Review

Models of Short Bowel Syndrome in Pigs: A Technical Review

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Key Words

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Abstract

Background: Short bowel syndrome (SBS) is still a life-threatening disease in both children and adults. Although the therapeutic options are improving, challenges still remain, and to overcome these challenges is a major focus of SBS research today. In order to simulate anatomical and physiological conditions similar to those in humans for research, porcine models of SBS are often used. Various approaches for generating SBS models have been described in the literature. **Methods/Results:** In this work, we present a review of different types of porcine models of SBS and outline the differences between those models regarding types of animals, surgical procedures, monitoring, and methods of assessment. **Conclusion:** The aim of this study was to select the most suitable SBS model regarding the purpose of the research.

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Introduction

Short bowel syndrome (SBS) is generally defined as a disorder in which the resorptive capacity of the intestine is not sufficient to provide an adequate alimentary supply due to anatomical or functional reasons [1, 2]. The incidence of SBS is increasing [3] and varies between 2 and 5 patients per million [1, 2, 4]. As total enteral alimentation is not possible in SBS patients, nutrition must be provided parenterally at least partially [1, 5]. The 5-year

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survival rate for patients receiving parental nutrition (PN) is 63% [6]. To optimize the patients' survival and quality of life, bowel-lengthening procedures, such as the Bianchi or serial transverse enteroplasty (STEP) technique [7, 8], or small bowel transplantation (SBTx) has been adopted. In the last decade, modern therapeutic options such as tissue engineering [9] have been among the topics of interest. Due to the anatomical and physiological similarities to humans, porcine models are useful for optimizing different therapeutic approaches [10–14]. There are various and sometimes not exact definitions of SBS in the literature. Moreover, different researchers have used different methods to assess their results. Therefore, an SBS researcher may find it difficult to find a standardized SBS model as well as assessment methods. The aim of this work was to present an overview of these different models regarding the techniques used to induce an SBS model and the variety of assessment methods employed, and to evaluate the advantages and disadvantages of each model in order to help the SBS researcher select the best suitable model according to the aim of their research.

Materials and Methods

An analysis of all MEDLINE-published porcine models of SBS up to December 2011 was performed. Search items included 'short bowel syndrome', 'model', 'intestinal failure', 'pig', 'swine', 'porcine', 'parenteral nutrition', 'small bowel transplantation', 'lengthening procedures', 'surgical options', 'stimulants', and 'intestinal transit'. We evaluated publications in English, German, Spanish, and French; articles published in other languages and those presenting insufficient data were excluded from the literature review. Particular attention was paid to the definition, surgical aspects and monitoring or assessment methods in the conducted SBS models. To avoid reviewing repetitive cases, review articles or double publications were omitted; however, the reference lists were cross-checked for additional useful articles. To optimize our search and the quality of analysis, the instructions of the Quality of Reports of Meta-analyses (QUOROM) [15] were followed. The MEDLINE analysis revealed 814 publications. Inclusion criteria were the use of a porcine SBS model and a description of how much bowel was resected. The application of these criteria resulted in 27 publications which were included in the final analysis (fig. 1).

Biometrical data, operative data (including different methods, the percentage and the anatomical location of resection), length of observation, as well as methods of monitoring the animals including nutritional assessment, weight changes, food intake, clinical status and lab data were evaluated. Functional, morphological, and molecular assessments were also evaluated, and the mortalities of the SBS models were outlined.

Results

Animals

The majority of studies used domestic pigs or piglets [5, 13, 16–19] mainly of female gender [10, 13, 16, 18, 20–29]. Regarding the exact breed, mostly landrace [10, 21, 22, 30, 31] or landrace × large white [5, 13, 16, 20, 24, 26, 32–34] animals were used. SBS models were seldom described in other types of pig [7, 23]. Male animals were used rarely [31, 34, 35].

The age as well as the weight [7, 10, 18, 25, 27, 28, 30, 31, 36] of the pigs at the time of surgery varied widely. In some cases, the pigs were younger than 7 days [21, 29, 34, 37], but in most cases they were between 3 and 8 weeks [13, 16, 18, 20, 24, 26–28, 32, 33]. In rare cases, older pigs (3–7 months) were chosen [5, 7]. Few authors used animals with less than 10 kg body weight [29, 34, 35], with the majority of animal models weighing 10–30 kg.

