ABSTRACT

Objective

In infants with gastroschisis, outcomes were compared between those where operative reduction and fascial closure were attempted ≤24 hours of age(PC), and those who underwent planned closure of their defect >24 hours of age following staged reduction with a pre-formed silo(SR).

Summary Background Data

Inadequate evidence exists to determine how best to treat infants with gastroschisis.

Methods

A secondary analysis was conducted of data collected 2006-2008 using the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System, and 2005-2016 using the Canadian Pediatric Surgery Network.

28-day outcomes were compared between infants undergoing PC and SR. Primary outcome was number of gastrointestinal complications. Interactions were investigated between infant characteristics and treatment to determine whether intervention effect varied in sub-groups of infants.

Results

Data from 341 British infants(27%) and 927 Canadian infants(73%) were used. 671 infants(42%) underwent PC and 597(37%) underwent SR. The effect of SR on outcome varied according to the presence/absence of intestinal perforation, intestinal matting and intestinal necrosis. In infants without these features, SR was associated with fewer gastrointestinal complications[aIRR 0.25(95% CI 0.09-0.67,p=0.006)], more operations[aIRR 1.40(95% CI 1.22-1.60,p<0.001)], more days PN[aIRR 1.08(95% CI 1.03-1.13,p<0.001)], and a higher infection risk[aOR 2.06(95% CI 1.10-3.87,p=0.025)]. In infants with these features, SR was associated with a greater number of operations[aIRR 1.30(95% CI 1.17–1.45,p<0.001)], and more days PN[aIRR 1.06(95% CI 1.02-1.10,p=0.003)].

Conclusions

In infants without intestinal perforation, matting or necrosis, the benefits of SR outweigh its drawbacks. In infants with these features, the opposite is true. Treatment choice should be based upon these features.

Management of gastroschisis: Results from the NETS^{2G} study, a joint British, Irish and Canadian prospective cohort study of 1268 infants

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Running Head: Decision making when treating gastroschisis

MINI-ABSTRACT

A joint British, Irish and Canadian cohort study was conducted in order to compare outcomes following common treatments for infants born with gastroschisis. Prospectively collected data from 1268 infants were included in the study. Based upon this data, we propose that infants ***without*** intestinal perforation, necrosis or matting at presentation should be treated using pre-formed silo placement, staged reduction and delayed closure, whilst infants ***with*** any of these features should undergo an examination under general anaesthetic, with primary closure performed if possible.

ABSTRACT

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In infants with gastroschisis, outcomes were compared between those where operative reduction and fascial closure were attempted ≤24 hours of age(PC), and those who underwent planned closure of their defect >24 hours of age following staged reduction with a pre-formed silo(SR).

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Data from 341 British and Irish infants(27%) and 927 Canadian infants(73%) were used. 671 infants(42%) underwent PC and 597(37%) underwent SR. The effect of SR on outcome varied according to the presence/absence of intestinal perforation, intestinal matting and intestinal necrosis. In infants without these features, SR was associated with fewer gastrointestinal complications[aIRR 0.25(95% CI 0.09-0.67,p=0.006)], more operations[aIRR 1.40(95% CI 1.22-1.60,p<0.001)], more days PN[aIRR 1.08(95% CI 1.03-1.13,p<0.001)], and a higher infection risk[aOR 2.06(95% CI 1.10-3.87,p=0.025)]. In infants with these features, SR was associated with a greater number of operations[aIRR 1.30(95% CI 1.17–1.45,p<0.001)], and more days PN[aIRR 1.06(95% CI 1.02-1.10,p=0.003)].

Conclusions

In infants without intestinal perforation, matting or necrosis, the benefits of SR outweigh its drawbacks. In infants with these features, the opposite is true. Treatment choice should be based upon these features.

INTRODUCTION

Affecting approximately 1 per 3000 live-births [1] in the British Isles, the congenital abdominal wall defect known as gastroschisis is one of the most common neonatal conditions managed by paediatric surgeons. Its aetiology is unknown, however there is widespread epidemiologic evidence of increased prevalence across international jurisdictions over the last 20 years[3]. It is characterised by early gestational herniation of the abdominal organs through a paraumbilical defect, almost always to right of umbilical cord. Clinical outcomes are influenced by the severity of injury incurred by the exposed fetal intestine and features of "complex" gastroschisis include the development of intestinal necrosis, perforation and atresia which increase the risk of short and long term morbidity and mortality[2].

In 2011, a National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) review of the organisational and clinical aspects of children's surgery in the UK highlighted two key findings. Firstly, when necrotising enterocolitis was excluded, infants who died under the care of paediatric surgeons had most commonly undergone surgery for gastroschisis, exomphalos or malrotation[4, 5]. Secondly, two of the drivers for outcomes not being as good as they could be in key paediatric surgical conditions were difficulties and delays in the surgical decision-making process[5]. Such difficulties and delays stemmed in part from the lack of robust evidence that was available to support surgeons in their decision-making, and one condition where this is likely to be impacting outcomes, is gastroschisis[6, 7].

