiotic courses they strongly increased again to 19.0 and 6.4 mol/ mol creatinine, respectively (all concomitant L-lactate excretions were <0.1 mol/ mol creatinine). Patient's mood, activity and condition increased concomitantly not only with the decrease of faecal lactobacilli and the urinary excretion of D-lactate, but also with the increase of faecal yeast. During the next years the frequency of acidotic/ encephalopathic episodes decreased. In December 2000 and January 2001 faecal samples contained 80-95% lactobacilli, 0-10% Gram-positive cocci, 0-5% Gram-negative rods, and 5-20% yeasts. The effect of the antibiotic cocktail on the microbial composition was lower than in 1995 and 1996, but still essentially the same.

**Identification of yeast isolates**

From 6 different faecal samples produced between the start and the end of 1996 and 4 samples produced in 2000 and 2001 we isolated and identified the yeast. All samples yielded identical isolates with the same biochemical profile in the Auxacolor test (Biorad; Marnes la Coquette, France; cf. 6); they were identified as *Candida glabrata*.

## DISCUSSION

Lactobacilli are generally considered to be non-pathogenic bacteria. However, this patient demonstrated that the massive intestinal overgrowth of lactobacilli in SSB-patients (maximal count: $10^{11}$ - $10^{12}$ cfu/g wet faeces) may disease the body due to the systemic acidification after massive uptake of especially D-lactic acid that is abundantly produced in the remaining bowel after resection. As SSB-patients become older, both the frequency and the height of D-lactic acid levels strongly decrease [3] probably due to the increase in the human body tissues of the enzyme D-2-hydroxyacid dehydrogenase that converts D-lactic acid to pyruvic acid [7,8]. This may explain why

in 2000/2001 the frequency of acidotic episodes was rather low. Consequently, the frequency of oral antibiotic therapy decreased, and also the intestinal yeast. *C. glabrata* is generally recognised as potentially pathogenic yeast, which may cause intestinal infections. However, this patient demonstrated that during the antibiotic therapy the massive intestinal overgrowth of C. glabrata (maximal count: $10^9$ - $10^{10}$ cfu/ g wet faeces) did not cause disease. As we observed no signs of fungaemia during the antibacterial therapy, patient's intestinal defence mechanism was considered adequate. The antibiotic cocktail inhibited the intestinal growth of lactobacilli and thus the lactobacilli-mediated lactic acid production. This enabled the yeast to grow out massively. Immediately after an antibiotic course the abundant intestinal concentration of yeast delayed the renewed outgrowth of lactobacilli, since the yeast consumed the major part of the substrates available for microbial growth. The more the lactobacilli acidify the intestinal environment and pH decreases again, the more the lower pH will inhibit the yeast to grow. With this explanation we want to emphasise that specific, metabolic processes of intestinal microbes are of essential importance in health and disease.

This case demonstrates that a massive amount of an intestinally present potentially pathogenic yeast, e.g., *C. glabrata* does not cause disease, if the body is in a healthy condition, and/or has body defence mechanisms. The main function of the selected yeast is even to act as both a metabolic and a microbiological buffer: in the competition for substrates, the majority of yeast prevents the minority of lactobacilli to grow out rapidly, and thus to acidify the body. The yeast also prevents lactobacilli to deconjugate cholic acids [9,10] and thus it strongly prevents the inhibition of cholic acid-mediated uptake of fats and especially of lipophilic vitamins.

This case also supports our hypothesis concerning the intestinal events of both probiotic bacteria and yeasts [11], and the use of probiotic yeast as alternative for antibiotic therapy [12,13]. Simultaneously, the question rises whether especially during childhood it may be a good choice to treat similar acidotic SSB-patients with a non-pathogenic yeast, e.g., the probiotic *Saccharomyces boulardii* [14,15], concomitantly with the antibiotic cocktail courses.

## CONCLUSION

This case study explains by an ecological competitive mechanism why the empirical procedure of intermittent antibiotic cocktail therapy mentioned above is effective to combat the symptoms of the SSB-syndrome, e.g., D-lactic acidosis and lack of lipophilic vitamins, and so justifies its use. However, this antibiotic therapy promotes massive outgrowth of yeast, possibly pathogenic. It can be considered to replace this yeast by a non-pathogenic one, like the probiotic *Saccharomyces boulardii* [16].

## REFERENCES

1. Vanderhoof JA, Langnas AN, Pinch LW, Thompson JS, Kaufman SS. Short bowel syndrome. J Pediatr Gastroenterol Nutr 1992; 14: 359-70.
2. Bongaerts GPA, Tolboom JJM, Naber AHJ, Sperl W, Severijnen RSVM, Bakkeren JAJM, Willems JL. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathogen 1997; 22: 285-93.
3. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems H. D-lactic acidemia and aciduria in pediatric and adult patients with short bowel syndrome. Clin Chem 1995; 41: 107-10.
4. Bongaerts G, Bakkeren J, Severijnen R, Sperl W, Willems H, Naber T, Wevers R, Van Meurs A, Tolboom J. *Lactobacilli* and acidosis in children with short small bowel. J Pediatr Gastroenterol Nutr 2001; 30: 288-93.
5. Bakkeren JAJM, De Abreu RA, Sengers RCA, Gabreëls FJM, Maas JM, Renier WO. Elevated urine, blood and cerebrospinal fluid levels of uracil and thymine in a child with dihydrothymine dehydrogenase deficiency. Clin Chim Acta 1984; 140: 247-56.
6. Verweij PE, Breuker IM, Rijs AJMM, Meis JFGM. Comparative study of seven commercial yeast identification systems. J Clin Pathol 1999; 52: 271-3.
7. Oh MS, Phelps KR, Traube M, Barbosa-Saldivar JL, Boxhill C, Carroll HJ. D-lactic acidosis in a man with the short-bowel syndrome. N Engl J Med 1979; 301: 249-52.
8. Yasuda T, Ozawa S, Shiba C, Maeba T, Kanazawa T, Sugiyama M, Owada S, Ishida M. D-lactate metabolism in patients with chronic renal failure undergoing CAPD. Nephron 1993; 63: 416-22.
9. De Smet I, Van Hoorde L, De Saeyer N, Vande Woestyne M, Verstraete W. In vitro study of bile salt hydrolase (BSH) activity of BSH isogenic *Lactobacillus plantarum* 80 strains and estimation of cholesterol lowering through enhanced BSH activity. Microb Ecol Health Dis 1994; 7: 315-29.
10. Bongaerts GPA, Severijnen RSVM, Tangerman A, Verrips A, Tolboom JJM. Bile acid deconjugation by *Lactobacilli* and its effects in patients with a short small bowel. J Gastroenterol 2000; 35: 801-4.
11. Bongaerts GPA, Severijnen RSVM. The beneficial, antimicrobial effect of probiotics. Medical Hypotheses 2001; 56: 174-7.

12. Bongaerts GPA, Severijnen RSVM. New strategies in antimicrobial therapy. Medical Hypotheses 2001; 56: 178-80.
13. Rodrigues ACP, Nardi RM, Bambirra EA, Vieira EC, Nicoli JR. Effect of Saccharomyces boulardii against experimental oral infection with Salmonella typhimurium and Shigella flexneri in conventional and gnotobiotic mice. J Appl Bacteriol 1996; 81: 251-6.
14. McFarland LV. Saccharomyces boulardii is not Saccharomyces cerevisiae. Clin Infect Dis 1996; 22: 200-1.
15. McFarland LV, Bernasconi P. Saccharomyces boulardii: a review of an innovative biotherapeutic agent. Microb Ecol Health Dis 1993; 6: 157-71.
16. Berg R, Bernasconi P, Fowler D, Gautreux M. Inhibition of *Candida albicans* translocation from the gastrointestinal tract of mice by oral administration of Saccharomyces boulardii. J Infect Dis 1993; 168: 1314-8.

# 4

# Consequences of a short small bowel

## 4.1 NORMAL DEVELOPMENT OF IMMUNITY IN YOUNG CHILDREN WITH A SHORT SMALL BOWEL

*RSVM Severijnen[1], JMJH van Krieken[2], IPJ van Wijk-Verschuure[3], GPA Bongaerts[4], JJM Tolboom[3], CMR Weemaes[3].*

*Department of [1]Paediatric Surgery, [2]Pathology, [3]Paediatrics and [4]Medical Microbiology, University Medical Centre Nijmegen, Nijmegen, The Netherlands*

*Submitted for publication*

### ABSTRACT

Many septic periods during parenteral nutrition were observed in five young children with a short small bowel. Immunological studies were performed in these patients. Serum immunoglobulins and T-cell subpopulations were normal according to age. In an ex-premature girl a normal development of mucosal immunity was demonstrated in the bowel. After removal of central venous catheters, sepsis did not occur in these children. Translocation due to enteric stasis, bacterial overgrowth, a central venous catheter and parenteral nutrition play a more decisive role in developing septicaemia than does immunity.

### INTRODUCTION

Protection of an individual against harmful agents entering the digestive system occurs in the first place via non-immune mechanisms like vomiting, gastric acid, small intestinal mucus, intestinal motility and colonic defense mechanisms like the balanced ecological system of the commensal flora.

Gut-associated lymphoid tissue (GALT), an important part of the lymphocyte based adaptive immune system, needs specific recognition of cells and memory. The immune response is predominantly humoral with IgA most prevalent in intestinal secretions. Gut associated immunity develops parallel with other lymphoid organs

and the development of the spleen and peripheral lymph nodes parallels the development of Peyer's patches in the intestine. T- cells do not populate the intestine until the thymus is ready to prime T-lymphocytes. This process starts during foetal development and further maturation continues after birth. Gastrointestinal immune function of the human infant is immature and remains so for the first months [1]. Within 1 or 2 weeks after birth IgA and IgM producing plasma cells are abundant in the lamina propria and T-cells also develop. The immaturity of the neonatal gut barrier may facilitate the passage of enteric bacteria across the intestinal mucosa [2]. GALT plays an integral role in regulating transepithelial passage of bacteria by synthesizing more immunoglobulins than any other lymphoid organ [3,4] and 80-90 % of this is secretory IgA. A significant level of IgA is produced by neonates at the end of the second week of life [1].

Short small bowel (SSB) is characterized by malabsorption and malnutrition as a result of inadequate bowel length. In children we consider the diagnosis SSB as a length of less than 75 cm for neonates born after 35 weeks of gestation and less then 50 cm at an earlier gestational age as measured during surgery [5].
In patients with an SSB, an extensive part of the mucosal immune system is removed together with the intestine. In most children resection has been performed shortly after birth when the mucosal immune system is immature. Systemic sepsis with gastrointestinal bacteria or fungi is frequently found [4,6]. It is generally assumed the reason for these multiple infections is a diminished immunologic capacity after extended resection. We therefore studied the immune competence in some children with an SSB (Table 1) and report the findings.

*Table 1. Patient data*

| *Patient* | *year of birth* | *gestational age* | *length of bowel* | *age on resection* |
|---|---|---|---|---|
| CH 4 | 1990 | at term | 45 cm and colon | 4 years |
| CH 5 | 1996 | 34 weeks | 25 cm and colon | 1 day |
| CH 7 | 1996 | 33 weeks | 50 cm and sigmoid | 11 days |
| CH 8 | 2001 | at term | 50 cm and colon | 3 weeks |
| CH 9 | 2001 | 31 weeks | 45 cm and colon | 1 day |

## PATIENTS

CH 4, a girl, was admitted at the age of four years with sepsis and fever caused by an ischaemic intestinal accident. She developed multiple abscesses both around the wound and intra-abdominally. After surgery she was totally parenteral nutrition (PN) dependent and growth was delayed.

After the bowel resection, she suffered from sepsis due to *Staphylococcus epidermidis* on six, and *Enterococcus faecalis* on three occasions. *Klebsiella oxytoca*, *Escherichia coli*, *Pseudomonas aeruginosa*, a fungus, Rhodotorula species, and the yeast, *Candida guilliermondii* were also identified in blood cultures at later occasions. Gram-positive rods, one time identified as *Lactobacillus species* were cultured on three occasions. In the last case she was on treatment with probiotic lactobacilli.
CH 5, a boy with a jejunal atresia developed diarrhoea and malabsorption after surgery. He became totally PN-dependant. Several episodes of sepsis occurred. On abdominal X-rays distended loops of bowel were often visible. Physical growth was delayed. Blood cultures at different times revealed *Klebsiella oxytoca*, *Enterococcus faecalis*, *Enterobacter cloacae* and *Citrobacter freundii*. Later *Staphylococcus aureus* was isolated from an implantable vascular access system and *Staphylococcus epidermidis* from a central venous line.

CH 7, a boy was born prematurely at gestational age of 33 weeks and a weight of 1510 grams. As a result of perinatal asphyxia he developed periventricular leucomalacia. He was mentally retarded, blind and deaf. The indication for surgery was necrotizing enterocolitis on day 11. His physical growth was delayed. He suffered from recurrent septic episodes with *Enterobacter cloacae* and *Enterococcus faecalis* during the first 14 months, with multiple positive cultures of *Staphylococcus aureus* from his gastrostomy.

CH 8, a boy, had only two umbilical vessels. At the age of three weeks he developed acute abdominal problems due to malrotation and volvulus. A bowel resection was performed. He received both PN and breast milk orally. Abdominal X-rays at the age of 1 and 2 years showed dilated intestinal loops. Between the ages of one and 18 months he suffered on nine occasions from a *Staphylococcus epidermidis* infection, as diagnosed by blood culture. At the point of skin entry of several central venous lines he was however, colonised with *Staphylococcus aureus*.

CH 9, a girl, prematurely born at 31 weeks, had a deteriorating condition in utero due to an antenatal volvulus because of a malrotation. Immediately after birth, sur-

gery was performed with resection of necrotic bowel and construction of a jejunostomy and ileostomy. PN was started and she was fed with breast milk.

*Table 2. Immunological data of the patients Immunoglobulins in g/l, cells in $10^9$/l*

| *Patient* | *age* | *IgG* | *IgA* | *IgM* | *CD3+* | *CD4+* | *CD8+* |
|---|---|---|---|---|---|---|---|
| CH 4 | 4 y | 8.26 | 0.46 | 0.70 | | | |
| | 12 y | 10.10 | 0.97 | 2.00 | 1.65 | 0.77 | 0.42 |
| CH 5 | 8 m | 4.12 | 0.64 | 0.77 | | | |
| | 2 y | 2.7 | 1.0 | 0.57 | | | |
| | 4 y | 12.5 | 1.74 | 0.82 | | | |
| CH 7 | 10 m | 1.47 | 0.13 | 1.23 | | | |
| | 15 m | 4.0 | 0.7 | 1.1 | | | |
| | 3 y | 4.3 | 0.7 | 0.7 | | | |
| CH 8 | 2m | 4.02 | 0.24 | 0.88 | 2.40 | 1.84 | 0.44 |
| | 5 m | 3.76 | 0.22 | 0.94 | | | |
| CH 9 | 1 m | 2.05 | <0.07 | 0.56 | 3.28 | 2.44 | 0.80 |
| | 1.5 m | 3.16 | 0.67 | 0.43 | | | |
| | 2 m | 3.80 | 0.44 | 2.12 | | | |
| *Normal values* | | | | | | | |
| *age* | *IgG* | *IgA* | *IgM* | *CD3+* | *CD4+* | *CD8+* | |
| newborn | 6.1-15.4 | 0.01-0.04 | 0.06-0.3 | 2.8-6.5 | 2.1-4.9 | 0.5-1.6 (1 wk-2 m) | |
| 3 months | 1.7-5.6 | 0.05-0.5 | 0.3-1.0 | 2.3-6.5 | 1.5-5.0 | 0.5-1.6 (2 m-6 m) | |
| 6 months | 2.0-6.7 | 0.08-0.7 | 0.3-1.0 | | | | |
| 1 year | 3.3-11.6 | 0.1-1.0 | 0.4-1.7 | | | | |
| 2-6 year | 4.0-11.0 | 0.1-1.6 | 0.5-1.8 | | | | |
| 7-12 year | 6.0-12.3 | 0.3-2.0 | 0.5-2.0 | 1.0-2.0 | 0.5-1.3 | 0.3-0.8 | |
| adult | 7-16 | 0.7-4 | 0.4-2.3 | | | | |

At the age of three weeks she had a sepsis with *Candida albicans* isolated in three blood cultures within one week and was treated with fluconazol. At the age of six weeks, after closure of her ileostomy, she again developed sepsis with *Morganella morganii*, isolated from eight blood cultures as well as from a culture of abdominal fluid. Despite treatment according to antibiotic susceptibility testing, eradication failed and she died two weeks later from ongoing sepsis.

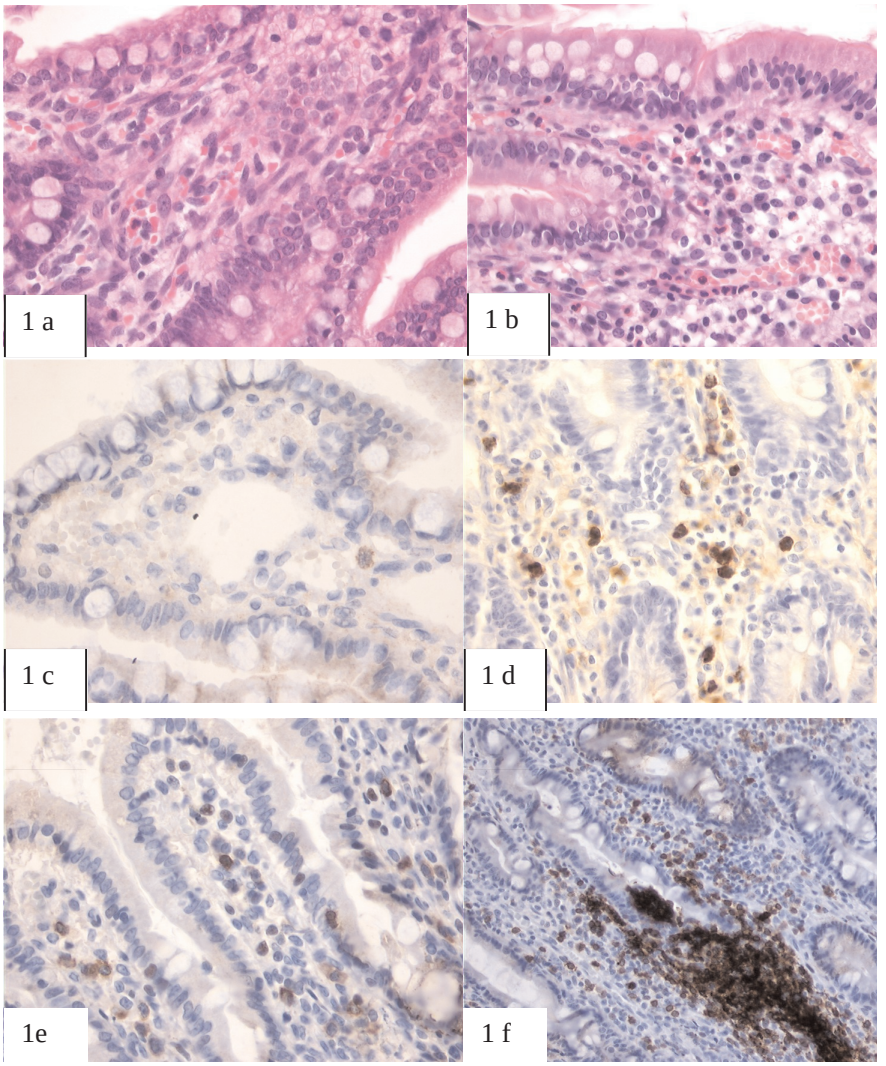



*Figure 1*. All figures are from the small bowel of CH9, figure a-e are 400 x, figure f is 200x enlarged. Fig. 1**a**. Normal small intestinal villus at birth showing only an occasional lymphocyte but no plasma cells. Fig. 1**b**. Normal villus at six weeks showing lymphocytes and plasmacells in the lamina propria and several intra-epithelial lymphocytes. Fig. 1**c**. Normal small intestinal villus at birth lacking lymphocytes and plasmacells. IgA staining is negative. Fig. 1**d**. Lamina propria at six weeks showing IgA-positive plasmacells. Fig. 1**e**. Normal villus at six weeks stained for CD 3 showing positive T- lymphocytes in the epithelium and the lamina propria. Fig. 1**f**. CD 20 staining showing the B- cells of a Peyer's patch in intimate relationship with the epithelium.

**Immunological results**

Immunological studies in all these children revealed normal values for immunoglobulins according to age and normal T-cell immunity (Table 2).

CH 9 showed a normal development of bowel immunity according to age. Lymphocyte and plasma-cell development and the IgA-presentation at six weeks with T- and B-cells are clearly visible (Figure 1). She also developed normal serum IgA levels at two months despite her prematurity. She had excretion of IgA and some IgG in the faecal fluid at the age of six weeks. All the children presented above had several episodes of sepsis, both with intestinal and skin flora. They all had central venous catheters and PN during this period. When parenteral feeding could be stopped and the lines removed, the septic episodes ceased.

## DISCUSSION

Development of serum immunoglobulins and T cell immunity was normal according to age in these young children. However, septicaemia was frequently demonstrated. The age at which bowel resection is performed appears to be unimportant. The eldest child CH 4 had similar problems with infections as the younger ones.

Even in young infants the immunity of the remaining bowel develops normally after surgery as CH 9 showed with normal mucosal immunity according to age (Figure 1, table 2). However, despite development of mucosal immunity and excretion of secretory IgA, she developed a fatal sepsis with species derived from intestinal flora.