Anesthesia

As anesthesia was not the focus of the analyzed models, it was often not described extensively and many authors did not explain how they performed anesthesia at all [20, 23, 26, 32,

Fig. 1. Screening design together with the summarized number of screened abstracts and the relevant and suitable articles identified during the review process, using the modified flow chart according to the QUOROM statement [15].

33, 36, 38–40]. If mentioned, most often anesthesia with halothane and oxygen [17, 18, 21, 24, 27] or isoflurane [19, 37] was performed, sometimes in combination with ketamine and azaperone [7]. In rare occasions, other strategies such as anesthesia with propofol, fentanyl and pancuronium [5], thiopental sodium and ketamine [7], or a combination of the mentioned drugs [29, 41] were chosen. Specific anesthesiologic problems concerning SBS have not been mentioned.

Surgical Procedures for Inducing SBS

Data concerning the extension and location of resection, associated interventions and period of observation are summarized in table 1.

The percentage of the resected small bowel ranged from 75 to 100%. Seventy-three percent of the authors performed a resection of 75% [10, 13, 16, 18, 21, 22, 24, 26–28, 32–34] or 80% of the small bowel [5, 29, 30, 35, 37], and in 8 and 19% of the articles, 90% [19, 23] and 95–100% [7, 25, 30, 31, 36] of the small bowel was resected, respectively. The bowel was resected in two main areas: most of the authors described a mid-intestinal resection in which the remaining small bowel consists of equal parts of the jejunum and ileum [5, 10, 18, 21, 22, 27–31, 34, 35]; other authors used a 75% resection model in which the jejunum was resected 0.5 [24, 26, 32] to 1 m [20, 33] distal of the ligament of Treitz proximally and the ileum up to 2.5 m proximal to the ileocecal valve distally [13, 16, 20, 24, 26, 32, 33]. No author described a resection of the ileocecal valve. In those publications that described the surgical technique in detail, only end-to-end anastomoses were reported [5, 21, 22, 24, 26, 29, 32, 34, 35, 37]; the anastomoses were mainly performed in a single-layer technique [5, 10, 19, 25–28, 32] with interrupted sutures [21, 22, 24, 26–28, 32, 34, 35, 37]. Running sutures were rarely observed [10, 18, 25]. While the use of 4-0, 5-0 and 8-0 silk sutures was reported, other nonabsorbable sutures such as 4-0 polypropylene were also described [19, 27, 28, 35, 37]. However, the material was predominantly nonmonofilament absorbable sutures such as 5-0 Dexon [24, 26, 32] or 4-0 Polysorb [21, 22]. Anastomoses with monofilament absorbable sutures such as 5-0 polyglyconate [25] or 3-0 polydioxanone [10] were also performed.

Surgical or nonsurgical interventions besides extended bowel resection included SBTx [25, 31, 36], bowel-lengthening procedures [18, 19, 23, 28], bowel dilatation [7, 28] or phar-

Table 1. Percentage and location of resection, interventions performed and time period of observation