In high income countries, the initial management of infants born with gastroschisis involves nasogastric decompression, antibiotics, intravenous fluid management, and prevention of hypothermia and evaporative fluid loss by bowel protection. Each of these steps is relatively uniformly performed regardless of where or by whom the infant is treated. There is, however, significant variation in how the eviscerated abdominal contents are reduced and the abdominal wall defect closed. The two most commonly used reduction and closure strategies are operative primary fascial closure (PC), and pre-formed silo placement with staged reduction and delayed closure (SR) [1, 8].

With PC, the abdominal contents are reduced on day one of life under a general anaesthetic, before the abdominal wall defect is closed using fascial sutures. In SR, the abdominal contents are placed in a pre-formed, spring-loaded, silastic silo, the volume of which is reduced over several days in order to gradually return the intestines to the abdominal cavity. Silos can be placed and reduced in volume on the Neonatal Intensive Care Unit (NICU) without requiring general anaesthetic. Once the abdominal contents are fully reduced, the abdominal wall defect can then either be closed under general anaesthetic using fascial sutures, or at the cot-side using a suture-less skin only closure. The final, less commonly used form of reduction and closure is ward-based reduction and sutureless closure, in which the abdominal contents are reduced on day one of life without general anaesthetic, and a skin only closure achieved using steri-strips. Only one randomised controlled trial has been attempted comparing operative management strategies for infants born with gastroschisis, and whilst this showed no difference in

ventilator days between the treatments compared, PC and SR, the study failed to recruit to target and was therefore under-powered to detect any differences [9].

The existing evidence-base comparing reduction and closure strategies for infants with gastroschisis is limited by the small size and retrospective nature of the majority of conducted studies, as well as two factors relating to outcome selection. Firstly, there is significant variation in the outcomes investigated by different studies, thereby preventing meta-analysis. Secondly, many of the outcomes investigated by studies, such as time to first feed, and number of transfusions, aren't relevant to clinical decision-making[10]. In order to address issues related to outcome selection, a gastroschisis core outcome set (COS) identifying the eight outcomes deemed most important in determining whether treatment of a child with gastroschisis has been successful, was recently developed[11]. All studies comparing interventions for infants with gastroschisis should now, as a minimum, report the outcomes included in this COS.

In order to improve the evidence-base supporting treatment of infants born with gastroschisis, the overall aim of this work was to investigate whether it was possible to use existing prospectively collected data to identify which infants with gastroschisis should be treated using each of the two most common surgical strategies, PC and SR.

METHODS

Research questions

In order to determine when to use PC and when to use SR, two research questions were addressed:

1. Are there specific characteristics that can be used to determine which reduction and closure strategy should be used for a particular infant?
2. Do the eight outcomes of importance identified in the previously developed gastroschisis core outcome set differ at 28 days of age between infants treated using PC, and infants treated using SR?

Summary

This study comprised a secondary analysis of data collected prospectively by three population-based systems, the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS)[1], the Canadian Pediatric Surgery Network (CAPSNet)[12], and the Canadian Neonatal Network (CNN)[13].

Data collection

Between October 2006 and March 2008, a British and Irish cohort study describing outcomes at 28 days of age for children born with gastroschisis was conducted using the BAPS-CASS infrastructure[1], and from May 2005 onwards, CAPSNet collected demographic, early management, operative and pre-discharge outcomes data for all infants diagnosed with gastroschisis in Canada. Infants

whose gastroschisis data were collected through CAPSNet also had data relating to any NICU admissions collected through the CNN. Data relating to all live-born infants diagnosed with gastroschisis in Canada between May 2005 and December 2016 were extracted from the CAPSNet/CNN databases and merged with data collected during the BAPS-CASS cohort study. Data collection methodology, duplicate checking and chasing of missing data have been described elsewhere [1, 12, 13]. Further details of the database merging strategy, variable definitions, outcomes where direct equivalence did not exist, and sensitivity analyses conducted to investigate the effect of the variable mapping process are described in supplementary materials 1-5. The conducted sensitivity analyses demonstrated that different variable mapping strategies did not affect the studies conclusions.

Interventions

Infants whose reduction and closure strategy did not meet one of the following definitions of PC or SR were excluded from the analysis. Intention to treat analyses were used throughout, such that all infants where PC was attempted were analysed in this group even if closure was unsuccessful, due for example to raised intra-abdominal pressure or abdomino-visceral disproportion, and a silo, either pre-formed or custom (i.e. fashioned from silastic sheeting and sutured to the defect margins), was placed instead.