Despite the normal development of the immune system, sepsis was common in the children with SSB. The microorganisms most frequently determined were Gram-negative rods and enterococci, originating from the bowel. These findings are in agreement with a significantly higher incidence of catheter sepsis described in children with SSB, with enteric organisms being responsible in 62% of these cases (6). Even *S. epidermidis* can originate in the intestines (7). Children with a small bowel shorter than 50 cm have a higher frequency of catheter-related sepsis, particular by enteric microorganisms. Terra and co-workers have proposed a relationship between the remaining length of the bowel and catheter-related sepsis (8). However, the length of the remaining bowel below a certain length did not appear to be an important factor in our patients. Extended small bowel resection is related to extensive loss of lymphoid tissue. Terra also suggested that the sepsis might be evidence of the occurrence of bacterial translocation (8). Bacterial translocation can be defined as the migration

of viable endogenous bacteria from the gastrointestinal lumen to the mesenteric lymph nodes of other organs (9). It is related to rupture of the gastrointestinal barrier, which occurs in situations as endotoxaemia, malnutrition, trauma and burns (10,11). PN is also described as a predisposing factor (12). A reduced villous height and frequent bacterial translocation in the group with a central venous catheters and PN has been described (13).

Our oldest patient CH 4 had lost a major part of her small bowel at the age of four years when she had already developed a normal immune response. Despite this, she had sepsis with intestinal microorganisms similar to the youngest child suggesting that immunity may be less important in translocation.

Animal studies have shown that translocation increases with enteric stasis, bacterial overgrowth and PN (2,11). Both enteric stasis and microbial overgrowth increase the contact and contact time between the luminal wall and microbes, such as bacteria and yeasts. This increases the chance that rupture of the gastrointestinal barrier may occur and microbes translocate. Reduced gut motility may therefore be a more important cause of translocation than reduced immunity. Our patients had dilatation of the bowel when septicaemic. This dilatation can be seen as indicative of both enteric stasis and bacterial overgrowth. However, after stopping PN and removal of the central venous catheters the children did not have septicaemia any more, even when they still showed dilatation of the small bowel.

These case histories suggest that the combination of a central venous catheter with PN and the poor condition of the remaining small bowel play a more decisive role in developing septicaemia due to microbial translocation than does a reduced immune response.

## ACKNOWLEDGEMENT

The authors thank Dr. E. Robertson anaesthesiologist, for the English language editing.

## REFERENCES

1. Mannick E, and Udall JN (1996) Neonatal Gastrointestinal Mucosal Immunity. Clin Perinatol 23: 287-304.
2. Wells CL, Maddaus MA, Simmons RL (1988) Proposed mechanisms for translocation of intestinal bacteria. Rev Infect Dis 10: 958-79.

3. Mestecky J and Russell MW (1997) Immunoglobulins and their contribution to defense mechanisms: an overview. Biochem Soc Trans 25: 457-62.
4. Dickinson EC, Gorga JC, Garrett M, et al. (1998) Immunoglobulin A supplementation abrogates bacterial translocation and preserves the architecture of the intestinal epithelium. Surg 124: 284-90.
5. Touloukian RJ, Walker Smith GJ (1983) Normal intestinal length in preterm infants. J Pediatr Surg 18: 720-3.
6. Kurkchubasche AG, Smith SD, Rowe MI (1992) Catheter sepsis in short-bowel syndrome. Arch Surg 127: 21-5.
7. Pierro A, van Saene HKF, Donnell SC, et al. (1996) Microbial translocation in neonates and infants receiving long-term parenteral nutrition. Arch Surg 131: 176-9.
8. Terra RM, Plopper C, Waitzberg DL, et al. (2000) Remaining small bowel length: association with catheter sepsis in patients receiving home parenteral nutrition: evidence of bacterial translocation. World J Surg 24: 1537-41.
9. Berg RD and Garlington AW (1979) Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. Infect Immun 23: 403-11.
10. O'Dwyer ST, Michie HR, Ziegler TR, et al. (1988) A single dose of endotoxin increases intestinal permeability in healthy humans. Arch Surg 123: 1459-64.
11. Deitch EA (1990) Intestinal permeability is increased in burned patients shortly after injury. Surg 107: 411-6.
12. Alverdy JC, Aoys E, Moss GS (1988) Total parenteral nutrition promotes bacterial translocation from the gut. Surg 104: 185-90.
13. McAndrew HF, Lloyd DA, Rintala R, et al. (1999) Intravenous glutamine or short-chain fatty acids reduce central venous catheter infection in a model of total parenteral nutrition. J Pediatr Surg 34: 281-5.

## 4.2 CONTRIBUTION OF GROWTH HORMONE TREATMENT IN CHILDREN WITH A SHORT SMALL BOWEL

*RSVM Severijnen[1], ECAM van Swieten[1], JJM Tolboom[2], GPA Bongaerts[3], EML Rammeloo[4], EJ Postema[5], CMR Weemaes[2].*

*Departments of [1]Paediatric Surgery, [2]Paediatrics, [3]Medical Microbiology and [5]Nuclear Medicine, University Medical Centre St. Radboud, Nijmegen, The Netherlands; [4]Bernhoven Hospital, Veghel, The Netherlands*

*Submitted for publication*

### ABSTRACT

Four children with a short small bowel and dependent on parenteral nutrition for more than six months received short-term treatment with growth hormone for seven to eighteen weeks in 1997. They all gained weight. One child achieved intestinal autonomy. Three other children stopped parenteral nutrition temporarily, two during the course and one three months later. Three years later these three children received further treatment with growth hormone for one and a half to three years. One of them almost achieved nutritional autonomy and a second child remained dependent on parenteral nutrition. In the third case parenteral nutrition did not need to be restarted. Growth hormone had a positive effect on anabolism and height in all children.
*Conclusion*: Treatment with growth hormone contributed to improving the intestinal function in these children with a short small bowel. There was an increase in height even though the children did not reach target height.

### INTRODUCTION

Short small bowel (SSB) is characterized by malabsorption and malnutrition as a result of inadequate bowel length. It can be defined either as resection of more than 70% of the small bowel, or as the need for parenteral nutrition (PN) for more than six weeks after small bowel resection [17,22]. We consider 75 cm remaining jejuno-ileal

segment for an infant born at term, and 50 cm for infants born between 28 and 35 weeks gestational age as our limits for an SSB. This is in accordance with the 30% remaining intestinal length according to the measurements of Touloukian and Walker Smith [20]. For children older than one year we keep 100 cm as the limit.

Due to the loss of intestinal absorptive surface, children develop malabsorption and malnutrition, which may lead to intestinal failure and dependency on PN. Frequent complications of long-term PN are infections, thrombosis and cholestasis [19].
The prognosis of children with SSB depends mostly on the length and function of the remaining part of the intestine and its adaptation. Patients who are dependent on PN, even when it is administered at home and at night, experience a reduced quality of life due to the impact of the administration of PN on daily life and the possible complications [10].

Since the publication by Byrne [6] in 1995, the short-term use of growth hormone (GH) has been proposed as a new treatment for children with SSB. The theoretical basis is that GH has an insulin-like growth factor (IGF) mediated skeletal effect and a direct non-IGF-mediated anabolic effect on muscle and fat tissue and thus probably also on intestinal tissue. In a meta-analysis of all trials published up till 2001 Ling concluded that the benefit of growth hormone and glutamine administration with or without a high carbohydrate low fat diet, was marginal or nonexistent [12]. In a six months trial on glucocorticosteroid-dependent children performed in 2002, Mauras showed that GH could influence body composition, bone metabolism and linear growth [13].

Scolapio commented on the lack of any significant increase in fat absorption in all published studies and advised against using growth hormone in patients with the short small bowel syndrome [16]. In one of our previous studies [5] we found an explanation for the disturbed fat absorption viz., the overwhelmingly high concentration of lactobacilli in the intestines of patients with SSB is able to deconjugate bile acids. This means that only small amounts of conjugated bile acids are available to facilitate the intestinal micellar uptake of triglycerides, fatty acids, cholesterol and lipophilic vitamins.

## PATIENTS AND METHODS

We studied treatment with growth hormone in SSB children dependent on PN for more than six months. All the patients have been described previously [4]. Below they are numbered in the same way.

Table 1 summarizes the history of the four children and the age at which they started GH treatment.

*Table 1. Histories of the four patients treated with GH for intestinal failure*

| | *Year of birth* | *Age at resection* | *Small bowel length* | *Ileo-caecal valve* | *Parenteral nutrition before short-term GH treatment* | *Time short-term GH-treatment* | *Parenteral nutrition restarted* |
|---|---|---|---|---|---|---|---|
| CH 4 | 1990 | 4 years | 45 cm + colon | Present | 3 years | 9 weeks | + after 15 months |
| CH 5 | 1996 | 1 day | 25 cm + colon | Resected | 1 year | 7 weeks | + after 10 days |
| CH 6 | 1996 | 11 weeks | 40 cm + colon | Present | 1 year | 9 weeks | - |
| CH 7 | 1996 | 11 days | 50 cm + sigmoid | Resected | 1 year | 18 weeks | - |

CH 4 was a healthy girl until the age of four years when she suffered an acute intestinal ischaemic accident and underwent bowel resection and several laparotomies. She spent six months in hospital and received PN via a central venous catheter. It was necessary to replace the central venous catheter eight times due to infections. She was discharged home where she received home-PN for 3 years. In 1997 she was treated with GH for a short term and 3 months later, after stopping PN a lack of growth occurred. In 1999, PN was reinstituted initially via central venous catheters, but this again caused frequent occlusion and infections, including one episode with a fungus (*Candida guilliermondii*) thrombus in the heart. An arteriovenous shunt was constructed in 2001 and several revision procedures were necessary. After removal of the central venous catheters, there were no more infections or septic episodes.

CH 5 was born with intestinal atresia. At the initial laparotomy stomata were created because of the difference in size between the jejunum and ileum. They could be closed after five weeks. A resection of the ileocaecal valve was performed later because of a nearly complete intestinal obstruction and suspected stenosis at that site. At the age of 11 months, he underwent a bowel lengthening procedure according to Bianchi [2] performed by professor K.L. Waag in Mannheim (Germany). This improved intestinal passage and enabled enteral nutrition. Short-term GH and gluta-

mine treatment for seven weeks was started two months later and because of the continuous need for PN, long-term GH treatment was started. He continuously receives, via gastrostomy, Neocate Advance® an oligomeric nutritional formula based on amino acids. This has improved bowel wall integrity, decreased the number of diarrhoeal episodes and thus prevented dehydration, which was a common problem until that time.

CH 6 was born prematurely at a gestational age of 31 weeks with a weight of 1185g. He suffered from bloody stools in the first week of life and sepsis at seven weeks. Necrotizing enterocolitis (NEC) was suspected. At laparotomy no necrosis or malrotation was discovered. He underwent seven more laparotomies for volvulus with necrosis, abdominal abscesses and fistulae. While receiving PN central venous catheters were replaced five times because of multiple infections and thrombosis of the subclavian vein.

CH 7 was born prematurely at a gestational age of 33 weeks with a weight of 1510 gram. After six days he was found to be suffering from NEC for which he underwent multiple bowel resections. He also had cerebral damage due to perinatal asphyxia and periventricular leucomalacia. We included this handicapped boy in the short-term and long-term treatment programmes in an attempt to stop and later to prevent the impending use of PN, as he had stopped growing in weight and height.

In 1997, the four children received subcutaneous GH (Genotropin®) at a dose of 0.4 $U/kg^{-1}/day^{-1}$ (0.14 $mg/kg^{-1}/day^{-1}$) for 7 to 18 weeks and intravenous glutamine (Dipeptiven®) 0.3 till 0.6 $g/kg^{-1}/day^{-1}$ in the PN solution depending on the amount of PN the child received [21].

In 2000, we started long-term GH administration in three of these children: CH 4, CH 5 and CH 7. They were treated with GH at a dose of 0.2 $U/kg^{-1}/day^{-1}$ (0.07 $mg/kg^{-1}/day^{-1}$) for one and a half years (CH 7) and three years (CH 4 and CH 5). Glutamine was not given in the long-term study.

In all the cases, bowel length had been measured at the time of the most recent intestinal resection (Table 1).

During long-term GH, height and weight were measured every three months, and IGF values were determined regularly. Patients CH 4 and CH 5 underwent total body Dual Energy X-ray Absorptiometry (DEXA) to estimate the body composition on four different occasions. For this purpose, a QDR4500 Elite (Hologic, Inc., Waltham, MA, USA) was used. Bone mineral densities (BMD) of the lumbar spine (L1-L4) and total body (tBMD) were determined, as well as the bone mineral content of the total body (tBMC) and percentage of fat (%Fat). The DEXA scan was performed with the

child lying lightly dressed on the pad. No sedation was used. Hologic's software and database were used to process the data.

## RESULTS

Table 1 summarizes the history of the four children and the age at which they started GH treatment. They all had growth failure with height and growth beneath the 5th percentile [1].

### Short-term GH results

CH 4 was still on PN at the end of the short-term treatment with GH, but later, the central venous catheter was removed and PN stopped. She had gained 1.2 kg during 9 weeks of GH therapy. We tried to do without any parenteral therapy for 15 months, but her condition deteriorated and we had to restart PN.

CH 5 showed a weight gain of 20% from 7.1 to 8.5 kg and we hoped he could manage without PN but this proved impossible. After 10 days and a weight loss of over 10%, he received another central venous catheter for PN.

CH 6 gained 20% in weight from 4.4 to 5.2 kg, he achieved intestinal autonomy and it was possible to stop all PN after 9 weeks. He did not receive any further GH treatment. He was discharged after spending ten months in hospital and has been doing well ever since.

CH 7 gained 2.5 kg or 35% in weight and was managing without PN.

CH 4 and CH 6 did not suffer from oedema or hand pain, which are described as side-effects of GH treatment [8, 18]. CH 7 showed a weight loss of 15% after stopping GH treatment, but one week earlier PN had also been stopped. CH 5 showed a 10% weight loss after stopping GH.

After the short-term treatment, all four children could be weaned from PN. Permanent intestinal autonomy was achieved in CH 6, while in CH 7 the result was temporarily. In CH 4, PN was stopped after three months for a period of 15 months; and in CH 5, PN could only be stopped for 10 days.

### Long-term results of GH treatment

Overall data recorded during the long-term treatment are presented in Table 2. Before the start of long-term GH treatment the height standard deviation (SD) scores of CH 4, CH 5 and CH 7 decreased in one to three years by 0.8, 1.6 and 2.3 SD, respectively.

After the start of long-term GH therapy, increases were seen in height SD scores. These were most obvious in the first year (0.7 to 1.0 SD) and became less in the second year (0.2 to 0.4 SD).

*Table 2. Height measurement and Body Mass Index in SSB-children on long-term GH treatment*

| | *Age at start long-term GH treatment* | *Height SD score* | | *Target height SD score* | *Weight for height SD score* | | *Body Mass Index SD score* | |
|---|---|---|---|---|---|---|---|---|
| | | *Start* | *End* | | *Start* | *End* | *Start* | *End* |
| CH 4 | 9 years | - 2.62 | - 1.77 | + 0.21 | - 0.51 | 0.30 | - 0.51 | 0.31 |
| CH 5 | 4 years | - 3.24 | - 1.78 | - 1.54 | - 0.28 | 0.50 | - 0.28 | 0.50 |
| CH 7 | 4 years | - 4.29 | - 2.92 | - 0.74 | - 0.87 | 0.06 | 0.86 | 0.91 |

At the age of 12 years CH 4 is still dependent on PN for over 50% of her caloric needs, but she has an anabolic status, reflected by greater muscular strength in sporting activities, such as swimming. She is also feeling much better, but her walking distance is restricted.

At the age of seven years, CH 5 is still on PN for 5-10%, but at the start he required over 50%. He receives home PN 1-2 nights a week.

CH 7 was treated with PN till the short term GH treatment and then stopped. Without PN his condition worsened but the severe difficulties with earlier central venous catheter insertion and complications made us decide to postpone PN administration and start GH again in an attempt to avoid restarting PN. He responded well and was kept on enteral nutrition only. Growth hormone treatment was stopped after one and a half years after reaching our goal of keeping him without PN.

The three patients showed an increase in height SD score of 0.85, 1.46 and 1.37, respectively. However, none of them reached the anticipated growth curve or target height. BMI values increased in all patients (Table 2).

Body composition was measured in two patients (Table 3). This could not be done in CH 7, because of psychomotor retardation. CH 4 showed an increase in BMD of the lumbar spine and total body. The increase in BMD of the lumbar spine was normal for her age; she remained on the same percentile. Total BMD did not increase as

much as was expected for a girl of that age [23]. Her total fat percentage decreased 7.2%. CH 5 showed an increase in Body Mass Index (BMI) and a decrease in fat of 6.5%. Bone mineral content values did not increase significantly when corrected for age. Indeed, the decreased. BMD of the lumbar spine did not increase over time, which is abnormal and the tBMD even decreased.

IGF values varied during long-term GH treatment, but showed an overall increase: in CH 4 from 9.4 to 16.6 nmol/l, in CH 5 from 11.1 to 19.5 and in CH 7 from 6.5 to 13.2 nmol/l. There were no significant changes in the other laboratory measurements during the treatment period.

*Table 3. DEXA (Dual Energy X-ray Absorptiometry) body composition during long-term GH*

| *CH 4* | *Bone Mineral Density lumbar spine (g/cm²)* | *Standard deviation of the mean* | *Bone Mineral Density total body (g/cm²)* | *Bone Mineral Content (g)* | *Fat %* |
|---|---|---|---|---|---|
| Start | 0.441 | -2.7 | 0.784 | 754.0 | 26.2 |
| 6 months | 0.462 | -2.6 | 0.770 | 765.8 | 18.2 |
| 11 months | 0.502 | -2.4 | 0.778 | 819.3 | 17.4 |
| 16 months | 0.517* | -2.8 | 0.811 | 1035.5 | 19.0 |
| ***CH 5*** | | | | | |
| Start | 0.420 | -1.8 | - | - | - |
| 8 months | 0.419 | -2.0 | 0.723 | 416.2 | 19.5 |
| 10 months | 0.436 | -1.8 | 0.693 | 409.7 | 18.2 |
| 16 months | 0.428 | -2.4 | 0.678 | 410.5 | 13 |

* means significant increase

## DISCUSSION

All children had positive effects from GH therapy since they could endure more enteral nutrition, and needed less PN, both in short and long-term treatment. Both high and low doses of GH had positive effects.

Most of the previous publications on this subject were short-term studies with GH dosages ranging from 0.024 [8] to 0.14 $mg/kg^{-1}/day^{-1}$ [23]. It was reported that 40% of the patients could be weaned from PN. Double blind studies [15, 18], however, did

not confirm these results. In our short-term study, we used GH dosages of 0.4 $U/kg^{-1}/day^{-1}$ (0.14 $mg/kg^{-1}/day^{-1}$) in combination with glutamine and could wean the patients from PN for some time.

Glutamine is described as preferential nutrition for the small intestine in infants. It provides energy for the enterocytes, promotes electrolyte absorption and supports immune function [9]. Intravenous glutamine treatment may be of value to support enterocyte metabolism in an effort to prevent infections from bacterial translocation while enteral intake and absorption is still restricted. When total intestinal autonomy has been reached after short-term GH and glutamine therapy it is not clear how much either of these products contributed to the process.

In our long-term GH treatment program for SSB children, we prescribed the dosage used normally in GH deficiency of 0.2 $U/kg^{-1}/day^{-1}$ (0.07 $mg/kg^{-1}/day^{-1}$) for one and a half years (CH 7) to three years (CH 4 and CH 5) without glutamine.

Long-term GH treatment may succeed in stimulating enteral absorption. This was the case in CH 7 in whom treatment could be stopped after one and a half years upon reaching our goal of intestinal autonomy. GH treatment without adequate enteral feeding will not help to improve bowel function. In CH 4, PN was necessary despite GH therapy. This might be explained on the basis of the nutritional problems of the patient. Continuous abdominal problems, possibly caused by $CO_2$ production of the lactobacilli [3], contributed to the decision to stop enteral nutrition and restart PN in the year before long-term GH therapy. She suffered frequent abdominal pain during enteral nutrition and regularly refused to eat.

CH 5 is currently almost without PN despite the very long adaptation period of seven years. This is in accordance with the hope of Schwartz et al. [14] that growth factors may lead to permanent enhancement of intestinal function, eliminate the need for PN and avoid intestinal transplantation.

Ladd et al. also observed a late effect of GH supplementation on nutritional independence in two children after treatment periods of 2.5 and 8 years respectively. One patient became independent of PN, in the other patient PN requirements were greatly reduced [11].

We saw fewer episodes of sepsis in CH 5 and after adding GH at the age of four years, they almost ceased. We are therefore not convinced that GH therapy facilitates bacterial translocation as was suggested by Eizaguirre et al. [7]. The combination of PN and a central venous catheter in children with SBB almost certainly leads to an increased susceptibility to infections and sepsis, especially if insufficient enteral nutri-

tion is provided to maintain integrity of the intestinal tract wall. No further infections were seen after the construction of an arterio-venous shunt for PN administration.

GH treatment increased height SD scores in our patients, but not to target height. Decreases in fat mass and increases in BMI were measured, suggesting an increase in lean body mass and thus anabolic condition as a result of GH treatment.

## CONCLUSION

On the basis of this very limited study, we advocate to try treatment with GH in children with SSB if their height and weight are without any gain for more than three months and the children are receiving at least 25% of their absorbed calories by the enteral route. We suggest starting with a high dose of 0.14 $mg/kg^{-1}/day^{-1}$ GH for six weeks to three months and continuing for as long as necessary, maybe for several years with a restricted dose of 0.07 $mg/kg^{-1}/day^{-1}$ GH to avoid as many side-effects as possible.

## REFERENCES

1. Barksdale EM, Koehler AN, Yaworski JA, Gardner M, Reyes J. (1999) Insulin-like growth factor 1 and insulin-like growth factor 3: indices of intestinal failure in children. J Pediatr Surg 34: 655-62.
2. Bianchi A. (1997) Longitudinal intestinal lengthening and tailoring: results in 20 children. J R Soc Med 90: 429-32.
3. Bongaerts GPA, Tolboom JJM, Naber AHJ, Sperl WJK, Severijnen RSVM, Bakkeren JAJM, Willems JL. (1997) Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathogen 22: 285-93.
4. Bongaerts G, Bakkeren J, Severijnen R, Sperl W, Willems H, Naber T, Wevers R, van Meurs A, Tolboom J. (2000) Lactobacilli and acidosis in children with short small bowel. J Pediatr Gastroenterol Nutr 30: 288-93.
5. Bongaerts GP, Severijnen RS, Tangerman A, Verrips A, Tolboom JJ. (2000) Bile acid deconjugation by Lactobacilli and its effects in patients with a short small bowel. J Gastroenterol 35: 801-4.
6. Byrne TA, Morrissy TB, Nattakom TV, Ziegler TR, Wilmore DW. (1995) Growth hormone, glutamine, and a modified diet enhance nutrient absorption in patients with severe short bowel syndrome. JPEN 19: 396-402.