First author	Resection		Additional intervention			Period of observation
	percent- age	location	further operation	type	sequence	
Llanos [36], 2006	100	jejunum and ileum	yes	SBTx	simultaneously	19 weeks
Sano [31], 2001	100	jejunum and ileum	yes	SBTx	simultaneously	14 days
Sano [30], 2002	100	not mentioned	no	no	–	19 weeks
Kimura [47], 1990	100	jejunum and ileum	no	no	–	>180 days
Pakarinen [25], 1996	>95	jejunum and ileum	yes	SBTx	simultaneously	12 weeks
Sacher [7], 1997	95	jejunum and ileum to 15 cm prox. to ileocecal valve	yes	intestinal banding	simultaneously	10 weeks
	95	jejunum and ileum to 5 cm prox. to ileocecal valve				
	95	jejunum and ileum to 5 cm prox. to ileocecal valve				
Chang [19], 2006	90	not mentioned	yes	STEP procedure	simultaneously	6 weeks
Modi [23], 2009	90	not mentioned	yes	STEP procedure	sequentially	18 weeks
Taguchi [29], 2005	80	same length of jejunum and ileum	yes	bypass operation	simultaneously	2 weeks
Digalakis [5], 2011	80	same length of jejunum and ileum	yes	reverse bowel segment	simultaneously	8 weeks
Bartholome [37], 2004	80	15 cm distal to ligament of Treitz to 75 cm prox. to ileocecal valve	no	no	–	7 days
Benhamou [35], 1997	80	same length of jejunum and ileum	no	no	–	4 weeks
Buie [18], 1993	75	same length of jejunum and ileum	yes	Bianchi procedure	sequentially	18 weeks
Sigalet [28], 2001	75	same length of jejunum and ileum	yes	bowel lengthening colon interposition cimetidine and codeine	sequentially sequentially	16 weeks
Pereira-Fantini [32], 2008	75	0.5 m distal to ligament of Treitz to 2.5 m prox. to ileocecal valve	no	GLP-2 application	–	6–8 weeks
Pereira-Fantini [16], 2008	75	1 m distal to ligament of Treitz to 2.5 m	no	no	–	8 weeks
Pereira-Fantini [13], 2011	75	prox. to ileocecal valve	no	no	–	6 weeks
Welters [10], 1996	75	same length of jejunum and ileum	no	butyrate application	–	3 weeks
Healey [20], 2010	75	1 m distal to ligament of Treitz to 2.5 m prox. to ileocecal valve	no	no	–	6 weeks
Heemskerk [21], 1999	75	same length of jejunum and ileum	no	no	–	4 weeks
Heemskerk [22], 2002	75	same length of jejunum and ileum	no	no	–	4 weeks
Nagy [24], 2004	75	0.5 m distal to ligament of Treitz to 2.5 m prox. to ileocecal valve	no	no	–	8 weeks
Paris [26], 2004	75	0.5 m distal to ligament of Treitz to 2.5 m prox. to ileocecal valve	no	no	–	8 weeks
Del Olmo [40], 1998	75	not mentioned	no	no	–	24 weeks
Sigalet [27], 1990	75	same length of jejunum and ileum	no	no	–	16 weeks
Stephens [33], 2010	75	1 m distal to ligament of Treitz to 2.5 m prox. to the ileocecal valve	no	no	–	6 weeks
Turner [34], 2011	75	same length of jejunum and ileum	no	no	–	17–21 days

maceutical treatments for SBS [10, 32], often in the course of weeks after the extended bowel resection.

The period of observation varied widely from 7 days [37] up to 19 weeks [30]. Many research groups chose a short-time model up to 4 weeks [10, 21, 22, 31, 34, 35, 37]. Few models selected a follow-up period of 2–3 months [5, 7, 16, 19, 24–26, 32, 33] or even longer (up to 4–5 months) [18, 23, 27, 28, 30].

Objectives of the Different Studies

The aim of the studies can be divided into the following categories:

- intestinal adaptation to SBS [10, 13, 26, 27, 33, 34];

- effects of nutritional [16, 17, 22, 24, 28, 37], hormonal [32, 35] or surgical [5, 36] treatment on intestinal adaption;
- intestinal functions in pigs with SBS [7, 18, 19, 23, 25];
- other objectives such as influences of SBS on liver function or the level of immunosuppressive medication [29–31].

According to the above-mentioned categories, different aspects were important in generating the models. The main differences were regarding nutrition of the animals, the use of histological and special analyses as well as different methods of animal monitoring after the induction of SBS (see below).