CAPSNet definitions

PC was defined as intended primary reduction of the eviscerated abdominal contents, with the first attempted reduction occurring within a day of birth, and sutured fascial closure being attempted. If the closure technique was unknown, the surgeon's intent to suture the fascia was assumed if the reduction and closure took place with an intubated or anaesthetised infant.

SR was defined as use of a silo to facilitate delayed closure, with closure taking place more than one day after birth. Where the primary intention was to facilitate staged reduction through use of a silo, and the type of silo was not known, the silo was assumed to be a pre-formed, spring loaded silo as opposed to a custom silo. This is because standard practice across Canada is to only use custom silos as a salvage operation where PC or use of a pre-formed silo has not been possible. It is therefore highly unlikely that any custom silos were used in cases where staged reduction was the intended treatment strategy.

BAPS-CASS definitions

For infants whose data were collected in the BAPS-CASS dataset, the first attempted reduction and closure strategy was classified as per the treating surgeon.

Outcome definition

Number of severe gastrointestinal complications in the first 28 days of life was investigated as the primary outcome. This was defined as per the recently

developed NETS[1G] gastroschisis COS[11] to include intestinal perforation (identified after treatment), unplanned intestinal resection regardless of amount of bowel removed or the indication for the resection, mechanical intestinal obstruction requiring laparotomy, abdominal compartment syndrome, and enterocolitis. For infants treated in Canada, abdominal compartment syndrome was defined as '*an increase in intra-abdominal pressure requiring surgery to relieve pressure*,' whilst for infants treated in Britain and Ireland, it was defined as per the treating clinician. Enterocolitis for both sets of infants was defined as per the treating clinician.

The secondary outcomes investigated were:

- Number of operations, including only;
    - Any procedure carried out under a general anaesthetic;
    - Any central venous catheter (including PICC line) insertion carried out without a general anaesthetic;
    - Any abdominal procedure, including placement of a silo, replacement of a silo, and sutureless abdominal wall closure carried out without general anaesthetic, but; ***Excluding*** all episodes of silo volume reduction unless carried out under a general anaesthetic
- Number of days of parenteral nutrition (PN) use
- Diagnosis of one or more episode of infection
- Number of episodes of infection
- Z-score for weight and z-score for head circumference,
- Mortality
- Liver disease.

Using the available data, it was not possible to apply a single definition of liver disease uniformly for both British and Irish, and Canadian infants, and therefore, in order to present the most severe estimate of the rate of liver disease, an infant was deemed to have been diagnosed with liver disease if they met the case definition for the study in which their data were originally used. Liver disease is defined by CAPSNet as two or more consecutive measurements of 50 μmol/l or greater of conjugated bilirubin over a period of at least 14 days at any point in the hospital stay, with no documented bacteremia over that time period. In the original BAPS-CASS study however, liver disease was diagnosed at the discretion of the treating clinician. Data relating to growth outcomes and number of episodes of infection were only collected for Canadian infants.

Statistical analysis

Propensity score calculation

Propensity scores predicting an infant's probability of being treated using a particular reduction and closure strategy were calculated using logistic regression. The characteristics used to develop the propensity score were gestational age at birth, birth weight, weight <10th centile for gestational age at birth, year of birth, country of treatment, transfer in to a surgical centre, antenatal diagnosis, gender, presence of an additional chromosomal or structural anomaly, intestinal necrosis, intestinal atresia, intestinal perforation, intestinal matting,

Apgar score at five minutes, and the composite variable, 'complex' gastroschisis, as per the definition by Molik et al[2].

Additional chromosomal or structural anomalies excluded those that were likely to be directly associated with evisceration of the abdominal contents, including intestinal atresia and undescended testes. Single minor anomalies such as *'accessory skin tags, congenital'* were not included as an additional chromosomal or structural anomaly. A full list of additional structural and congenital anomalies is described in supplementary material 5. The subjective variables intestinal matting and intestinal necrosis were defined as per the treating surgeon. In the BAPS-CASS dataset surgeons were asked to describe the bowel as pink/healthy, meconium stained/healthy, dusky/ischaemic, or black/necrotic, and the degree of matting as none, less than 50% intestinal matting, ≥50% intestinal matting, and adherent mass. There is no direct equivalence between these two systems of categorisation. In the CAPSNet database, abstractors had access to web-based pictorial guidance and text-based descriptions to help them determine whether necrosis and matting were present, and the categories to which they should be assigned (none, focal and diffuse, and none, moderate and severe, respectively). (http://www.capsnetwork.org/portal/ForAbstractorsSiteInvestigators/AbstractorManualsFAQsandTimesheet.aspx). Mapping of these variables and sensitivity analyses conducted are described in supplementary material 3.

