A Comprehensive Evaluation of the Perinatal Management of Gastroschisis

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**Contribution of Authors:**

This is a manuscript based thesis. All of the four included manuscripts were published in the *Journal of Pediatric Surgery*.

The student is the first author in all four included manuscripts. For each manuscript, the corresponding author contributed to the conception, the design of the work, and the critical revision of the article. All the co-authors contributed to the final approval of the article to be published. The student contributed to data collection, data analysis, data interpretation and drafting the manuscripts.
Acknowledgements:

This work was carried out in the Department of Pediatric General and Thoracic Surgery at the Montreal Children’s Hospital. I am mostly grateful to my supervisors Dr. Robert Baird and Dr. Jean-Martin Laberge for their guidance through the days of work and their invaluable advice and patience. I would like to extend equal gratitude to Dr. Sherif Emil, whose direction, supervision, and personal care have been critical for this project. I’d also like to extend my deepest gratitude to all the team members of the Montreal Children’s hospital, department of Pediatric Surgery for their great support during the years of work with them.

I am deeply grateful to the Canadian people for embracing me and my family when we first arrived in Canada.

Lastly, I’d like to thank my wife, family and friends for their understanding and support.
Abstract:

Although the literature has extensive research on Gastrochisis (GS), there are still many essential questions needed to be addressed about the perinatal management of GS; Some of these are the optimal time of delivery, the best method to close the abdominal defect, the potential effects of the healthcare system on the outcomes of GS and the determinants of the outcomes in patients with simple GS. Through the four studies included in this thesis we concluded that in patients with GS, there is no correlation between the time spent in utero and the degree of the bowel injury, that there is no difference in short term outcomes between the umbilical cord flap and the fascial suturing techniques to close the abdominal defect, that the mortality rates and the use of C-section to deliver patients with GS are significantly higher in the United states compared to Canada, and Central Line Associated Blood Stream Infection is the most important determinant of outcomes in patients with simple GS.
Résumé:

Bien qu'il existe des recherches approfondies sur le Gastroscisis (GS), il reste encore beaucoup de questions essentielles à propos du traitement périnatal des GS, entre autres, le moment optimal de l'accouchement, la meilleure méthode pour réparer le défaut abdominal, les effets potentiels du système de santé sur les résultats des GS et les facteurs responsables des résultats chez les patients avec GS simple. Nous avons conclu que chez les patients avec GS, il n'y a pas de corrélation entre le temps passé dans l'utérus et le degré de dommage intestinal, qu’il n'y a pas de différence dans les résultats à court terme entre les techniques avec ou sans sutures pour fermer le défaut abdominal, que les taux de mortalité et d'utilisation de la césarienne pour accoucher ces patients sont significativement plus élevés aux États-Unis par rapport au Canada, et que les infections associées aux cathéters veineux centraux sont le facteur le plus important des résultats chez les patients porteurs de GS simple.
I. Introduction

Most of the children did not contribute to the causes of their diseases. This fact is more readily apparent in newborns with congenital malformations. The burden of an incidence of a congenital malformation not only influences the patient’s life but also threatens the whole family’s well being.

According to their medical and social consequences, congenital malformations are divided into major and minor. The incidence of major malformations is approximately 24 per 1000 total births according to data from more than 1.5 million births in 22 countries. [1] With such a high incidence of major malformations and the chronic nature of some of their sequelae, it is always necessary to put our best efforts to enhance the quality of life in incurable cases and to improve the outcomes in curable ones. One of the curable major malformations is Gastroschisis (GS).

GS is a full thickness, abdominal wall defect through which parts of the intra-abdominal organs herniate prenatally. Although parts of the stomach and the liver could also herniate through this defect, intestines are more commonly seen. This type of neonatal defect needs urgent and highly specialized medical care. With no gender differences in the incidence of GS, it is one of the most common abdominal wall anomalies with a prevalence of approximately 4 per 10000 live births [2]. For unknown reasons, the incidence of GS has been increasing on both national and international levels [2,3]. According a Public Health Agency of Canada report, the incidence of GS in Canada increased from 3.1 to 4.4 per 10000 total births between 2002 and 2009. Of note, the incidence of GS differed significantly across Canada and ranged from 19.6 in Nunavut to 1.6 per 10000 total births in Quebec. [3] The same increasing trend of the incidence of GS has been reported in the United States [2] and
many other countries. [4] Although GS patients enjoy excellent survival rates of approximately 96% in Canada, [5] specific subtypes of GS patients have less than optimal outcomes including prolonged length of stay and delayed intestinal function. The aim of the treatment of patients with GS is to reduce the herniated bowels back into the abdominal cavity and to close the abdominal defect with the best outcomes. This reduction is feasible immediately after birth in some cases, while in other cases, the herniated bowels should to be covered with a silastic pouch (called a “silo”) and gradually reduced into the abdominal cavity. After the successful reduction of the herniated bowels, there are two available techniques to close the abdominal defect: fascial closure, which is the classical closure of the fascia with sutures under general anesthesia, and flap closure which is the simple use of the remnant of the umbilical cord to cover the abdominal defect supported by adhesive tapes without any use of suture materials, which can be carried out at the bedside with minimal sedation. [6]

Many prenatal and postnatal factors may affect the outcomes in patients with GS. Prenatally, the possible adverse effects of amniotic fluid on the exposed intestines has been a point of controversy that made some surgeons change their practice towards the early induction of labor in the presence of GS. Patients born with gastroschisis often have a thick peel covering the intestines, the etiology of which is not fully elucidated; this results in bowel matting and may be related to delayed intestinal function postnatally. On the other hand, prematurity itself may lead to complications and increased length of stay (LOS). Postnatally, the most important determinant of outcomes has been the presence or absence of intestinal related complications, namely perforation, atresia, and necrosis. The patients with any of these complications are classified as complex GS patients and they have shown worse outcomes compared to patients with simple GS [7,8]. It is not clear however, why some patients with simple GS have worse outcomes than others. In addition to the intestinal complications, the outcomes might be affected by many other factors such as the timing of delivery, bowel matting, the postnatal management, including the closure technique, and the type of the healthcare system.
With the increasing incidence and the suboptimal outcomes in specific groups of patients with GS, there is still a need for intensive research efforts given the persistent gaps in our knowledge and the continuous controversies on several points of prenatal and postnatal management of newborns with GS. This thesis aimed to answer the following questions.

1. **In patients with GS, is there any correlation between the gestational age and the degree of injury in the exposed intestines?** Thus, is it a justified practice to induce the delivery solely to protect the intestines? In Canada, most cases of GS are diagnosed prenatally. The evidence has been growing that the pregnancy should be carefully pursued until the fetus is safe from the consequences of prematurity; [9,10,11] however, once the pregnancy reaches term, a tendency towards an elective induction of delivery has been reported in some centers, pushed by the concerns of possible damage that the contents of amniotic fluid might bring to the exposed bowels. [12,13,14,15] But is this a justified practice? To answer this question, we used the data from the Canadian Pediatric Surgery Network (CAPSNet) which is a national, disease specific registry of all patients with GS and congenital diaphragmatic hernia diagnosed pre or postnatally in tertiary care centers in Canada. This data has been prospectively collected since 2005. The use of this data enabled us to conduct the first study included in this thesis “The correlation between the time spent in utero and the severity of bowel matting in newborns with gastroschisis”.

2. **What is the best surgical method to accomplish the final closure of the abdominal defect?**
   
   After reduction of the herniated bowels, the two available options to close the abdominal defect are fascial and flap closures. The use of flap closure has been steadily growing over the last decade [5], but compared to the classical fascial closure, which technique has better outcomes and is more cost-effective in patients with GS? To answer this question, we performed the second study included in this
thesis “Flap versus fascial closure for gastroschisis: a systematic review and meta-analysis”.

3. **What are the determinants of the short-term outcomes in patients with simple GS? Is severe bowel matting a significant predictor of prolonged LOS in patients with “simple” GS?**

   To answer this question, we performed the third study included in this thesis “Determinants of outcomes in patients with simple gastroschisis” using the CAPSNet database.

4. **What are the effects of the healthcare system on the short-term outcomes in patients with GS?**

   To answer this question, we performed the fourth study included in this thesis “Gastroschisis Outcomes in North America: A Comparison of Canada and the United States”. We used the CAPSNet database for the Canadian cohort and for the American cohort, we used the Kids Inpatient Database (KID’s) which is the largest inpatient, publicly available database in the United States.

After a literature review of the management of GS in the prenatal and postnatal periods (Chapter 2), the results generated from the four included studies are presented in Chapters 3, 4, 5 and 6 in the form of manuscripts. Finally, Chapter 7 summarizes the findings of the whole research work and comes to a global conclusion.
References

II. Literature Review

This chapter includes a review of the literature regarding the management of neonates with GS. We will first give a historical perspective and then the topics of pathogenesis, incidence and risk factors, prenatal diagnosis, time and mode of delivery, and post natal management will be visited.

1) **Historical Perspective:**

The first two reported cases of GS were in 1733 by Calder. [1] At the time when Calder reported his two cases, there were no differentiation among the various types of anterior abdominal wall deformities. The report of the first case of survival of GS came in 1878 by Dr. William Fear. [2]

The term Gastrochisis (GS) is of a Greek origin (Gastro: belly; Schisis: separation or cleft). This term has been invented for the first time by the Italian pathologist Tarrufi in 1894 who also did a sub classification of GS according to the part of the anterior abdominal wall involving in it. [3] About 50 years later in 1943, Dr. Edward Watkins published his method of treating what he considered a case of Gastrochisis. [4] At that time, and during the first hour of the patient’s life, Dr. Watkins expanded the 1 inch abdominal defect into a 2 inches incision and this enabled him to reduce the herniated viscera inside the abdomen, and eventually, the incision was closed with sutures. Then the patient was hospitalized for 6 days, and discharged and followed up for one month. By this report, Dr. Watkins outlined the first successful surgical management of GS.

With the success of the primary surgical closure of GS, concerns started about the effective coverage of exposed intestines in cases where the reduction and the primary closure were not possible.
In 1975, Shermeta et al. described the use of preformed silo to cover the exposed intestines after several attempts to cover the unprotected intestines by skin flaps, teflon, and abdominal layers expansion. [5] The use of preformed silo has significantly improved the outcomes of patients with GS. [6] Another milestone in the history of the treatment of GS was in 1995 when Fischer et al. used the spring loaded silo for the first time. This allowed for applying the silo at the bedside with minimal or even no sedation. [7]

Whether using a silo for gradual intestinal reduction or immediate closure, definitive fascial closure is classically performed in the operating room under general anesthesia using sutures to close the defect in various ways (vertical, transverse, pursestring). There is another alternative, called “flap closure”, which is the simple use of the remnant of the umbilical cord to cover the abdominal defect supported by adhesive tapes without any use of suture materials, using the natural ability of the umbilical ring to close spontaneously and allowing the skin defect to heal by secondary intention.

The first case series of bedside reduction without general anesthesia in infants with GS was reported by Bianchi [8] in 1998. In this report, Bianchi et al. demonstrated the feasibility of intestinal reduction without anesthesia within a few hours of delivery using only local anesthesia and sutures to place the umbilical cord as a “plug” over the abdominal defect. After concerns were voiced about the associated discomfort and complications of the procedure [9], several modifications to the ‘Bianchi technique’ were adopted until a large series describing a sutureless ward reduction was published in 2001 [10]. Ward reduction was limited to selected cases of simple GS with the defect partially closed with adhesive strips. Bianchi published a similar case series shortly thereafter, followed by the description by Sandler et al. of a ‘plastic closure’ using a clear, adhesive dressing to secure the umbilical cord within the defect without formal skin or fascial closure [11,12].
2) **Pathogenesis:**
There is no confirmed etiology of GS but there are many theories regarding its pathogenesis. Many of these reports mention a defect in the formation of the abdominal wall as the initial event with consequent herniation of the abdominal viscera. The possible aetiologies of the abdominal defect include either a failure to form the abdominal wall or a weakness after this formation. Regarding the formation, the mesoderm might fail to form the abdominal wall [13] or the body wall might fail to fold properly [14]. However, this may apply more to omphalocele than GS, in which the abdominal wall, including the rectus muscles, appear well formed. Other theories mention a local weakness of the abdominal wall, which might be caused by a breach of the amniotic membrane near the base of the umbilical cord [15], or a weakness caused either at the site of involution of the right umbilical vein [16] or by the occlusion of the omphalomesenteric artery [17]. The involuting right umbilical vein theory is the only one that explains the fact that the defect is nearly always right-sided. In one report, a small omphalocele/hernia at the base of the cord was observed early in gestation, with later rupture and a typical GS appearance further in gestation and after birth [17a]. Generally GS is considered as an accident occurring during fetal life rather than an embryological developmental anomaly, since there is a low percentage of associated malformations, most of which can be considered secondary to the defect (such as intestinal atresias and undescended testicles). [18]

3) **Incidence and risk factors**
The incidence of GS is about 4-4.5 cases per 10,000 live births [19]. An unexplained increase in the incidence of GS has been reported during the last decade in Canada, the United States and many other countries including Europe [20-22]. Several risk factors have been studied in different categories: Congenital, individual and environmental.