Care and Monitoring of the Animals

Nutrition

Nutrition was provided to the animals in different ways. PN was used in some [29, 34, 37] but not all studies. How and in which vein intravenous lines were placed was frequently not described. Taguchi et al. [29] utilized PN consisting of 64 kcal/kg/day (15 g/kg/day glucose, 1.0 g/kg/day amino acid) in addition to enteral alimentation. Turner et al. [34] fed their piglets only by PN with target nutrient intakes of 16 g/kg/day amino acids, 1.1 MJ/kg/day energy, 10 g/kg/day lipid, and 324 ml/kg/day fluid. Bartholome et al. [37] used dextrose (50% glucose monohydrate; Baxter Healthcare Corporation, Deerfield, Ill., USA), amino acids (8.5% Travasol with electrolytes; Baxter Healthcare Corporation) and lipids (30% Intralipid; Baxter Healthcare Corporation) equaling 307 kcal/kg/day and 15.5 g/kg/day amino acids for postoperative days 0–3 and 253 kcal/kg/day and 12.8 g/kg/day for postoperative days 4–7. In models analyzing the influence of enteral nutrition, different diets such as elemental/polymeric formula or chow were provided [13, 16, 17, 20], often supplemented with colostrum [16, 22, 24]. Rarely, other forms of alimentation such as Pezzullo dough pellets (Sun Company, Milan, Italy) [5], Nutrison Steriflo HP (Nutricia, Zoetermeer, The Netherlands) [10], modified infant formula (Nutrilon Premium; Nutricia) or further types were mentioned [5, 10, 21, 32]. Enteral alimentation was sometimes only described unspecifically as a ‘standard grower diet’ [27, 28, 35] or ‘free access to food’ [7, 18, 19, 31] without any detailed dietary information.

Monitoring

Body weight, food intake, stool output, the general condition of the animal and blood tests were used as monitoring criteria. Nearly all of the research groups used body weight to monitor the effect of SBS. In addition to body weight, food intake was also frequently recorded. It was usually measured once a day [17, 24, 26, 34, 35] or once a week [18, 25, 27]. One group also described measuring the food intake once in a fortnight [28]. The evaluation of stool output once a day [17, 24] or once a week [25] and obtaining stool samples for microscopic analyses [20, 32] (every fortnight) or nutritional studies [18, 34] (days to weeks after the first operation) were also often conducted. The general well-being of the animals was only described by a limited number of research groups [17, 24–26, 36, 37]. Where it was analyzed, it was most often recorded once a day [17, 24, 26, 37]. Blood samples were analyzed very irregularly [7, 17–20, 25, 28, 32–34, 36]. The majority of samples were analyzed on the day of the first surgical procedure [5, 7, 16, 18, 19, 25, 28, 29, 33, 36] but postoperative analysis of blood samples varied widely from some days [20, 29, 32, 34] to 18 weeks after the first surgical procedure [5, 18]. Also, the values measured were very inhomogeneous.

Functional, Morphological, and Molecular Assessment

Measurements of the disaccharidase activity (maltase, sucrase, lactase) [17, 24, 26, 32] in the intestinal tissue as a marker of intestinal function [26], plasma glucagon-like peptide-2

Table 2. Laboratory assessment

First author	Blood samples
Kimura [47], 1990	'routine laboratory chemistry': not mentioned how often
Buie [18], 1993	at 0, 6, and 18 weeks: Hb, Hct, WBC, albumin, protein, Ca, P
Pakarinen [25], 1996	Hb 1×/week 1× weeks 1–4, 1× weeks 5–12: cholesterol, triglyceride, protein, ALP, ALAT, ASAT, creatinine, sodium, potassium, Cl
Sacher [7], 1997	weeks 0 and 10: Hct, protein, sodium, potassium, Cl, iron
Sigalet [28], 2001	weeks 6–10: blood count, total protein, albumin, glucose, alkaline, phosphatase, creatinine, LDH, ASAT
Bines [17], 2002	'frequently': albumin, protein, glucose, calcium, cholesterol, urea, electrolyte, iron, ASAT, ALAT, GGT
Taguchi [29], 2005	days 7 and 14: bilirubin, ASAT, ALAT, bile acid
Chang [19], 2006	weeks 6 and 12: 'baseline hematologic parameters', albumin, vitamin D, triglycerides
Llanos [36], 2006	day of surgery, last measure: total protein, albumin, triglycerides, cholesterol, glycemia, urea, creatinine
Pereira-Fantini [32], 2008	2×/month: albumin
Digalakis [5], 2011	4–8 weeks preop.: albumin
Healey [20], 2010	2×/month: Ca, total protein, Hb
Stephens [33], 2010	weeks 2, 4, and 6: bile acid, cholesterol, triglycerides
Turner [34], 2011	days 0–17/21: bilirubin, ALAT, ALP, GGT

(GLP-2) concentrations [32, 37], and rarely additional measurements of nutrient uptake [18, 27, 28], D-xylose absorption test [19], motility test [23] or other methods [10, 17, 29] have been described. Concerning the measurement of vitamins, only in one publication [19] was the measurement of vitamin D recorded. The measurement of other vitamins or folic acid was not described. Concerning selenium, zinc or iron measurements, only iron was analyzed in two of the publications evaluated [7, 17].