Assessment of interaction

Statistical interactions between reduction and closure strategy, and key infant characteristics, were investigated in a covariate and propensity score adjusted model describing the association between reduction and closure strategies and the number of incident severe gastrointestinal complications. Where clinically or statistically significant interactions were identified, these were used to define two sub-groups of infants in which all subsequent analyses were conducted.

A statistically significant interaction was defined as one in which including the interaction term improved the fit of the covariate and propensity score adjusted model, as defined by a p-value of <0.05 on likelihood ratio testing. A clinically significant interaction was defined as one in which the treatment effects were in opposing directions at each level of the interaction, even if including the interaction term did not meet the level of statistical significance for improving the fit of the model.

Comparison of reduction and closure strategies

The impact of treatment choice on outcome was investigated in each of the sub-groups using appropriate regression analyses. Negative binomial regression was used for outcomes with over-dispersed count data, including number of severe gastrointestinal complications and number of episodes of sepsis. Poisson regression was used where the outcome was count data, but was not over-dispersed, including number of operations and number of days of PN use. Logistic regression was used for binary outcomes, including mortality, liver disease and one or more episode of sepsis, and linear regression was used for growth

outcomes where the data were continuous and normally distributed. Crude and propensity score plus covariate-adjusted estimates of effect were calculated. Covariates that were adjusted for were gestational age at birth, birthweight, intestinal perforation identified at presentation, and intestinal atresia, as these characteristics have been demonstrated in this cohort to be associated with variation in outcome.

RESULTS

Infant characteristics

A total of 1600 live-born infants with gastroschisis were identified during the defined reporting periods, 393 (25%) from Britain and Ireland, and 1207 (75%) from Canada. Of these, 671 (42%) underwent PC as their first attempted reduction and closure strategy, and 597 (37%) underwent SR. Of the remaining 332 infants who were excluded from the analysis, 183 (11%) underwent ward-based reduction with sutureless closure, 16 (1%) underwent staged reduction facilitated by a custom silo, 71 (4%) underwent operative primary reduction with suture-less closure, and 11 infants (1%) had a mesh sutured in place at their first reduction and closure procedure. The first reduction and closure strategy was unknown for 51 infants (3%) (Figure 1). Of the 671 infants where PC was attempted, 106 (16%) were unable to be closed primarily and therefore had a silo placed. Characteristics of infants in the PC and SR treatment groups are shown in table 1.

Severe gastrointestinal complications

In the first 28 days of life, the 671 infants in the PC group experienced 105 severe gastrointestinal complications between them, whilst the 597 infants in the SR group experienced 68 severe gastrointestinal complications between them. Overall, in the PC group, 586 infants (88%) experienced no complications, 67 (10%) experienced one, 13 (2%) experienced two, and 4 (1%) experienced three or more. In comparison, in the SR group, 549 infants (92%) experienced no complications, 35 (6%) experienced two, 9 (2%) experienced two, and 4 (1%) experienced three or more. A breakdown of the types of severe gastrointestinal complications experienced by infants in each group is given in Table 2.

Interactions and sub-group definition

A clinically plausible interaction was identified between intestinal perforation identified at time of presentation and treatment, with SR associated with an incidence rate ratio (IRR) of severe gastrointestinal complications of 0.65 in those without perforation, and an IRR of 1.96 in those with perforation. Similarly, a clinically plausible interaction was identified between presence of intestinal matting and treatment, with SR associated with an IRR of severe gastrointestinal complications of 0.31 in those without intestinal matting, and 1.10 in those with severe matting. Finally, a clinically plausible interaction was also identified between intestinal necrosis and treatment, with SR associated with an IRR of severe gastrointestinal complications of 0.66 in those without intestinal necrosis, and 2.54 in those with intestinal necrosis. No interaction was identified between intestinal atresia and treatment type, with SR associated with an IRR of severe

gastrointestinal complications of 0.70 in those without intestinal atresia, and 0.75 in those with intestinal atresia. No other interactions between key characteristics and the effect of treatment on outcome were identified. The effect of treatment on outcome therefore varies according to the presence or absence of each of intestinal perforation, intestinal matting and intestinal necrosis.

As the effect of SR on number of severe gastrointestinal complications differed between infants with and without intestinal perforation, intestinal matting or intestinal necrosis, two sub-groups were defined. The first sub-group included infants without intestinal necrosis, perforation or matting, and the second included infants with one or more of these features of bowel injury. All subsequent analyses were undertaken in these two sub-groups.

Infants without intestinal necrosis, perforation or matting

In the sub-group of 443 infants without intestinal necrosis, perforation or matting, infants who underwent SR experienced statistically significantly fewer severe gastrointestinal complications in the first 28 days of life than those who underwent PC, adjusted IRR 0.25 (95% CI 0.09-0.67, p=0.006), but underwent a greater number of operations, adjusted IRR 1.40 (95% CI 1.22-1.60, p<0.001), and required a marginally greater number of days of PN, adjusted IRR 1.08 (95% CI 1.03-1.13, p<0.001), and were more likely to experience one or more infection, adjusted OR 2.06 (95% CI 1.10-3.87 p=0.025) (Table 3). There were no differences in any other outcomes between infants who underwent SR, and those who underwent PC.