3-1. **Age group:** Young maternal age has been linked to GS for several decades. This was confirmed in recent publications with relatively good evidence, emphasizing that young maternal age (less than 20 years old) is one of the strongest risk factors associated with GS. [23,24]
3-2. **Ethnicity:** Whites and Hispanics appear to have a higher risk of GS. [24]

3-3. **Socioeconomic status:** Some studies suggested that lower socioeconomic status is associated with a higher risk of GS. It is not clear if this is related to the lifestyle of this population group. [25]

3-4. **Geographic:** Interestingly, there is a significant variation of GS between countries and sometimes even among provinces or regions in the same country. [26] Some studies suggested that agriculture chemicals (Atrazine) which are found in the local surface water might be responsible for such significant geographic variation. [27]

3-5. **Nutrition:** GS incidence has not been associated with any maternal deficiency or intake of any micro or macro nutrient. [28]

3-6. **Substance abuse:** Smoking has been found to be associated with GS. [29] Several reports also demonstrate an increased incidence of GS with the abuse of cocaine, amphetamines, and some specific medications like antidepressants. [24, 30, 31, 32]

4) **Prenatal diagnosis**

In developed countries, the prenatal diagnosis rate of patients with GS is more than 90%. [33] The wide use of prenatal obstetric US and the routine detection of other genetic deformities by measuring Alfa fetoprotein (AFP) and the measurement of nuchal fold during the first trimester are among the factors of this high detection rate. It is critical however, to differentiate between GS and omphalocele given the different associated malformations between the two. The site of the abdominal wall defect (on the right side of the umbilical cord in GS vs through the base of the umbilical cord in Omphalocele), the type of herniated viscera (solid organs more commonly found in Omphalocele) and the presence of covering amniotic membrane in omphalocele are the most useful differentiating signs.

Other investigations such as a karyotype are usually indicated in case of omphalocele where the risk of associated malformations is as high as 50%, unlike GS which has a low risk of other malformations. [18,34] It is relevant to mention some rare syndromes associated with GS such as arthrogryposis. [35]

The ability to predict postnatal outcomes depending on the prenatal imaging has been a major area of interest. Complex GS is defined by the presence of any of the following intestinal
related complications postnatally (atresia, necrosis, or perforation), but this may not be fully determined until several weeks after birth. With inconsistent results, efforts have been made to predict the postnatal prognosis depending on prenatal measurements. The following prenatal ultrasonography signs have been suggested to be associated with complex GS: oligohydramnios or polyhydramnios, intra and extra abdominal bowel loop dilatation, bowel wall thickening, stomach dilatation. [36] A recent systematic review found a correlation between intra-abdominal bowel dilatation with polyhydramnios and the incidence of intestinal atresia, and between gastric dilatation and infant mortality. [37] GS is almost always associated with elevation of maternal AFP [38]. While US is still the standard method of evaluating GS prenatally, fetal MRI has shown promising results especially in featuring the intra-abdominal organs in cases of complicated GS and in detecting other possible deformities [39].

5) **Delivery time and mode:**
Despite extensive literature around this area, the best time of delivery in patient with GS is still controversial. There is an increasing evidence however that elective preterm delivery in fetuses less than 36 weeks is harmful and should be strongly discouraged. [40]. The evidence regarding the type of delivery has been established for a longer time, with good evidence that elective C-section with its known complications as a surgical intervention adds no benefit over a normal vaginal delivery. Thus, the recommendation is to reserve C-section only for the traditional obstetrical indications, including fetal distress, which is a common occurrence in GS. [41,42] Since preterm delivery is common in GS, prenatal diagnosis allows maternal transportation close to a tertiary care facility with a neonatal unit and pediatric surgery availability. For families living in remote areas, it is usually advised to stay close to such a facility from 30-32 weeks of gestation in case of premature labor and to allow for more frequent US monitoring.

There is no consensus on the possible benefit of labour induction for pregnancies complicated with GS. Some reports indicated that near-term delivery induction is protective for the exposed bowel against the contents of the amniotic fluid, [43] while other reports
support expectant management. **Part of this thesis is dedicated to address this specific point.**

Postnatal diagnosis relies on the physical examination of the newborn. In cases with GS, there should be a full thickness defect of the abdominal wall, usually to the right of a normally inserted umbilical cord, associated with uncovered visceral herniation. Again, it is of paramount importance to differentiate between GS and ruptured omphalocele since the latter is associated with other congenital anomalies which should be investigated.

6) **Surgical postnatal management:**

Once the neonate with GS is born, the highest care in the hospital should be offered which includes Neonatal Intensive Care Unit (NICU). Initially, the newborn should be resuscitated like any other newborn regarding his Airway, Breathing, and Circulation with a special attention to third space fluid loss, hypothermia, gastric decompression and avoidance of mesenteric kinking at the level of the defect. The decision is then made to either reduce the herniated bowel or to cover them with a silo. [44] If the baby has to be transported after birth, special precautions include the provision of intravenous fluids, nasogastric tube decompression (to avoid gastric herniation with compression of the mesentery of the herniated bowel, and decrease the risk of vomiting and aspiration), bowel coverage with a waterproof protection (silo, bowel bag or even saran wrap to prevent fluid and temperature losses), and transportation in the right lateral decubitus position to avoid mesenteric kinking. Clear cases of intestinal perforation or necrosis are indications for urgent surgical intervention. In the absence of these indications, intestines will be reduced back to the abdomen if possible or covered with a silo for gradual reduction.
6-1. Abdominal defect closure

Either as an urgent primary closure after birth or after gradual silo reduction, there are two methods to close the fascial defect of the abdominal wall; fascial closure and flap closure. Fascial closure is the classic method of closing any fascial defect, by taking the patient to the operation room and under general anesthesia, closing the fascial defect using sutures (purse-string, vertical interrupted or transverse). The other method to close the defect is the flap closure which involves the sutureless covering of the fascial defect with the umbilical cord stump using adhesive tapes at the bedside under minimal or no sedation. In the cases when the umbilical cord stump is not salvaged, the surrounding skin flaps can be used to cover the defect. Until now it was not clear which method is the best to achieve the closure. Part of this thesis is dedicated to address this question.

6-2. Silo staged reduction

Silos were initially used in cases where the immediate reduction of the herniated bowel was not possible or thought to be unsafe. The silo covers the intestines to maintain the integrity, the temperature and prevent water loss. Many centers have elected to routinely use silos to accomplish a more gentle reduction of the herniated intestines to avoid bowel ischemia and an abdominal compartment syndrome that can sometimes occur after aggressive primary closure. The silo allows the treating team to see the bowel through the silo in order to evaluate for any ischemic signs. After gradual reduction using the silo, the surgical closure of the defect is indicated either by fascial or flap closure.
References

3. G. Taruffi :Storia della teratologica, 7 (1894), p. 403


III. The Correlation between the time spent in utero and the severity of bowel matting in newborns with gastroschisis

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This paper was published in the Journal of Pediatric Surgery.

Corresponding author *
Abstract

Background: Optimal timing of delivery in fetuses with gastroschisis (GS) is unknown. Some favor early induced delivery to prevent bowel injury. This study evaluates the correlation between bowel injury and the gestational age at birth using the Gastrochisis Prognostic Score (GPS).

Methods: A national database was analyzed from 2005 to 2013. Patients were pooled based on their gestational age at birth. The mean GPS and % of patients with severe bowel matting were tabulated for each week in utero. Regression modeling was used to evaluate the relationship between the dependent (severe matting and GPS) and independent (gestational age) variables and the $R^2$ coefficient of determination was derived to evaluate model strength. Additional factors influencing the timing of delivery were evaluated.

Results: Of 780 cases, 88 were excluded because of missing data. A linear relationship is seen between increasing gestational age and decreasing bowel matting ($R^2 = 0.66$) and GPS ($R^2 = 0.72$). For every week in utero, the % of patients with severe matting decreases by 3.6%.

Conclusion: Early induced delivery simply to protect the bowel from ongoing in utero damage appears unfounded and should be reserved for evidence of closing gastroschisis or traditional obstetrical/fetal indications.
Gastroschisis (GS) is one of the most common congenital abdominal wall defects and is usually detected in the prenatal period in developed countries during routine fetal ultrasound and selective maternal serum screening [1–3]. Despite frequent intrauterine growth restriction (IUGR) and premature delivery, most babies with GS survive with an excellent outcome; only 5%–10% have severe bowel damage and require prolonged intravenous nutrition [4]. The exact cause of bowel injury remains unknown. Putative causes include chemical irritation by urine, meconium or regurgitated digestive enzymes in the amniotic fluid; other possibilities include the restriction of venous and lymphatic outflow because of a narrow abdominal wall defect [5–8]. A few authors have blamed prolonged labor as the cause of bowel edema and have advocated for routine cesarean section (CS) as a consequence [9–12].

Several authors have advocated for preterm delivery to prevent potential serious complications including ongoing bowel damage in utero as well as third trimester fetal demise, fetal distress with neurological sequelae [13] and a risk of “closing gastroschisis” leading to massive midgut loss [14,15]. Elective preterm delivery has been associated with a shorter hospital stay, faster initiation to oral feeding [16,17], a higher proportion of successful primary repair, and a shorter duration of mechanical ventilation [9,17]. On the other hand, preterm delivery has conversely been shown to increase the duration of hospitalization and delay the time required to reach full oral feeding [18–20].

In addition, premature GS babies are at higher risk of developing sepsis and cholestasis [4,21,22]. Many studies have been underpowered to detect significant outcome differences based on delivery practices, including the only prospective randomized trial published to date [23–25]. Additional limitations of the salient literature include the prolonged time span included in most studies resulting in the comparison of patients treated in different eras, inclusion of emergency and elective deliveries as well as the evaluation of patients without stratification based on disease severity.

In order to assess whether preterm delivery protects the bowel from ongoing damage in utero, the Canadian Pediatric Surgery Network (CAPSNet) database was used to correlate the
time spent in utero with the severity of bowel matting and Gastrochisis Prognostic Score (GPS) in newborns with gastroschisis [26]. The study hypothesis was that if the proponents of preterm delivery were correct, we should see a higher percentage of severe matting and high-risk GPS with increasing gestational age.

1. Methods

1.1. Study population

The Canadian Pediatric Surgery Network includes all tertiary care Canadian perinatal centers and has collected data on all congenital diaphragmatic hernia and GS cases from fetal diagnosis until hospital discharge or death since May 2005. CAPSNet is nested within a national, universal health care delivery plan without appreciable private maternal or neonatal hospital care. Screening maternal ultrasounds are routinely performed during the second trimester, and often in the first and third trimesters for low-risk pregnancies; private ultrasounds remain available as desired. The diagnosis of GS on prenatal screening typically triggers a prompt referral to a CAPSNet center for further surveillance, counseling and antenatal care.

After obtaining approval from the CAPSNet steering committee and our hospital's Research Ethics Board (14-081-PED), the CAPSNet data registry for cases of GS for the years 2005–2013 was accessed and analyzed. Individual patient data was prospectively collected in the registry as previously described [3]. Briefly, a trained research assistant at each participating center abstracted prenatal and postnatal data using a customized data entry program and a standardized manual of operations and definitions with built-in error checking. The coded, de-identified data were then transmitted electronically to a centralized, secure database for cleaning and storing. This process was overseen by a study coordinator and a multidisciplinary, geographically representative, steering committee consisting of a neonatologist, pediatric surgeon, a maternal fetal medicine specialist, and an epidemiologist.
Prospectively collected clinical findings at first patient encounter were assigned a numerical score based on logistic regression analysis. Patients with a GPS b2 are considered at low risk for morbidity and mortality. A GPS ≥2 identifies patients with higher risks of morbidity and mortality. Reproduced with permission from Cowan et al. [26].

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<td>Suspected (1)</td>
<td>Present (2)</td>
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<td>Perforation</td>
<td>Absent (0)</td>
<td></td>
<td>Present (2)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Absent (0)</td>
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<td>Present (4)</td>
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**Table 1**
Gastroschisis Prognostic Score (GPS).

**Table 2**
Demographic information and select outcomes for gastroschisis patients included in analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>Male, n (%)</td>
<td>365 (52.8)</td>
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<tr>
<td>Gestational age, weeks (median; IQR)</td>
<td>36 (35–37)</td>
</tr>
<tr>
<td>Birth weight, grams (mean ± SD)</td>
<td>2538 ± 516</td>
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<tr>
<td>GPS, median (IQR)</td>
<td>1 (0–1)</td>
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<td>GPS low risk, n (%)</td>
<td>534 (78)</td>
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<tr>
<td>LOS, median days (IQR)</td>
<td>36 (25–62)</td>
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<tr>
<td>Survival, n (%)</td>
<td>679 (98)</td>
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<td>Severe bowel matting, n (%)</td>
<td>83 (12)</td>
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<tr>
<td>1st attempt successful closure, n (%)</td>
<td>582 (84)</td>
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<tr>
<td>Delivery type, vaginal, n (%)</td>
<td>470 (68)</td>
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</tbody>
</table>

IQR = interquartile range (1st quartile–3rd quartile); GPS = Gastroschisis Prognostic Score; LOS = length of stay.
1.2 Bowel injury assessment:

Before the onset of CAPSNet data collection, standard definitions for bowel matting, necrosis, atresia and perforation were agreed upon (available at http://www.capsnetwork.org/portal/Resources/ EducationfortheGSBowelInjuryScore.aspx). For each GS patient, a bowel injury assessment form was prospectively filled at the time of first clinical evaluation by the treating surgeon or surgical fellow: (http://www.capsnetwork.org/portal/Portals/0/CAPSNet/Worksheets/GS%20PreOp%20Record%20-%20V1.1.1_Nov%202013.pdf). After several years of data collection, the GPS tool was developed and validated, providing a prospectively collected risk-stratification tool (Table 1) [26]. A GPS score of 0 or 1 is considered low-risk, while 2 or more places the child at higher risk of mortality and morbidity including a prolonged length of stay.