For the purpose of morphological assessment, 72% of the studies performed histological examinations. The samples were mainly referred to as 'small bowel' without any further specifications [22] or a declaration of the exact location of resection [19, 21, 27, 35, 37]. Specific location descriptions included mainly the duodenum, jejunum and ileum [5, 13, 17, 24, 28, 32, 34]. Colonic samples were rarely used for histological assessment [20]. For the histological assessment, 56% (9/16) of the research groups analyzed villus height and crypt depth [17, 21, 22, 24, 26, 28, 32, 34, 35, 37]. Additionally, in 18% (3/16) of the studies, measurements of the thickness of the intestinal muscle layer were also performed [17, 32, 35]. Furthermore, 18% of the groups recorded villus and crypt cell proliferation as well as apoptosis [13, 20, 32]. Midvillus width, villus surface area [13, 37], villus diameter [35] and total number of villi [13, 28] were also analyzed by about 12% of the research groups. In very rare cases, other analyses such as the evaluation of the total number of cells within the colon crypts, enterocyte cell levels [20, 36] or liver biopsies were performed additionally [29, 34].

Molecular assessment was performed in approximately 37% (6/22) of the reviewed articles. In 50%, DNA or RNA concentrations and ratios were measured in mucosal scrapings taken from different locations of the intestine [21, 22, 37] to analyze changes on the molecular or the protein level. In addition to these assessments, special genetic analyses such as proglucagon gene expression [17] and different protein analyses were performed. The sampling location for these studies varied widely [20–22, 33, 37]. Measurement of the total protein content in the entire intestinal tissue [37] or mucosa alone [21, 22], or analysis of special

Table 3. Functional assessment

First author	Functional assessment
Sigalet [27], 1990	in vitro glucose/lipid uptake of the tissue
Buie [18], 1993	in vitro glucose uptake and transmural electrical studies digestibility coefficients
Welters [10], 1996	portal efflux (glucose, amino acids)
Sigalet [28], 2001	in vivo protein, carbohydrate, fat
Bines [17], 2002	disaccharidase in tissue transepithelial conductance Cr-EDTA flux
Bartholome [37], 2004	plasma GLP-2 concentrations
Nagy [24], 2004	disaccharidase activity
Taguchi [29], 2005	hepatic circulation/tissue sample
Chang [19], 2006	D-xylose test, fat absorptive capacity (vitamin D, triglyceride levels)
Pereira-Fantini [32], 2008	GLP-2 plasma levels disaccharidase activity
Modi [23], 2009	motility testing
Digalakis [5], 2011	transit time
Turner [34], 2011	fecal fat collections liver biopsy

Table 4. Molecular assessment

First author	Molecular assessment
Del Olmo [40], 1998	plasma levels of vasoactive intestinal peptide
Heemskerk [21], 1999	protein concentration of mucosa DNA and RNA concentrations and ratios in mucosa scrapings
Bines [17], 2002	proglucagon gene expression (intestinal tissue)
Heemskerk [22], 2002	protein concentration of mucosa DNA and RNA concentrations and ratios in mucosa scrapings
Bartholome [37], 2004	DNA, RNA, protein content (intestinal tissue) protein analysis (apoptotic protein and proliferating cell nuclear antigen protein abundance in intestinal tissue)
Pereira-Fantini [16], 2008	concentration of growth hormone/IGF-1 (serum) RNA content of ileal tissue
Healey [20], 2010	analysis of colon mucosa proteins
Stephens [33], 2010	protein analysis (difference gel electrophoresis, immunoblotting, immunohistological analysis) of ileal tissue

proteins [33, 37] including the use of difference gel electrophoresis, immunoblotting and immunohistological methods [33] was also performed.