7. Eizaguirre I, Aldazabal P, Barrena MJ, Garcia-Arenzana JM, Ariz C, Candelas S, Tovar JA (1999) Effect of growth hormone on bacterial translocation in experimental short bowel syndrome. Pediatr Surg Int 15: 160-3.
8. Ellegård L, Bosaeus I, Nordgren S, Bengtsson BA. (1997) Low-dose recombinant human growth hormone increases body weight and lean body mass in patients with short bowel syndrome. Ann Surg 225: 88-96.
9. Hankard R, Goulet O, Ricour C, Rongier M, Colomb V, Darmaun D. (1994) Glutamine metabolism in children with short-bowel syndrome: a stable isotope study. Pediatr Res 36: 202-6.
10. Jeppesen PB, Langholz E, Mortensen PB (1999) Quality of life in patients receiving home parenteral nutrition. Gut 44: 844-52.
11. Ladd AP, Grosfeld JL, Pescovitz OH, Johnson N. The effect of the growth hormone supplementation on late nutritional independence in unadapted pediatric patients with short bowel syndrome. BAPS 50th international congress July 2003 Estoril, Portugal.
12. Ling L, Irving M. (2001) The effectiveness of growth hormone, glutamine and a low-fat diet containing high-carbohydrate on the enhancement of the function of remnant intestine among patients with short bowel syndrome: a review of published trials. Clinical Nutrition 20: 199-204.
13. Mauras N, George D, Evans J, Milov D, Abrams S, Rini A, Welch S, Haymond MW. (2002) Growth hormone has anabolic effects in glucocorticosteroid dependent children with inflammatory bowel disease: a pilot study. Metabolism 51: 127-35.
14. Schwartz MA and Kuenzler KA. (2001) Pharmacotherapy and growth factors in the treatment of short bowel syndrome. Sem Pediatr Surg 10: 81-90.
15. Scolapio JS. (1999) Effect of growth hormone, glutamine, and diet on body composition in short bowel syndrome: A Randomised, Controlled Study. JPEN 23: 309-13.
16. Scolapio JS. (2003) Tales from the crypt. Gastroenterology 124: 561-65.
17. Sigalet DL. (2001) Short bowel syndrome in infants and children: an overview. Sem Pediatr Surg 10: 49-55.
18. Szkudlarek J, Jeppesen PB, Mortensen PB. (2000) Effect of high dose growth hormone with glutamine and no change in diet on intestinal absorption in short bowel patients: a randomised, double blind, crossover and placebo-controlled study. Gut 47: 199-205.
19. Teitelbaum DH, Tracy T. (2001) Parenteral nutrition-associated cholestasis. Sem Pediatr Surg 10: 72-80.
20. Touloukian RJ, Walker Smith GJ. (1983) Normal intestinal length in preterm infants. J Pediatr Surg; 18: 720-3.

21. Van den Bos SN, Severijnen RSVM, Tolboom JJM, Otten BJ, Rammeloo EML, Bongaerts GPA, Rieu PNMA, Festen C. (1998) Combined growth hormone treatment and glutamine treatment in three children with a short small bowel. Proceedings of the 6th Southeast European Congress on Pediatric Surgery. Short Bowel. Graz Austria.
22. Vanderhoof JA, Langnas AN. (1997) Short-Bowel Syndrome in children and adults. Gastroenterology 113:1767-1778.
23. Van der Sluis IM, De Ridder MAJ, Boot AM, Krenning EP, De Muinck Keizer-Schrama MPF. (2002) Reference data for bone density and body composition measured with dual energy x-ray absorptiometry in white children and young adults. Arch Dis Child 87: 341-347.

## 4.3 ENTERAL DRUG ABSORPTION IN PATIENTS WITH SHORT SMALL BOWEL. A REVIEW.

*R. Severijnen[1], N. Bayat[1], H. Bakker[2], J. Tolboom[3], G. Bongaerts[4].*

*Department of [1]Paediatric Surgery, [2]Clinical Pharmacy, [3]Paediatrics and [4]Medical Microbiology, University Medical Centre St. Radboud, Nijmegen, The Netherlands*

*Accepted for publication in Clinical Pharmacokinetics*

### ABSTRACT

Drug therapy may become difficult, when a significant amount of the small intestine is resected as in patients with a short small bowel. Drug absorption from the gastrointestinal tract is altered in these patients. However, this effect is variable in patients and differs with each drug. Literature regarding clinical outcomes of normal or alternative administration routes in patients with a short small bowel is limited. We explored what is written about the normal absorption of commonly used drugs and what difference the resection of different but substantial parts of the small intestine makes. Changes in the gastrointestinal tract after resection of more than 50% of the small intestine cause malabsorption of macronutrients and micronutrients and may alter the drug absorption process. The metabolic activity of the abundantly present intestinal lactobacilli also can affect the enteral drug absorption in patients with short small bowel, as this results in production of lactic acid, gaseous $CO_2$, ethanol and an increased bile acid deconjugation. Accelerated intestinal luminal transit time causes a reduction in absorption of certain antimicrobial agents, digoxin, hydrochlorothiazide, cyclosporin, cimetidine, mesalazine, oral contraceptives and levothyroxine. Gastric hypersecretion and lack of sufficient contact time with the intestinal mucosa in short small bowel patients leads to insufficient absorption of drugs such as omeprazole. Successful treatment with warfarin, tricyclic antidepressants, metronidazole, fluconazole, procainemide, sotalol and pindolol are reported in several studies. Many different factors cause this variability in drug absorption in such patients. Monitoring

the serum drug concentration in these patients may ease dealing with the management problems.

## INTRODUCTION

The American Gastroenterological Association writes in a medical position statement on Short bowel syndrome and intestinal transplantation: "Oral medication absorption is often impaired and larger doses, intravenous, or sublingual delivery may be required; significant interpatient variability may be observed" [1].

The management of patients with malabsorption after massive resection of small intestine and oral medication remains a difficult clinical problem. Many medications are available only as oral dosage forms, which limits the pharmacotherapy choice. To understand the absorption of orally administered drugs in patients with short small bowel (SSB), it is essential to understand not only the concept of normal absorption and factors contributing to this, but also the consequences of the changed intestinal flora with up to 100% lactobacilli. For many drugs, it is not clear in what part of the intestine the absorption takes place and what the contributing factors are. This article will discuss studies that have investigated the concept of drug absorption in the patients with SSB.

We count 75 cm remaining jejuno-ileal segment for an infant born at term, and 50 cm for infants born between 28 and 35 weeks gestational age as our limits for a short small bowel in accordance with 30% remaining intestinal length according to the measurements of Touloukian and Walker Smith [2]. For children above one year we keep 100 cm as the limit of an SSB. The American Gastroenterological Assocation states that less than 200 cm. of functional small intestine is its definition of short bowel syndrome [1].

Malabsorption of orally administered nutrition, vitamins, minerals and drugs occurs, because of the incapability of the remaining small intestine to absorb enough. The consequences in an individual depend upon a variety of factors such as the location and extent of the resection, the state of the remaining bowel and existence of other systemic diseases.

## DRUG ABSORPTION FROM THE GASTROINTESTINAL TRACT

### Sites of absorption

There is little absorption in the mouth, because it is difficult to keep solutions in contact with the oral mucosa for any length of time. Sublingual administration is an effective method of administration. Following absorption within the oral cavity, the drug gains access to the general circulation without first passing the liver. Nitroglycerin is administered sublingually for a rapid relief of the pain of angina pectoris. Some substances such as nicotine may be administered in chewing gum, containing the substance [3].

The stomach primarily functions as an organ of digestion, but some drugs will be absorbed [4]. At normal gastric pH, weak acids, such as aspirin, non- ionised drugs and lipophilic substances are absorbed from the stomach [5].

The small intestine represents the area with the greatest absorptive capacity. The upper small intestine (duodenum and jejunum) plays the most important role in the process of absorption of drugs because of its large surface area, its generous blood supply and its permeable mucosa. The rate at which the stomach empties its contents into the intestine affects the rate at which drugs reach the blood and the hepatic circulation. The absorption of weak bases, which constitute the majority of commonly used drugs, is particularly dependent on the speed with which they reach the intestine. Slowing the rate of stomach emptying decreases the overall rate of intestinal absorption. Many agents are preferably administered on an empty stomach with sufficient water to ensure their rapid passage into the intestine [4,6].

The main function of the colon is that of reabsorbing sodium and water. Even though the function of the colon is not fundamentally that of absorption, drugs that escape absorption in the small intestine may continue to be absorbed in the colon. Drugs such as diclofenac, metoprolol, isosorbide nitrate, nifedipine and oxprenolol are completely absorbed in the colon. So there will be a normal bioavailability of these drugs when the colon is intact and that means that patients with a jejunocolic anastomosis should not have problems when receiving these drugs [7].

The rectum can serve as a useful site for drug administration particularly when the oral route is unsuitable. The ease of access makes this route popular. The bioavailability of drugs given rectally is better because of the partial avoidance of the hepatic first- pass metabolism. However, absorption is not as rapid or complete as in oral administration because of the restricted mucosa surface area and not all drugs are available in this

form [6]. Drugs that can be given rectally are antiemetics such as metoclopramide and analgetics like indomethacin, diclofenac, paracetamol and morphine [7]. Other commonly used modes of drug administration are intramuscular, subcutaneous, inhalational, intravenous and transdermal. These forms of administration are not discussed in this paper.

*Table 1. Factors affecting drug absorption from the gastrointestinal tract*

**1** Formulation and characteristics of drug product:
- a)Tablet disintegration time
- b) Drug concentration
- c) Dissolution time
- d) Presence of excipients in tablet or capsule formulation
- e) Stability in gastrointestinal tract
- f) pH of the drug

**2** Patient characteristics:
- a) pH of lumen
- b) Gastric emptying time
- c) Intestinal transit time
- d) Surface area of gastrointestinal tract and motility
- e) Gastrointestinal disease
- f) Mesenteric blood flow
- g) Presence of bile salts

**3** Presence of other substances in the gastrointestinal tract:
- a) Interaction with other drugs, ions
- b) Exogenous substances (Food)

**4** Pharmacokinetic characteristics of drug:
- a) Drug metabolism by gut bacteria
- b) Drug metabolism in gut wall
- c) Enterohepatic recycling

**5** Effect of the lactobacilli
- a) Acidification due to fermentative lactic acid production
- b) Increased intestinal passage due to production of gaseous $CO_2$
- c) Effect of D- lactic acid on intestinal epithelia
- d) Effect of ethanol on intestinal epithelia
- e) Deconjugation of primary cholic acid with decreased uptake of lipophilic compounds

**Drug Absorption Process**

Drug absorption is mostly a passive, first- order process. The bioavailability, being the fraction of the administered dose which is absorbed into the bloodstream, is another important parameter [4]. Many factors influence the absorption of drugs across membranes (Table 1). Absorption is dependent on drug solubility and the concentration of the given drug. Drugs given in aqueous solution are more rapidly absorbed than those given in oily solution, suspension or solid form, because aqueous drug forms do not have to be disintegrated and dissolved [8]. Other factors influencing drug absorption are: the site of absorption and the length of the (remaining) absorbing surface, the circulation at the site of absorption and the permeability of the absorbing membrane, gastric emptying time which affects the rate and extent of the absorption, changes in pH, intestinal luminal transit time, ileocoecal valve function and intestinal adaptation [9].

## SHORT SMALL BOWEL AND DRUG ABSORPTION

The mean length of the normal human small intestine is 575 cm, ranging from 400 to 800 cm in adults [10]. The intestines have a large reserve capacity. When more than 50% of the midsection of the small intestine is resected there may be a few symptoms, however when smaller parts of duodenum or the terminal part of ileum are resected malabsorption may follow.

Common causes in adults are Crohn's disease and bowel infarction due to vascular occlusion. Volvulus in patients with a malrotation, atresia and necrotizing enterocolitis are common precipitants in children and infants [11].

Massive resection of the small intestine may result in clinical consequences known as short bowel syndrome with malabsorption of nutrition, drugs and micronutrients (vitamins, electrolytes and minerals). Macronutrient absorption of protein and carbohydrates may be undisturbed, but fat malabsorption may lead to steatorrhoea. In patients with SSB enteral drug absorption may be adversely affected by the consequences of the metabolic activity of the abundantly present intestinal lactobacilli, producing lactic acid from sugars. The enteral uptake of drugs that must be protonated may be affected due to the lactic acid production. Some heterolactic lactobacilli produce also $CO_2$ and ethanol. The gas may accelerate intestinal passage of food and drugs and cause diarrhoea.

When only a small part of the ileum, the site for lipid uptake by conjugated bile acid, is left, the enterohepatic absorption of intact bile acid will be reduced and these

molecules will arrive in the colon and influence absorptive capacity. Stasis is also a pathological consequence of small bowel resection, that may interfere with adequate absorption [12]. The degree of malabsorption after intestinal resection varies. It is not only depen-dent on the extension of resection, but also on factors such as patient's age at the time of the first resection [13].

Within 24 hours after its resection, the remaining small intestine begins to undergo significant structural and physiologic changes leading to an increase in the absorptive capacity [14-16]. Resection of the jejunum results in changes in the ileum, which takes on the structural and functional characteristics of the jejunum. This great adaptive capacity of ileum may be due to the shorter villi and superficial crypts in the distal part of the small intestine. The jejunum shows less adaptive response after resection of the ileum [17].

Another significant change after bowel resection is the rate at which food passes through the intestinal lumen, which affects the intestinal absorptive capacity. Normally the motility in the ileum is three times slower than in the jejunum. A faster intestinal motility after ileal or ileocaecal resection leads to diarrhoea and malabsorption [16].

Jejunostomy and ileum resection both can cause a loss of bile salt reabsorption which can lead to a poor absorption of drugs because bile salts are necessary for absorption of drugs such as cyclosporine [18-20]. Lactobacilli have comparable effects [12]. In these situations enterocoated cholestyramine tablets that are not absorbed can be given. These tablets minimise the diarrhoea induced by bile salts, because they disintegrate in the colon and can sequester the bile salts there without having any effect on jejunal fat absorption or bile salts malabsorption [21].

## DRUGS AFFECTED BY SHORT SMALL BOWEL

### Drugs affecting the gastrointestinal tract and metabolism

*Cimetidine*

Cimetidine is an $H_2$-receptor antagonist, that inhibits the secretion of gastric acid. One of the characteristics in patients with an SSB is gastric hypersecretion in the first months because of the decreased gastrin activity and a decreased level of the intestinal hormones that inhibit gastrin activity [22]. Animal studies suggest that cimetedine is absorbed in the ileum. Russo et al. reported a patient with a massive bowel resection (20 cm distal to the duodenojejunal juncture to the midtransverse colon).

This patient received cimetidine for gastrointestinal symptoms. A reduced bioavailability of cimetidine due to the rapid transit time was seen. Slowing the emptying time may improve drug bioavailability [23].

Cimetidine reduces the gastric acid load to the duodenum. In a pilot study, Aly et al. showed a reduction of faecal fluid loss in patients with diarrhoea after massive ileal resection. They also mentioned that because of decreased drug absorption a higher dosage might be necessary [24] .

Inhibition of gastric acid secretion will make the intestine vulnerable to micro-organisms and yeast.

*Omeprazole*

Omeprazole is a proton pump inhibitor. It slows gastric acid secretion and suppresses the actions of Helicobacter pylori [25]. Omeprazole absorption may not be adequate in patients with SSB because of a lack of sufficient contact with the intestinal mucosa and because of gastric acid hypersecretion, which leads to a low pH in the duodenum and upper jejunum. Nightingale et al. showed a reduction of intestinal output in patients with SSB and a net decrease of secretory output after taking omeprazole orally before breakfast. This effect however, was not enough to replace parenteral fluid and electrolyte supplements [26].

*Mesalazine (5-Aminosalicylic Acid)*

5-ASA is administered to patients with chronic inflammatory bowel disease like ulcerative colitis or Crohn's disease. Tablets of 5-ASA are coated with a pH sensitive enteric soluble film that is degraded in the distal part of the small intestine. Without this coating 5-ASA is absorbed in the stomach and duodenum and would have little effect in the treatment of distal small intestinal diseases. The absorbed fraction is redelivered to the intestinal lumen via the enterohepatic circulation. 5-ASA itself can cause systemic toxicity or irritation of the GI tract when given orally in effective dosage to achieve sufficient effect in the colon [27].

Mcleod et al. found a release of 5-ASA in the small intestine after administration of Rowasa I (a 5-ASA preparation) in patients with small bowel resection. However the authors could not draw any conclusions about its therapeutic effectiveness [28].

Oral 5-ASA administered soon after resection of the distal small intestine and proximal colon delays the recurrence of Crohn's disease of the neoterminal ileum and reduces its severity. Frieri et al. studied two groups of patients who received pro-

phylactic treatment with 5-ASA after surgery. The rate of recurrence was significantly higher in the group with an end- to-end anastomosis compared with an end-to-side or side-to-side anastomosis. The mucosal concentration of 5-ASA in the neoterminal ileum was significantly lower in patients with an end-to-end anastomosis. Drug absorption was increased in the patients with end-to-side and side-to-side anastomosis, suggesting that increased segmental transit time leads to a higher mucosal concentration and absorption in these patients [29].

*Loperamide*

Loperamide is a synthetic anti-diarrhoea drug. It slows gastrointestinal motility, accelerates gastric emptying and reduces gastrointestinal secretion and so it has an antidiarrhoeal effect. This effect is opiate receptor mediated [30-32]. Loperamide is widely used in the management of chronic diarrhoea in patients with SSB. It has no extraintestinal opiate effects on the central nervous system and no addictive characteristics. However there may be a reduction in pancreatic and biliary secretions in the patients with extensive bowel resection and this is not desirable in such patients [33]. Several studies have suggested loperamide to be effective in the treatment of diarrhoea in patients with SSB [34-39]. The enhancing effect of produced $CO_2$ gas on the peristalsis may influence the effect of drugs that slow peristalsis.

*Other anti-diarrhoeal drugs*

Other recommended agents in the treatment of diarrhoea in patients with SSB are opiates and octroide. Opiates slow down the intestinal transit time but are addictive so patients should be monitored closely. Octroide, a somatostatin analogue, acts by slowing the intestinal transit, and has an anti-secretory effect but also inhibits intestinal absorption. Octroide can not be administered orally [39,40]. Rectal and colonic administration of medications in SSB patients with severe diarrhoea has an unpredictable effect.

**Drugs affecting the Cardiovascular System**

*Antiarrythmics*

Procainamide is an antiarrythmic agent that is almost completely ionised in the stomach and absorbed in the small intestine. In a male SSB patient 26 cm of small intestine was left and the patient had ventricular arrhythmias. Despite a reduced intestinal transit time, minimal absorptive area and insufficient time for adaptation, therapeutic levels

of procainamide were achieved in this patient. This could be partly due to the absence of other intestinal diseases and partly because of the possible contribution of colonic absorption [41]. Sotalol is a non- selective hydrophilic beta- adrenergic blocking agent that is almost completely absorbed after oral administration. It undergoes no first-pass hepatic metabolism and therefore its bioavailability is 90%-100%. Bioavailability is reduced by 20% when food is present in the gastrointestinal tract [42]. In two patients with atrial fibrillation and reduced intestinal length, normal plasma concentrations were achieved after oral administration. In patients with severe SSB (stomach, duodenum and only 50cm of jejunum) adjustment of the daily dose led to a substantial increase of sotalol plasma concentrations [43].

*Cardiac Glycosides*

Digoxin, a cardiac glycoside is absorbed in the upper intestine and in small amounts in the stomach. A minimal length of duodenum and upper jejunum is necessary for absorption. In subjects with a normal functioning GI tract digoxin has a bioavailability of almost 80%. Digoxin malabsorption seems to occur in patients with an extremely short length of functioning small intestine [44,45].

Digoxin is partly absorbed when administered directly into the lower jejunum or upper ileum, the transverse colon and the sigmoid colon. Its poor solubility is the critical rate-limiting factor in its bioavailibility. Patients with SSB seem to have altered blood levels of digoxin when they use digoxin in the tablet dosage form. This may be related to inadequate dissolution of the tablet before it passes the absorption sites and not necessarily to a defect at the absorption site. Several studies suggest that digoxin absorption may be improved in patients with intestinal resection when given in liquid dosage form such as elixir [46-48], also after radiation induced malabsorption [47]. Even in a patient with an end jejunostomy and only 12-15 cm of remaining jejunum a diminished absorption of oral digoxin was observed, but digoxin elixir achieved a therapeutic serum concentration [45].

In another study oral digoxin tablet absorption was investigated in 14 patients in whom varying amounts of ileum were resected. No correlation was found between drug absorption (measured as the area under the serum concentration-time curve after oral administration of single 0.5 mg doses) and the length of the resected intestine [44]. Other studies suggest that the compensatory ability of the colon to absorb digoxin achieves therapeutic concentrations in patients after resection of the total small intestine [7].

Ehrenpreis et al. reported a patient with only 18 cm jejunum and without continuity of small intestine and colon. The authors explain that patients with an end jejunostomy experience severe digoxin malabsorption and may need intravenous administration, because of the inability to achieve the efficient therapeutic concentration after oral administration [49].

Digoxin absorption may be influenced by other drugs like propantheline, which decreases gastrointestinal motility. Propantheline appears to increase contact time of digoxin with the absorption site, thereby increasing the amount of digoxin absorbed from the administered tablets. Metoclopramide, which increases the gastrointestinal motility, seems to decrease the amount of digoxin absorbed [46].