1.3. Statistical analysis

The analysis was restricted to neonates with complete data regarding GPS and gestational age (GA) at birth. To evaluate the relationship between gestational age at birth and matting/GPS, regression modeling was performed for all gestational weeks with at least 3 patients within (excluding b29 weeks and N40 weeks gestational age). Since isolated mild bowel matting has previously been demonstrated not to influence prognosis [26], only severe bowel matting was examined as a dependant variable, as well as overall GPS. Linear and nonlinear regression models were tested to investigate the association between the dependent (matting and GPS) and independent (gestational age) variables; the $R^2$ coefficient of determination was derived to evaluate model strength, with $R^2 = 1$ indicative of a perfect correlation.

Secondary variables investigated include other parameters that significantly influence timing of delivery, including the mode of delivery (cesarean or vaginal delivery), the presence and adherence to a birth plan, and whether or not an induction was performed. For each of these, the incidence (%) of severe bowel matting, high-risk GPS score, and the percentage of successful primary closure were evaluated. For the secondary outcomes, the data obtained were analyzed using Fisher's
exact and two-tailed Student's t-tests for categorical and continuous variables, respectively (p<0.05 significant).

Fig. 1. Regression graph showing a linear relationship between increasing gestational age and decreasing incidence of severe bowel matting and overall Gastroschisis Prognostic Score.

Fig. 2. Percentage of patients with high-risk GPS according to gestational age at birth, with total number of patients for each gestational age in brackets.
2. Results

2.1. Patient demographics

Of the 780 GS patients in the CAPSNet data registry born in the period from 2005 to 2013, 88 were excluded because of missing data, leaving 692 patients for analysis. Table 2 presents patient demographics and selected neonatal outcomes for the included cohort.

2.2. Gestational age, GPS and % severe bowel matting

The regression model results represent the association between gestational age at birth, the GPS and the incidence of severe bowel matting (Fig. 1). While nonlinear models were tested without significant correlation (not shown), a linear relationship is demonstrated between increasing gestational age and decreasing bowel matting ($R^2 = 0.66$) and GPS ($R^2 = 0.72$), indicative of a strong linear correlation. For every week of increasing gestation age, the mean GPS decreases by 0.39, while the % of patients with severe matting decreases by 3.6%. Fig. 2 demonstrates the percentage of patients with high-risk GPS according to gestational age at birth.

2.3. Secondary outcomes

Fig. 3 demonstrates the prenatal delivery plan as established at 30–32 weeks gestation. While delivery plans vary widely, in many instances the plan changed because of fetal or obstetrical reasons. For example, in 284 planned inductions, just over 50% (143) had a change in their original birth plan. Overall, 222 mothers underwent cesarean section (CS); the percentage of patient undergoing CS at each gestational age is represented in Fig. 4. Fig. 5 shows abdominal wall closure success stratified by gestational age, with minimal variation between 32 weeks and term.
Fig. 3. Total patient cohort with delivery plan as established at 30–32 weeks gestation.

Fig. 4. Percentage of cesarean delivery according to gestational age, with total number of patients for each gestational age in brackets.
Fig. 5. Percentage of successful abdominal closure according to gestational age, with total number of patients for each gestational age in brackets.

Table 3 compares patients whose delivery plan was a spontaneous vaginal delivery (SVD) to those with a planned induction. Although their gestational ages at delivery were comparable, patients who had a planned SVD had more severe matting and a worse mean GPS when compared to their induced counterparts, although the percentage of high-risk GPS was similar. This difference is accentuated in patients who had no alteration in their birth plan during the course of their induction, with greatly improved GPS (0.9 ± 1.2 versus 1.6 ± 2.3, p = 0.001) and severe bowel matting (4.25% versus 18.5%, p < 0.001) when compared to the SVD cohort.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SVD (199)</th>
<th>Planned induction (284)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPS, mean ± SD</td>
<td>1.64 ± 2.36</td>
<td>1.19 ± 1.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Gestational age, weeks, median (IQR)</td>
<td>36 (35–37)</td>
<td>36 (35–37)</td>
<td>0.62</td>
</tr>
<tr>
<td>LOS, days, median (IQR)</td>
<td>37 (25–60)</td>
<td>35 (25–62)</td>
<td>0.74</td>
</tr>
<tr>
<td>Severe bowel matting, n (%)</td>
<td>37 (18.5)</td>
<td>25 (9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Delivery type (vaginal), n (%)</td>
<td>144 (72.3)</td>
<td>202 (71.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>High risk GPS, n (%)</td>
<td>50 (25.1)</td>
<td>56 (19.7)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

SVD = planned spontaneous vaginal delivery; GPS = Gastrochisis Prognostic Score, LOS = length of stay in hospital. High risk GPS is ≥2.
3. Discussion

For certain congenital anomalies, prenatal identification and intervention has improved patient outcomes and saved children's lives.

Cystic lung lesions, congenital diaphragmatic hernia, myelomeningocele and many other conditions all have recognized prenatal therapeutic options depending on in utero disease severity. For gastroschisis, no such prenatal intervention has been demonstrated to be of value. Although amnio-exchange has been investigated under several experimental conditions [27,28] and used in clinical pilot studies [8], it has not proven effective in reducing the inflammatory status of amniotic fluid or in improving patient outcomes [29]. The clinician's only current recourse to treat the unborn child with gastroschisis is to deliver the baby. The debate about the mode of delivery has been gradually settled, with routine CS having shown no benefit [30,31]. The debate regarding timing of delivery is ongoing.

Fears of in utero fetal demise or massive bowel loss as a consequence of a closing gastroschisis ring clearly influence obstetrical decision-making. Burge and Ade-Ajayi's [13] review demonstrated a 10.6% rate of prenatal death for patient with GS—a figure that is a severe outlier when compared to contemporary series. The CAPSNet database has demonstrated a rate of fetal loss of 1.4% (10 in more than 700 cases) (www.capsnetwork.org). The study by Burge and Ade-Ajayi has unduly and inadvertently influenced decisions regarding the timing of delivery for fetuses with GS; indeed the authors argued only for enhanced surveillance as opposed to early delivery [13]. Thus, while obstetrical indications may always prompt early delivery, when should a well maternal–fetal dyad be delivered and should that delivery be coerced?

Data from this study indicate that there is no reason to proceed with early delivery for patients with GS to prevent bowel damage. Indeed, the percentage of patients with severe matting (previously correlated with neonatal outcomes) decreases with increasing gestational age. Furthermore, the GPS has also been shown to decrease in a linear fashion with increasing gestational age. While these findings represent aggregated patients and not individual patient
trajectories, they argue against elective early delivery for the sake of improved neonatal outcomes. Our study clearly refutes a correlation between increased duration of amniotic fluid exposure and worsening bowel damage.

Bowel damage is likely multifactorial and may occur at any gestational age. Interestingly, a recent study also using CAPSNet data concluded that delivery at ≥38 weeks gestation was associated with increased bowel matting, without any adverse prognostic markers such as hospital length of stay [32]. However, the authors included any matting, as their work was carried out before the development of the GPS and the realization that only severe matting affects prognosis [26]. The fact that prognosis was not affected in their study confirms our findings.

Another significant observation of this investigation is that neonatal outcomes appear improved (less severe matting, improved GPS) in patients who undergo induction as opposed to patients who have a spontaneous vaginal delivery. This may be explained by the fact that both matting and worse GPS reflect a fetus in distress, which in turn may lead to a spontaneous onset of labor. Those fetuses in good condition will have a tendency to delay the onset of labor until closer to term—patients in our cohort who had an uneventful induction as planned had a mean GPS nearly half the SVD group, and demonstrated severe matting more than 4 times less often.

This study represents the largest, prospectively collected dataset of patients with GS reported thus far. By evaluating disease-specific information (matting, atresia, necrosis and perforation), adequate risk stratification can be performed and correlations between gestational age and outcomes can be sought. Nonetheless, certain caveats must be acknowledged. Details regarding induction practices, and the factors that alter delivery plans are unavailable to this analysis. Decision-making for individual patients remains inherently complex and signs of fetal distress should prompt urgent delivery. The risks associated with a closing gastroschisis with subsequent midgut infarction, are often cited as an indication for early delivery. The findings on ultrasound include distended intraabdominal bowel loops [15], but in a recent review only 25% of such patients were actually found to have complex gastroschisis [19]. Furthermore, the ultrasound signs are often present before 30 weeks gestation, at a time when delivery would invariably add
the complications of prematurity [33]. Unfortunately, intraabdominal bowel dilatation, with extraabdominal dilatation or collapse, does not allow differentiation between simple atresia and necrosis [19]. Delivering a premature GS baby with an already established intestinal atresia only adds insult to injury. Until now, more direct signs of a closing gastroschisis such as the diameter of the defect and mesenteric vascular flow of the exteriorized bowel have not proven useful [34].

In summary, we have shown that early induced delivery simply to protect the bowel from ongoing in utero damage is unfounded. The induction of labor at term is not necessarily associated with negative consequences. Indeed, a recent meta-analysis suggests that induction for pregnancies in general reduced the overall CS rate and may even be associated with improved neonatal outcomes [35]. Labor induction at term for babies with GS may be the preferred delivery mode in some centers for logistical reasons, but should not be chosen under the false pretence of preventing bowel damage.
References


[13] Burge D, Ade-Ajayi N. Adverse outcome after prenatal diagnosis of gastroschisis: the


IV. Flap versus fascial closure for gastroschisis: a systematic review and meta-analysis

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Corresponding author *
Abstract:

**Background:** Flap closure represents an alternative to fascial closure for gastroschisis. We performed a systematic review and meta-analysis of outcomes comparing these techniques.

**Methods:** A registered systematic review (PROSPERO: CRD42015016745) of comparative studies was performed, querying multiple databases without language or date restrictions. Gray literature was sought. Outcomes analyzed included: mortality, ventilation days, feeding parameters, length of stay (LOS), wound infection, resource utilization, and umbilical hernia incidence. Multiple reviewers independently assessed study eligibility and literature quality. Meta-analysis of outcomes was performed where appropriate (RevMan 5.2).

**Results:** Twelve studies met inclusion criteria, of which three were multi-institutional. Quality assessment revealed unbiased patient selection and exposure, but group comparability was suboptimal in four studies. Over all, 1124 patients were evaluated, of which 350 underwent flap closure (210 immediately; 140 post-silo). Meta-analysis revealed no significant differences in mortality, LOS, or feeding parameters between groups. Flap patients had less wound infections (OR 0.40 [95%CI 0.22–0.74], P = 0.003). While flap patients had an increased risk of umbilical hernia, they were less likely to undergo repair (19% vs. 41%; P = 0.01).

**Conclusions:** Flap closure has equivalent or superior outcomes to fascial closure for patients with gastroschisis. Given potential advantages of bedside closure and reduced sedation requirements, flap closure may represent the preferred closure strategy.

Gastroschisis (GS) is a congenital full thickness defect of the abdominal wall that is increasing in prevalence worldwide [1,2]. Although the survival rate of neonates with GS is high, the burden of survivor morbidity remains considerable [3]. Various techniques have been described to close the defect, with the two most common methods being an operative fascial closure with sutures and a non-operative sutureless ‘flap’ closure [4]. The ‘flap’ closure has gained increasing popularity since its original description by Bianchi [5] and subsequent modifications by Kimble [6], and Sandler [7]. Indeed, the Canadian Pediatric Surgery Network (CAPSNet) reported an increase in flap closure use from 7% to 26% between 2006 and 2013; [4] a recent study from the United States has revealed a similar trend [8]. The relative ease of bedside closure with minimal or no sedation, coupled with cost effectiveness based on reduced operating room utilization, is among the cited reasons for increased acceptance.
of the flap technique. Moreover, while early reports restricted the use of the flap closure in uncomplicated GS [6,9], flap closure has also been applied in a growing number of complicated cases with reasonable results [10].

With significant reported treatment variability of patients with GS and a lack of consensus regarding the best method to close the abdominal wall defect [11,12], the objective of this investigation was to compare the short-term outcomes of flap closure and fascial closure through a formal systematic literature review and meta-analysis.

1. Materials and methods

1.1. Search strategy

The protocol of this review was prospectively published in the PROSPERO registry (CRD42015016745) [13]. Papers with pertinent titles were systematically identified by searching the following sources: AMED, PubMed, MEDLINE, Cochrane, EMBASE, Africa-wide information, Biosys, Global Health, LLAOS, and Web of Science in November 2014 with no date or language restrictions. For each of these databases, a search strategy guided by our institution's scientific librarian was established according to the database design (Appendix A). A hand check of reference lists of the included articles was performed to identify any further relevant papers. Gray literature was sought, where appropriate, by probing the abstracts of relevant conferences and contacting the authors for any unpublished results. After the literature search, only comparative studies were included in the final qualitative and quantitative analyses.

1.2. Definitions

During the conduct of this review, the following definitions were used:

A. Flap closure: The sutureless use of either the umbilical cord remnant or skin flaps as an autologous dressing to cover the abdominal defect, with support from adhesive material to either keep the cord in place or to approximate the skin.

B. Fascial closure: The operative closure of the abdominal wall defect with sutures under general anesthesia.

C. Primary closure: Abdominal defect closure immediately after birth without using a silo, either by flap or fascial techniques.

D. Secondary closure: Abdominal defect closure after serial reduction using a silo, either by flap or fascial techniques.
E. Complicated GS: Any case of GS with one or more of the following bowel-related complications: necrosis, atresia, perforation, or severe bowel matting [10].
F. Simple GS: Any case of GS without a bowel-related complication as listed above.