Tables 2–5 give an overview of the functional, morphological and molecular assessments conducted in the different published models.

Discussion

For the purpose of animal research, pig models are the experimental method of choice because of the substantial anatomical and physiological similarities to humans [14, 17, 20, 26, 42, 43]. Moreover, pigs can reliably tolerate extended pathophysiological stress like the

Table 5. Morphological assessment

First author	Morphological assessment
Heemskerk [21], 1999	villus height, crypt depth
Nagy [24], 2004	villus height, crypt depth
Paris [16], 2004	villus height, crypt depth
Pereira-Fantini [32], 2008	villus height, crypt depth
Turner [34], 2011	villus height, crypt depth
Bines [17], 2002	villus height, crypt depth + mucosal and muscle layer thickness
Bartholome [37], 2004	villus height, crypt depth + villus width and surface
Digalakis [5], 2011	villus height, crypt depth + muscular layer thickness, crypt cell proliferation, apoptosis rate
Benhamou [38], 1997	villus height, crypt depth + crypt to villus ratio, number of mitosis per field, intestinal muscular layer and wall thickness
Healey [20], 2010	increase of number of crypt colon cells and of apoptotic colon cells, enterocytes within colonic crypts, enteroendocrine cells and goblet cells in colon
Pereira [13], 2011	bowel length and width, increase in crypt and villus surface, number of crypt and villus cells
Sigalet [28], 2001	number of villi
Heemskerk [22], 2002	mitotic index
Kimura [47], 1990	mucosal integrity, significant lymphocyte infiltration
Chang [19], 2006	'structural differences between groups'
Llanos [39], 2006	histologic grading rejection (Murase)
Pereira-Fantini [16], 2008	bowel length, increase in circular muscle area

resection of the small bowel for the purpose of SBS research [27]. Through the analysis of the different porcine models currently in use, we have found that a unanimous definition of SBS, as a disorder, in which an adequate alimentary supply cannot be provided enterally [1, 2], still does not exist in the field of surgical research. Therefore, an overview of the various porcine models used seems to be important.

Biometrical Data of the Used Pigs

Concerning the type and gender of the animals, mainly female landrace pigs were used. This could be due to practical reasons such as easier laparotomy and less risk of urethral injury in female pigs, whereas the urethra in male pigs runs along the laparotomy line. However, this fact has not been mentioned clearly in the literature. In the different experimental models, the following three age groups of animals became evident.

(1) Neonatal pigs up to 7 days of age: neonatal pigs show a similar anatomy, physiology, and metabolism to human neonates [34]. In the neonatal state, nutrient demand is much higher than in older animals [21]. Using 7-day-old piglets, the full clinical spectrum of intestinal failure, as with human neonatal SBS, can be simulated [34]. The size of neonatal piglets permits surgical interventions as well as further treatments and invasive monitoring. Furthermore, these pigs tolerate major surgery and anesthesia easily [21]. Although some groups argue that piglets younger than 7 days may have theoretical advantages for studies analyzing intestinal adaption [34], others advocate the use of 7-day-old piglets in intervention studies due to the high mortality (50% within 48 h after surgery) in the group of younger piglets [21].

(2) Pigs between 3 and 8 weeks of age: at the age of 3 weeks, piglets can be weaned from suckling [44]. At 4 weeks of age, those confounding factors which occur at the time of weaning might be avoided [17] and the juvenile pig has anatomical, physiological and biochemical

similarities to humans and reflects the condition of SBS in infants and children [13, 17, 24, 26]. The growing pig gains weight rapidly and therefore alterations in weight gain can demonstrate the effects of surgical interventions as an objective parameter following the efficacy of adaptation of nutrient absorption [28]. Additionally, pigs up to 20 kg can be quickly restrained manually [45, 46].

(3) Pigs older than 8 weeks: the rationale for using these pigs is that body weight encompasses the effects of surgery and growth development in this age group [5].