*Betablockers: Pindolol*

Pindolol is a beta-adrenoreceptor antagonist, used for treatment of hypertension, angina pectoris, cardiac arrhythmias and prevention of a second myocardial infarction. The bioavailability of pindolol is high because of a rapid digestive absorption and its low first pass effect. Evard et al. studied the bioavailability of pindolol in patients with malabsorption syndrome. The average length of the remaining small intestine after resection was 137 +/- 15 cm. Their study subjects included 7 patients with SSB after ileal or jejuno-ileal resection. Oral pindolol was well absorbed in the majority of the patients. In two patients there was a decreased absorption of pindolol after total ileal resection, the authors could not explain this [50].

*Diuretics: Hydrochlorothiazide*

Hydrochlorothiazide is a commonly used thiazide diuretic agent with a relatively long half-life [51]. The major part of the hydrochlorothiazide absorption takes place in the duodenum and upper jejunum [52]. Backman et al. investigated the absorption of hydrochlorothiazide in patients with a jejunoileostomy and ileocaecostomy after intestinal shunt operations for obesity. The mean length of the remaining jejunum was 43 cm and of the remaining ileum 14.4cm. The total urinary recovery of hydrochlorothiazide was measured to determine its gastrointestinal uptake. They found a 50 % decrease in uptake and suggest the malabsorption of hydrochlorothiazid may be due to a shortened intestinal transit time [53].

*Anticoagulants: Warfarin*

Warfarin is an oral anticoagulant. Its bioavailibility is nearly complete when the drug is administered orally, intramuscularly, intravenously or rectally. Warfarin is usually detectable in the plasma within one hour after oral administration. Case reports claim that warfarin absorption is not affected by SSB [54,55].

Drug-drug interactions may prevent absorption, increase metabolism or antagonise the effects of warfarin. Antacids such as magnesium or aluminium hydroxide have no effect on the therapeutic serum concentrations of warfarin [56].

A precipitating factor in warfarin resistance may be intravenous lipid administration. Warfarin is absorbed in the stomach and proximal the small intestine, the presence of food in the gastrointestinal tract may decrease the rate of absorption. Excessive vitamin K may cause prolonged warfarine resistance. In a patient with SSB the small intestine was resected with only 30 cm of jejunum left. The patient received subcutaneous vitamin K1. The bioavailibility values for warfarin were normal, which ruled out any decrease in warfarin absorption. The investigators suggested exogenous vitamin K to be responsible for warfarin resistance [54]

Lehman et al reported a patient with 15 cm jejunum, the ileum and proximal right colon were also resected, and warfarin was almost completely absorbed in this patient [57].

A more recent study reported warfarin resistance due to reduced surface area for drug absorption secondary to resection of duodenum and gastrojejunostomy. A patient with total duodenectomy and gastrojejunostomy, but with intact ileum was treated with oral warfarin for deep vein thrombosis. The decreased absorptive surface area of his upper small intestine could be the reason for the warfarin resistance in this case [58]. Lutomski suggests that it may be more practical to use intravenous or subcutaneous warfarin in the patients with malabsorption and resistance [59].

**Drugs affecting Behaviour, Psychotic State, Pain Sensation and Muscle Control**

*Tricyclic antidepressants*

Amitriptyline is a tricyclic antidepressant widely used for the treatment of major depression. It is absorbed through the stomach and small intestine and its elimination half-life is 15 hours. A case study reported good oral absorption and therapeutic serum concentrations of amitriptyline after crushing the dose and allowing the powder to dissolve in the mouth of the patient, having only 40 cm of proximal small intestine [60].

Nortriptyline, also a tricyclic antidepressant, is rapidly absorbed in the gastrointestinal tract and is almost completely ionised in the stomach. Little is known about the exact site of nortriptyline absorption within the intestines. Nortriptyline was well absorbed in a patient with SSB after oral administration [61].

*Paracetamol*

Paracetamol is absorbed rapidly from the small intestine. The rate of absorption of paracetamol seems to be dependent on the gastric emptying [62,63]. The most important absorption site of paracetamol is the jejunum [64,65]. Patient's posture influences the absorption of paracetamol, when the patient is lying down the absorption is slowed [66]. Ueno et al investigated the absorption of paracetamol in patients with SSB who had a duodenostomy or a jejunostomy (15-60 cm left after resection). Paracetamol was mixed with a 200 ml liquid meal. They found a decreased absorption of paracetamol in these patients. The authors concluded that jejunum distal from the duodenojejunal flexure is the site of absorption for paracetamol [64]. Paracetamol can be administered rectally, but the absorption is slower in healthy people.

**Hormones and Related Compounds**

*Oral Contraceptives*

Oral contraceptive steroids are mainly absorbed in the small intestine. The bioavailability of these drugs depends on the absorptive capacity of the small intestine.
Higher risk for contraceptive failure is reported in women with an ileostomy because of the rapid gastrointestinal passage and the loss of enterohepatic recirculation of steroids. The lowest levels of levonorgestrel were found in the patients with the largest small bowel resection. Jejunoileal bypass may lead to a reduced bioavailability of norethisterone and levonorgestrel [67].

*Levothyroxine*

Levothyroxine (L-Thyroxine) is prescribed in patients with hypothyroidism. Stone et al. studied the absorption of L-Thyroxine in patients with SSB. The patients had a normal functioning duodenum and variable lengths of jejunum with an absent ileum. After receiving sodium L-T4, the amount of radiolabelled T4 was measured in the patient's circulation. There was no absorption of labeled T4 in-patients with a duodenum only and a lower T4 absorption in patients with shortened bowel. The authors concluded that the duodenum is not an important site for the absorption of L-Thyroxine and that

in the patients with resected bowel there may be malabsorption of T4. They suggest treatment with a higher dosage of this hormone. The authors were unable to draw any conclusion concerning the involvement of ileum in the absorption of T4, because none of the patients had an intact ileum [68]. As L-T4 absorption is better in the fasting state, food intake should be avoided with L- thyroxine medication [69].

**Drugs affecting the immune system: Cyclosporin**

Cyclosporin is an immunosuppressant that is used to prevent rejection of organ transplants and to treat severe autoimmune diseases that are resistant to other therapeutic agents [70]. After oral administration, its absorption is slow and incomplete [71]. Cyclosporin absorption takes place in the duodenum and the jejunum [72]. Factors affecting cyclosporin absorption are food, bile flow, gastrointestinal drug metabolism, small intestinal transit time and absorption surface area [73]. Oral cyclosporin was given in two patients with SSB, one with a renal transplantation and Crohn's disease in the other. The investigators compared the drugs pharmacokinetics after intravenous and oral administration. A therapeutic serum concentration was achieved after intravenous administration, but both cases failed to achieve therapeutic cyclosporine serum concentrations after oral administration. The critical limiting factor in cyclosporine absorption in both cases was the rapid intestinal transit time [74].

**Antimicrobial Agents**

Cefaclor is a cephalosporin that is administered orally. It is well absorbed throughout the whole intestinal tract and its bioavailability is not significantly affected by food. Oral cefaclor was not rapidly absorbed in a child with SSB who suffered from otitis media, because of rapid transit through the shortened intestine and its half-life (36-46 min) [75].

Under normal circumstances cephalexin is extremely well absorbed enterally. Trimethoprim is an antibacterial agent that is well absorbed from the gastrointestinal tract [76]. Oral cephalexin and trimethoprim-sulfa both are used in children with SSB. This was investigated in a study of five children with extensive resection of small intestine in the neonatal period. The authors observed a reduction in absorption of 10% to 50%, although therapeutic serum concentrations were achieved. They explained that the fast passage in the upper small intestine might be the reason for this decrease. The investigators also found that aminopenicillin and drugs with comparable absorption rates such as penicillin, acidocillin, isoxicillin and macrolides are not

absorbed sufficiently in children with resection of more than 100 cm of the small intestine. This means that therapeutic concentrations are not achievable and it is advisable to give these medicines when necessary as parenteral therapy [77].

Fluconazole is soluble in water and rapidly absorbed from the gastrointestinal tract after oral administration, with about a 90% bioavailability [78]. Fluconazole was rapidly absorbed in a patient with SSB. The gastric antrum, duodenum and ileum had been removed, but the jejunum and colon were left intact [79].

Iacono et al reported a successful treatment with orally administered metronizadol (20-30 mg/kg/day) in an infant with only 11cm of the intestine remaining [80]. Parson et al reported the absorption of several antimicrobial agents in patients with Crohn's disease that had undergone intestinal resection. They noted a decrease in absorption of cephalexin, lincomycin, erythromycin stearate and rifampicin. They found an increase in absorption of clindamycin, sodium fusidate and sulfamethoxazole [81].

Massive resection of the small intestine may lead to the loss of activity of mucosal enzymes and enzymes produced by bacteria. This results in a reduction of the biotransformation of ester prodrugs to the active form, such as erythromycin, chloramphenicol, pivampicillin, but also steroids and other esthers [82]. Successful treatment with orally administered antimicrobial agents is reported in most of the mentioned studies. However, the undesirable disturbing effect of these drugs on the intestinal microflora should be taken in consideration. Probiotics (*lactobacillus casei* and *bifidobacterium brevis*) and prebiotic galactooligosaccharides are suggested in the treatment of antibiotic induced diarrhoea in patients with SSB [83].

## CONCLUSION

There are a few case reports of drug absorption in single SSB patients and some studies with only small populations. Their findings and conclusions cannot be reflected onto a larger population. The major characteristics of SSB patients are the short bowel itself and the intestinal flora with up to 100% lactobacilli. These bacteria may adversely affect intestinal events including drug absorption. This effect should be added to the already existing variability in drug absorption in patients with SSB. Because of this and the different remaining lengths and function of the remaining small intestine in these patients, predicting drug dosage is difficult.

A patient with SSB requires alert pharmacotherapeutic care. It is of a great importance for clinicians to be aware of the variable drug absorption and the pharmacoki-

netics involved in the treatment of these patients. Monitoring of serum drug levels in these patients with SSB is essential.

**ACKNOWLEDGEMENT**

The authors thank Dr. E. Robertson, anesthesiologist, for the English language editing.

**REFERENCES**

1. American Gastroenterological Association Medical Position Statement: Short Bowel Syndrome and Intestinal Transplantation. Gastroenterology 2003; 124: 1105-10.
2. Touloukian RJ, Walker Smith GJ. Normal intestinal length in preterm infants. J Pediatr Surg 1983; 18 720-3.
3. Zhang H, Zhang J and Streisand J.B. Oral mucosal drug delivery; clinical pharmacokinetic. Therapeutic Applications 2002; 41: 661-80.
4. Benet LZ, Kroetz DL, Sheiner LB. The dynamics of drug absorption, distribution and eliminition. In :Gilman AG, Goodman LS, Gilman A, eds. Goodman and Gilman's the pharmacological basis of therapeutics 1996; 9th ed. New York.
5. DeSesso JM and Jacobson CF. Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats. Food and Chemical Toxicology 2001; 39: 209-28.
6. Sjöqvist F, Borga O, Dahl ML et al. Fundamentals of clinical pharmacology. In : Speight TM and Holford NHG, editor. Avery's drug treatment .A guide to the properties, choice, therapeutic use and economic value of drugs in disease management. Adis international 1997: 15-20.
7. Kennedy JM and Van Riji M. Effects of surgery on the pharmacokinetic parameters of drugs. Clin Pharmacokinetics 1998; 35: 293-312.
8. Gubbins PO, Bertch KE.Drug absorption in gastrointestinal disease and surgery. Pharmacotherapy.1989; 9: 285-95.
9. Seidner DL. Short Bowel Syndrome: etiology, pathophysiology and management. The Cleveland clinic centre for continuing education 2001 at: www.clevelandclinicmed.com.
10. Weaver LT, Austin S, Cole JT. Small intestinal length: a factor essential for gut adaptation. Gut 1991; 32: 1321-3.
11. Höllwarth ME. Short bowel syndrome: pathophysiological and clinical aspects. Review article Pathophysiology 1999; 6: 1-19.
12. Bongaerts GPA, Severijnen RSVM, Tangerman A et al. Bile acid deconjugation by *lactobacilli* and its effects in patients with a short small bowel. J Gastroenterol 2000; 35: 801-4.

13. Warner BW, Vanderhoof JA, Reyes JD. Whats new in the management of short gut syndrome in children. J Am Coll Surg 2000, 725-36.
14. Debru E, Martin GR, Sigalet DL. Invivo measurement of intestinal absorption using 3-0 methylglucose in short bowel syndrome. J Paediatr surg 2001; 36: 745-9.
15. Shike M. The short bowel syndrome. In. Winawer SJ,editor. Management of gastrointestinal diseases. Gower medical publishing 1992; 1:16.2.
16. Jeejeebhoy KN. Nutritional aspects of inflammatory bowel disease. In: Kirsner JB, Shorter RG, editor. Inflammatory bowel disease.Williams & Wilkins 1995: 734-49.
17. Kvietys PR. Intestinal physiology relevant to short-bowel syndrome. Eur J Pediatr Surg 1999 ; 9: 196-9.
18. Mehta MU, Venkataramanan R, Burckart GJ. Effect of bile on cyclosporin absorption in liver transplant patients. Br J Clin Pharmacol 1988; 25: 579-84.
19. Muller EA, Kallay Z, Kovarik JM. Bile independent absorption of cyclosporine from a microemulsion formulation in liver transplant patients. Transplantation 1995; 60: 515-7.
20. Nyhlin H, Merrick MV, Eastwood MA. Bile acid malbsoption in Crohn's disease and indications for its assessment using SeHCAT. Gut 1994; 35: 90-3.
21. Jacobsen O, Hojgaard L, Moller HE et al. Effect of enterocoated cholestyramine on bowel habit after ileal resection: a double blind crossover study. Br Med J 1985; 290: 1315-8.
22. Wesser E. Nutritional aspects of malabsorption. Americ J Med 1979; 67: 1014-20
23. Russo J Jr, Watson WA, Nelson EW et al. Cimetidine bioavailability after massive small bowel resection. Clin Pharm 1982; 1: 558-61.
24. Aly A, Barany F, Kollberg B et al. Effect of an $H_2$-receptor blocking agent on diarrhoeas after extensive small bowel resection in Crohn's disease. Acta Med Scand 1980; 207: 119-22.
25. Piper DW, de Carle DJ, Talley NJ et al. Gastrointestinal and hepatic diseases. In: Speigh TM, Holford NHG, editors. Avery's drug treatment. A guide to the properties, choice, therapeutic use and economic value of drugs in disease management. Adis international 1997: 934-1021.
26. Nightingale JMD, Walker ER, Farthing MJG et al. Effect of omeprazole on intestinal output in the short bowel syndrome. Alimen Pharmacol Therap 1991; 5: 405-12.
27. Altman DF. Drug used in gastrointestinal diseases. In: Katzun BG, editor. Basic & Clinical Pharmacology. Prentice-Hall International Inc 1992: 895-6.
28. Mc Leod RS, Cohen Z, Vari BJ et al. The release profile of a controlled release preparation of 5-aminosalicyclic acid(Rowasa I)in humans. Dis Col & Rect 1990; 33: 21-5.
29. Frieri G, Pimpo MT, Palumbo G et al. Anastomotic configuration and mucosal 5-aminosalicylic acid (5-ASA) concentrations in patients with Crohn's disease: a GISC study. Am J Gasteroent 2000; 95: 1486-90.

30. Jaffe JH, Martin WR. Opiod analgesics and antagonists. In: Gilman AG, Rall TW, Nies AS et al. editors, Goodman and Gilman's. The Pharmacological basic of therapeutics. Pergamon Press 1990; p507-8.
31. Cann PA, Read NW, Holh CD. Loperamide improves dyspeptic symptoms and accelerates gastric emptying in patients with irritable bowel syndrome. Gut 1982; 25: 437.
32. Awouters F, Megens A, Verlinden M et al. Loperamide. Survey of studies on mechanism of its antidiarrheal activity. Dig Dis Sci 1993; 38: 977-95.
33. Remington M, Fleming CR, Malagelada JR. Inhibition of postprandial pancreatic and biliary secretion by loperamide in patients with short bowel syndrome. Gut 1982; 23: 98-102.
34. Remington M, Malagelada JR, Zinsmeister A et al. Abnormalities in gastrointestinal motor activity in patients with short bowels: effect of a synthetic opiate. Gasteroent 1983; 85: 629-36.
35. Galambos JT, Hersh T, Schroder S et al. Loperamide: a new antidiarrheal agent in the treatment of chronic diarrhea. Gasteroent 1976; 70: 1026-9.
36. Lennard-Jones JE. Review article: practical management of the short bowel. Aliment Pharmacol Ther 1994; 8: 563-77.
37. Lentze MJ. Intestinal adaptation in short-bowel syndrome. Eur J Pediatr 1989; 148: 294-9.
38. Nightingale JMD. Management of patients with a short bowel. Nutrition 1999;15: 633-7.
39. Schiller LR. Review article: anti-diarrhoeal pharmacology and therapeutics. Aliment Pharmacol Ther 1995; 9: 87-106.
40. Fried M. Octreoide in the treatment of refractory diarrhea. Digestion 1999; 60 Suppl 2: 42-6.
41. Felser J, Hui KK. Procainamide absorption in short bowel syndrome. JPEN 1983; 9: 154-5.
42. Hanyok JJ.Clinical pharmacokinetics of sotalol. Am J Cardiol 1993; 72: 19A-26A.
43. Silomon M, Bach F, Juckenhofel S et al. Bioavailability of sotalol in short bowel syndrome.(abstract) Med Klin 1999; 94: 638-41.
44. Gerson CD, Lowe EH, Lindenbaum J. Bioavailability of digoxin tablets in patients with gastrointestinal dysfunction. Am J Med 1980; 69: 43-9.
45. Vetticaden SJ, Lehman ME, Barnhart GR et al. Digoxin absorption in a patient with short-bowel syndrome. Clin Pharm 1986; 5: 62-4.
46. Kumer KP, Nwangwu JT, Nwangwu PU. Perspectives on digoxin absorption from small bowel resections. Drug Intel Clin Pharm 1983; 7: 121-3.
47. Hall WH, Doherty JE, Gammill J et al. Tritiated digoxin XXII. Absorption and excretion in malabsorption syndrome. Am J Med 1974; 56: 437-42.
48. Jusko WJ, Conti DR, Molson A et al. Digoxin absorption from tablet elixir. JAMA 1974; 230: 1554-5.

49. Ehrenpreis ED, Guerriero S, Nogueras JJ et al. Malabsorption of digoxin tablets, gel caps and elixir in a patient with an end jejunostomy. Ann Pharmacother 1994; 28: 1239-40.
50. Evard D, Aubry JP, Le Quintrec Y et al. Study of the bioavailability of pindolol in malabsorption syndromes. Br J clin Pharmac 1984; 18: 632-7.
51. Mc Neil JJ, Krum H. Cardiovascular diseases. In: Speigh TM, Holford HG, editors.Avery's drug treatment. Adis international 1997: 809-96.
52. Beerman B, Groschinsky- Grind M, Rosen A. Absorption, metabolism and excretion of C-hydrochlorothiazid. Clin Pharmaco Therap 1976; 19: 531-7.
53. Backman L, Beerman B, Groschinsky- Grind M et al. Malabsorption of hydrochlorothiazide following intestinal shunt surgery. Clin. Pharmacokinetics 1979; 4: 63-8.
54. Kearns PJ, O'Reily RA. Bioavaiability of warfarin in a Patient with severe short bowel syndrome.JPEN 1986; 10: 100-1.
55. Mitchell JF, Maas LC, Barger RC. Successful oral anticoagulant therapy in a patiënt with short bowel syndrome. Am J Hosp Pharm 1977; 34: 171-2.
56. Neuvonen PJ, Kivistö KT. Enhancement of drug absorption by antacids. An unrecognised drug interaction. Clin Pharmacokinet 1994; 27: 120-8.
57. Lehman ME, Kolb KW, Barnhart GR et al. Warfarin absorption in a patient with short-bowel syndrome. Clin Pharm 1985; 4: 325-6.
58. Brophy DF, Ford SL, Crouch MA. Warfarin resistance in a patient with short bowel syndrome. Pharmacotherapy 1998; 18: 646-9.
59. Lutomski DM, LaFrance RJ, Bower RH et al. Warfarin absorption after massive small bowel resection. Am J Gasteroenterol 1985; 80: 99-102.
60. Robbins B, Reiss RA. Amitriptyline absorption in a patient with short bowel syndrome. AM J Gastroenterol 1999; 94: 2302-4.
61. Broyles JE, Brown RO, Self TH et al. Nortriptiline absorption in short bowel syndrome. JPEN 1990; 14: 326-7.
62. Heading RC, Nimmo J, Prescott LF et al. The dependence of paracetamol absorption on the rate of gastric emptying.Br J Pharmacol 1973; 47: 415-21.
63. Holt S, Heading RC, Clements JA et al. Acetaminophen absorption and metabolism in celiac disease and Crohn's disease. Clin Pharmacol Ther 1981; 30: 232-8.
64. Ueno T, Tanaka A, Hamanaka Y et al. Serum drug concentrations after oral administration of paracetamol to patients with surgical resection of the gastrointestinal tract. Br J Clin Pharmac 1995; 39 : 330-2.
65. Nelson EB, Abernethy DR, Greenblatt DJ et al. Paracetamol absorption from a feeding jejunostomy. Br J clin Pharmac 1986; 22 : 111-3.
66. Nimmo WS, Prescott LF. The influence of posture on paracetamol absorption. Br J Clin Pharmacol 1978; 5: 291-334.