1.3. Inclusion and exclusion criteria
Our inclusion criteria were formulated according to the ‘PICOS’ format as follows:
• Population: All infants born alive with the diagnosis of GS and who underwent abdominal defect closure.
• Intervention: Sutureless flap closure either primarily or after silo reduction, in simple and complex GS cases.
• Control: Operative fascial closure under general anesthesia either primarily or after a silo, in simple and complex GS cases.
• Outcomes: The primary outcome was mortality rate. Secondary outcomes included the length of hospital stay, the number of post-intervention days on mechanical ventilation, the number of post-intervention days on total parenteral nutrition (TPN), the number of Nil Per Os days (NPO), the incidence of surgical site infection, the incidence of umbilical hernia, the need for umbilical hernia repair, and markers of resource utilization.
• Study type: Only comparative studies (retrospective or prospective) that included both the intervention and control group and that reported at least one outcome of interest were included.

All the resulting titles were twice inspected independently; papers were excluded if one of the following exclusion criteria were met: basic science or animal studies, non-comparative studies or case reports, or papers that did not include GS patients. Abstracts were then reviewed and papers further excluded based on irrelevant methods of closure, whether the method of the closure was clearly explained or not, and any study that did not include either the primary or the secondary outcomes of this review. Full texts of all titles that were deemed relevant by either reviewer (where possible) were then retrieved. One instance of a duplication of relevant data was identified and excluded [14]. Full agreement of included titles was then reached through discussion under the guidance of the senior author (RB).

1.4. Quality of included studies
The literature search did not yield any randomized control trials or cohort studies. Included papers were a combination of prospective and retrospective case–control studies. The Newcastle-Ottawa Scale (NOS) for case–control studies was used to critically appraise the quality of included papers [15]. This scale is designed to assess the quality of the study under three broad categories: the selection of the study groups, the comparability between the groups, and the ascertainment of exposure. Stars are awarded for each of the quality items met by the study; the highest quality studies are awarded up to nine stars.

1.5 Statistical analysis
Meta-analysis was performed for primary and secondary outcomes using RevMan 5.2 (Copenhagen) [16]. Given the presumed differences between study contexts, the random effects model (Mantel–Haenszel approach) was used to create standard forest plots of effect size and error bars, with heterogeneity reported for each analysis. Publication bias was evaluated through the generation of a funnel plot of standard error against the log odds ratio. P b 0.05 was considered statistically significant for all analyses.

2. Results
The search results are shown in the PRISMA flow chart in Fig. 1. Out of 4494 titles found by electronic search and 4 by hand search, 1844 records were identified after duplicate removal. Title and abstracts screening subsequently excluded 1824 records. Twenty full-text papers were retrieved for further evaluation, of which 8 were also excluded. Finally, twelve studies (1 prospective [10] and 11 retrospective studies [17–27]) were included for qualitative and quantitative analyses.

2.1. Qualitative analysis
The characteristics of the included studies are highlighted in Table 1. The years of publication ranged from 2008 to 2015. Sample sizes varied between 8 and 565 cases/study. Three studies were multi-institutional [10,20,26]. Only one study reported the use of flap closure in complicated cases of GS [10] while four studies explicitly limited their cohorts to cases of simple GS [17,20,26,27]. Overall, a total of 1124 patients (774 fascial closure and 350 flap closure)
were included in this study. Of cases that underwent flap closure, 140 underwent closure after silo placement.
The quality of included studies was evaluated by the Newcastle-Ottawa Scale (NOS) for Assessing the case–control studies shown in Table 2. Included studies were of moderate to high quality, scoring between 6 and 9 out of possible nine stars. Three studies demonstrated significant differences in subject comparability between the intervention (flap) and the control (fascial closure) groups [17,19,24].

2.2. Quantitative analysis

2.2.1. Mortality rate
All but three studies [17,26,27] compared the mortality rate between flap and fascia groups. These nine studies [10,18–25] individually showed comparable results for mortality between the two groups. Pooled data (919 patients) demonstrated similar mortality rates between the flap and fascia groups (OR: 1.04; 95% CI: 0.45 to 2.41; P = 0.92) (Fig. 2A). A Funnel plot of the log odds ratio against the standard error for these nine studies demonstrated relative asymmetry, suggesting potential publication bias (Fig. 2B).

2.2.2. Length of the hospital stay
All included studies included data on the length of the hospital stay [10,17–27] with only one study [19] favoring flap closure. A meta-analysis of data (835 patients) [10,17,19,22,23,26] revealed no significant mean differences (MD) in the length of hospital stay (Fig. 3).

2.2.3. Feeding parameters
All included studies included data regarding days on TPN, although only five reported means and standard deviations amenable to pooling [10,17,19,22,26]. One study [19] individually favored flap closure. Meta-analysis revealed the time on TPN to be shorter in the flap closure by 3.9 days, but this difference failed to reach statistical significance (MD: −3.97; 95% CI: −8.14 to 0.19; P = 0.06) (Fig. 4A). Machida et al. [19] also demonstrated significantly fewer days of NPO in the flap group. Pooled data from the three studies [10,19,22] reporting this data demonstrated no statistically significant difference (Fig. 4B).
Fig. 1.


<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Dates included</th>
<th>Flap (n)</th>
<th>Fascia (n)</th>
<th>Mortality</th>
<th>LOS</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
<td>No SSD</td>
<td>Days on vent.</td>
</tr>
<tr>
<td>Choi. (2012)</td>
<td>Ret, MC</td>
<td>1999–2010</td>
<td>44</td>
<td>26</td>
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<td>No SSD</td>
<td>N/A</td>
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<td>McNamar. (2011)</td>
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<td>2002–2008</td>
<td>3</td>
<td>5</td>
<td>No SSD</td>
<td>No SSD</td>
<td>N/A</td>
</tr>
<tr>
<td>Riboh. (2009)</td>
<td>Ret, SC</td>
<td>2004–2008</td>
<td>24</td>
<td>19</td>
<td>N/A</td>
<td>No SSD</td>
<td>More in fascia</td>
</tr>
<tr>
<td>Bonnard. (2008)</td>
<td>Ret, SC</td>
<td>2000–2005</td>
<td>11</td>
<td>22</td>
<td>N/A</td>
<td>No SSD</td>
<td>No SSD</td>
</tr>
</tbody>
</table>
2.2.4. Days on mechanical ventilation

Eight studies compared the number of days on ventilation between flap and fascia closure cohorts [10,18,19,23–27], four of which favored the flap cohort [10,23,25,26]. There were 13.4% of flap patients in Emami et al. [10] and 40% of the same cohort in Dariel et al. [18] that completely avoided intubation. For pooled estimates, only studies that presented data in the form of mean and standard deviation were analyzed [10,19,23,26]. With 698 included patients, the meta-analysis demonstrated that the number of ventilation days was 2.6 days less in the flap group when compared to the fascial group. This difference did not reach statistical significance using the random effects model (P = 0.06) but did so when analyzed using the fixed effects model (P = 0.02, data not shown). Considerable heterogeneity was noted across the included studies (I² = 60%) (Fig. 5).

2.2.5. Surgical site infection

Three studies reported the incidence of surgical site infection (SSI) [10,17,18], with two [17,18] favoring the flap group. Schlueter et al. defined SSI as an infection of the skin and/or tissues surrounding the surgical site, characterized by the presence of erythema, localized swelling, and purulent drainage. In both Emami et al. and Dariel et al., SSI was defined by the use of antibiotics to treat wound redness or purulent discharge. Emami et al. [10] (the single largest series) found no significant difference in the SSI incidence between flap and fascia groups. With a total of 758 included patients, the meta-analysis significantly favored the flap group (P = 0.003; Fig. 6A). A subgroup analysis of studies reporting SSI outcomes for flap or fascial closure exclusively after silo placement was also performed [10,17,18]. The pooled analysis for SSI (460 patients) again favored the flap closure group (OR: 0.44; 95% CI: 0.24 to 0.82; P = 0.01) (Fig. 6B).
Table 2
Newcastle Ottawa Scale (NOS) for quality assessment of included studies.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Selection</th>
<th>Comparability of groups</th>
<th>Exposure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4</td>
<td>5</td>
<td>6 7 8</td>
<td></td>
</tr>
<tr>
<td>Schlueter et al. (2015)</td>
<td>* * * *</td>
<td>* * * *</td>
<td></td>
<td>7*</td>
</tr>
<tr>
<td>Emami et al. (2015)</td>
<td>* * * *</td>
<td>* * * *</td>
<td></td>
<td>9*</td>
</tr>
<tr>
<td>Dariel et al. (2015)</td>
<td>* * * *</td>
<td>* * * *</td>
<td></td>
<td>9*</td>
</tr>
<tr>
<td>Machida et al. (2013)</td>
<td>* * * *</td>
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<td></td>
<td>7*</td>
</tr>
<tr>
<td>Choi et al. (2012)</td>
<td>* * * *</td>
<td>* * * *</td>
<td></td>
<td>9*</td>
</tr>
<tr>
<td>Erdogan et al. (2012)</td>
<td>* * * *</td>
<td>* * * *</td>
<td></td>
<td>6*</td>
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<tr>
<td>McNamara et al. (2011)</td>
<td>* * * *</td>
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<td></td>
<td>9*</td>
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<tr>
<td>Orion et al. (2011)</td>
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<tr>
<td>Kandasamy et al. (2010)</td>
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<td>7*</td>
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<tr>
<td>Rao et al. (2009)</td>
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<tr>
<td>Riboh et al. (2009)</td>
<td>* * * *</td>
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<tr>
<td>Bonnard et al. (2008)</td>
<td>* * * *</td>
<td></td>
<td></td>
<td>9*</td>
</tr>
</tbody>
</table>

Selection: 1 = Case definition; 2 = Case representativeness; 3 = Controls selection; 4 = Definition of controls.
Comparability of groups: 5 = Comparability of cases and controls on the basis of the design or analysis.
Exposure: 6 = Ascertainment of exposure; 7 = Same method of ascertainment for cases and controls; 8 = Non-Response rate.
An asterisk indicates that a point has been allotted for this category.

A

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Flap Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Choi 2012</td>
<td>2</td>
<td>44</td>
<td>2 26</td>
<td>17.3%</td>
<td>0.57 [0.08, 4.32]</td>
</tr>
<tr>
<td>Dariel 2015</td>
<td>0</td>
<td>23</td>
<td>1 41</td>
<td>6.7%</td>
<td>0.57 [0.02, 14.68]</td>
</tr>
<tr>
<td>Emami 2015</td>
<td>2</td>
<td>129</td>
<td>4 436</td>
<td>24.2%</td>
<td>1.70 [0.31, 9.39]</td>
</tr>
<tr>
<td>Erdogan 2012</td>
<td>5</td>
<td>11</td>
<td>5 18</td>
<td>28.6%</td>
<td>2.17 [0.45, 10.44]</td>
</tr>
<tr>
<td>Kandasamy 2010</td>
<td>0</td>
<td>16</td>
<td>3 34</td>
<td>7.7%</td>
<td>0.27 [0.01, 5.60]</td>
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<td>Machida 2013</td>
<td>0</td>
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<td>0 10</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>McNamara 2011</td>
<td>0</td>
<td>3</td>
<td>0 5</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Orion 2011</td>
<td>1</td>
<td>52</td>
<td>1 28</td>
<td>8.9%</td>
<td>0.53 [0.03, 8.80]</td>
</tr>
<tr>
<td>Rao 2009</td>
<td>0</td>
<td>11</td>
<td>1 27</td>
<td>6.6%</td>
<td>0.77 [0.03, 20.30]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>294</td>
<td>625</td>
<td>100%</td>
<td>1.04 [0.45, 2.41]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 10 17
Heterogeneity: Tau² = 0.00; Chi² = 2.65, df = 6 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)
2.2.6. Umbilical hernia incidence
Six studies reported the incidence of post-intervention umbilical hernia [18,19,20,23,26,27]. Only studies that reported the median time of follow-up and the percentage of hernias requiring repair were included in the pooled data for meta-analysis [18,20,23,27]. With a total of 247 patients, the incidence of post-intervention umbilical hernia was significantly higher in the flap group ($P = 0.005$). However, significant heterogeneity between studies was evident ($I^2 = 77\%$) (Fig. 7). While the follow-up time in these studies ranged between 168 and 3266 days, the exact time of umbilical hernia repair was not reported in the included studies. Nonetheless, the overall percentage of umbilical hernias that needed repair was significantly higher in the fascia group compared to the flap group (41% vs. 19%; $P = 0.001$) which indicates that the umbilical hernias after flap closure are more likely to close spontaneously.

2.2.7. Markers of resource utilization
Only one study reported data on the mean charges of hospitalization [23], and it showed no significant difference between the flap ($174,000$ US dollars; range: $34,000–$1,681,000) and fascial closure groups ($199,000$ US dollars; range: $35,000–$643,000).
Fig. 4. A: Forest plot of total parenteral nutrition (TPN) days comparing flap and fascia groups. B: Forest plot of Nil Per Os (NPO) days comparing flap and fascia groups.

3. Discussion

While the sutured fascial technique has been the classical method of abdominal defect closure in patients with GS, the flap “sutureless” closure has been increasingly adopted as a viable alternative by a growing number of surgeons for both simple and complex GS [4,8,10]. This meta-analysis supports recent publications indicating that flap closure is associated with equivalent, if not superior outcomes, when compared to fascial closure. Indeed, this analysis reveals that the primary outcome of mortality was equivalent between groups as were several other secondary outcomes, including TPN days, length of hospital stay, and markers of resource utilization. Importantly, however, the true advantage of flap closure was related to a significantly
reduced risk of surgical site infections and a clinically significant reduction of ventilator days for flap closure patients. Finally, a number of patients achieved complete abdominal wall closure without general anesthesia.

Fig. 5. Forest plot of mechanical ventilation days comparing flap and fascia groups.