Surgical Procedure

The mode of surgical intervention ranges widely concerning the percentage and the location of the resected bowel as well as associated procedures in addition to massive bowel resection. Most frequently, a midintestinal resection of 75% of the bowel was performed. Resections up to 100% and resections of parts other than the midintestinal part were also described. Selecting the mode of resection depended highly on the authors' definition of SBS, the study aims and the planned period of observation. Sacher and Stauffer [7] defined SBS by weight *loss*, which was achieved by a 95% distal intestinal resection preserving the ileocecal valve including a jejunoileal anastomosis. Turner et al. [34] performed different types of resection and presented an SBS model of 75% distal intestinal resection followed by significantly less weight *gain*, greater malabsorption and more cholestatic liver disease compared to a midintestinal 75% resection. Furthermore, Turner et al. [34] selected the *distal* intestinal resection because this is a common type of resection performed in human neonates. However, Bines et al. [17] justified performing a *proximal* 75% intestinal resection for the same reason.

Nonetheless, it was usually not explained why the authors selected a specific type of resection. The duration of the observation period also varied greatly. To evaluate levels of an immunosuppressive drug (FK 506) in SBS after oral application, 7 days of observation seemed adequate [30]. Healey et al. [20] and Pereira-Fantini et al. [13] examined the animals 2, 4 and 6 weeks postoperatively to analyze early and late adaptational responses. In a separate study, Pereira-Fantini et al. [32] chose a period of 6–8 weeks to analyze the influences of GLP-2 treatment on SBS. In contrast to that, Pakarinen et al. [25] declared a period of 5–12 weeks to be necessary for the evaluation of 'long-term effects' after inducing SBS. Kimura et al. [47] defined 'long-term survival' as a period of 180 days. Sigalet et al. [28] observed their pigs for 10 weeks to analyze nutritional effects on SBS, but 16 weeks to monitor the physiology of adaptational processes [27]. This agrees with the findings of Bartholome et al. [37] that functional adaptation takes place during the first months after resection and reaches a plateau after 1–2 years [37]. None of the publications mentioned why a special method of anastomosis was chosen. To improve interventions treating SBS, associated surgical procedures were often performed and SBS itself was not analyzed. This has to be taken into account, especially when complication rates (see above) or different types of monitoring animals are discussed.

Care and Monitoring of Animals

Intestinal adaptation, as the pivotal process occurring after extended intestinal resection, proved to be influenced by the amount [5, 20, 35, 48] and quality of enterally applied nutrients [5]. To allow for comparison between animals in similar conditions, Benhamou et al. [35] chose the pair feeding method. Some other authors monitored food intake for at least a week [18, 25, 27] to control nutrient uptake. Besides the quantity of food, the type of food also seems to be important. To simulate the conditions in infants and children, polymeric infant formula and elemental formula designed for infants were used [17, 20]. Polymeric diet was associated with a better adaptational response [17, 24]. A diet supplemented with bovine colostrum protein concentrate also showed influences on intestinal adaptation such as

trophic effects on bowel mucosa [24] and hypertrophy of the smooth muscle of the intestine [16]. Polymeric infant formula together with colostrum protein was found to produce the optimal effects on intestinal adaptation [16, 24]. Also, nonnutritive components of different feedings which result in better uptake of nutrients may promote the physiologic adaptation process in neonates [22].

Body weight is one of the most frequently measured parameters in SBS. Most often, it is measured daily or at least weekly. Generally, failure to gain weight [10, 17–21, 23, 24, 26, 27, 32–35] would be adequate for an SBS model, although some authors only accepted weight loss [7, 25, 31, 36]. An increase in body weight was also described as the most important end-stage clinical parameter of a successful bowel adaptation in animals [22] with SBS. However, some studies did not even compare weight differences between case and control groups and associated SBS with severe transient diarrhea after massive bowel resection [29]. Besides diarrhea [21, 24, 25, 29, 31], a lower efficacy of the feed-to-weight ratio [18] and a lower absorptive function [7, 19, 34] measurable in decreased nutritional parameters [36] were other common indicators for SBS after extended bowel resection.

Assessment of SBS

It is important to distinguish two different objectives in publications: the analysis of SBS itself or the effects of interventions on SBS and the use of an SBS model to evaluate other surgical interventions. Assessment criteria of the former are based on the processes which take place after inducing an SBS. Following the loss of extended parts of the small bowel, an upregulation of the ability of the intestine to absorb nutrients occurs [28] resulting in a process called ‘intestinal adaptation’. This process is characterized by functional and morphological changes as well as changes in the protein and molecular level [5, 13, 17, 21, 22].