Infants with intestinal necrosis, perforation or matting

When outcomes for the group of 697 infants with intestinal necrosis, perforation or matting were compared between PC and SR, two statistically significant differences were identified. Use of SR was associated with a greater number of operations in the first 28 days of life, adjusted IRR 1.30 (95% CI 1.17 – 1.45, p<0.001), and a marginally greater number of days on which PN was used in the first 28 days of life, adjusted IRR 1.06 (95% CI 1.02-1.10, p=0.003) (Table 4)

Types of operation performed

Overall, in the group of 671 infants who underwent PC, 1537 operations were performed, 73(4.7%) of which were abdominal operations performed without a general anaesthetic. In comparison, in the 597 infants who underwent SR, 1839 operations were performed, 401 (21.8%) of which were abdominal operations performed without general anaesthetic (table 5).

DISCUSSION

In comparison to PC, use of SR in infants without intestinal necrosis, perforation, or matting was associated with an approximately 75% reduction in the incidence of severe gastrointestinal complications in the first 28 days of life, but at the expense of a 40% increase in number of operations, a doubling in the risk of experiencing one or more infections, and potentially an 8% increase in number of days on which PN was received over the same time period. In contrast to its effect in infants without intestinal perforation, necrosis or matting, the use of SR in infants with any of these features was associated with a 30% increase in the number of operations infants undergo in the first 28 days of life, and potentially a 6% increase in the number of days on which they receive PN, but no reduction in number of severe gastrointestinal complications.

Three key strengths of this study are the size of the cohort, the patient-centred nature of the outcomes investigated, and the detailed, prospective data collection methodology utilised. The collection of nuanced data relating to an infant's physiology, degree of bowel injury and operative management allowed estimates of effect to be adjusted for infant's propensity scores and previously identified confounding factors, thereby ensuring that the results presented are as close as possible using observational data to those that would be seen in a randomised controlled trial. As the outcomes investigated were identified as important by key stakeholders, the results of the comparison between PC and SR hold direct relevance to clinical practice.

Three limitations affected this work. The first is that definitions of some outcomes varied between the databases, making it difficult to ensure comparability when creating the unified dataset. The second, is that as demonstrated by the differences in characteristics seen between infants who underwent PC and those who underwent SR, allocation to treatment has been confounded by intention. However, the use of covariate and propensity score adjusted analyses should have, if sufficient factors were taken account of and accurately measured, accounted for much of this confounding [14-16]. A third limitation is that outcomes are reported at 28 days of age, and therefore only represent early outcomes for each intervention. This is particularly relevant for the outcome of parenteral nutrition use. A large proportion of infants remained on parenteral nutrition at 28 days of age, and therefore, whilst statistically significant differences in parenteral nutrition use have been demonstrated, it is difficult to robustly define the clinical significance of these differences. Because many infants were still parenterally fed as opposed to enterally fed at the time of outcome reporting, there is also the potential that further severe gastrointestinal complications would occur following the reintroduction of enteral feeding. However, as the proportion of infants requiring parenteral nutrition at 28 days of age is similar between the treatment groups, we would not expect this to significantly affect the conclusions of the study.

Two recently conducted systematic reviews[6, 7] reported that multiple outcomes were better for infants who underwent PC than for those who underwent SR. However, there were significant limitations with the primary data upon which those conclusions were based, and. it is therefore difficult to use these reviews to

inform clinical decision making. It is also impossible to draw any robust conclusions from the one RCT that has been conducted comparing PC to SR[9] as the trial was abandoned due to a failure to recruit to target[9]. In contrast to the existing literature, this study has been able to at least in part address issues arising from selection bias and confounding that weaken the published systematic reviews [6, 7], and also achieve sufficient statistical power to detect differences in meaningful outcomes[9].

Many surgeons opt to use SR over PC due to the fact that it is felt to reduce the number of operations that children required. This work has suggested the opposite to be true. This difference is likely due to the definition of operation we have used. Traditionally, many surgeons class an operation as a procedure performed under a general anaesthetic, and therefore count infants who have had an uncomplicated silo repair and sutureless abdominal wall closure, as undergoing zero operations. However, when the gastroschisis COS was developed, the clear message from all stakeholder groups was that the definition of an operation should include all silo placements, replacements, and abdominal wall closures, regardless of whether these were performed under general anaesthetic or not. This definition did not however include episodes of silo volume reduction. This expanded definition of operation likely accounts for the discrepancy seen between the results of this work and established thinking.