67. Hanker JP. Gastrrointestinal disease and oral contraception. Am J Obstet Gyneacol 1990; 163: 2204-7.
68. Stone E, Leiter LA, Lambert JR et al. L- Thyroxine absorption in patients with short bowel. Clin Endocrinol Metab 1984 ; 59: 139-41.
69. Wenzel KW, Kirschsieper HE. Aspects of the absorption of oral L-thyroxine in normal man. Metabolism 1977; 26: 1-8.
70. Brenner GM. Antineoplastic and immunomodulating drugs in: George M. Brenner Pharmacology. W.B. Saunders Company 2000; p 488.
71. Ptachcinski RJ, Venkataramanan R, Burckart GJ. Clinical pharmacokinetics of cyclosporin. Clin Pharmacokinet 1986; 11: 107-32.
72. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Internat J Pharmac 1996; 136: 117-39.
73. Gubbins PO, Bertch KE. Drug absorption in gastrointestinal disease and surgery, clinical pharmacokinetics and therapeutic implications. Pharmacokin 1991; 21: 431-47.
74. Roberts R, Sketris IS, Abraham I et al. Cyclosporine absorption in two patients with short-bowel syndrome. Drug Intel Clin Pharm 1988; 22: 570-2.
75. Nahata MC, Freimer N, Hilty MD. Decreased absorption of cefaclor in short bowel syndrome. Drug Intel Clin Pharm 1983; 17: 201-2.
76. Thielman NM, Neu HC. Bacterial cell wall inhibitors. In: Brody TM, Larner J, Minneman KP, editor. Human pharmacology. Mosby-Year Book, Inc.1998: 655-82.
77. Menardi G, Guggenbichler JP. Bioavailability of oral antibiotics in children with short-bowel syndrome. J Pediatric Surg 1984; 19: 84-6.
78. Thielman NM, Neu HC. Antimicrobacterial agents. In: Brody TM, Lerner J, Minneman KP, editor. Human pharmacology. Mosby-Year Book, Inc. 1998: 723-33.
79. Joe LA, Jacobs RA, Guglielmo BJ. Systemic absorption of oral fluconazole after gastrointestinal resection. J Antimicrob Chemother 1994; 33: 1070.
80. Iacono G, Carroccio A, Montalto G et al. Extreme short bowel syndrome: a case for reviewing the guidelines for predicting survival. J Ped Gasteroent Nutr 1993; 16: 216-9.
81. Parsons RL. Drug absorption in gastrointestinal disease with particular reference to malabsorption syndromes. Clin Pharmacokin 1977; 2: 45-60.
82. Dressman JB, Bass P, Ritschel WA et al. Gastrointestinal parameters that influence oral medications. J Pharm Sci 1993; 82: 857-72.
83. Kanamori Y, Hashizume K, Sugiyama M et al. Combination therapy with bifidobacterium breve, *lactobacillus casei*, and galactooligosaccharides dramatically improved the intestinal function in a girl with short bowel syndrome. A novel synbiotics therapy for intestinal failure. Dig Dis Scienc 2001; 46: 2010-6.

## 4.4 INTESTINAL TRANSPLANTATION FOR THE TREATMENT OF PERMANENT INTESTINAL FAILURE IN CHILDREN

*JJM Tolboom[1], RSVM Severijnen[2], PNMA Rieu[2], GPA Bongaerts[3], MJ Verheyen[4], AT Naber[5].*

*Department of [1]Paediatrics, [2]Paediatric Surgery, [3]Medical Microbiology, [4]Dietics and [5]Gastroenterology, University Medical Centre St Radboud, Nijmegen, The Netherlands*

*Tijdschrift voor Kindergeneeskunde 2000; 68: 157-163*
*Darmtransplantatie voor behandeling van blijvend darmfalen bij kinderen*



### SUMMARY

Intestinal transplantation has been available in other countries since 1985, but has not yet been introduced in the Netherlands. We reviewed the literature on: (a) causes of intestinal failure in children; (b) indications for intestinal transplantation and combined liver-intestinal transplantation; (c) transplantation technique; (d) post-transplant immunosuppressive treatment and its complications; (e) clinical course after transplantation; (f) short-term and medium-term results of intestinal transplantation. Implications of these data and developments for patients in the Netherlands with permanent intestinal failure and dependency on total parenteral nutrition (TPN) are discussed. We emphasize that close cooperation between the two centres that are planning to perform the transplantations and the centres with expertise in the field of TPN at home and in hospital is absolutely essential for the success of the national intestinal transplantation programme. It is expected that in the Netherlands, the first intestinal transplantation will take place in the year 2000.

## INTRODUCTION

A child with small bowel failure must be fed parenterally, so-called total parenteral nutrition (TPN). If TPN is not started immediately, persistent diarrhoea and steatorrhoea can lead to growth retardation, vitamin and trace element deficiencies, hypoproteinaemia, electrolyte disturbances and metabolic acidosis [1-3]. The aim of total or partial parenteral nutrition is to achieve adequate growth, prevent malnutrition and metabolic disturbances, while maintaining an optimal quality of life. If a child has permanent intestinal failure, the prognosis of survival depends fully on being able to administer TPN in the long-term with as few complications and side-effects as possible [1-4]. Complications associated with the means of administration, chiefly via a central venous catheter (CVC), include thrombosis and catheter infections. These can be fatal owing to embolism and sepsis, respectively.

In young children, a major side-effect of TPN is disturbed liver function with cholestasis; its pathophysiological mechanism is as yet unknown. Both intestinal and TPN-associated factors seem to play a role. Examples of the former are multiple surgical interventions, hypoperistalsis, bacterial overgrowth and disturbance of the enterohepatic circulation. TPN-associated factors include catheter sepsis, inadequate administration of glucose, fat and amino acids, macrophage activation by fats and toxicity from trace elements (e.g. Al, Mn and Fe) [4-7].

In older children and adults, cholestasis is far less common; their complaints are almost exclusively fatty degeneration of the liver and liver fibrosis.

TPN-associated cholestatic liver disease in young children is usually progressive and leads irrevocably to biliary cirrhosis and ultimately to liver failure. This complication is a major cause of death in patients with permanent intestinal failure. Over the past 15 years, children who could no longer receive TPN, whether or not they had reached end stage liver failure, had a chance of further survival if they underwent intestinal transplantation or combined liver-intestinal transplantation [7-13].

## CAUSES OF PERMANENT INTESTINAL FAILURE

In children, there are important, but fairly rare, causes of permanent intestinal failure besides the well-known short bowel syndrome (SBS), microvillus inclusion disease (MID) and the chronic intestinal pseudo-obstruction (CIPO) syndrome. For example, epithelial dysplasia is an extremely rare cause, in which intestinal failure occurs in the

same way as in MID, as a result of massive intestinal malabsorption. Total aganglionosis of the small and large intestine leads to symptoms that resemble the CIPO.

*Table 1. Causes of the short bowel syndrome in children*

| *Congenital anomalies* | *Acquired disorders* |
|---|---|
| Gastroschisis | Necrotizing enterocolitis |
| Intestinal atresia | Crohn's disease |
| Malrotation/volvulus | Trauma |
| Aganglionosis | Infarction (arteriosclerosis) |
| Meconium ileus (in cystic fibrosis) | |

**The short bowel syndrome**

This is the most important cause of permanent intestinal failure in children and adults. The length of the small bowel in full-term neonates is 250 to 300 cm, increasing to 600 to 800 cm in adults. Its absorptive surface is 950 and 7500 $cm^2$, respectively. The presence of intestinal villi and microvilli greatly increase the surface area [2]. In the SBS, the small bowel is so short that its functional loss leads to complaints and abnormalities. Insufficient absorption of nutrients causes growth retardation, micronutrient deficiencies and metabolic disturbances. A short small bowel is nearly always the result of extensive intestinal resection and is very seldom a congenital anomaly. In children, the indication for resection is a congenital anomaly of the digestive tract or damage to the intestinal wall by inflammation, ischaemia or sometimes trauma (Table 1). The presence of volvulus can inhibit the blood supply to the intestine and lead to infarction (ischaemic necrosis). Intestinal infections caused by arteriosclerosis are very uncommon in children. Severe abdominal trauma can sometimes necessitate extensive intestinal resection. Children with the SBS have the best prognosis when their duodenum, distal ileum and the ileocaecal valve (Bauhini's valve) remain intact [1-3,14]. By leaving the ileocaecal valve in situ there is less risk of bacterial overgrowth. In young infants, even the presence of 10-20 cm residual small bowel, including the ileocaecal valve, improves their prognosis of becoming independent of TPN. If the ileocaecal valve is removed, at least 40 cm of residual small bowel is necessary. In a study on 27 neonatal intestinal resections, the presence or

absence of the ileocaecal valve was not a determining factor in whether or not the children became independent of TPN in the long-term [15]. Besides the length of the remaining intestine, its state is also important (normal or abnormal calibre, presence of inflammation, bacterial overgrowth) and plays a role in whether or not TPN is permanent. If a child with the SBS is still dependent on TPN at the age of 36 to 48 months, then there is no chance at all that he or she will be able to function without it in the future [15]. Intestinal transplantation might ultimately be the only solution.

**Microvillus inclusion disease**

The congenital anomaly MID was first described in 1978 [16]; it is a hereditary intestinal disease. The microvilli of the enterocyte are morphologically abnormal in number and form. With the aid of electron microscopy, intracytoplasmic inclusions are visible, in which the microvilli are partly recognisable. In addition, the enterocyte displays an increase in secretory granules, especially apical and lysosomal bodies [2,17]. Research into the genetic defect underlying this autosomal recessive hereditary disease is well underway. The syndrome presents with secretory diarrhoea from birth or shortly afterwards and threatened dehydration or weight loss if parenteral rehydration and nutrition are not started immediately. In 1992, more than 30 patients were reported to have MID worldwide [17]. Until now, six cases of MID have been encountered in the Netherlands, of whom five died at the age of one or two years [18].

**The chronic intestinal pseudo-obstruction syndrome**

The CIPO syndrome refers to a heterogeneous group of disorders that are all characterised by signs and symptoms of intestinal obstruction, without there being any indications of mechanical obstruction [19-21]. In children, the CIPO is mainly a primary disorder that is congenital or acquired. Secondary CIPO occurs in a number of systemic diseases (e.g. scleroderma) and chiefly affects adults. Depending on the pathoanatomical substrate, the disease is classified as neuropathic, myopathic or idiopathic. The small bowel is always involved, but other parts of the digestive tract can also be affected. Complaints and signs of functional intestinal obstruction dominate the clinical symptoms. In 50% of the children, the first symptoms arise in the neonatal period and vary from ileus (bilious vomiting, swollen abdomen) and total food intolerance, to severe chronic recurrent abdominal pain and persistent constipation. In some cases, secretory diarrhoea occurs instead of constipation. The myopathic form involves

more risk of intestinal perforation. Primary CIPO can be accompanied by a megabladder and megaureters.

## INDICATIONS FOR INTESTINAL TRANSPLANTATION

In children, the major indication for transplantation of the small bowel is the SBS when it is very difficult to treat or untreatable [7-13]. In addition, intestinal transplantation is chiefly applied to children with MID or CIPO [22-26]. If it is no longer possible to administer TPN for permanent intestinal failure, then intestinal transplantation is the only option left. The former indication arises when there are no more venous access points for TPN; the second indication arises when life-threatening complications occur repeatedly, such as recurrent sepsis. In order to avoid being presented with a fait accompli, it is necessary to consult the transplantation team at an early stage to establish whether the patient should be and is a suitable candidate for such a procedure. In children with comorbid liver disease and liver failure associated with the administration of TPN, it must also be established whether it would be better to perform combined liver-intestinal transplantation instead of intestinal transplantation alone [11,27].

## INTESTINAL TRANSPLANTATION TECHNIQUE

The abdominal viscera can be compared with a bunch of grapes. It is possible to replace any organ (one grape) or a group of organs (a sprig of grapes) by means of transplantation [28]. Blood is supplied to the abdominal viscera via two main routes: the coeliac axis and the superior mesenteric artery. Both blood steams can be anastomosed with the aorta in the supracoeliac area or intrarenal area. Venous drainage of the combined liver-intestinal transplant occurs via the hepatic vein, which runs from the isolated small bowel transplant via the portal vein, splenic vein, or directly into the inferior vena cava (mesocaval shunt). It is possible to transplant the ileocaecal valve and the colon of the donor at the same time. This promotes the absorbtion of water and electrolytes.

## POST-TRANSPLANT TREATMENT WITH IMMUNOSUPPRESSIVE DRUGS

It was not until after the introduction of the powerful immunosuppressive drug tacrolimus (FK506) that intestinal transplantation became reasonably successful. Tacrolimus is much more powerful than cyclosporine and moreover, is absorbed in the upper part of the digestive tract [11,29,30].

Just as cyclosporine, tacrolimus is a T-cell inhibitor that depresses the production of interleukins 2, 3 and 4 and also granulocyte factor and interferon-alpha. Just as cyclosporine, tacrolimus has many side-effects. Well-known side-effects from tacrolimus are increased susceptibility to infection, tremors, headaches, paraesthesia, hyperglycaemia, diabetes mellitus, hypertension and renal function disorders. Less frequent are electrocardiographic changes, tachycardia, peripheral oedema, electrolyte imbalance and central disturbances, such as agitation, anxiety, confusion and depression. In young children who are Epstein-Barr-virus seronegative, there is an increased risk of lymphadenopathy and lymphomas [29]. Very rare side-effects are (usually reversible) white matter disorders (leukoencephalopathy) that are associated with the occurrence of convulsions [31]. Blood serum levels of tacrolimus must be checked periodically. They must be checked frequently under the following conditions: directly after transplantation, after adjusting the dosage, after switching to a different immunosuppressive drug and after the administration of any drugs that (might) interact with tacrolimus. Examples of these are cyclosporine, amphotericin B (nephrotoxic), acyclovir and ganciclovir (neurotoxic). In the initial stages, tacrolimus is given intravenously (IV administration). As soon as possible after the disappearance of postoperative ileus, oral administration should be started. Target blood serum levels should not exceed 20 ng/ml (ELISA assay) [29]. Besides tacrolimus, cortico-steroids are administered for several weeks. To support immunosuppression, prostaglandin $E_I$ is administered for five days. In addition, support treatment with azathioprine is given, initially intravenously [11,30].

## COURSE AFTER TRANSPLANTATION

The condition of the liver transplant is monitored regularly by analysing the liver enzymes and periodically by taking biopsies. Findings suspicious of intestinal transplant rejection are: deterioration in clinical condition, increase or decrease in stomal

production, abnormal endoscopic findings and histological changes that correlate with rejection. Biopsies can be taken endoscopically by means of gastroduodenoscopy, endoscopy via the stoma or colonoscopy. In the initial stages or if the patient's condition weakens, biopsies should be taken twice a week [11,33]. Rejection is characterised by macroscopic and microscopic changes in the intestinal mucosa. Initially, there is merely oedema, erythema, mucosal membrane fragility and loss of peristalsis. This is followed by the development of aphthoid ulcerations and ultimately by broad-based ulceration covered by pseudomembranes. Histologically there is an increase in lymphocytes in the epithelium of the crypts and patchy epithelial apoptosis. In the case of severe rejection, epithelial desquamation occurs together with diffuse pseudomembranous enterocolitis [34]. Threatened rejection requires adjustment of the immunosuppressive drugs and a short course of steroids. In some patients, OKT3 is administered, which is a monoclonal mouse antibody directed against the CD3 antigen of T-lymphocytes [11,29,30].

Infection prevention plays a central role in the success of intestinal transplantation [11,27]. The compromised condition of the intestine and weakened defence easily lead to Gram-negative bacterial infections. Translocation of Escherichia coli, Klebsiella and Pseudomonas may cause life-threatening sepsis. To prevent this, selective intestinal decontamination can be applied, i.e. reducing the numbers of Gram-negative aerobes in favour of the proliferation of anaerobes. To prevent infection from Pneumocystis, cytomegalo virus and herpes, prophylactic medication can be administered in the form of cotrimoxazole, ganciclovir and acyclovir, respectively. As mentioned above, the latter two drugs can increase the neurotoxic action of tacrolimus [30]. Once the postoperative ileus has subsided, feeding can begin via the jejunostomy [11]. Preference is given to continuous drip-feeding with oligomeric nutrition; its constitution depends on the age of the patient. Absorption capacity of the transplant is reflected by the quantity and constitution of the stoma production. Fat balance is useful once enteral long chain fatty acids administration has started. In the absence of TPN, an increase in serum albumin level and the onset of body growth indicate adequate intestinal function. Other useful parameters for the onset of absorption by the small bowel are serum levels of calcium, phosphate, magnesium, iron and trace elements and the serum tacrolimus level with oral administration. As long as the absorption capacity remains below par, TPN must be continued [11,27].

## RESULTS OF INTESTINAL TRANSPLANTATION IN THE SHORT AND MEDIUM-TERM

In 1996, Grant reported the results of intestinal transplantation over the period 1985 to June 1995 on behalf of the International Intestinal Transplantation Registry [8]. A total of 180 intestinal transplantations were conducted on 170 patients in 24 programmes; two thirds of the patients were children. The most important indication for intestinal transplantation was SBS (64% of the cases), in 13% it was a malignancy (Table 2). In 38% of the patients, the small bowel was transplanted with or without large bowel, in 46% the intestine and liver, while 16% underwent multivisceral transplantation.

*Table 2. Data from the International Transplantation Registry on 180 intestinal transplantations in 178 patients (52% male, 48% female), 1985-1995 [8]*

| *Age (yrs)* | *No.* | *Indications* | *(n=178)* | *Year* | *No.* |
|---|---|---|---|---|---|
| 0-5 | 79 | Short bowel | 114 (64%) | 1985 | 1 |
| > 5-10 | 19 | Malabsorption | 23 (13%) | 1986 | 1 |
| > 10-20 | 19 | Motility disorder | 15 (8%) | 1987 | 3 |
| > 20-40 | 44 | Rejection | 10 (6%) | 1988 | 7 |
| > 40 | 17 | Tumour | 23(13%) | 1989 | 11 |
| | | Other | 1 | 1990 | 11 |
| | | | | 1991 | 14 |
| | | | | 1992 | 27 |
| | | | | 1993 | 40 |
| | | | | 1994 | 34 |
| | | | | 1995 (June) | 31 |

In the latter case, abdominal evisceration was necessary because of aggressive tumours. In the total group of intestinal transplantations, survival of the transplant and patient survival were considerably poorer in the patients treated with cyclosporine (n=49, 28% of the cases) than in the patients treated with tacrolimus immunosuppression (n=129, 72% of the cases). Table 3 summarizes the results. In the total group of 86 survivors, 78% were no longer on TPN, but were receiving oral nutrition. The

majority of patients in the report had been followed-up for a relatively short time. Survival was better after isolated intestinal transplantation than after combined liver-intestinal transplantation or multivisceral transplantation. This might be related to the difference in technical complexity of the interventions (isolated intestinal transplantation is in principle "more simple"), or to differences in the condition of the patients. Nevertheless the mortality rate two years after isolated intestinal transplantation was only 40%.

*Table 3. Results of 180 intestinal transplantations (isolated bowel, liver-intestine and multivisceral) in 178 patients (52% male, 48% female), 1985-1995. Survival of transplant and patient with cyclosporine or tacrolimus [8].*

| Cyclosporine (n=49) | After 1 yr % Trpl.*&pat.** | After 3 yrs % Trpl.*&pat.** | Tacrolimus (n=129) | After 1 yr % Trpl.*&pat.** | After 3 yrs % Trpl.*&pat.** |
|---|---|---|---|---|---|
| Intestine | 17 and 57 | 11 and 50 | Intestine | 65 and 83 | 29 and 47 |
| Liver-intestine | 44 and 44 | 28 and 28 | Liver-intestine | 64 and 66 | 38 and 40 |
| Multiviscera | 41 and 41 | 41 and 41 | Multivisceral | 51 and 59 | 37 and 43 |

** transplant survival; ** patient survival*

The next report from the International Transplantation Registry was published in 1999 [9]. In the last two years of the period from 1985 to February 1997, the number of transplant centres increased from 24 to 33, the number of transplants increased from 180 to 273 and the number of patients increased from 170 to 260; two thirds of whom were children or adolescents. Since 1990, there has been a linear increase in the number of transplantations, with a total of 58 in 1996. After February 1995, the one-year survival rates for the transplant and patient in patients with isolated intestinal transplants were 55% and 69%; in liver-intestinal transplants these rates were 63% and 65% and in multivisceral transplant patients, 63% and 63%, respectively. Transplants carried out since 1990 and centres that had conducted at least 10 transplants had significantly better transplant survival rates and patient survival rates; 77% of the survivors no longer required TPN. The five-year survival rates were similar to those for lung transplantation. An important aspect to prevent mortality in the case of rejection was to remove the transplant at an early stage and restart TPN. The more

complicated clinical course had clear repercussions in the occurrence of more complications than in heart, liver and kidney transplantation. Recently published results from the major European intestinal transplantation centre that forms part of the Hospital Necker-Enfants Malades in Paris on 26 children over the period 1987-1998 also showed improvement in the survival of both the transplant and the patient after the introduction of tacrolimus [13]. In addition, less rejection was observed in combined liver-intestinal transplantations, without increased mortality and morbidity. On the basis of these results, it can be concluded that (liver-)intestinal transplantation is a valid option for patients with permanent intestinal failure and life-threatening complications from TPN.

An important consideration in intestinal transplantation is the burden on the child and family. None of the studies mentioned above explicitly investigated quality of life after intestinal transplantation. However, there is evidence that intestinal transplantation is associated with a clearly higher burden on the family [34]. On the other hand, dependency on home-TPN is also associated with a considerable psychological burden and decreased quality of life [35,36].

## DEVELOPMENTS IN EUROPE AND THE NETHERLANDS

Only a limited number of European centres perform intestinal transplantation in children. This also reflects a limited need. At the end of 1998 there were eight centres: in Paris, Birmingham, London, Geneva, Strasbourg, Uppsala, Kiel and Coimbra (Portugal). The vast majority of (liver-)intestinal transplantations in children (n=26) were performed in Paris. At the end of 1998, seven children were still on the waiting list for the intervention. In Birmingham, a total of seven transplants had been conducted, but at the other centres only two, one or none [7].