To analyze functional changes, body weight, as mentioned before, plays a pivotal role [28]. Additionally, nutrient uptake after extensive intestinal resection was demonstrated to be diminished in fat [19, 27, 28], protein [28], carbohydrate [18, 27, 28] and total energy absorption and was therefore measured [18, 27, 28, 49].

Morphological changes occurring in the process of intestinal adaptation [27] have frequently been analyzed. These include macroscopic alterations such as increased length, dilatation and thickening of the intestinal lumen [5, 34]. Most studies focused on histological changes and showed that mucosal hyperplasia (associated with an increase in villus height), diameter and depth of the crypts [5, 21, 24, 34, 35] were parameters for intestinal adaptation [21].

In addition to morphological evaluations, molecular analyses are also important. The histological alterations described previously correlate with an increase in weight and protein as well as RNA and DNA content of the mucosa [5, 33]. SBS animals showed alterations in protein levels compared to the other animals [33]. An analysis of concentrations of growth hormone and IGF-1 [16] as well as plasma levels of vasoactive intestinal peptide [40] and proglucagon gene expression [17] were also reported.

Complications of the Different Models

The SBS model has to harbor a low rate of complications. In the literature, complication rates differ widely depending on the surgical procedures performed. In models where only extended small bowel resection was performed, complication rates ranged from 0 [7, 20, 35] to 18% [34]. In models combining the SBS model with procedures such as SBTx (44%) [25] or bowel lengthening (30–69%) [18, 19], the complication rate often increased [18, 19, 25, 28, 36]. In contrast, other authors reported no complications in combination models [29, 31]. In some studies, it was not declared whether or not complications occurred following surgery [10, 23, 26, 30, 32, 33, 37]. Those studies reporting fatal complications are summarized in table 6.

Table 6. Fatal complications using a porcine SBS model

First author	With/without intervention	Total, n	Death, n	Fatal complication
Llanos [36], 2006	with/without SBTx	21	6	sepsis (n = 6)
Pakarinen [25], 1996	with/without SBTx	27	8	anastomotic leak (n = 1), internal hernia (n = 3), stoma prolapse (n = 1), ileus (n = 2), arterial mesenteric thrombosis (n = 1)
Buie [18], 1993	with/without Bianchi procedure 6 weeks after resection	24	7	intussusception (n = 1 sham), acute gastric dilation (n = 1 SB), obstruction (n = 1 SB, n = 2 SB + Bianchi), sudden death (n = 1 SB + Bianchi), anastomotic leak (n = 1 SB + Bianchi)
Chang [19], 2006	with/without dilatation Op, bowel resection, STEP	10	3	technical error (n = 1), massive upper gastrointestinal hemorrhage (n = 2)
Sigalet [28], 2001	with/without cimetidine and codeine with/without isoperistaltic interposition of distal colon with/without bowel lengthening	24	3	bowel obstruction (n = 3)
Heemskerk [21], 1999	no	16	1	?
Heemskerk [22], 2002	no	24	3	?
Nagy [24], 2004	no	37	2	bowel perforation (n = 1), mesenteric torsion (n = 1)
Sigalet [27], 1990	no	14	2	anastomotic stricture (n = 1), bowel obstruction (n = 1)
Turner [34], 2011	no	28	5	anastomotic leak (n = 1), sepsis (n = 4)

Conclusion

In order to choose an appropriate SBS model, it is important to consider that the descriptions of those models currently in use are very heterogeneous, sometimes imprecise and highly dependent on the aim of the planned study. A uniform definition of SBS is missing along with a consistent method of induction in an animal model. As enteral alimentation is not sufficient to provide an adequate nutrient supply in SBS, the most important point for the induction of SBS in an animal model would be the reduction of weight gain in growing pigs or weight loss in pigs with stable weight. The majority of authors tried to establish this model through a 75% midintestinal resection with the preservation of the ileocecal valve. This may define a common practical model of SBS in pigs. However, it remains pivotal to tailor the model according to the aim of the study.

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Disclosure Statement

None of the authors have any conflicts of interest.

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