We hypothesise that the benefit seen in this study to treating infants with intestinal necrosis, perforation or matting using PC is seen because undergoing general anaesthetic allows a thorough assessment of the infant's intestines and

abdomino-visceral ratio, and then based on those findings, individual tailoring of the reduction and closure strategy. In contrast, in those infants with less complex disease, i.e. no necrosis, perforation, or matting, where individualised treatment is less necessary, we hypothesise that the gradual reduction of the abdominal contents that is associated with SR reduces the risk of increased intra-abdominal pressure and development of the severe gastrointestinal complications associated with it, but the staged nature of the procedure increases the number of operations that infants require, and the greater period of time over which the bowel is exposed increases the risk of systemic infections.

Based upon the results of this study, parents of infants born with gastroschisis who do not have intestinal perforation, intestinal necrosis or matted bowel at delivery should be counselled that treatment with SR has both pros and cons. However, as the magnitude of reduction in number of severe gastrointestinal complications outweighs the drawbacks of treatment with SR, we propose that these parents should be cautiously counselled that SR is the most appropriate treatment for their children. In contrast, parents of children with intestinal necrosis, perforation or matting should be advised that at present, it appears that PC is the operation of choice, as there are demonstrable benefits to its use, but no demonstrable drawbacks. Parents must however also be informed that centres or individual practitioners within a centre may have different levels of expertise with each approach, and therefore until there is a transition towards more standardised care, counselling should be contextualised in a centre or practitioner-specific manner.

Whilst this work has provided evidence that can be utilised to begin developing a decision-making pathway for infants born with gastroschisis, further research is still required. We would advocate for conduct of a joint British, Irish and Canadian RCT comparing PC to SR in infants without intestinal necrosis, perforation or matting. Such an RCT should include a cost-utility analysis, and would require approximately 250 infants to be randomised to demonstrate a statistically significant difference between treatments in the number of severe gastrointestinal complications. We believe that such a trial is feasible and necessary to conduct. Further work is also necessary to ascertain the relative merits of other treatment strategies including ward-based reduction and sutureless closure, which were not specifically addressed in this study. However, until the point that such trial data is available, we propose that infants without intestinal necrosis, perforation or matting are managed using placement of a pre-formed silo, staged reduction and delayed closure, whilst those infants with intestinal necrosis, perforation or matting undergo examination under general anaesthetic, appropriate management of the injured bowel, and primary closure if feasible, safe, and not precluded by signs of raised intra-abdominal pressure.

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FIGURE LEGENDS

Figure one - Reduction and closure strategies utilised

SUPPLEMENTAL DIGITAL CONTENT

SUPPLEMENTAL MATERIAL ONE - CREATION OF A UNIFIED DATABASE

SUPPLEMENTARY MATERIAL TWO- VARIABLES WITHOUT DIRECT EQUIVALENCE BETWEEN BAPS-CASS AND CAPSNET DATASETS

Table 1: Characteristics of infants in each treatment group

	PC	SR
	N=671	N=597
	Median (IQR)	Median (IQR)
Birthweight		
Grams	2490 (2140-2820)	2450 (2170-2790)
Gestational age at birth		
Completed weeks	36 (35-37)	36 (35-37)
	n(%)*	n(%)*
Reporting year		
2005-2008	408 (60.9%)	266 (44.6%)
2009-2012	151 (22.5%)	202 (33.8%)
2013-2016	111 (16.6%)	129 (21.6%)
Country of treatment		
British Isles	203 (30.3%)	138 (23.1%)
Canada	468 (69.7%)	459 (76.9%)
Transferred in to surgical centre		
No	497 (74.1%)	240 (40.2%)
Yes	174 (25.9%)	357 (59.8%)
Antenatal diagnosis		
No	5 (0.8%)	9 (1.6%)
Yes	642 (99.2%)	555 (98.4%)
Maternal age		
<25	421 (69.1%)	333 (65.7%)
25-34	169 (27.8%)	168 (33.1%)
35 and above	19 (3.1%)	6 (1.2%)
Caesarean section delivery		
No	364 (65.0%)	357 (65.3%)
Yes	196 (35.0%)	190 (34.7%)
Ethnicity		
White	424 (84.8%)	285 (70.4%)
BME	76 (15.2%)	120 (29.6%)
Sex		
Male	349 (52.5%)	297 (50.3%)
Female	316 (47.5%)	294 (49.7%)

*Percentage of those with complete data
BME – Black or minority ethnicity, PC– Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure,