Fig. 6. A: Forest plot of surgical site infection (SSI) rates comparing flap and fascia groups. B: Forest plot of surgical site infection (SSI) for sub-group of patients underwent the closure after silo reduction comparing flap closure with fascial closure.

The first case series of bedside reduction without general anesthesia in infants with GS was reported by Bianchi [5] in 1998. In this report, Bianchi et al. demonstrated the feasibility of intestinal reduction without anesthesia within a few hours of delivery using only local anesthesia and sutures to place the umbilical cord as a “plug” over the abdominal defect. After concerns were voiced about the associated discomfort of the procedure [28], several modifications to the ‘Bianchi technique’ were adopted until a large series describing a sutureless ward reduction was published in 2001 [6]. Ward reduction was limited to selected cases of
simple GS with the defect partially closed with adhesive strips. Bianchi published a similar case series shortly thereafter, followed by the description by Sandler et al. of a ‘plastic closure’ using a clear, adhesive dressing to secure the umbilical cord within the defect without formal skin or fascial closure [7,9].

The purported advantages of the flap closure include the reduced need for sedation and/or general anesthesia, the avoidance of operating room delay or transfer, and the potential for an improved cosmetic result. In addition, the risk of abdominal compartment syndrome immediately after intestinal reduction and defect closure may theoretically be diminished with the flap technique since signs of increased abdominal pressure can be more easily relieved by removing the closure and (re)placing a silo. Flap closure may also prove to be less costly than traditional operative closure given the potential to avoid operating room costs. While these presumed advantages likely underlie the increasing adoption of flap closure, they have not been well documented to date. Several investigations have evaluated the effectiveness of preformed silos in the closing strategy of patients with GS; [29] this study is the first systematic review that looks specifically at the method rather than the timing of abdominal closure.

While a previous investigation demonstrated no difference in surgical site infections (SSI) when comparing GS closures performed in the operating room versus the neonatal intensive care unit, concerns remain about the potential to increase infections at the site of closure if not performed under optimal conditions in the OR [30]. This meta-analysis revealed a decrease in SSI rates with the sutureless technique when compared to fascial closure. Several caveats require acknowledgement when considering this conclusion: not all flap closures were performed in the NICU and the definition of an SSI was non-standardized across studies. Indeed, most closure sites appear erythematous and may grow skin flora if cultured; the diagnosis of a true infection is, therefore, challenging to make. Nonetheless, fascial cases act as internal controls within each study framework, suggesting that true differences likely exist favoring flap closure. This advantage may be because of the avoidance of surgical trauma to the area, although This meta-analysis also identified a trend towards a reduction in overall ventilator days favoring flap closure (P = 0.06). A point estimate of 2.6 fewer mechanical ventilation days clearly meets the definition of clinical significance and is likely because of the important number of patients who
are not intubated at all. Given the anticipated lack of difference in other short-term outcomes (mortality, length of stay and feeding parameters), this finding represents the greatest inherent advantage of the flap closure. Recent editorials have begun to identify early exposure to general anesthesia as a potential contributor to differences in long-term neurocognitive performance [31]. While the exact magnitude of the neurotoxic effects of general anesthesia is unclear and undergoing intense study [32–34], the call for deferring, delaying or avoiding anesthesia altogether is becoming harder to ignore. Similar to the ALARA (As Low As Reasonably Achievable) principle adopted by radiologists [35], it will not be long before anesthesiologists, pediatricians and neonatologists adopt a similar mantra. Irrespective of some surgeon's current preference to use general anesthesia with flap closure, this technique represents the only reasonable method to close the abdominal defect without general anesthesia.

![Forest plot of post intervention umbilical hernia incidence comparing flap and fascia groups](Image)

**Fig. 7.** Forest plot of post intervention umbilical hernia incidence comparing flap and fascia groups

While a previous single centre study identified that a significant majority of GS patients undergoing flap closure will develop an umbilical hernia [27], additional studies have reported that many ultimately do not require operative repair [7,20]. The results of this meta-analysis confirmed this finding. Importantly, however, our analysis demonstrated that the percentage of hernias that had to be repaired after flap closure was significantly lower than their counterparts after fascial closure. The exact mechanisms for this are unclear but it may be related to iatrogenic abdominal wall trauma inherent in fascial closure, rendering any subsequent hernia more akin to an incisional hernia and, therefore further mechanistic studies are required to clarify this issue.
unlikely to close spontaneously. This contrasts with the flap closure where the umbilical fascia is undamaged and may behave more like a typical umbilical hernia that often closes without intervention. Even if a delayed umbilical hernia repair is required, the best existing evidence regarding neurotoxicity after anesthesia suggests that procedures after the age of 2–3 (when an umbilical hernia is typically performed), is less harmful [36,37].

The extensive literature search of 10 databases, the inclusion of non-English literature, the structured methodology and the appraisal of included studies are among the strengths of this review. However, qualitative analysis of these studies demonstrates heterogeneity in patient selection (simple vs. complex GS patients), the timing of repair (immediate or after silo), and reported outcomes. The limitations of this review reflect the paucity of published comparative studies on the reviewed topic, the relatively low level of existing evidence, as well as a small sample size for most of the included studies. In addition, the identification of potential publication bias suggests that further, preferably prospective, investigations on the subject are required.

4. Conclusion
Available evidence justifies the increasing use of flap closure as a method to close the abdominal defect in patients with GS. It results in comparable short-term outcomes when compared to fascial closure, and obviates the need for general anesthesia in some cases. It also appears to reduce the rate of surgical site infections, and while the incidence of umbilical hernias is unsurprisingly higher, these may not need operative correction. The results of this review are limited by the quality of included studies and further prospective evidence is needed to clarify the role of flap closure for patients with gastroschisis.

Acknowledgments
We are indebted to Elena Guadagno, the librarian at the Montreal Children's Hospital for her help with the literature search. We also recognize Dr. Robert A. Cusick the corresponding author.
at University of Nebraska Medical Center, Omaha, NE, USA for his cooperation by providing unpublished data from one of the included studies in this review [17].
References


Appendix: Search Strategy (PubMed)

PubMed [NLM] (November 18, 2014)

Search Query

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#51  #46 NOT #49

#49  #45 NOT #48

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#47 slugs*[Title/Abstract]) OR pigeon*[Title/Abstract]) OR pigeons*[Title/Abstract]) OR rabbit*[Title/Abstract]) OR horse*[Title/Abstract]) OR mouse*[Title/Abstract]) OR

— mice*[Title/Abstract]) OR llama*[Title/Abstract]) OR monkey*[Title/Abstract]) OR zebra*[Title/Abstract]) OR dalmation*[Title/Abstract]) OR swine*[Title/Abstract]) OR feline*[Title/Abstract]) OR canine*[Title/Abstract]) OR hamster*[Title/Abstract]) OR
cow*[Title/Abstract]) OR cows*[Title/Abstract]) OR bovine*[Title/Abstract]) OR

#46 #43 AND #44 Filters: Humans #45 #43 AND #44

#44  #3 AND #24

— #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR

#43

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#42

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post-natal*[Transliterated Title]) OR

OR post natal*[Title/Abstract]) OR

perinatal*[Title/Abstract]) OR

peri-natal*[Title/Abstract]) OR peri

natal*[Title/Abstract]) OR preg*n*[Title/Abstract]) OR gestation*[Title/Abstract]) OR

fetus*[Title/Abstract]) OR

fetal*[Title/Abstract]) OR

Search Query
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#39 “Postnatal Care”[Mesh]
#38 “Prenatal Diagnosis”[Mesh]
#37 “Perinatal Care”[Mesh]
#36 “Obstetrics”[Mesh]
#35 “Pregnancy Complications”[Mesh]
#34 “Pregnancy Trimester, Third”[Mesh]
#33 “Pregnancy Trimester, Second”[Mesh]
#32 “Pregnant Women”[Mesh]
#31 “Pregnancy”[Mesh]
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closure*[Title/Abstract]
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(((Vacuum therap*[Title/Abstract]) OR vacuum assist*[Title/Abstract]) OR vacuum closure*[Title/Abstract]
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#2 schis*[Title/Abstract]) OR gastro-
   schies*[Title/Abstract]) OR gastro-
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   schiasis*[Title/Abstract]) OR gastro-
   schisis[Title/Abstract]
#1 “Gastroschisis”[Mesh]
V. Gastrochisis outcomes in North America: a comparison of Canada and the United States

Fouad Youssef, Li Hsia Alicia Cheong, Sherif Emil*, The Canadian Pediatric Surgery Network (CAPSNet)

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Abstract

Background: Care of infants with gastroschisis is centralized in Canada and noncentralized in the United States. We conducted an outcomes comparison between the two countries and analyzed the determinants of such outcomes. Methods: Inpatient mortality and hospital stay of gastroschisis patients from the Canadian Pediatric Surgery Network prospective clinical database for the period 2005–2013 were compared with those from the US Kids Inpatient Database for the period 2003–2012. Potential outcome determinants were analyzed using univariate and multivariate analyses.

Results: A comparison was made between 695 Canadian patients and 5216 American patients. Complex gastroschisis was found in 16.0% and 13.7% of patients in Canada and the US, respectively; P = 0.11. Canada had less premature births, more normal birth weight (BW) infants, less cesarean section deliveries, and more inborn patients compared to the US. For simple gastroschisis, Canadian mortality was lower (1.4% vs. 3.4%; P = .008) and hospital stay was longer (45 ± 38 vs. 41 ± 32 days; P = .04). US mortality correlated strongly with low BW (P = .002) and marginally with cesarean section delivery (P = .08). A longer Canadian hospital stay was associated with lower gestational age (P = 0.01) and western region (P = 0.04), while a longer American hospital stay was associated with medium neonatal intensive care unit gastroschisis volume (P = .03), low socioeconomic status (P = .06), low BW (P = 0.06), and public insurance (P = 0.07). Outcomes for complex gastroschisis did not differ between Canada and the US.

Conclusions: Mortality for simple gastroschisis is higher in the US than in Canada, whereas no outcome differences exist for complex gastroschisis. Outcome determinants are different between the 2 countries.
The American and Canadian health care systems are significantly different. The Canadian system is best described as a single payer system, where all nationals and legal residents are insured under provincial plans, while the American system is a multipayer system with a large number of public and private insurers as well as a significant proportion of uninsured patients. These differences directly influence medical practice, health care delivery, and access to health care [1]. There has been interest in comparing health care outcomes between countries, in an effort to understand how health care systems may influence outcomes [2–4]. The first study comparing a pediatric surgical outcome was recently published, demonstrating that the outcomes of Canadian patients with appendicitis fall in between those of American patients who are noninsured or publicly insured and those who are privately insured [4]. Gastrochisis (GS) is a relatively common congenital anomaly, requiring highly specialized medical and surgical care. The condition has increased in incidence over the last two decades in both Canada and the United States [5,6]. The differences in health care systems and delivery between the two countries are strongly reflected in the care of neonates with this condition. In the United States, GS is treated at multiple different types of hospitals, including free-standing children's hospitals, children's hospitals within general hospitals, and neonatal units within community hospitals. The role of the pediatric surgeon is often dependent on the type of unit. In Canada, on the other hand, treatment of all GS patients occurs only in university free-standing children's hospitals and medical centers with established pediatric surgical services. We compared GS populations in Canada and the US to test the hypothesis that centralization positively influences the outcomes of GS patients.

1. Methods

1.1. Data sources

After obtaining approval from the Montreal Children's Hospital Research Ethics Board (14-420-PED) and from the Canadian Pediatric Surgery Network (CAPSNet) steering committee, two
databases from Canada (CAPSNet) and the United States (Kids' Inpatient Database [KID]) were accessed and analyzed.

1.1.1. Canadian Pediatric Surgery Network

The CAPSNet is a national, disease-specific registry of all GS and congenital diaphragmatic hernia patients born in Canada, which collects prospective data starting from prenatal diagnosis and ending with discharge [7]. Data from CAPSNet were accessed from inception of the database to the last iteration of data, 2005–2013.

1.1.2. Kids' Inpatient Database

The KID is the largest publicly available all-payer pediatric inpatient care database in the United States [8]. Data from KID have been collected every 3 years, starting in 1997 and ending with the last iteration in 2012. The database includes discharges from more than 4100 hospitals in 44 states. We accessed KID data for the years 2003, 2006, 2009, and 2012, in order to obtain a patient cohort overlapping chronologically with the CAPSNet data.

1.2. Patient selection

All registered GS patients in CAPSNet during the period 2005–2013 were included. In the KID, GS patients were identified using an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure code specific to GS repair (54.71). The application of this code to identify GS patients has been previously validated [9]. Patients with unrelated procedure codes were excluded. Patients with missing data from specific fields (eg, gestational age [GA], birth weight [BW]) were excluded from analysis of that variable. Relevant ICD-9 codes were used to identify demographic parameters, complications, and concomitant congenital anomalies.
1.2.1. Risk stratification

The patient cohort of each database was divided into two populations for separate analyses, simple GS and complex GS. Complex GS was defined as GS with one of the following intestinal complications: atresia, necrosis, or perforation. These complications are each tabulated in individual fields in CAPSNet. In KID, the following ICD-9 codes, 751.1, 557.0, and 777.6, were used to identify intestinal atresia, intestinal necrosis, and intestinal perforation, respectively.