In the Netherlands, policy regarding organ transplantation is prescribed by the Guidance Committee on Organ Transplantation (Begeleidingscommissie Orgaantransplantatie (BOTX)). It is probable that the first Dutch intestinal transplant will take place in the year 2000 and it is very unlikely to be in a child. Two Dutch centres will perform intestinal transplants: University Hospital Groningen (UHG) and Leiden University Medical Centre (LUMC). Working groups have been formed at both centres and have identified themselves via symposia, publications in popular scientific literature and the lay press. It is of great importance that both groups have formulated clear selection criteria and that both centres work in close collaboration with Dutch

centres that have wide experience in the field of TPN, at home and in hospital. The University Medical Centre Nijmegen St. Radboud supervises about two thirds of all Dutch adults on long-term TPN at home. In addition, over the course of time, extensive knowledge has been built up in the field of the metabolic aspects of the SBS in children and adults [37,38]. Close cooperation between the transplant centres and the centres with TPN expertise is of importance for several reasons. Firstly, candidates for intestinal transplantation must be selected from the group of patients receiving TPN. Secondly, it is necessary to continue TPN for some time after transplantation. Thirdly, if intestinal failure recurs because of rejection of the transplant, then TPN must be restarted at an early stage.

The Netherlands Society for Gastroenterology (NVG), the Section Gastroenterology and Nutrition of the Netherlands Paediatric Association (NVK) and the Netherlands Society for Paediatric Surgery are attempting to formulate and introduce national protocols for TPN in children and adults. This is intended to contribute to achieving optimal administration of TPN, with as few complications as possible. Only patients with permanent intestinal failure, in whom TPN administration is impossible or no longer desirable, form suitable candidates for transplantation. In children with permanent intestinal failure and threatened total liver failure, liver-intestinal transplantation should be considered at an early stage [7,11,13].

## CONCLUSION

World-wide, two thirds of all the intestinal transplantations for permanent intestinal failure are carried out on children. Despite improvements in immunosuppression, intestinal transplantation and combined liver-intestinal transplantation are still associated with considerable mortality, particularly in the medium-term. None of the major studies published in the literature explicitly evaluated quality of life. However, it can be assumed that in survivors, being able to live at home without TPN will at the very least lead to clear improvements in quality of life. Intestinal transplantation causes a heavy burden on the family. At present, intestinal transplantation cannot be considered the standard treatment for permanent intestinal failure and should only be reserved for a carefully selected group of patients. TPN must be totally impossible in these patients, or clearly no longer desirable. Children with permanent intestinal failure who develop early threatened liver failure should be considered for combined liver-intestinal transplantation.

## REFERENCES


1. American Academy of Pediatrics. Pediatric Nutrition Handbook, 4th ed. Elk Grove Village: American Academy of Pediatrics, 1998.
2. Walker-Smith J, Murch S. Diseases of the small intestine in childhood. 4th Ed. Oxford: Isis Medical Media, 1999.
3. Preston PP, Kirby DF. Short-bowel syndrome: a review of the role of nutrition support JPEN 1991; 15: 93-101.
4. Manginello FP, Javitt NB. Parenteral nutrition and neonatal cholestasis. J Pediatr 1981; 99: 445-9.
5. Das JB, Cosentino CM, Levy MF et al. Early hepatobiliary dysfunction during total parenteral nutrition: an experimental study. J Pediatr Surg 1993; 28: 14-8.
6. Moukarzel AA, Haddad I, Ament ME et al. 230 patient years of experience with home long-term parenteral nutrition in childhood: natural history and life of central venous catheter. J Pediatr Surg 1994; 29: 1323-7.
7. Goulet O. Selection of small bowel transplantation candidates and timing of transplantation. In: Ploeg RJ, Bijleveld C, Dullmen H van (eds). Small bowel transplantation in the Netherlands: fiction becomes fact? Report of a national workshop. Dec 8,1998 (CD-Rom). Groningen: University hospital Groningen and K.F. Wenckebach Institute, 2000.
8. Grant D. International Intestinal Transplant Registry. Current results of intestinal transplantation. Lancet 1996; 347: 1801-3.
9. Grant D. Intestinal transplantation: 1997 Report of the International Registry. Intestinal Transplant Registry. Transplantation 1999; 67: 1061-4.
10. Langnas AN, Shaw BW, Antonson DL et al. Preliminary experience with intestinal transplantation in infants and children. Pediatrics 1996; 97: 443-8.
11. Kocoshis SA, Reyes J, Todo S, Starzl TE. Small intestinal transplantation for irreversible intestinal failure in children. Dig Dis Sc 1997; 42: 1997-2008.
12. Reyes J et al. Current status of intestinal transplantation in children. J Pediatr Surg 1998; 33: 243-54.
13. Jan D, Goulet O, Sarnacki S et al. Up-to-date evolution of small bowel transplantation in children with intestinal failure. J Pediatr Surg 1999; 34: 841-3.
14. Stringer MD, Puntis JWL. Short bowel syndrome. Arch Dis Child 1995; 73: 170-3.
15. Sondheimer JM, Cadnapaphornchai M, Sontag M, Zerbe GO. Predicting the duration of dependence on parenteral nutrition after neonatal intestinal resection. J Pediatr 1998; 132: 80-4.
16. Davidson GP, Cutz E, Hamilton JR, Gall DG. Familial enteropathy: a syndrome of protracted diarrhea from birth, failure to thrive and hypoplastic villus atrophy. Gastroenterology 1978; 75: 783-90.

17. Phillips AD, Schmitz J. Familial microvillus atrophy: a clinicopathological survey of 23 cases. J Pediatr Gastroenterol Nutr 1992; 14: 380-96.
18. Jacobs MJ, Tolboom JJM, Bosman DK, Haelst UGJM van, Bult P, Kneepkens CMF, Taminau JAJM. Microvillusziekte, een zeldzame oorzaak van ernstige aangeboren diarree. Ned Tijdschr Geneesk 2002; 146: 1448-52.
19. Vargas JH, Sachas P, Ament ME. Chronic intestinal pseudo-obstruction syndrome in pediatrics: results of a national survey by members of the North American Society of Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 1989; 7: 323-32.
20. Rudolph CD, Hyman PE, Altschuler SM et al. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of a consensus workshop. J Pediatr Gastrenterol Nutr 1997; 24: 102-12.
21. Mousa H, Cocjin J, Flores AF et al. Multicenter experience with congenital intestinal pseudo-obstruction in children. J Pediatr Gastroenterol Nutr 1998; 26: 558.
22. Oliva MM, Perman JA, Saavedra JM, Young-Ramsaran J, Swarz KB. Successful intestinal transplantation for microvillus inclusion disease. Gastroenterology 1994; 106: 771-4.
23. Herzog D, Atkinson P, Grant D, Paradis K, Williams S, Seidman E. Combined bowel-liver transplantation in an infant with microvillus inclusion disease. J Pediatr Gastroenterol Nutr 1996; 22: 405-8.
24. Randak C, Langnas A, Kaufman S, Phillips A, Wisecarver J, Hadorn H, Vanderhoof J. Pretransplant Management and Small Bowel-liver Transplantation in an infant with Microvillus Inclusion Disease. J Pediatr Gastroenterol Nutr 1998; 27: 333-7.
25. Sigurdsson L, Kocoshis SA, Mzariegos G et al. Intestinal transplantation in children with chronic intestinal pseudo-obstruction. Gut 1999; 45: 570-4.
26. Ville de Goyet J de. Pseudo-obstruction in children: transplant or wait? Gut 1999; 45: 479.
27. Bueno J, Ohwada S, Kocoshis S et al. Factors impacting the survival of children with intestinal failure referred for intestinal transplantation. J Pediatr Surg 1999; 34: 27-33.
28. Starzl TE, Todo S, Tzakis A, Murase N. Multivisceral and intestinal transplantation. Transplant Proc 1992; 24: 1217-23.
29. Kuy A van der (red). Farmacotherapeutisch kompas. Amstelveen: Ziekenfondsraad, 1999.
30. Denton MD, Magee CC, Sayegh MH. Immunosuppressive strategies in transplantation. Lancet 1999; 353: 1083-90.
31. Torocsik HV, Curless RG, Ost J, Tzakis AG, Pearse L. FK506-induced leukoencephalopathy in children with organ transplants. Neurology 1999; 52: 1497-1500.
32. Garau P, Orenstein SR, Neigut PE et al. Role of endoscopy following small intestinal transplantation in children. Transplant Proc 1994;26:136-37.
33. Sigurdsson L, Kocoshis SA, Reyes J, et al. Severe exfoliative rejection after intestinal transplantation in children. Transplant Proc 1996; 28: 2783-4.

34. Tarbell SE, Kosbach B. Parental psychosocial outcomes in pediatric liver and/or intestinal transplantation: pretransplantation and the early postoperative period. Liver Transpl Surg 1998; 4: 378-87.
35. Brook G. Quality of life issues: parenteral nutrition to small bowel transplantation; a review. Nutrition 1998; 14: 813-6.
36. Wong C, Akobeng AK, Miller V, Thomas AG. Quality of life of parents and children on home parenteral nutrition. Gut 2000; 46: 294-5.
37. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems J. D-lactic acidemia and aciduria in pediatric and adult patients with a short bowel. Clin Chem 1995; 41:107-10.
38. Bongaerts G, Bakkeren J, Severijnen R, Sperl W, Willems H, Naber T, Wevers R, Meurs A van, Tolboom J. *Lactobacilli* and acidosis in children with short small bowel. J Pediatr Gastroenterol Nutr 2000; 30: 288-93.

## 4.5 ACUTE LOSS OF THE SMALL BOWEL IN A SCHOOL-AGE BOY. DIFFICULT CHOICES: TO SUSTAIN LIFE OR TO STOP TREATMENT?

*René Severijnen[1], Ineke Hulstijn-Dirkmaat[2], Bert Gordijn[3], Leo Bakker[4], Ger Bongaerts[5].*

*Department of [1]Paediatric Surgery, [2]Medical Psychology, [3]Medical Ethics, [4]Paediatric Intensive Care Unit and [5]Department of Medical Microbiology, University Medical Centre St. Radboud, Nijmegen, The Netherlands*

*European Journal of Pediatrics 2003; 162: 794-798*


### ABSTRACT

A 9-year-old boy lost almost all his small bowel after an acute volvulus due to a congenital, but previously unsuspected malrotation. Survival using total parenteral nutrition is possible in these cases, but the medical burden is heavy. Small intestinal transplantation was performed for the first time in the Netherlands in 2001 and this patient was treated 3 years earlier. The results of bowel transplantation are not as good as in kidney or liver transplantation. A method of Ethical Case Deliberation helped to elucidate the importance of each contribution in the discussion and provided space and a broad basis for decision-making. The parents refused to allow parenteral nutrition to be started because of the bad prospects for quality of life in the future and the medical team, after thorough deliberation with specialists throughout the country, and consultation of the literature, agreed.
*Conclusion*: Despite the many different opinions, the parents felt accepted in their refusal of treatment for their son and the team accepted the decision.

## INTRODUCTION

When the whole small bowel is lost, treatment with total parenteral nutrition (PN) and small bowel transplantation in the future should be considered. The results of intestinal transplantation are not as good as for other organ transplants in terms of mortality and certainly not in morbidity [1,2]. How can we reach a decision to maintain a child on PN and await transplantation or to deny such "extraordinary" treatment? [1]. In a 9-year old boy with sudden loss of the entire small bowel, a choice had to be made whether to start treatment of the intestinal failure or not. The quest for optimal treatment requires careful evaluation of all factors surrounding the child [1]. Discussion in the team according to a model of Ethical Case Deliberation (ECD) gave everyone involved adequate time to discuss and contribute and in the end to reach a decision with the parents. The decision led afterwards to much discussion on the ward.

### The Nijmegen method of ethical case deliberation

The Nijmegen method of ECD was developed in the Department of Ethics in co-operation with different clinical departments of our hospital in the early 1990s to facilitate decision-making through multidisciplinary case discussions (see Appendix). It allows professionals to articulate, analyse and evaluate medical, psychological, social and ethical aspects of problems in medical decision-making in clinical practice. The aim is to improve the quality of medical decision-making in ethically difficult situations [7]. The deliberation procedure consists of four steps: 1. The formulation of the ethical problem; 2. Gathering the relevant facts from the different professional viewpoints, taking into account the medical, nursing, social, psychological and organisational dimensions; 3. Weighing the relevant moral considerations; 4. Decision-making.

The moderator, preferably an ethicist and not a member of the team, has the important role of giving members of each professional group equal opportunity to express their views. Because the facilitation follows a systematic protocol, the different professional perspectives (of physicians, nurses, psychologists and social workers) can be articulated at a foreseeable point in the process, thereby conveying the active participation of all the relevant professional groups. In this way, the Nijmegen method structures moral reflections into multidisciplinary team conferences. It aims to find what is an acceptable and responsible action in what are often open and new situations. As such, the method is not based on a specific normative theory in ethics. The assumption, however, is that there is intuitive access to moral questions. Moral ques-

tions and problems arise in daily life and practice. Almost everyone has some sense of right and wrong and, as a rule, perceives the moral dimension of actions and situations. ECD tries to shed light on this dimension.

Both in ordinary language and in moral philosophy, the phenomenon of the intuitively accessible moral dimension of life has been interpreted in various ways. One way depicts moral issues as questions of conscience which is understood both as a reservoir of intuitive moral knowledge and as a trial court of ethical arguments. An ECD using the Nijmegen protocol always starts on an intuitive level of moral conscience. After that, it gathers all the necessary facts in order to think about the moral problem being presented in a well-informed way. Next, it proceeds to more rational arguments in favour of or against certain moral assumptions. In this way, initial moral assumptions are critically assessed and weighed in a structured multidisciplinary process of moral reflection.

## CASE REPORT

A 9-year-old boy experienced acute severe abdominal pain one evening. On examination in the local hospital that night the boy was in shock and had a painful abdomen. At emergency laparotomy, a volvulus of the entire small bowel with necrosis due to a malrotation, was found. After an unavoidable resection, a duodenostomy was created and the ileum was closed 2 cm proximal to the ileocaecal valve. For postoperative ventilation and treatment of septic shock, the child was transferred to the paediatric intensive care unit of our university hospital. The next day a planned relaparotomy was performed and the duodenum sutured to the last centimetre of ileum to avoid high output stoma problems.

After the second operation the parents considered all the information provided and chose to refuse treatment of the intestinal failure as proposed by the medical team. The firmness of the parents' view to withhold treatment and the problems with this decision of the nursing and medical team, led to the consultation of a psychologist to facilitate the deadlocked positions [14]. On the 6th day after prolonged and intensive discussions between the parents, the hospital ethics team, doctors and nurses, medical treatment and artificial respiration were stopped. Sedation and pain treatment were continued. The boy died the next morning with a high fever due to ongoing sepsis.

## DISCUSSION

### The moral problem

The choice was to agree with the parents' wish to stop treatment or to start the usual treatment with total PN against the parents' will [15]. All possible medical strategies were considered [3,6] including total PN or as long as the boy should live or starting PN and considering small bowel transplantation in the future. The last possibility was to keep the child under sedation and see what happened without active treatment by PN or respiratory support, offering only "comfort care" [1].

### Medical dimension

The duodenum alone is not enough to survive on without intravenous nutrition, even if the whole colon is present [8]. After survival of the acute illness the child could be kept alive for a long time on PN, but normal feeding and drinking would be restricted for the rest of his life. The quality of life in these cases is dominated by the complications of intravenous access to the great vessels. Liver failure occurring as another complication of long-term PN, may require a combined liver and intestinal transplant. Without total PN this patient would soon die.

The results of intestinal transplantation in 1998 were reported to lead to a 55% patient survival [11], and the morbidity is still very high [5]. The first bowel transplantation on an adult in the Netherlands was performed in 2001, 3 years after this child was treated. With little possibility at that time of future bowel transplantation, starting a child on PN for an unknown number of years needs careful consideration [4,12].

### Nursing dimension

Optimal care for children in the Paediatric Intensive Care Unit requires good co-operation between parents and nurses and the confidence they have in each other can help the child to withstand the severe illness that led to the admission to the intensive care unit. In this patient, the parents believed there was no cure only palliation and prolonged illness with the possibility of an unpleasant life and death. The nurses invited the parents, who were present all the time, to assist with the daily care, but this was too much for them. It made communication with the parents difficult [9]. The parents also did not want the sedation of their child to be stopped.

**Social and psychological dimension**

After gaining the confidence of the parents, the psychologist started the discussion about "to treat or not to treat". The patient was a healthy boy, with a normal development but few social contacts. His parents assessed that he would never accept and cope with chronic disease, physical limitations, dependency on medical and invasive treatment without any prospect of a normal life and being "not the same" as other children of his age. They expected that he would blame his parents for having agreed to prolong his life. They were very concerned about the way in which he would cope with the fear for death and about their own coping with their son's illness. They also worried about the emotional impact on the development and functioning of their 14-year-old son.

The patient was brought up in a rather closed family in a small traditional community. The parents were only formally affiliated to a protestant community. The social network consisted of the father's family and neighbours, from whom the parents experienced practical but not strong emotional support. The father used few words but showed his grief and emotions and underlined his concern and doubts about his son's coping capacity. The mother was the only child of parents who both suffered from serious chronic diseases. She cared for her parents until they died and had seen her father suffer a great deal. She attributed his suffering to what she called meaningless inhuman medical treatment that prolonged his life without any perspective. She was determined not to treat her son likewise. Both parents gave the impression that they fully understood the information of the doctors and they consulted their general practitioner twice for additional information and support.

The conclusion of the psychologist was that both parents, each from a different frame of reference, were sincere and convinced that no treatment should be in their son's interest. They said: if we were told that there would be a good chance for successful transplantation in the long-term, we would never leave him and wait for a better life. Now we are convinced death means a better outcome for him and we have to cope with our grief and loss.

**Organisational dimension**

After survival of the acute postoperative and respiratory care on the paediatric intensive care unit, a transfer to a paediatric ward should be possible. When the medical conditions were stable and the boy and his parents were accustomed to the "life-line", parents can be taught the care of the central venous catheter and home administration

of PN was foreseen. The medical system in The Netherlands o.ers every possibility to start these children on PN and if necessary to continue this at night at home for the rest of their lives, whatever the financial cost.

**Ethical considerations**

In the multidisciplinary discussion, some members of the team argued that active treatment should be withheld while others pleaded to the contrary [13]. Arguments in favour stated that if this boy would receive further lifesaving treatment, he would be confronted with continuous medical care for the rest of his life and the parents of the boy refused this [2]. To further assess the future quality of life, advice was sought from paediatric surgical centres throughout the Netherlands, and the literature was consulted. Nearly all consultants agreed that the quality of life would be strongly diminished. PN is a medical treatment such as ventilation and its use should be clearly decided upon. Therefore it should not be assumed that the patient or in this case the parents wanted this without official consent [4,6]. Other members, arguing against withholding active treatment, stated that everybody has a right to live. According to them, the parents in this case should not deny this and decide for him. Because short-term cure seemed possible and long-term support of life was available, treatment should be started. They did not consider PN to be an "extraordinary" treatment [1]. Moreover, they were of the opinion that the benefits would outweigh the burdens for the patient.

**Decision**

The more important role of the parents arguments in cases where there is a strong doubt about prognosis and outcome, are supported by Molenaar [10]. The right of the parents to refuse PN without consulting their 9-year old son is in accordance with the law in the Netherlands. Allowing the child to regain consciousness so that he could express his feelings and participate in the decisionmaking seemed unethical. It was doubted whether a boy of his age would be able to take responsibility in such a complex and burdening decision.

After difficult deliberations, the nurses, physicians, psychologist and the ethicist decided to comply with the parents' wish not to start nutritional treatment and consequently accept the inevitability of death. The alternative was a judicial review which would have led to the responsibility for the child being temporarily removed from the parents and given to the Council for Child Protection. After the acute hospital treat-

ment, the care of the child, then dependent on PN and continuous medical intervention, would have been returned to the parents and they would have had to live and cope with that for the rest of the child's life.

The parents' decision did not alter after extensive discussions with the doctors, nurses or the psychologist. The information on the subject of a future transplantation, which was weighed and explained by different doctors was most important for their decision [9]. Structured analysis of all the arguments and conflicting values made it possible to reach an agreement with the present members of the team and with the parents. Despite that, the death of this young boy placed a heavy burden on all members of the team. The quality of life in children with a gastroenterological handicap can be poor, but in most cases there is no opportunity to take a decision not to treat. This boy was being actively treated for sepsis and kept sedated whilst on the ventilator. This artificial support made it possible to choose carefully the option to stop treatment and not to start unwanted PN.

## ACKNOWLEDGEMENTS

The authors thank Dr. J. Tolboom, paediatric gastroenterologist for his comments and Dr. E. Robertson, anaesthesiologist, for the English language editing.

## REFERENCES

1. Beals DA (2001) Virtue ethics in a pluralistic world. Semin Pediatr Surg 10: 179-85.
2. Booij LHDJ, van Leeuwen SJ (1997) Ethics in anaesthesia and intensive care. Curr Opin Anaesthesiol 10: 147-53.
3. Caniano DA, Kanoti GA (1988) New-borns with massive intestinal loss: difficult choices. N Engl J Med 318: 703-7.
4. Ells C (2001) Culture, ethics and pediatric surgery. Semin Pediatr Surg 10: 186-91.
5. Georgeson K, Brown P (1998) Short bowel syndrome. In: Stringer MD, Oldham K, Moriquand PDE et al (eds) Pediatric surgery and urology: long term outcomes. Saunders, Philadelphia, pp 237-43.
6. Glover JJ, Caniano DA, Balint J (2001) Ethical challenges in the care of infants with intestinal failure and lifelong total parenteral nutrition. Semin Pediatr Surg 10: 230-6 .
7. Gordijn B (2000) Ethik in der Pflege. Ethische Diskussionen im Team. Nimweger Modell der multidisziplinische Fallbesprechung. Die Schwester, der Pfleger 39: 114-7.
8. Hancock BJ, Wiseman NE (1990) Lethal short bowel syndrome. J Pediatr Surg 11: 1131-4.