Table 1: Characteristics of infants in each treatment group - continued

	PC	SR
	N=671	N=597
	n(%)*	n(%)*
Small for gestational age at birth		
No	542 (81.9%)	466 (79.5%)
Yes	120 (18.1%)	120 (20.5%)
Additional chromosomal or structural anomaly		
No	566 (88.6%)	469 (82.9%)
Yes	73 (11.4%)	97 (17.1%)
APGAR score at five minutes		
≥7	570 (88.4%)	513 (88.8%)
4-6	61 (9.5%)	53 (9.2%)
0-3	14 (2.2%)	12 (2.1%)
Necrosis at admission		
No	571 (95.0%)	552 (98.7%)
Yes	30 (5.0%)	7 (1.3%)
Intestinal matting		
None	257 (43.5%)	205 (37.2%)
Mild	265 (44.8%)	256 (46.5%)
Severe	69 (11.7%)	90 (16.3%)
Intestinal atresia		
No	577 (86.1%)	546 (92.5%)
Yes	93 (13.9%)	44 (7.5%)
Intestinal Perforation		
No	578 (95.1%)	551 (97.9%)
Yes	30 (4.9%)	12 (2.1%)
Complex gastroschisis		
Simple	499 (74.4%)	510 (85.4%)
Complex	110 (16.4%)	53 (8.9%)
Unknown	62 (9.2%)	34 (5.7%)
Grade of surgeon		
Consultant	290 (62.5%)	233 (52.2%)
Trainee	139 (30.0%)	166 (37.2%)
Consultant and Trainee	35 (7.5%)	47 (10.5%)

*Percentage of those with complete data
BME – Black or minority ethnicity, PC– Operative Primary Fascial Closure, SR – Silo placement with staged reduction and delayed closure,

Table 2: Numbers and types of severe gastrointestinal complications in each reduction and closure group

	PC		**SR**	
	671 infants		**597 infants**	
	N=105 complications		**N=68 complications**	
	n (% of total complications)	n/100 infants	n (% of total complications)	n/100 infants
Type of complication				
Mechanical obstruction	7 (6.7%)	1.04	7 (10.3%)	1.17
De novo Intestinal perforation	19 (18.1%)	2.83	10 (14.7%)	1.67
Unplanned Intestinal resection	41 (39.0%)	6.11	22 (32.4%)	3.68
Abdominal compartment syndrome	10 (9.5%)	1.49	8 (11.8%)	1.34
Enterocolitis	28 (26.7%)	4.17	21 (30.9%)	3.51

OPFC – Operative Primary Fascial Closure,
SR – Silo placement with staged reduction and delayed closure
WBR - Ward Based Reduction

Table 3

Table 3: Outcomes in infants without intestinal necrosis, perforation or matting

	PC	SR				
	N=241	N=202	Crude estimate of effect		Adjusted estimate of effect~	
	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Severe gastrointestinal complications						
None	215 (89.2%)	194 (96.0%)	0.29 (0.12-0.68)	0.005	0.25 (0.09-0.67)	0.006
One	21 (8.7%)	8 (4.0%)				
Two	3 (1.2%)	0 (0.0%)				
Three or more	2 (0.8%)	0 (0.0%)				
Operations						
One	0 (0%)	0 (0%)	1.42 (1.26-1.59)	<0.001	1.40 (1.22-1.60)	<0.001
Two	192 (81.0%)	2 (1.0%)				
Three	39 (16.5%)	168 (86.6%)				
Four or more	6 (2.5%)	24 (12.4%)				
Number of episodes of infection						
None	107 (86.3%)	93 (77.5%)	1.55 (0.82-2.94)	0.179	1.57 (0.76-3.23)	0.219
One	14 (11.3%)	23 (19.2%)				
Two	2 (1.6%)	3 (2.5%)				
Three or more	1 (0.8%)	1 (0.8%)				
	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality						
No	237 (98.3%)	201 (99.5%)	0.29 (0.03 - 2.66)	0.276		
Yes	4 (1.7%)	1 (0.5%)				
Infection in first 28 days						
No	180 (87.0%)	149 (81.0%)	1.57 (0.91-2.71)	0.108	2.06 (1.10-3.87)	0.025
Yes	27 (13.0%)	35 (19.0%)				
Liver disease						
No	215 (95.1%)	193 (99.5%)	0.10 (0.013 - 0.79)	0.029	0.14 (0.017-1.23)	0.076
Yes	11 (4.9%)	1 (0.5%)				

* Percentage of those with complete data

~Adjusted for propensity score, gestational age at birth, birthweight, intestinal atresia and intestinal perforation at presentation

Table 3: Outcomes in infants without intestinal necrosis, perforation or matting - continued