1.3. Outcomes and variables of interest

The primary outcomes were inpatient mortality and length of hospital stay, expressed as the mean ± SD. An attempt to assess classic GS secondary outcomes, such as duration of mechanical ventilation or duration of ileus, was unsuccessful due to the limitations of KID. The following demographic data were collected: gender, BW, GA, prevalence of other anomalies, inborn status, and delivery mode. Gestational age and BW were delineated as categorical variables for both countries, as they are provided in KID. Only congenital anomalies of the heart (mitral insufficiency, sub aortic stenosis, cor triatriatum, infundibular pulmonic stenosis, obstructive anomalies of heart not otherwise specified [NOS], coronary artery anomalies NOS, malposition of the heart and cardiac apex, congenital anomaly of heart NOS, and heart disease NOS) and lung (hypoplasia, aplasia, or agenesis) were tabulated, as they have previously been shown to adversely affect GS outcomes [10].

Several potential determinants of primary and secondary outcomes were also analyzed. Birth weight, GA, delivery mode, inborn or outborn status, hospital type (children's vs. nonchildren's), and neonatal intensive care unit (NICU) gastroschisis volume were common factors to both countries. Neonatal intensive care gastroschisis volume was determined by the average of GS cases per year during the study period: low volume (≤3 per year), medium volume (4–8 per year), and high volume (≥9 per year). This classification was adapted from CAPSNet and applied to both countries [11].
Geographic region was analyzed in both countries. Canada was divided into four regions: Quebec, Ontario, western region (Alberta, British Columbia, Manitoba, and Saskatchewan), and Maritimes (New Brunswick, Nova Scotia, Prince Edward Island, and New Foundland). The US was also divided into four regions: Northeast, Midwest, South, and West. Socioeconomic status and insurance status were assessed only for US patients, as Canadian patients all had the same insurance coverage, and socioeconomic status is not a CAPSNet variable. United States Insurance status was divided into three categories: private, public, and noninsured. United States socioeconomic status was reported by the estimated median household income quartiles for residential zip code from the lowest (first) to the highest (fourth) quartiles.

1.4. Statistical analyses

The differences in patient demographics and clinical characteristics between the US and Canada were reported for each category of GS (simple and complex). Categorical variables were tabulated in frequencies by subgroups. Continuous variables were presented using summary statistics (median, mean, and SD) by groups. χ² Test (for categorical variables) or Wilcoxon rank sum test (for continuous variables) was performed to assess homogeneity of relevant characteristics or outcomes between subgroups. All comparisons between groups were carried out using a 2-sided test at an alpha level of 0.05 unless otherwise specified. Median regression analyses were employed to explore the associations between relevant factors (BW, GA, delivery mode, inborn/ outborn, NICU gastroschisis volume, region, hospital type, insurance status, and socioeconomic status), and estimates for regression slope parameters were produced. Since mortality rate was very low in all 4 subpopulations (US simple, US complex, Canada simple, and Canada complex), we used a stepwise model building procedure with a significance level of .30 for entry and .35 for removal of variables, to determine the covariates which were likely associated with mortality in each subgroup. All analyses were performed in SAS 9.3 (SAS Institute Inc., Cary, NC).
2. Results

2.1. Study cohorts

Overall, 695 patients in Canada and 5216 patients in the US met inclusion criteria for the study. Missing data were excluded wherever applicable. The proportion of missing BW and GA data (44.6% and 41.9%, respectively) was high in the American cohort.

2.2. Comparison of Canada and US GS populations

The characteristics of the Canadian and American cohorts are shown in Table 1. In Canada, there were 16 treating hospitals, including 6 (37%), 7 (44%), and 3 (19%) hospitals with low, medium, and high NICU GS volume, respectively. In the US, the number of treating hospitals was 345, including 213 (62%), 100 (29%), and 32 (9%) hospitals with low, medium, and high NICU GS volume, respectively. Of the Canadian hospitals, 7 (44%) of 16 were children's hospitals, whereas 39 (12%) of 345 of the American hospitals that treated GS patients were children's hospitals. Prematurity and low BW were significantly lower in the Canadian cohort. The Canadian cesarean section (c-section) rate was approximately half that of the US, and the proportion of inborn patients was significantly higher in Canada. The percentage of complex GS was comparable between Canada and the US.

2.3. Comparison of Canada and US populations by type of GS

Table 2 shows the outcome differences between the Canadian and US populations, stratified by type of GS. A survival advantage was seen in Canada for the simple GS patients, along with a longer length of stay. No significant differences were found in the complex GS patients between the two countries.
2.4. Univariate analysis

In the Canadian simple GS population, none of the variables tested were significantly different between survivors and nonsurvivors. A longer hospital stay was associated with lower GA (P = .01) and care in the western region of the country (P = .04). In the US, simple GS population, mortality was higher in patients who were delivered by c-section (P < .0001) and born outside the reporting hospital (P < .0002). A longer hospital stay was associated with lower BW (P = .0002) and public insurance (P = .03).

In both the Canadian and US complex GS population, none of the variables demonstrated significant effects on mortality or length of stay.
2.5. Multivariate analysis

Table 3 demonstrates the results of the multiple regression analysis for all 4 cohorts. The influence of GA and western region on hospital stay persisted in the Canadian simple GS cohort. No other effects of any of the variables were found either in simple or complex GS. For simple GS, US mortality correlated strongly with low BW and marginally with C-section delivery. A longer American hospital stay was significantly associated with medium NICU gastroschisis volume and marginally associated with low socioeconomic status, low BW, and public insurance. For complex GS, American mortality correlated with low BW and longer American hospital stay correlated with lower GA.

Discussion

Cross-border outcomes comparisons between Canada and the United States have been a point of interest in several medical fields [2–4]. Our group has recently reported the first outcomes comparison of a pediatric surgical disease, appendicitis, between the two countries [4]. We failed to show an overall advantage in outcomes of this very common condition within the Canadian single payer system, but did show advantages when Canadian patients were compared to US patients with public or no insurance as well as advantages in the youngest patients [4]. In the present study, we aimed to extend this approach to gastroschisis, a common congenital anomaly treated by pediatric surgeons. A recent effort in the United States to evaluate and appropriately designate institutions providing neonatal and pediatric surgical care based on their resources
stems from strong evidence that many neonatal surgical patients are treated in institutions with suboptimal resources [12]. This is largely the product of an environment where tertiary care remains generally decentralized and reimbursed by multiple public and private insurers. The Canadian neonatal surgical care environment provides a very different model, where care is centralized to university children's hospitals and medical centers exclusively and occurs in a relatively homogenous insurance environment that covers all neonates equally. Our primary aim was to investigate whether this difference in health care delivery systems is associated with an overall difference in outcomes. Our secondary aim was to investigate potential outcome determinants relevant to the patient populations and the health care environment in each country.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Multivariate analysis results of determinants of mortality and hospital stay in GS cohorts.</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Canada</td>
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<tr>
<td></td>
<td>Simple GS</td>
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<tr>
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<td>–5.8</td>
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</table>

Abbreviations: CI, Confidence interval; OR, odds ratio; SES, socioeconomic status.

Patient-related variables, the most important of which is the presence or absence of complex GS, defined by concurrent bowel atresia, necrosis, or perforation, clearly have the most significant effect on the outcome of this disease [13–15]. We therefore separated patients in each country into simple and complex categories to remove this major confounding factor.

This study found a higher mortality rate among simple GS patients in the US vs. those in Canada. Although it may be argued that the difference in mortality rates may not be clinically significant, the US rate is more than double that of Canada’s. With modern medical and surgical care, the death of a GS patient without intestinal complications should be a rare event. Interestingly, mortality of simple GS patients in the US correlated quite strongly on univariate analysis and marginally on multivariate analysis, with C-section delivery, which was twice as likely to be used to deliver a GS baby in the US vs. Canada. Previous studies have quite conclusively shown that C-section deliveries do not improve the outcomes of GS patients [16–18]. It is therefore surprising that most GS babies in the US are still delivered by C-section. Our
study strongly suggests an actual disadvantage to C-section delivery and hopefully can stimulate a change in practice patterns.

Two other risk factors for poor outcomes in GS are low BW and prematurity, which were again more prevalent in the US [19–21]. The reason for the difference in demographics between the populations is not clear but may reflect access to prenatal care or other factors not examined in this study. We found a trend toward increased US hospital stay in simple GS patients who were of lower socioeconomic status or publicly insured. Recent CAPSNet studies have shown socioeconomic status not to significantly affect GS outcomes in Canada [22].

In terms of potential health care system determinants, our study was limited by our inability to identify the NICU level in KID. We therefore used NICU GS volume as a potential surrogate for experience of the individual unit. The only effect of volume was an increased hospital stay in US simple GS patients treated at moderate volume NICUs. We also looked at hospital type, hospital of birth, and insurance status. A patient with GS born in Canada or the US may be transferred after birth to another facility due to absence of a birthing center at a receiving free-standing children's hospital. Lack of a prenatal diagnosis or insurance restrictions that dictated a delivery site may have contributed to the higher outborn rate in the US, which correlated with mortality on univariate analysis. Previous studies suggested that outborn status may be associated with adverse outcomes in patients with GS and supported delivery in tertiary care centers [23–25]. We believe this difference may have also influenced the slightly longer length of stay for simple GS patients in Canada, where GS patients are typically discharged home rather than returned to a referring facility to continue their recovery, as sometimes happens in the US. Designation of levels of care may facilitate birth of GS babies at appropriate facilities in the US and decrease the outborn rate. Canadian hospital stay for simple GS patients was longer in the western provinces, which may represent a regional practice variation or longer distances between the treating hospitals and patients’ domiciles [26].

There were no differences in outcomes of complex GS between the two countries. This was not surprising, given that the outcomes of these patients are largely driven by the severity of their bowel insult [14,27]. In addition, it is very likely that the care of these infants in the US almost
exclusively occurs at level III NICUs, a de facto centralization. For the same reason, no health care system factors were shown to influence the outcomes of these patients.

Several limitations should be acknowledged in this study. The two databases used were quite disparate in their comprehensiveness with respect to GS. Whereas CAPSNet is a prospectively acquired, disease-specific, national database, KID, despite its large cohorts, is a general discharge database gathered every three years. A significant amount of data on patient characteristics was missing from KID, as was noted earlier. It also did not allow us to collect accurate data on other interventions, such as closure method, which could have been compared to CAPSNet to examine additional potential outcome determinants. Despite these limitations, we were able to perform the first cross-border comparison of GS patients treated under different health care systems in North America, delineating differences in outcome that may in fact be at least partially influenced by health care delivery and practice patterns.

Acknowledgement
We would like to thank Dr. Xianming Tan of the Biostatistics Core Facility, McGill University Health Centre Research Institute, for providing assistance with the statistical analyses.
References


VI. Determinants of outcomes in patients with simple gastroschisis

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Abstract

Purpose: We analyzed the determinants of outcomes in simple gastroschisis (GS) not complicated by intestinal atresia, perforation, or necrosis.

Methods: All simple GS patients enrolled in a national prospective registry from 2005 to 2013 were studied. Patients below the median for total parenteral nutrition (TPN) duration (26 days) and hospital stay (34 days) were compared to those above. Univariate and multivariate logistic and linear regression analyses were employed using maternal, patient, postnatal, and treatment variables.

Results: Of 700 patients with simple GS, representing 76.8% of all GS patients, 690 (98.6%) survived. TPN was used in 352 (51.6%) and 330 (48.4%) patients for ≤26 and N26 days, respectively. Hospital stay for 356 (51.9%) and 330 (48.1%) infants was ≤34 and N34 days, respectively. Univariate analysis revealed significant differences in several patient, treatment, and postnatal factors. On multivariate analysis, prenatal sonographic bowel dilation, older age at closure, necrotizing enterocolitis, longer mechanical ventilation, and central-line associated bloodstream infection (CLABSI) were independently associated with longer TPN duration and hospital stay, with CLABSI being the strongest predictor.

Conclusions: Prenatal bowel dilation is associated with increased morbidity in simple GS. CLABSI is the strongest predictor of outcomes. Bowel matting is not an independent risk factor.

Gastroschisis (GS) is a congenital anomaly with increasing incidence over the last few decades [1,2]. Although the survival rate for newborns with GS is high, morbidity is still considerable
The role of several potential determinants of outcomes has been assessed in neonates with GS. The most important determinant has been consistently found to be the presence or absence of intestinal complications, namely atresia, necrosis, and perforation. Patients with these complications are classified as complex GS, and have consistently worse outcomes than those without these complications, classified as simple GS [3,4]. Unfortunately, the presence of intestinal complications is a patient-determined factor, amenable to limited manipulation [4,5]. Modifiable treatment factors, such as mode of delivery and method of abdominal closure, have also been studied, but not consistently found to affect outcomes [6,7].

In the absence of intestinal complications, it is not clear why some simple GS patients have worse outcomes than others, with longer bowel dysfunction, typically resulting in a longer hospital stay [6,7]. Candidates for outcome determinants in these patients include gestational age, delivery mode, age at closure, closure method, the degree of bowel matting, necrotizing enterocolitis (NEC), cardiac anomalies, and lung hypoplasia [8,9]. However, risk stratification has focused mostly on predicting mortality, and has typically included both simple and complex gastroschisis [8,9]. This included the gastroschisis prognostic score, or GPS, created using the Canadian Pediatric Surgery Network (CAPSNet) database [9,10].

The goal of our study was to identify factors that influence outcomes in patients with simple GS, using the most recent iteration of the CAPSNet database. We also specifically investigated whether the severity of bowel matting independently predicts increased morbidity.
1. Methods

1.1. Study population

CAPSNet is a prospectively collected database of all patients with GS and congenital diaphragmatic hernia born in Canada [10]. GS patients entered into the database between 2005 and 2013 formed the base cohort. Patients with necrosis, perforation or confirmed atresia were excluded from the analysis.