9. Hedrick HL, Nelson RM (2001) Handling ethical conflicts in the clinical setting. Semin Pediatr Surg 10: 192-7.
10. Molenaar JC (1996) Ethics in pediatric surgery. Eur J Pediatr Surg 6: 132-5.
11. Reyes J, Bueno J, Kocoshis S, Green M, Abu-Elmagd K, Furukawa H, Barksdale EM, Strom S, Fung JJ, Todo S, Irish W, Starzl TE (1998) Current status of intestinal transplantation in children. J Pediatr Surg 33: 243-54.
12. Shambogue LK, Molenaar JC (1994) Short bowel syndrome: metabolic and surgical complications. Br J Surg 81: 486-99.
13. Sigalet DL (2001) Short bowel syndrome in infants and children: an overview. Semin Pediatr Surg 10: 49-55.
14. Shooter M, Watson A (2000) The ethics of withholding and withdrawing dialysis therapy in infants. Pediatr Nephrol 14: 347-51.
15. Truogg R, Burns J, Rogers MC (1996) Ethics. In: Tibboel D, van der Voort E (eds) Intensive care in childhood: a challenge to the future (update in intensive care and emergency medicine). Springer, Berlin Heidelberg New York.

**APPENDIX: THE NIJMEGEN METHOD OF ETHICAL CASE DELIBERATION**

**PROBLEM**
What is the moral problem?

**FACTS**
**Medical dimension**
How has the patient been diagnosed and what is the prognosis?
What kind of treatment can be suggested?
Does this treatment have a positive effect on the prognosis? To what extent?
What will be the prognosis when this treatment is not prolonged?
What are the chances of success with the treatment?
Could the treatment be harmful to the patient's health?
How do these positive and negative aspects lie with each other?

**Nursing dimension**
What is the nursing diagnosis of the patient?
What kind of nursing plan is suggested?
To what extent is the patient able to take care of him/herself? Is volunteer aid available?
What arrangements have been made with regard to the division of tasks in care?

**Patient's values and social dimension**
What is known about the patient's outlook on life?
Is the patient a member of a religious community?
How does the patient view illness? Has a need for pastoral care been expressed?
What is the patient's social background?
What are the consequences of the illness and treatment for the family, lifestyle and social position?
Do these consequences go beyond the strength of the patient and his/her environment?

**Organisational dimension**
Can the patient's need of care be realised? (capacity, staff, equipment)

**ASSESSMENT**
**Welfare of the patient**
What are the consequences of illness and treatment for the wellbeing of the patient? (joy in life, freedom of movement, physical and mental wellbeing; pain, shortening of life, fear etc.)

**Autonomy of the patient**
Has the patient been well informed about his/her situation?
Has the patient been sufficiently involved in the decision-making process until now?
What is his/her judgement on the pros and cons of the treatment?
Which values and opinions of the patient are relevant?
What is his/her view on life-sustaining or intensive therapy?
Is it right to leave the decision whether to treat or not to the patient?

**Responsibility of the health care professionals**
Are there differences of opinion between physicians, other health care professionals, the patient and relatives about what should be done?
Is it possible to solve this conflict by choosing a particular kind of health care policy? Has there been sufficient consultation between the health care professionals involved?
Have their responsibilities been sufficiently demarcated?
How do health care professionals deal with confidential information (confidentiality)?
Has the patient been truthfully informed of his/her situation (sincerity)?
Has the case given rise to tensions within the team the health care institute? (collegiality)?
Can the suggested policy be accounted for in relation to other patients (justice)?
Should health care providers take into account the interests of a third party? What are the relevant guidelines of the health care institute?

**Decision-making**
What is the moral problem in this case?
Are there important facts still unknown? Is it nevertheless possible to take a responsible decision?
Could the problem be interpreted in terms of (conflicting) values?
Is there a way out of this dilemma?
Which alternative way of acting is most in keeping with the patient's values?
What other arguments are relevant to this decision?
Which act is preferable, on the basis of the afore mentioned arguments? (treatment, changes in care, consultation, referral, awaiting etc.)
What are the actual obligations of the persons involved?
Which questions remain unanswered?
In which cases should the decision be revised?
In what way can the decision and the evaluation be summarised?

**Special circumstances**
*Incapable patients*
How and by whom has incapability been established?
In what way is the patient incapable?
Is it of a temporary or a permanent character?
Is there a prospect of recuperation of capability?
Is it possible to postpone decisions until that time?
What is known about the values the patient holds?
Is there a capable representative of the interests of the patient?
*Children*
Has the child been given enough attention?
Is the child capable of deciding for itself with regard to the treatment?
Which alternative way of acting is most in keeping with the parents' set of values?
What are the consequences for the child if the parents' view is or is not adhered to?
*Long-term treatment*
In which situations does the policy of care need to be evaluated and possibly revised?
What is the patient's attitude with regard to policy changes?

# 5

# General discussion

## GENERAL DISCUSSION

Children suffering from a short small bowel are often hospitalised for long periods. They suffer from invasive medical treatment and are exposed to many complications. This disturbs their physical and mental development and restricts and reduces the quality of life of these children and their families.

Every effort should be made to achieve nutritional autonomy in children with a short small bowel. We have learned over the years to start enteral feeding early in all these children by gradually increasing the amount and frequency of food. Since the enteral absorption is abnormally low, the decrease in intravenous nutrition should not be of equal caloric or fluid amounts as the increase of enteral feeding. Extra enteral feeding may be needed to compensate for this insufficient absorption.

After neonatal intestinal resection and sometimes also in older children, the infant is started with mother's milk and this is continued for the first year or even longer. Oligomeric nutrition on an amino acid basis can be provided if a child cannot tolerate other enteral nutrition, such as protein hydrolysates [1]. For adequate adaptation more complex enteral feeding is necessary. Glutamine is described as preferential nutrition for the small intestine in infants. It provides energy for the enterocytes, promotes electrolyte absorption and supports immune function [2]. As the amino acid based enteral nutrition such as Neocate® contains over 10% of glutamine as part of its total protein content, no additional glutamine administration is necessary.

All enteral nutrition, especially if the child needs continuous feeding over 24 hours, is administered by gastrostomy to avoid the negative effects of a nasogastric tube, such as gastrooesophageal reflux, pulmonary infections and feeding or speech disturbances. Still a small amount is always presented orally, but in some cases this may not be enough to teach the child to eat everything by mouth when we think the stomach and intestines can handle normal oral feeding. A child's feeding team consisting of a paediatric gastroenterologist, dietician, specialised nurse, psychologist, speech language therapist, paediatric physiotherapist and paediatric surgeon, is necessary to advise how to overcome the eating problems of these children who have lost the ability to eat normally.

### Surgery

Animal experiments were performed to evaluate at that time recommended operative techniques to improve the rapid small bowel transit and the reduced absorption

of nutrients. The results showed the best way to repair the intestines, was an end-to-end anastomosis and we decided after that not to perform any extra surgery in children to improve absorption.

As loss of fluids and nutrients from a jejunostomy is difficult to deal with in children, we close intestinal stomas early, 3-4 weeks after their construction, if the condition of the child allows it. Since then we have had no child with a short bowel syndrome and persistent jejunostomy or ileostomy.

Various operations are advocated nowadays to combat intestinal dilatation and improve absorption. We very occasionally taper the small bowel but only when stasis makes enteral feeding impossible, an operation is necessary.

In 1997 in a case of extreme dilatation and stasis of the intestine in a boy of 11 months a lengthening procedure of the distended small bowel with longitudinal splitting according to Bianchi was performed in Mannheim, Germany. In 2002 we performed the same operation in our clinic in a girl of 6 months. Both children ameliorated with regard to the passage of intestinal contents and it became possible to start enteral feeding.

Parenteral nutrition, if possible at night and at home is the first choice of treatment if intestinal autonomy cannot be achieved. This can be given to adult patients for prolonged periods if no complications occur, as is proven in the University Medical Centre Nijmegen, where some adults are treated for over 25 years with home parenteral nutrition (Naber, personal communication).

The choice for intestinal transplantation might be made if all intravenous access possibilities fail or there is no prospect of reaching intestinal autonomy in the coming years after maximal supporting medical and surgical measures like lengthening operations.

**Bacterial flora**

The major part (up to 100%) of the intestinal flora in our children with a short small bowel consists of non-pathogenic lactobacilli. These bacteria are generally considered to be beneficial for the health of our patients. For this reason these bacteria should not be killed by antibiotics.

The explanation for this highly characteristic flora in children with a short small bowel lies in the appropriate environment for the acid-tolerant lactobacilli in the duodenum. The pH is still low and there is - with enteral nutrition - enough malabsorbed sugar available, which can be fermented by lactobacilli to lactic acid. This increases

the acidic surroundings and promotes further growth of lactobacilli. The neutralizing capacity of the pancreatic juice may soon be overcome and the acidic contents will result in faeces with up to 100% of lactobacilli in a number of $10^{12}$ cfu/g faeces (normal count: $10^{11}$ cfu/g faeces) and a pH that may be as low as 3.9. Lactobacilli need sugars for growth, which may intestinally have been produced from polymerised carbohydrates, e.g. starch; otherwise their numbers decrease rapidly. We observed this in a child who, after stopping oral feeding when her abdominal distension caused unbearable pain, had quick symptomatic relief.

It is just the high molecular volume of $CO_2$ gas (22,4 l/mole gas) produced by heterolactic lactobacilli that leads to a distended abdomen and diarrhoea.

The produced lactic acid (two moles lactic acid from one mole glucose by homolactic strains, one by heterolactic strains) may be D- or L-lactic acid. L-lactic acid is harmless and broken down easily in children. In neonates and young children we observed a very high serum D-lactic acid and a high urinary D-lactic acid excretion. In contrast in adults only high serum D-lactic acid values were found. This is due to the enzyme D-2-OH-acid dehydrogenase, which seems to clear D-lactic acid from the blood in adults and children from about four to five years of age. If too much of the produced D-lactic acid is not excreted in time, it causes D-lactic acidosis.

Abdominal complaints, acidosis and even encephalopathy may occur. In the past patients with a short small bowel and these complaints were treated with antibiotics or starvation. However, the selection of other bacteria or even yeast by antibiotic treatment can also be harmful and this brought us to probiotic treatment. When normal intestinal flora is disturbed by antibiotics, or when lactobacilli cause D-lactic acidosis and gas problems, oral administration of probiotic *Lactobacillus casei* that produce only limited amounts of $CO_2$, as replacement of the naturally occurring lactobacilli, may alleviate the problem.

Lactobacilli in the duodenum resist the killing effect of bile acids by producing a cholic acid deconjugating enzyme. The deconjugated cholic acid cannot be absorbed by the intestine and so the normal enterohepatic cycle of cholic acids is severely disturbed. This makes fat absorption difficult and creates steatorrhoea with loss of absorptive capacity for the lipophilic vitamins, A, D, E and K. As lactobacilli do not degrade proteins like many other bacteria, their effect on mucin is limited and this spares the intestinal defence mechanism of mucin on the intestinal wall.

If proton pump inhibitors are used to treat the gastric hyperacidity that occurs initially after bowel resection, they should be stopped as soon as possible after an adap-

tation period. These inhibitors disturb the natural protection of the gastrointestinal tract against all kinds of ingested microorganisms. Abnormal bacterial growth in the small bowel may disturb the already compromised absorption of nutrients and medicine.

If antibiotics are used to treat lactobacilli overgrowth and acidosis, a change of the intestinal flora and thus of patient's metabolism is quite normal. During such long-term treatment pathogenic yeasts, e.g. *Candida glabrata* may emerge. In such cases we advocate the yeast *Saccharomyces cerevisiae* subspecies *boulardii* as a useful probiotic that may be safer than the naturally occurring yeasts in a child.

Treatments should be aimed at dietary manipulation of the natural lactobacillus flora or at replacement of this flora by a probiotic lactobacillus flora. In children with a short small bowel and oral feeding consisting of a high carbohydrate, low fat diet the major part of the intestinal flora consists of non-pathogenic lactobacilli as long as no oral antibiotic treatment, neutralisation of gastric acid or inhibition of gastric acid production has been induced. Replacement of the high carbohydrate low fat diet by a low carbohydrate high fat diet may greatly reduce the many typical symptoms related to lactobacilli-mediated sugar fermentation and even the percentage of lactobacilli in the intestinal flora.

Replacement of the natural *lactobacillus* flora of patients with a short small bowel by probiotic L-lactic acid producing facultative heterolactic lactobacilli will reduce also problems, which are due to intestinal sugar fermentation.

**Venous access and infections**

The administration of parenteral nutritional solutions requires intravenous catheters, subcutaneous portals or arterio-venous shunts, all with their own problems and complications. The parenteral solution itself may also be harmful and may lack some necessary nutrients. Technology is constantly improving these solutions but intravenous access remains the greatest challenge in such children.

Children with a short small bowel often suffer from serious systemic bacterial or mycotic infections. Septicaemia is often due to translocation of intestinal bacteria. The infection may cause a temporary ileus, and so enteral feeding has to be stopped. It worsens liver function and promotes cholestatic icterus. A disturbance in the development of immune reactivity in some children could not be demonstrated. The combination of parenteral nutrition by a central venous catheter and bacterial translocation from distended bowel seems to be the main problem since infections did not occur

after removal of the central venous catheter, despite the continuing bowel dilatation. Subcutaneous portals produce the same problems. Repeat intravenous antibiotic treatments and selective intestinal decontamination may also lead to unwanted and resistant bacteria or yeasts. These can be difficult to treat and can be life threatening to the patient. Selective intestinal decontamination has to be used, when the antimicrobial action of the spontaneously occurring lactobacilli will not suffice for eradication of possible pathogens, or when a small bowel biopsy shows a villous atrophy, ascribed to bacterial overgrowth.

**Growth**

Children with a short small bowel are in general shorter than children with a normal length of intestine. Growth hormone treatment was used in a child to increase her restricted length. Later four children were treated with growth hormone for a short term in combination with glutamine and complete intestinal autonomy could be achieved in one child, temporarily in the others. In our long-term use of growth hormone alone in three children, height could be improved in all three. All children achieved a better anabolic condition. The exact contribution of growth hormone to intestinal autonomy needs further study.

Different strategies are often applied together when treating children with an SSB. The bowel lengthening operation in a boy at 11 months (CH 5) improved the peristalsis and made enteral feeding possible. The start of enteral oligomeric amino acid solution at the age of two and a half years improved bowel wall integrity, decreased the number of diarrhoeal episodes and prevented dehydration, which had been a common problem until that time. We also saw fewer episodes of sepsis and after adding growth hormone at the age of four years, they almost ceased. Therefore, we are convinced that growth hormone therapy is not facilitating bacterial translocation. However, it was only after the start of selective intestinal decontamination that parenteral nutrition could be diminished from seven to two times a week. Since then there have only been a few periods of serious illness. We assume that in order to achieve complete intestinal autonomy, it will be necessary to change to another oral diet, which contains more nutrients that are known to stimulate bowel adaptation, as this boy is currently almost on complete enteral nutrition after a very long adaptation period of seven years.

**Ethics**

In an ethical study we considered the rights and motives of parents who refused the starting of parenteral nutrition for their child. This was done in complete accordance with Dutch law. This decision was taken by the parents and supported in the end by the team. This family and boy would have been subjected to the long and difficult administration of prolonged parenteral nutrition and even eventually transplantation. Stopping all active treatment led to the death of the child and this was very difficult for all the involved health care workers. A good functioning ethical team with proper judgement of all viewpoints was essential in reaching a decision acceptable to all people involved.

## CONCLUSIONS

Each patient with a short small bowel needs individual judgment and individual therapy by a dedicated committee for nutrition and feeding problems in order to prevent complications, achieve an early anabolic state and help to reach the ultimate goal of complete intestinal autonomy.

Satisfactory height and weight growth on enteral nutrition remains the cornerstone of the evaluation of children with a short small bowel. A careful estimation of the child's wellbeing by an experienced team not only of nurses and doctors, but also many other child health care providers involved, is essential. Maximal support for these children and their families is invaluable.

## FUTURE PERSPECTIVES

Prevention of a short small bowel will not be possible in all cases. Improvements in neonatal care with attention to an adequate intestinal circulation in premature babies may help to prevent loss of intestine. Volvulus of the bowel in malrotation can sometimes be recognised earlier especially when associated with other anomalies and operated in time.

Increased interest in diet therapy with a high fat diet in contrast to high carbohydrate might help to improve intestinal function faster than at this moment.

Growth hormone therapy deserves another trial as a general anabolic medicament with an increased growth and improvement of bowel absorption.

Further study of the microbiological flora in the intestines of children with a short small bowel during parenteral nutrition is necessary. It may help to prevent the disastrous effects of translocation and sepsis or present a better insight in therapeutic possibilities. Probiotics such as *Lactobacillus casei* or *Saccharomyces boulardii* reduce gas formation and thus abdominal complaints and dilatation [3].
Severe dilatation without stasis is no indication to operate but stasis of intestinal contents with severe dilatation of the bowel may be treated surgically by serial transverse enteroplasty, a novel bowel lengthening procedure described by Kim [4]. This operation seems to improve bowel passage even better than the longitudinal splitting and lengthening operation described by Bianchi [5].

## REFERENCES

1. Vanderhoof JA and Young RJ. Enteral nutrition in short bowel syndrome. Sem Pediatr Surg 2001; 10: 65-71.
2. Hankard R, Goulet O, Ricour C, Rongier M, Colomb V, Darmaun D. Glutamine metabolism in children with short-bowel syndrome: a stable isotope study. Pediatr Res 1994; 36: 202-6.
3. Bongaerts GPA, Severijnen RSVM. The beneficial, antimicrobial effect of probiotics. Med Hypotheses. 2001; 56: 174-7.
4. Kim HB, Fauza D, Garza J, Oh J-T, Nurko S, Jaksic T. Serial transverse enteroplasty (STEP): a novel bowel lengthening procedure. J Pediatr Surg 2003; 38: 425-9.
5. Bianchi A. Longitudinal intestinal lengthening and tailoring: Results in 20 children. J R Soc Med 1997; 90: 429-32.

# Summary

## SUMMARY

In the introduction the definition of a short bowel syndrome and the normal length of small bowel is described. The causes and some consequences in children with a short small bowel are explained. The aim of the study and the contents of the different chapters are also presented.

Chapter 2.1 describes our work on dogs in the animal laboratory where we tried to find ways to slow down the rapid transit through the short small bowel and improve intestinal absorption. Creating antiperistaltic segments or circular loops did not help. Stasis of the intestinal contents that occurred in the reversed segments worsened the condition of the dogs. A simple end-to-end anastomosis was best. We therefore decided not to add any constructive surgical techniques to the end-to-end anastomosis.

Chapter 2.2 explains our definition of a short small bowel and how surgical treatment can contribute to the short small bowel and the vascular access problems. We identify the paediatric patients, as they appear numbered in the different studies. An overview is presented of the problems we had to deal with and the important morbidity and mortality we encountered in these children.

Chapter 2.3 presents the results of 33 children who underwent surgery for malrotation within a study period of one year. In two infants, resection of the twisted part of the intestine led to a short small bowel. We think that all children with malrotation should undergo surgery in order to prevent life-threatening volvulus. However, the intestinal motility problems that these children have will not be cured by this operation and this should be explained to the parents.

Chapter 3 is the heart of our work and explains the important role of the microbiological flora in patients with a short small bowel.

Normal intestinal flora development is discussed in Chapter 3.1.

Chapter 3.2 gives biochemical and microbiological explanations for the high concentrations of intestinal lactobacilli flora found in our patients.

Chapter 3.3 explains the role of lactobacilli in the mechanism that involves deconjugation of the bile acids.

Chapter 3.4 describes a side-effect of heterolactic strains of lactobacilli i.e., the production of $CO_2$. This gas formation causes abdominal pain and diarrhoea.

Treatment with antibiotics is often necessary in children with acidosis but this may lead to the overgrowth of yeast, which is considered to be detrimental. In the case presented in Chapter 3.5, the girl improved and functioned well despite a high concentration of potentially pathogenic yeast in her intestinal flora.

Chapter 4 describes various consequences of a short small bowel.

Chapter 4.1 considers the immune status of some children, because we thought it would be disturbed by the lack of a large part of the small bowel. Despite the fact that we observed normal development of the immune system in a premature child, she died of untreatable septicaemia. We assume that the combination of bacterial translocation with parenteral nutrition and a central venous catheter contributed to the problem of sepsis. Development of immunity was normal in the children studied.

In Chapter 4.2 four children with a short small bowel received short-term treatment with growth hormone. Three of them later had long-term treatment in an attempt to improve intestinal absorption and to find a solution for their catabolic state. Their height improved, but two of them have not yet obtained intestinal autonomy and still need parenteral nutrition.

Patients with a short small bowel also need medication. However, after enteral administration, no one knows whether it is absorbed or how it will work. In Chapter 4.3 we review the limited literature to find an answer to this question.

If all treatments fail, bowel transplantation can be performed. We considered the results achieved with intestinal transplantation in children worldwide in Chapter 4.4. In a very low birth weight infant with a completely necrotic intestine, the decision not to treat may seem reasonable. But, what do you do if the parents of a school-age boy, with acute loss of all small bowel, refuse parenteral nutrition? Options are discussed in Chapter 4.5.

Chapter 5 describes what we have learned from our biochemical and microbiological examinations and considers various strategies for the future. The treatment of children with a short small bowel must be performed within a team of different professionals and will continue to be a long and difficult process.

# Samenvatting

## SAMENVATTING

In de inleiding wordt een definitie van het korte darm syndroom gegeven en onderzoek naar de normale lengte van de dunne darm bekeken. De oorzaak en enkele gevolgen van een korte dunne darm bij kinderen worden besproken. Het doel van de studie en de richting van de verschillende bijdragen worden hier aangegeven.