1.2. Outcomes

The two primary outcomes were duration of TPN and length of hospital stay. Both of these outcomes had a non-normal distribution skewed to the left. The median of each outcome was utilized to create categorical variables for analysis, and in fact resulted in two groups with widely divergent outcomes. The duration of TPN was therefore analyzed as a dichotomous variable using the median duration, 26 days, as a cut off, as well as a continuous variable. Likewise, the length of hospital stay was analyzed as a dichotomous variable using median stay, 34 days, as a cut-off, as well as a continuous variable. The primary outcomes analysis included only survivors to discharge.

NEC was studied both as a secondary outcome, as well as a potential determinant of primary outcomes.

1.3. Independent variables

The independent variables analyzed were classified as maternal variables, patient variables, treatment variables, and postnatal complications. Maternal variables included maternal age, ethnicity (Caucasian, first nations, others), smoking, alcohol consumption, illicit drug use, and delivery mode. Patient variables included gender, gestational age, gestational weight, Apgar score at 1 min, Apgar score at 5 min, the incidence of bowel dilation on the last prenatal ultrasound that reported this information, the degree of bowel matting (none, mild, or severe),
and the presence of a cardiac anomaly. Treatment factors included transfer status (inborn or outborn), success of attempted closure, age at closure, hospital GS volume per year [(low, \( \leq 3 \)), (medium, 3–9), (high, \( \geq 9 \))], duration of mechanical ventilation, and the year of admission (2005–2009 vs. 2010–2014). Postnatal complications included the incidence of central line associated blood stream infection (CLABSI) and the incidence of NEC.

1.4. Analysis of the effect of bowel matting

To further assess the effect of bowel matting, a univariate analysis was performed comparing patients with no or mild mating to those with severe matting.

1.5. Statistical analyses

Thresholds of TPN duration and hospital stay were set at the median for each, 26 days and 34 days, respectively. Infants in study were categorized by their TPN duration, hospital stay, NEC, or severe bowel matting. Maternal, patient, treatment, and complication data were compared between groups. Frequency (percentage), mean (standard deviation) or median (inter quintile range) were reported. Significance across groups was assessed by Pearson's chi square test for categorical variables, and ANOVA or Wilcoxon rank test for continuous variables.

Multivariate logistic analyses were applied for TPN duration and hospital stay to explore associated factors. Odds ratios and 95% confidence intervals (CI) were estimated. General linear regression was used to assess the TPN duration and hospital stay as continuous outcomes, and coefficient (95% CI) was estimated. The use of both logistic regression and linear regression analyses optimized the detection of any potential independent outcome determinants. All analyses were conducted using SAS v.9.2 (SAS Institute Inc., Cary, NC) with significance level 0.05.

1.6. Study approval
The study underwent scientific review and approval by the CAPSNet steering committee. Institutional approval was obtained from the Pediatric Research Ethics Board of the McGill University Health Centre (15–144-MUHC).

2. Results

2.1. Study cohort

During the period of study, a total of 912 patients with GS were prospectively enrolled in the CAPSNet database, with complete data to discharge. Of those, 700 met the inclusion criteria for simple GS, representing 76.8% of all GS patients. 690 (98.6%) patients survived to discharge. Average duration of TPN and hospital stay for the non-survivors was 33.9 ± 50.8, and 36.3 ± 53.3, respectively. Among the 690 survivors, data for TPN duration and hospital stay were available for 682 (98.8%) and 686 (99.4%), respectively. Duration of TPN was 35.1 ± 33.0 days, with a median of 26 days. Hospital stay was 47.0 ± 46.3 days, with a median of 34 days. Twenty-six patients (3.8%) developed NEC. Mechanical ventilation was employed in 653 (94.6%) of patients, for an average of 6.3 ± 5.5 days. The first enteral feed was started at 15.2 ± 11.8 days. Comorbidities at discharge included cholestatic liver disease in 124 (18.0%), gastroesophageal reflux disease in 148 (21.4%), and intestinal failure in 17 (2.5%). Discharge feeding status was full oral feeding in 457 (66.2%), some component of tube feedings in 129 (18.7%), some component of TPN in 86 (12.5%), and unknown in 18 (2.6%).

2.2. Primary outcomes: univariate analyses

The univariate analyses of primary outcomes as dichotomous variables are shown in Table 1. 352 (51.6%) patients at or below the median for TPN duration were on TPN for 18.9 ± 4.9 days, and 330 (48.4%) above the median were on TPN for 52.5 ± 40.6 days. 356 (51.9%) patients at or below the median for hospital stay had a stay of 24.3 ± 6.5 days, and 330 (48.1%) above the
median had a hospital stay of 71.5 ± 57.1 days. None of the maternal variables had a significant effect on outcomes in univariate analysis. There were several patient, treatment, and complication variables significantly associated with worse outcomes, as highlighted in italics in Table 1.

2.3. Primary outcomes: multivariate logistic regression analyses

The multivariate logistic regression analyses of primary outcomes as dichotomous variables are shown in Table 2. Essentially the same variables were found to be independent predictors of both TPN duration and hospital stay. Sonographic bowel dilatation emerged as an independent predictor of morbidity. Severe bowel matting was not an independent predictor of morbidity. Interestingly, moderate versus large hospital volume appeared to confer a small outcome advantage. The complications of CLABSI and NEC had the greatest effects on morbidity.

2.4. Primary outcomes: multivariate linear regression analyses

The multivariate linear regression analyses of primary outcomes as continuous variables showed the following variables to be associated with a longer TPN duration: sonographic bowel dilation [5.01 (0.81–9.21), p = 0.02], severe bowel matting [6.62 (0.08–13.2), p ≤ 0.01], longer ventilation period [1.27 (0.94–1.64), p ≤ 0.01], CLABSI [23.7 (17.7–29.8), p ≤ 0.01], and NEC [27.5 (17.3–37.8), p ≤ 0.01]. The same analysis revealed that the following variables were associated with longer hospital stay: lower gestational age [−2.93 (−4.62–−1.25), p ≤ 0.01], longer ventilation days [2.04 (1.49–2.59), p ≤ 0.01], CLABSI [41.5 (32.8–50.2), p ≤ 0.01], and NEC [21.7 (6.25–37.1), p ≤ 0.01].
2.5. Secondary outcome

The univariate analysis of NEC as a secondary outcome is shown in Table 3. Outborn status, CLABSI, and admission after 2009 were significantly associated with NEC. All three variables persisted as independent predictors of NEC on multivariate logistic regression: outborn status [7.01 (3.05–16.10), p ≤ 0.01], CLABSI [3.11 (1.24–7.83), p = 0.04], and admission after 2009 [3.12 (1.25–7.76), p = 0.01]. Severe matting was not associated with an increased risk of NEC.

Table 1
Univariate analyses of outcomes.

<table>
<thead>
<tr>
<th>Maternal variables</th>
<th>TPN duration</th>
<th>Hospital stay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤26 days (N = 352)</td>
<td>&gt;26 days (N = 330)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.5 ± 4.8</td>
<td>23.2 ± 4.7</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>150 (70.1)</td>
<td>134 (72.8)</td>
</tr>
<tr>
<td>First nations</td>
<td>40 (18.7)</td>
<td>27 (14.7)</td>
</tr>
<tr>
<td>Other</td>
<td>24 (11.2)</td>
<td>23 (12.5)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>108 (30.7)</td>
<td>109 (33.0)</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>17 (4.8)</td>
<td>22 (6.7)</td>
</tr>
<tr>
<td>Illicit drug use, n (%)</td>
<td>54 (15.3)</td>
<td>54 (16.4)</td>
</tr>
<tr>
<td>C-section, n (%)</td>
<td>114 (32.4)</td>
<td>99 (30.6)</td>
</tr>
</tbody>
</table>

| Patient variables |                      |                      | |                      |                      | |
|--------------------|-----------------------|-----------------------| |-----------------------|-----------------------| |
| Male, n (%)        | 190 (54.3) | 167 (50.8) | 0.35 | 190 (53.5) | 169 (51.5) | 0.60 |
| Gestational age (weeks) | 36.3 ± 1.7 | 35.9 ± 2.0 | <0.01 | 36.4 ± 1.5 | 35.8 ± 2.1 | <0.01 |
| Gestational weight (grams) | 2605 ± 486 | 2489 ± 536 | <0.01 | 2622 ± 477 | 2471 ± 536 | <0.01 |
| Apgar, median (IQR) | 8 (6-9) | 8 (5-9) | 0.02 | 8 (6-9) | 8 (5-9) | 0.07 |
| Cord respiration, n (%) | 8 (8-9) | 9 (8-9) | 0.70 | 9 (8-9) | 9 (8-9) | 0.91 |
| Severe bowel matting, n (%) | 24 (6.8) | 35 (10.6) | 0.08 | 23 (6.5) | 36 (10.9) | 0.04 |
| Severe bowel matting, n (%) | 21 (6.0) | 44 (13.3) | <0.01 | 21 (5.9) | 46 (13.9) | <0.01 |

| Treatment variables |                      |                      | |                      |                      | |
|---------------------|-----------------------|-----------------------| |-----------------------|-----------------------| |
| Outborn, n (%)      | 61 (17.3) | 65 (19.7) | 0.43 | 61 (17.1) | 64 (19.4) | 0.44 |
| Attempted closure success, n (%) | 317 (90.1) | 256 (80.6) | <0.01 | 320 (89.9) | 268 (81.2) | <0.01 |
| Age at closure (days) | 1.8 ± 2.8 | 4.0 ± 4.2 | <0.01 | 2.1 ± 2.9 | 3.8 ± 4.2 | <0.01 |
| Mechanical ventilation (days) | 4.6 ± 3.1 | 8.8 ± 6.7 | <0.01 | 4.8 ± 3.0 | 7.5 ± 6.8 | <0.01 |
| Hospital volume     |                      |                      | |                      |                      | |
| Small, n (%)        | 21 (5.9) | 25 (7.6) | 0.29 | 18 (5.1) | 27 (8.2) | 0.29 |
| Medium, n (%)        | 152 (43.1) | 124 (37.6) | 0.29 | 159 (44.7) | 119 (36.1) | 0.29 |
| Large, n (%)         | 179 (51.0) | 181 (54.8) |      | 179 (50.3) | 184 (55.7) |      |
| Year of treatment, n (%) | 0.21 | 0.21 |      | 0.21 | 0.21 |      |
| 2005 to 2006         | 188 (53.4) | 192 (58.2) |      | 191 (53.7) | 188 (57.0) |      |
| 2010 to 2015         | 164 (46.6) | 138 (41.8) |      | 165 (46.3) | 142 (43.0) |      |
| Complications        |                      |                      | |                      |                      | |
| CLABSI, n (%)        | 15 (4.3) | 21 (5.7) | <0.01 | 15 (4.2) | 22 (6.7) | <0.01 |
| NEC, n (%)           | 6 (1.7) | 17 (5.3) | 0.01 | 7 (2.0) | 17 (5.3) | 0.02 |

IQR, interquartile range; CLABSI, central line associated blood stream infection; NEC, necrotizing enterocolitis.
2.6. Analysis of the effect of bowel matting

Table 4 shows the results of the univariate analysis of the simple GS cohorts with no or mild bowel matting compared to the cohort with severe bowel matting. In this analysis, severe bowel matting was associated with male gender, less successful and delayed abdominal closures, and longer ventilation period. An association with CLABSI closely approached statistical significance. Severe matting was associated with worse primary outcomes, namely longer TPN duration, and longer hospital stay.

![Table 4](image)

Table 2
Multivariate logistic regression analyses of outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPN duration &gt; 26 days odds ratio (95% CI), P</th>
<th>Hospital stay &gt; 34 days odds ratio (95% CI), P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower gestational age</td>
<td>1.13 (0.99–1.31), 0.06</td>
<td>1.18 (1.03–1.34), 0.01</td>
</tr>
<tr>
<td>Sonographic bowel dilation</td>
<td>2.06 (1.31–3.24), &lt;0.01</td>
<td>1.79 (1.16–2.75), 0.01</td>
</tr>
<tr>
<td>Older age at closure</td>
<td>1.13 (1.05–1.21), &lt;0.01</td>
<td>1.10 (1.03–1.17), 0.01</td>
</tr>
<tr>
<td>Longer mechanical ventilation</td>
<td>1.17 (1.10–1.25), &lt;0.01</td>
<td>1.15 (1.09–1.22), &lt;0.01</td>
</tr>
<tr>
<td>Hospital volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small vs. high</td>
<td>1.27 (0.53–3.02), 0.59</td>
<td>1.37 (0.60–3.14), 0.46</td>
</tr>
<tr>
<td>Medium vs. high</td>
<td>0.59 (0.38–0.92), 0.02</td>
<td>0.61 (0.40–0.93), 0.02</td>
</tr>
<tr>
<td>CLABSI</td>
<td>8.03 (3.59–17.96), &lt;0.01</td>
<td>8.66 (3.96–18.91), &lt;0.01</td>
</tr>
<tr>
<td>NEC</td>
<td>3.49 (1.10–11.65), 0.04</td>
<td>3.65 (1.09–11.90), 0.03</td>
</tr>
</tbody>
</table>

CI, confidence interval; CLABSI, central line associated blood stream infection; NEC, necrotizing enterocolitis.

3. Discussion

The current study once again points to the high survival rate of patients with GS, one of the triumphs of modern neonatal medicine and surgery in high-income countries [11,12]. In fact, mortality of patients with simple GS is now consistently in the low single digits in high resource settings, a level that does not allow mortality to be studied as a primary outcome [13]. However, this high survival rate is still accompanied by significant morbidity and very high resource utilization [14]. As seen in this most recent analysis of the CAPSNet data, approximately 20% of patients with simple GS are discharged with cholestasis or gastroesophageal reflux disease. Some type of enteral or parenteral nutritional support is required in one third of patients. TPN
support and hospital stay, because of intestinal failure, last a median of 26 days and 34 days, respectively.

Risk stratification in gastroschisis has essentially two goals. The first goal is to identify prenatal or neonatal patient features that allow prognostication of outcome, in order to appropriately counsel parents and anticipate resource utilization. The second is to identify factors that may be

Table 3
Univariate analysis of NEC.

<table>
<thead>
<tr>
<th></th>
<th>NEC (N = 26)</th>
<th>No NEC (N = 656)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maternal variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.4 ± 3.6</td>
<td>23.4 ± 4.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
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<td>0.33</td>
</tr>
<tr>
<td>Caucasian</td>
<td>13 (81.3)</td>
<td>277 (71.6)</td>
<td></td>
</tr>
<tr>
<td>First nations</td>
<td>3 (18.7)</td>
<td>63 (16.3)</td>
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<tr>
<td>Other</td>
<td>0 (0)</td>
<td>47 (12.1)</td>
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<tr>
<td>Smoking, n (%)</td>
<td>10 (38.5)</td>
<td>214 (32.6)</td>
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</tr>
<tr>
<td>Alcohol consumption, n (%)</td>
<td>3 (11.5)</td>
<td>103 (15.7)</td>
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</tr>
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<td>Illicit drug use, n (%)</td>
<td>7 (26.9)</td>
<td>208 (31.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>C-section, n (%)</td>
<td>7 (28.0)</td>
<td>208 (31.8)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Patient variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>10 (38.5)</td>
<td>351 (53.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>35.9 ± 1.9</td>
<td>36.1 ± 1.8</td>
<td>0.53</td>
</tr>
<tr>
<td>Gestational weight (grams)</td>
<td>2413 ± 457</td>
<td>2548 ± 517</td>
<td>0.19</td>
</tr>
<tr>
<td>Apgar 1, median (IQR)</td>
<td>8 (5.8)</td>
<td>8 (6.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Apgar 5, median (IQR)</td>
<td>9 (8.9)</td>
<td>9 (8.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>Bowel dilatation, n (%)</td>
<td>14 (63.6)</td>
<td>394 (69.1)</td>
<td>0.59</td>
</tr>
<tr>
<td>Cardiac anomaly, n (%)</td>
<td>2 (7.7)</td>
<td>58 (8.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Severe bowel matting, n (%)</td>
<td>1 (3.9)</td>
<td>66 (10.1)</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Treatment variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outborn, n (%)</td>
<td>16 (61.5)</td>
<td>105 (16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Attempted closure success, n (%)</td>
<td>24 (92.3)</td>
<td>561 (85.5)</td>
<td>0.56</td>
</tr>
<tr>
<td>Age at closure (days)</td>
<td>3.5 ± 3.6</td>
<td>2.9 ± 3.7</td>
<td>0.37</td>
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<tr>
<td>Mechanical ventilation (days)</td>
<td>8.4 ± 7.2</td>
<td>6.4 ± 5.9</td>
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<td>Hospital volume</td>
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<tr>
<td>Small, n (%)</td>
<td>1 (3.9)</td>
<td>47 (7.2)</td>
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<tr>
<td>Medium, n (%)</td>
<td>7 (26.9)</td>
<td>262 (39.9)</td>
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<tr>
<td>Large, n (%)</td>
<td>18 (69.2)</td>
<td>347 (52.9)</td>
<td></td>
</tr>
<tr>
<td>Year of treatment, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>2005 to 2009</td>
<td>7 (26.9)</td>
<td>373 (56.9)</td>
<td></td>
</tr>
<tr>
<td>2010 to 2014</td>
<td>19 (73.1)</td>
<td>283 (43.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLABSI, n (%)</td>
<td>8 (30.8)</td>
<td>79 (12.0)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

IQR, interquartile range; CLABSI, central line associated blood stream infection; NEC, necrotizing enterocolitis.
amenable to intervention or manipulation in order to improve outcomes. Most risk stratification studies have focused on separating patients with complex gastroschisis, those with bowel ischemia or volvulus resulting in atresia, necrosis, or perforation, from the remainder of GS patients [3,8,9,15]. It has been shown repeatedly that these patients have inferior outcomes, when compared to their counterparts without intestinal complications. However, they represent only 10–25% of all GS patients, their outcomes are largely determined by the degree of bowel insult, and there are limited opportunities for medical or surgical interventions that may improve these outcomes [3–5,13]. The majority of GS patients fall in the simple category. It is unclear what independently predicts outcome in these patients, and what opportunities exist for medical interventions that may improve outcomes. Candidates for prognostic variables have included the degree of bowel matting, as well as comorbidities such as pulmonary hypoplasia or congenital cardiac anomalies [8,9]. Previous studies from regional and national collaborative groups have not shown that variability in surgical practices, such as method or timing of closure, have a significant effect on outcomes [6,7]. The current study is one of few that have specifically targeted patients with simple GS, in order to elucidate the effect of maternal factors, patient factors, treatment factors, and postnatal events, on the overall outcomes of these patients.

In this study, outcomes were not dependent on any maternal variables, a finding previously reported in GS [16]. On univariate analysis, lower gestational age and weight, lower 1-min APGAR, prenatal sonographic bowel dilatation, and severe bowel matting, were all associated with longer TPN duration, longer hospital stay, or both. The coexistence of a cardiac anomaly was marginally associated with worse outcomes. Of all these patient factors, only prenatal sonographic dilation persisted as an independent predictor of both longer TPN duration and hospital stay. Multiple studies have looked at prenatal sonographic findings, including amniotic volume, intra and extra abdominal bowel dilation, stomach dilation or herniation, and intestinal wall thickening as possible predictors of complex GS [17–20]. The most recent data indicate that third trimester intraabdominal bowel dilation may be the most reliable predictor of complex GS, despite limited sensitivity, specificity, and predictive values [17–20]. We are not aware of any studies that have looked at the value of prenatal US, specifically bowel dilation, in predicting morbidity in patients with simple GS. The results reported here should prompt a prospective validation of this variable.
Treatment variables, including earlier closure, shorter period of mechanical ventilation, and medium hospital volume all were independently associated with better outcomes in our study, although the magnitude of the improvement was quite modest for each. The issue of GS hospital volume has been previously looked at in CAPSNet and was not found to influence outcome [6].
Recent data from a state wide California database showed a survival advantage, and a nearly significant shorter hospital stay, in high volume hospitals [21]. Interestingly, in the present study, the best outcomes were realized in medium volume (3–8 GS cases per year) hospitals, not in those with the highest volume. Approximately one third of Canadian centers are designated as high-volume centers (≥ 9 cases per year) in CAPSNet.

The largest effects on outcomes by far were the two post-natal infectious complications, NEC and CLABSI, with the latter showing the largest effect in logistic regression analysis. Although longer TPN duration and hospital stay may themselves predispose to CLABSI, it is highly likely that the infectious complications in fact caused the prolonged TPN dependence and hospitalization. The deleterious effect of infectious complications, including CLABSI, in patients with any form of GS has recently been reported [22]. This may represent one of the few opportunities to improve outcomes through meticulous placement and care of central venous lines, and their removal as soon as possible [23,24]. In our study, there was an 8-day difference between the median TPN duration and the median hospital stay. Since the main indication for a central venous line in GS patients is TPN, there is an opportunity to remove the source of CLABSI during a significant portion of the patient's NICU stay.

We found the occurrence of NEC in a simple GS patient to independently predict worse outcomes. Previous reports indicated that neonates with GS are at a higher risk of NEC [25,26]. Patients with complex GS often have a global ischemic insult to the intestine that may increase their risk of NEC. However, it is not known what disposes patients with simple GS to NEC. We therefore studied NEC as both a prognostic variable, and a secondary outcome. We could not identify any maternal or patient variables associated with NEC. The epidemiology of NEC in GS is therefore different from that in the general neonatal population, and is not related to prematurity, low birth weight, or cardiac anomalies. The three factors associated with increased incidence of NEC on univariate and multivariate analyses were outborn status, admission after 2009, and CLABSI. The latter is most likely a result of NEC as an infectious source, and not an etiologic factor for the disease. Outborn status and transfer may expose the patient to more diverse flora early in life, and certainly prolongs the time to definitive bowel coverage. Recent
studies have shown outcome disadvantages associated with transfer of GS patients for definitive care [13,27,28]. This new finding of higher rates of NEC in outborn GS patients strengthens the call for delivery of GS infants in mother–child centers that possess appropriate resources, whenever possible. We were surprised to find an increased incidence of NEC in GS patients during the last 4 years of the study, as there is no evidence of increased NEC incidence in Canadian neonates during the past 5 years. This may be because of more aggressive feeding practices in patients with simple GS, but it is an observation that requires further monitoring.

The gastroschisis prognostic score (GPS) is one of the few grading systems that has been prospectively validated as a prognostic indicator of mortality and morbidity for the entire spectrum of gastroschisis [9]. Three of the four components of the score, atresia, necrosis, and perforation, are not applicable to patients with simple GS. The only applicable component, matting, is scored as 0, 1, or 4 for patients with no, mild, or severe matting, respectively [9]. In the creation of the GPS, severe matting was identified as an independent predictor of morbidity [9]. We were therefore interested in specifically investigating this patient-defined factor's ability to continue predicting outcome. Although severe matting occurred twice as often in patients above the median for TPN duration and hospital stay, as those below, and was statistically significant in univariate analysis, it was not found to be predictive of longer TPN duration, longer hospital stay, or NEC incidence in multivariate logistic regression analysis. A weak association with longer TPN duration, but not hospital stay, was identified on linear regression analysis. A univariate analysis separating patients into two groups, no or mild matting versus severe matting, found that those with severe matting were more likely to fail attempted primary closure, achieve closure at an older age, and require longer mechanical ventilation. These same factors were found to independently increase TPN duration and length of stay. A higher incidence of CLABSI, approaching statistical significance was also found in those with severe matting. Although severe matting cannot be considered an independent risk factor based on our results, it likely exerts its effects through resulting in more difficult closure, longer ventilator days, and increased infectious complications. Moreover, the statistical methods used here are different from those used by Cowan et al., which were focused on developing and validating a weighted scale, without controlling for treatment variables or complications [9]. In addition, our
current study contains almost twice as many patients as the original data set used to develop the GPS [9].

Our study has several limitations. We are unable to report the intermediate or long-term morbidity of simple GS, as post discharge data are not included in CAPSNet. There are several fields in CAPSNet for prenatal US findings. We did not use any specific cutoff for bowel diameter, and only studied prenatal sonographic dilatation as a binary variable. We did not investigate the details of CLABSI to examine if the timing, type, method of placement, or duration of central venous lines contributed to morbidity. Despite these limitations, the study suggests an association between prenatal sonographic bowel dilatation and postnatal intestinal function in patients with simple GS and establishes the infectious complications of NEC and CLABSI as the strongest determinants of outcomes. Vigilance and meticulous care to decrease these complications may provide rare opportunities to improve outcomes in this patient population.

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References


VIII. Conclusion

Several conclusions can be drawn from the studies included in this thesis regarding the time of delivery, the best method to close the abdominal defect, the outcomes of GS patients in North America and the determinants of outcomes in patients with simple GS.

Firstly, although the evidence is still conflicting, our work argues against the practice of inducing the delivery in pregnancies complicated with GS aiming to protect the exposed bowel from the contents of the amniotic fluid. Actually, the percentage of patients with severe bowel matting decreases as the pregnancy continues. There is more than one factor contributing to the incidence of bowel damage, and most likely the exposure to the amniotic fluid is not one of them. Conversely, previous studies showed improvement in the outcomes in patients who underwent induction compared to patients who had spontaneous delivery, this proposed improvement misled the practice and gave the impression that the induction itself improved the outcomes. Indeed, this can be explained by the fact that bowel matting and GPS score reflect a fetus in distress that will eventually lead to spontaneous delivery before the induction.

Secondly, our study justifies the increasing adoption of umbilical flap closure as the simplest and most cost-effective method to close the abdominal defect in patients with GS. Flap closure showed comparable outcomes as opposed to the classical fascial closure in mortality, TPN days, the length of hospital stay and resource utilization. Of note, flap closure showed significantly less surgical site infection rate and clinically significant reduction in ventilator days. The most inherent benefit of flap closure is the ability to close the abdominal defect without the need to expose the neonate to general anesthesia.

Thirdly, our results showed that the rate of the C-section use to deliver GS babies in the United States of America is more than double of that Canada’s. This use correlated strongly in univariate analysis and marginally in multivariate analysis as a determinant of mortality in the cohort of simple GS patients in the US. The other two determinants of poor outcomes are low birth weight and prematurity which were also more prevalent in the US. While simple GS outcomes were
better in Canada compared to the United States, the outcomes of complex GS cohorts in the two countries showed comparable results.

Finally, our work demonstrated that in patients with simple GS no maternal variables affected the outcomes, prenatal sonographic bowel dilatation persisted as independent factor for longer TPN period and length of stay, CLABSI had the largest effect on outcomes in patients with simple GS and this latter conclusion presents a unique opportunity to improve the outcomes in the cohort of simple GS patients.

The management of gastroschisis, like that of many other uncommon congenital anomalies, remains controversial in many aspects. Large multicenter cohort studies are sometimes the only way to gather relevant information that allows confirmation of current practices or changes according to best evidence. In this thesis, CAPSNet enabled us to draw some conclusions on various aspects of both prenatal and postnatal treatment of GS, but some of the controversies will persist and many other areas deserve exploration.