Hoofdstuk 2.1 beschrijft ons werk in het dierenlaboratorium, waar we een manier zochten om de absorptie in de darm te verbeteren door de versnelde darmpassage te vertragen. Antiperistaltische of cirkelvormige darmlissen maken, bleek niet te helpen. Stasis van de darminhoud als gevolg van het omgekeerde stukje van de dunne darm, werd slecht verdragen. Een eenvoudige directe verbinding tussen de darmuiteinden na verwijderen van het grootste deel van de dunne darm, functioneerde het beste. Daarom hebben we besloten geen andere operaties erbij te verrichten.

Hoofdstuk 2.2 geeft onze definitie van een korte dunne darm en legt de chirurgische bijdrage aan het probleem van de korte dunne darm uit en de problemen met de toegang tot het vaatstelsel. Het geeft meer uitleg over de kinderen, zoals ze onder nummer in de verschillende publicaties voorkomen en een overzicht van de belangrijkste ziekteproblemen en de oorzaak van het overlijden van sommige kinderen.

Hoofdstuk 2.3 presenteert de 33 kinderen die wij in 2001 behandelden voor een malrotatie. Twee baby's hielden na resectie van de gedraaide en afgestorven darm een korte dunne darm over. De vraag of alle kinderen met een malrotatie geopereerd moeten worden, moet volgens ons bevestigend beantwoord worden. Hiermee kan een levensbedreigende draaiing worden voorkomen. Ouders moeten gewaarschuwd worden dat problemen van obstipatie door een verminderde beweeglijkheid van de darm, niet opgelost worden door de operatie.

Hoofdstuk 3 vormt de basis van ons werk en geeft een verklaring voor de zeer belangrijke rol van darmbacteriën bij patiënten met een korte dunne darm.

De normale ontwikkeling van de darmflora wordt besproken in hoofdstuk 3.1.

De biochemische en microbiologische verklaring voor de flora met een zeer grote hoeveelheid melkzuurbacteriën, die wij in de darm van onze patiënten ontdekten, wordt in hoofdstuk 3.2 beschreven.

De rol die de melkzuurbacteriën spelen in het mechanisme van de afbraak van galzuren en de gevolgen daarvan wordt in hoofdstuk 3.3 uitgelegd.

Een van de bijkomende effecten van bepaalde stammen van melkzuurbacteriën is het maken van koolzuurgas: de klachten van buikpijn en diarree, die daardoor worden veroorzaakt, worden in hoofdstuk 3.4 beschreven.

Behandeling met antibiotica is vaak nodig en kan leiden tot een schadelijke overgroei van gisten in de darm. Het meisje in hoofdstuk 3.5 werd juist beter en voelde zich goed met een grote hoeveelheid mogelijk schadelijke gisten in de darm.

Hoofdstuk 4 behandelt de gevolgen van een korte dunne darm.

In hoofdstuk 4.1 hebben we de afweer van sommige kinderen onderzocht, omdat we aannamen dat die gestoord zou zijn als een groot deel van de dunne darm, waarin een belangrijk deel van het immuunweefsel zit, verwijderd werd. Ondanks een normale ontwikkeling van de afweer overleed een te vroeg geboren kind aan een onbehandelbare sepsis door een normaal in de darm voorkomende bacterie. Voeding via een infuus verandert de doorlaatbaarheid van de darm voor bacteriën. Bij een direct in de bloedbaan gelegen lijn kunnen de bacteriën daarop gaan groeien.

Om de opname van voedingsmiddelen in de darm, de katabole toestand en de verminderde lengtegroei te verbeteren, beschrijven we in hoofdstuk 4.2 een proef waarbij vier kinderen kortdurend en drie ervan later langdurig groeihormoon toegediend kregen. Hun lengtegroei nam wel toe, maar een complete aanpassing van de darm, zodat voeding via het infuus niet meer nodig was, werd niet bereikt bij twee kinderen.

Patiënten met een korte dunne darm hebben soms ook geneesmiddelen nodig, maar niemand weet wat de opnamemogelijkheden zijn en wat daar invloed op heeft. We hebben uitgezocht hoe weinig en wat er over geschreven is. Dat staat in hoofdstuk 4.3.

Als iedere behandeling mislukt, kan nog een dunne darmtransplantatie worden verricht. We hebben de resultaten bij kinderen van een darmtransplantatie in de literatuur bestudeerd en beschreven in hoofdstuk 4.4.

Bij een te vroeg geboren kind met een heel laag geboortegewicht en een totaal afgestorven dunne darm, kan de beslissing om niet te behandelen moeilijk zijn. Bij een kind op de lagere school met plotseling verlies van zijn hele dunne darm, weigerden de ouders levensreddende behandeling met voeding via een infuus. Dit veroorzaakt ethische vragen. Deze worden in hoofdstuk 4.5 behandeld.

Hoofdstuk 5 beschrijft wat we geleerd hebben van alle biochemische en microbiologische onderzoekingen en geeft een aanwijzing voor toekomstig beleid. Behandeling van kinderen met een korte dunne darm zal altijd in multidisciplinair verband moeten gebeuren en langdurig en moeizaam blijven.

# Publications

## PUBLICATIONS WITH COOPERATION OF THE AUTHOR, RELATED TO THE SUBJECT


1. Festen C, Severijnen RSVM, van der Staak FHJM. Early closure of enterostomy after exteriorization of the small intestine for abdominal catastrophies. J Pediatr Surg 1987; 22:144-5.
2. Festen C, Severijnen RSVM, van der Staak FHJM. Enterostomy complications in infants. Acta Chir Scand 1988; 154: 525-7.
3. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems H. D-lacic acidemia and aciduria in pediatric and adult patients with short bowel syndrome. Clin Chem 1995; 41: 107-10.
4. Bongaerts G, Tolboom J, Naber A, Bakkeren J, Severijnen R, Willems, J. D-Lactic acidosis in patients with short bowel syndrome. Clin Chem 1995; 41: 767-9.
5. Bongaerts GPA, Tolboom JJM, Naber AH, Sperl WJ, Severijnen RSVM, Bakkeren JA, Willems JL. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathog 1997; 22: 285-93.
6. Bongaerts GPA, Tolboom JJM, Naber AH, Bakkeren JA, Severijnen RSVM, Willems JL, Sperl WJ. Lactobacillus flora in short bowel syndrome. Dig Dis Sci 1997; 42: 1611-2.
7. Agbeko RS, Semmekrot BA, Bongaerts GPA, Neeleman C, Severijnen RSVM. A newborn with cyanosis. Eur J Pediatr. 1998; 157: 1026-9.
8. Bongaerts G, Bakkeren J, Severijnen R, Sperl W, Willems H, Naber T, Wevers R, van Meurs A, Tolboom J. Lactobacilli and acidosis in children with short small bowel. J Pediatr Gastroenterol Nutr. 2000; 30: 288-93.
9. Bongaerts GPA, Severijnen RSVM, Tangerman A, Verrips A, Tolboom JJM. Bile acid deconjugation by Lactobacilli and its effects in patients with a short small bowel. J Gastroenterol. 2000; 35: 801-4.
10. Tolboom JJM, Severijnen RSVM, Rieu PNMA, Bongaerts GPA, Verheyen MJ, Naber AT. Darmtransplantatie voor behandeling van blijvend darmfalen bij kinderen. Tijdschrift voor Kindergeneeskunde 2000; 68: 157-63.
11. Bongaerts GPA, Severijnen RSVM. The beneficial, antimicrobial effect of probiotics. Med Hypotheses. 2001; 56: 174-7.
12. Bongaerts GPA, Severijnen RSVM. New strategies in antimicrobial therapy. Med Hypotheses. 2001; 56: 178-80.

13. Tangerman A, Bongaerts G, Agbeko R, Semmekrot B, Severijnen R. The origin of hydrogen sulfide in a newborn with sulfhaemoglobin induced cyanosis.J Clin Pathol. 2002; 55: 631-3.
14. René Severijnen, Ineke Hulstijn-Dirkmaat, Bert Gordijn, Leo Bakker, Ger Bongaerts. Acute loss of the small bowel in a school-age boy. Difficult choices: to sustain life or to stop treatment? Eur J Pediatr 2003; 162: 794-8.
15. R. Severijnen, N. Bayat, H. Bakker, J. Tolboom, G. Bongaerts. Enteral drug absorption in patients with short small bowel. A review. Clinical Pharmacokinetics accepted.

**Werkboek kindergastro-enterologie**

Kneepkens CMF, Taminiau JAJM, Polman HA. Tweede druk VU Uitgeverij Amsterdam 2002. *Hoofdstuk 25 Kortedarmsyndroom.* Tolboom JJM, van Wetten-van den Bos SN, Severijnen RSVM.

**6th Southeast European Symposium of Paediatric Surgery**

Short Bowel Syndrome Graz May 1998

1. Van den Bos SN, Severijnen RSVM, Tolboom JJM, Otten BJ, Rammeloo EML, Bongaerts GPA, Rieu PNMA, Festen C. Combined growth hormone and glutamine treatment in three children with short bowel syndrome.
2. Severijnen RSVM, Tolboom JJM, Bongaerts GPA. Intestinal stasis in short bowel patients.
3. Bongaerts G, Severijnen R, Sperl W, Naber T, Bakkeren J, Wevers R, Willems H, van Meurs A, Tolboom J. Role of organic acids in SBS-associated metabolic acidosis.
4. Bongaerts G, Naber T, Severijnen R, Willems H. Role of bacterial fermentation in SBS-associated diarrhea.

# Dankwoord

## DANKWOORD

Professor Kees Festen wil ik bedanken voor de gelegenheid om onder zijn leiding het uiterst boeiende vak van kinderchirurg te leren. Zijn absolute toewijding aan de kinderen en het vak vormde de basis, waaruit dit proefschrift is voortgekomen.

Zonder de inspiratie tijdens ons wekelijkse overleg in de afgelopen 16 jaar met co-promotor Ger Bongaerts zouden veel ideeën in dit proefschrift niet zijn uitgewerkt.

In Corry Weemaes vond ik een stimulerende co-promotor, die met haar aanwijzingen en ondersteuning absoluut noodzakelijk was om het werk tot een goed einde te brengen.

Professor Jan Jansen bedank ik voor zijn bereidheid om als promotor bij dit voor een belangrijk deel gastro-enterologische werk op te treden.

Jules Tolboom leverde aan veel artikelen en bij bijna alle patiënten een grote bijdrage. Hij controleert de kinderen nog vele jaren, als wij allang weer met andere kinderen bezig zijn.

Mijn collega's Frans van der Staak en Paul Rieu hebben een zeer groot aandeel in de dagelijkse klinische behandeling en operaties van deze kinderen gehad. Aan de jongere collega's René Wijnen, Marc Wijnen en Ivo de Blaauw zullen wij onze kennis zo overdragen dat de kinderen met een korte dunne darm, ook als wij met pensioen zijn, een optimale behandeling krijgen in het Radboud Kinderziekenhuis.

De stimulerende hulp van Eric Robertson was niet alleen tijdens vele nachtelijke gezamenlijke operaties, maar ook verder als "native speaker" onmisbaar voor veel aanpassingen en vaker ook aanvullingen van de Engelse tekst.

Binnen de operatiekamers laten wij de directe zorg voor een belangrijk deel over aan anesthesiologen en hun assistenten, terwijl wij ons concentreren op onze operatie met hulp van de operatieassistenten. Dankzij de hulp en bijstand, die aan beide kanten geboden wordt, kunnen wij heel veel bereiken bij heel zieke kinderen.

Aan laboratoriumpersoneel zijn in de tijd van computers en telefoons vaak geen gezichten gekoppeld, maar de vele bepalingen op klinisch-chemische en microbiologische laboratoria zowel tijdens de acute problemen als erna tijdens de langdurige follow-up, zijn onmisbaar voor een kwalitatief hoogstaande zorg. Ook binnen de klinische farmacie werd veel zorg besteed aan de parenterale voeding en medicatie voor deze kinderen met regelmatig overleg als wij weer iets wilden veranderen aan de samenstelling. Bedankt voor de samenwerking.

Ook de vele andere dienstverleners in ons ziekenhuis zoals de radiologen, die altijd voor ons klaarstonden en hun laborantes, die steeds weer mochten opdraven voor de zoveelste centraal veneuze lijn bij deze kinderen, bedank ik hartelijk voor de prettige samenwerking.

Darm en voeding zijn onlosmakelijk verbonden, wij pretenderen er iets van te weten, maar zonder de hulp van diëtisten, zouden wij toch erg tekort schieten in onze begeleiding met name bij de overgang van parenterale naar enterale voeding. Ook het eet- en voedingsteam voor kinderen met zijn deelnemers uit uiteenlopende specialismen is soms nodig voor de uiteindelijke zorg, als kinderen weer mogen eten, maar vergeten zijn hoe dat moet.

Als kinderen met parenterale voeding naar huis mogen, is voor het regelen van de parenterale voeding thuis de hulp van de afdeling gastro-enterologie met hun voedingsteam onmisbaar.

Intensieve samenwerking met alle kinderspecialisten en vooral de assistenten in opleiding tot kinderarts, die een groot deel van de dagelijkse zorg op hun nek krijgen, is noodzakelijk om deze kinderen een leven te verschaffen dat de moeite waard is om geleefd te worden. Ik kan niet alle kinderspecialismen en - specialisten noemen, maar we hebben ze hard nodig bij de zeer uiteenlopende problemen van deze kinderen.
Zonder de liefdevolle begeleiding van toegewijde en uitstekend geschoolde verpleegkundigen op onze kinderchirurgische afdeling maar ook op de neonatale intensive care, de intensive care voor kinderen en de andere kinderafdelingen, die deze kinderen verplegen en daarnaast oog hebben voor de noden van de ouders, zou het niet mogelijk zijn voor ons als artsen, deze groep kinderen adequaat te behandelen. Met het noemen van enkele namen zou ik teveel verpleegkundigen tekort doen, daarom van ganser harte, bedankt allemaal.

Zonder steun van alle anderen bij de behandeling betrokkenen, waaronder pedagogisch medewerkers, kinderfysiotherapeuten en psychologen, die de natuurlijke ontwikkeling van de kinderen in het ziekenhuis voor zover mogelijk ondersteunen, zou het meestal langdurig en vaak terugkomende ziekenhuisverblijf een nog veel grotere invloed gehad hebben.

De zorg, in het dierenlaboratorium besteed aan het welzijn van de te opereren dieren onder de leiding van Theo Arts, was voortreffelijk.

In dit ziekenhuis werken heel veel mensen van schoonmakers tot leden van de Raad van Bestuur en van de staf Financiën en Economie tot medewerkers van de telefoon-

centrale. Zonder de inzet van elk van hen zou ons klinische werk niet mogelijk zijn en dan waren studies als deze ook niet mogelijk.

Omdat onze tijd voor wetenschap vaak uiterst beperkt is, prijzen we ons gelukkig dat verschillende studenten in een wetenschappelijke stage een stukje van de problemen wilden uitzoeken.

Mijn kinderen Karen en Maaike hebben altijd gezegd, dat ze paranimf wilden worden: het gaat dan eindelijk gebeuren.

Zonder de stimulans van mijn vrouw Assina Haan zou dit proefschrift niet tot stand zijn gekomen. Zij forceerde de beslissing: doen, maar dan ook doorzetten of niet doen, maar er dan ook niet meer over praten.

Marilyn French
Our Father
1994 Belles-Lettres, Inc
Little, Brown and company, Boston

So many wonderful things in life, she leaves all that out of her accounting. Economics she calls it, a science she says, it's a peculiar science if it leaves out half of the existence, more than half, but maybe all sciences do that, certainly medicine does it, watch the doctors at St. Mary's, they forget the spirit, they forget how important it is to be held and touched and consoled. Also they forget nutrition, at St. Mary's at least. The terrible food they serve patients, don't they think they would get better faster with healthier food? All they can see is medication and surgery, well my clinic will do a better job, will have fresh food there for patients who need that more than they need a pill. Fruit, vegetables, rice and beans, and there will always be a pot of soup cooking in my clinic.

Marilyn French
Onze Vader
1994 JM Meulenhoff bv. Amsterdam

Zoveel heerlijke dingen in het leven, die laat ze allemaal buiten beschouwing. Economie noemt ze het, een wetenschap zegt ze, een merkwaardige wetenschap als die de helft van het bestaan negeert, meer dan de helft, maar misschien doet iedere wetenschap dat, vast, geneeskunde doet het zeker, ik zie de artsen in het St.-Mary, ze vergeten de geest, ze vergeten hoe belangrijk het is omhelsd, aangeraakt en getroost te worden. Ze vergeten ook de voeding, in het St.-Mary tenminste. Het vreselijke eten dat ze de patiënten voorzetten, snappen ze niet dat ze sneller beter zouden worden met gezonder voedsel? Ze hebben alleen oog voor medicijnen en chirurgie, nou, mijn kliniek zal het beter aanpakken, wij zullen vers voedsel hebben voor de patiënten die dat harder nodig hebben dan pillen. Vruchten, groenten, rijst, bonen, en in mijn kliniek zal altijd een pan soep op het vuur staan.

# Curriculum Vitae

## CURRICULUM VITAE

René Severijnen was born in 1942 in Boekel (Noord-Brabant, the Netherlands). After primary school, he attended the Episcopal College, a boarding school in Weert, where he obtained at the Gymnasium ß diploma in 1959. The medical study was followed at the University of Utrecht and after an active student life, he graduated as a medical doctor in 1969. He worked for one year at the surgical department of the St. Anna Hospital in Oss and was taught the principles of surgery by dr. M. Bauer and dr. J. Logeman.

After a course in tropical medicine, he was the only doctor in Igogwe, a 72-bed mission hospital run by the Franciscan Sisters of Denekamp in the Mbeya district of southwest Tanzania from 1970 till 1972.

At the St Radboud Hospital of the Catholic University in Nijmegen he received his surgical training from 1972 to 1978 under prof. dr. W. Schmidt and prof. dr. H. de Boer, including intervals of three to six months at the departments of anesthesiology, intensive care, plastic surgery, orthopaedics, urology, thoracic and vascular surgery and paediatric surgery. For non-university practical training, he spent six months at the Canisius-Wilhelmina Hospital in Nijmegen under dr. H. Joosten.

Since October 1978, he has been working at the Paediatric Surgery Department of the University Hospital Nijmegen, first under prof. dr. C. Festen and since March 2000 as head of the Department of Paediatric Surgery of the University Medical Centre St Radboud in Nijmegen.

At the animal laboratory, he tried different operation techniques on pigs with anal atresia to choose the best operation to perform later on children.

In the multidisciplinary team for children with defaecation problems after anal atresia and Hirschsprung's disease, he looks after medication and surgery to complement the contributions of the psychologist and paediatric physiotherapist. He is also a member of the paediatric feeding team.

As a teacher in general and paediatric surgery at all the hospitals, where he trained and worked, he also contributed to the primary and secondary training of nurses and operation assistants. He is actively involved in education programmes for medical students and postgraduate programmes for doctors.

He has been serving on the Hospital Ethical Committee for eight years.

In the founding of societies for the parents of children with anal atresia, Hirschsprung's disease and oesophageal atresia, he took an active part.

He has two daughters, Karen and Maaike and four grandchildren, Tim, Sterre, Mees and Nova. Assina Haan, creative regression and past lives therapist for children, is his wife.

**Stellingen bij het proefschrift "Short small bowel in children" van René Severijnen 2004**

1. The man who made time, made plenty of it (Old Irish Proverb).

2. Moedermelk is ideale voeding, ook voor patiënten met een korte dunne darm.

3. Een kind met een korte dunne darm vormt een levend probiotisch model (Jules Tolboom).

4. Spontane selectie van lactobacillen in patiënten met een korte dunne darm veroorzaakt door de lage pH een bijna ideale aanvulling op de natuurlijke verdedigingsmechanismen van de dunne darm, als artsen die groei niet verstoren door remming van het maagzuur en antibiotica.

5. Transplantatie van de dunne darm is een acceptabele optie bij kinderen met een korte dunne darm die afhankelijk blijven van parenterale voeding, als na vele jaren geen verdere adaptatie van de darmfunctie meer te verwachten is.

6. Het is niet het verlies van de ileocoecaalklep en door de terugvloed van faeces veroorzaakte bacteriële overgroei, maar het verlies van de laatste ileumlis wat meestal ermee gepaard gaat, dat problemen veroorzaakt.

7. Lichaam en geest zijn niet te scheiden, niet door "westerse" artsen en evenmin door patiënten, die alles van de arts verwachten en niet zelf een emotionele bijdrage willen of kunnen leveren.

8. Artsen zijn onvoldoende toegerust om chronische pijn bij kinderen zoals veroorzaakt wordt door posttraumatische dystrofie (CRPS Complex Regionaal Pijn Syndroom) te behandelen, ze kunnen niet zonder de hulp van psychologen en fysiotherapeuten.

9. Staande leren plassen kan onzindelijk blijven voor ontlasting in de hand werken (Agnes Brugman).

10. Rode en kapotte billen bij kinderen die tanden krijgen, kunnen worden veroorzaakt door enzymen uit het speeksel, die normaal voor de doorbraak van de tanden zorgen en die als ze niet in de darm onschadelijk gemaakt worden, de huid op de billen aantasten.

11. Kinderen zijn onze echte leraren. Luister zorgvuldig en ze zullen je leren over de verloren wereld van een bestaan zonder zorgen in het hier en nu (Tibetaanse wijsheid).

12. De patiënt die goed eet, heeft geen medicijnen nodig en de patiënt die slecht eet ook niet (Handboek Ayurveda van Robert Swami Persaud).

13. Zonder enthousiasme is het onmogelijk blijvend kennis over te dragen of om te inspireren.

14. Een diepgaand gesprek op een onverwacht ogenblik is een te koesteren geschenk en een voortdurende inspiratiebron.

15. Het Universitair Kinderziekenhuis in Nijmegen moet kiezen voor de naam "Radboud Kinderziekenhuis"om de bekende en goede naam van het "Radboud" in Nederland optimaal te gebruiken. Daarnaast zal een eenduidige keuze van het UMC St Radboud te Nijmegen voor dezelfde naam in binnen- en buitenland, Radboud Universitair Medisch Centrum Nijmegen veel verwarring in toekomstige publicaties kunnen voorkomen.