	PC	SR				
	N=241	**N=202**	**Crude estimate of effect**		**Adjusted estimate of effect~**	
	n(%)*	**n(%)***	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Head circumference						
z-score	-0.35 (-2.62 to 1.92)	-.68 (-2.42 to 1.06)	-0.33 (-0.77 to 0.11)	0.147	-0.32 (-0.72 to 0.09)	0.127
Weight						
z-score	-.87 (-2.87 to 1.13)	-1.04 (-2.49 to 0.41)	-0.18 (-0.50 to 0.15)	0.285	-0.08 (-0.30 to 0.13)	0.448
	Median (IQR)	**Median (IQR)**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Parenteral nutrition						
Number of days use	23 (16, 28)	27 (20, 28)	1.10 (1.06 - 1.15)	<0.001	1.08 (1.03-1.13)	0.001

* Percentage of those with complete data

~Adjusted for propensity score, gestational age at birth, birthweight, intestinal atresia and intestinal perforation at presentation

Table 4

Table 4: Outcomes in infants with intestinal necrosis, perforation or matting

	PC	SR				
	N=349	N=348	Unadjusted estimate of effect		Adjusted estimate of effect~	
	n(%)*	n(%)*	IRR (95% CI)	p-value	IRR (95% CI)	p-value
Number of severe GI complications						
None	300 (86.0%)	316 (90.8%)	0.78 (0.49-1.24)	0.298	1.02 (0.60-1.74)	0.950
One	37 (10.6%)	21 (6.0%)				
Two	10 (2.9%)	8 (2.3%)				
Three or more	2 (0.6%)	3 (0.9%)				
Number of operations						
One	0 (0%)	0(0%)	1.29 (1.18-1.42)	<0.001	1.30 (1.17-1.45)	<0.001
Two	208 (62.1%)	4 (1.2%)				
Three	96 (28.7%)	273 (82.2%)				
Four or more	31 (9.3%)	55 (16.6%)				
Number of episodes of infection						
None	158 (81.4%)	202 (80.8%)	1.1 (0.65-1.57)	0.975	1.07 (0.65-1.79)	0.782
One	29 (14.9%)	36 (14.4%)				
Two	5 (2.6%)	11 (4.4%)				
Three or more	2 (1.0%)	1 (0.4%)				
	n(%)*	n(%)*	OR (95% CI)	p-value	OR (95% CI)	p-value
Mortality						
No	342 (98.3%)	336 (97.4%)	1.53 (0.54-4.33)	0.427	2,37 (0.71-7.92)	
Yes	6 (1.7%)	9 (2.6%)				
Infection in first 28 days						
No	247 (82.6%)	240 (78.7%)	1.29 (0.86-1.92)	0.224	1.41 (0.88 - 2.27)	0.159
Yes	52 (17.4%)	65 (21.3%)				
Liver Disease						
No	321 (95.3%)	331 (98.8%)	1.24 (0.08-0.73)	0.012	0.60 (0.18-2.06)	0.420
Yes	16 (4.7%)	4 (1.2%)				

* Percentage of those with complete data

~Adjusted for propensity score, gestational age at birth, birthweight, intestinal atresia and intestinal perforation at presentation

Table 4: Outcomes in infants with intestinal necrosis, perforation or matting - Continued

	PC	SR				
	N=349	N=348	Unadjusted estimate of effect		Adjusted estimate of effect~	
	Mean (95% CI)	Mean (95% CI)	Difference in z-score (95% CI)	p-value	Difference in z-score (95% CI)	p-value
Head circumference						
z-score	-.74 (-3.15 to 1.67)	-.0.62 (-3.12 to 1.89)	0.12 (-0.32 to 0.55)	0.597	0.32 -0.11 to 0.76)	0.145
Weight						
z-score	-..90 (-2.84 to 1.04)	-1.03 (-3.21 to 1.15)	-.032 (-0.19 to 0.12)	0.675	0.05 (-0.12 to 0.22)	0.541
	Median (IQR)	**Median (IQR)**	**IRR (95% CI)**	**p-value**	**IRR (95% CI)**	**p-value**
Parenteral nutrition						
Number of days use	28 (20, 28)	28 (22, 28)	1.06 (1.02-1.09)	<0.001	1.06 (1.02-1.10)	0.003

* Percentage of those with complete data

~Adjusted for propensity score, gestational age at birth, birthweight, intestinal atresia and intestinal perforation at presentation

Table 5

Table 5: Numbers and types of operations performed

	PC		SR	
	671 infants		**597 infants**	
	N=1537 operations		**N=1839 operations**	
	n(% of total operations)*	**n/100 infants**	**n(% of total operations)***	**n/100 infants**
Under general anaesthetic				
Abdominal operation	780 (50.7%)	116.2	817 (44.4%)	136.9
Central venous catheter insertion	31 (2.0%)	4.6	70 (3.8%)	11.7
Other	20 (1.3%)	3	10 (0.5%)	1.7
Without general anaesthetic				
Abdominal operation	73 (4.7%)	10.9	401 (21.8%)	67.2
Central venous catheter insertion	624 (40.6%)	93	518 (28.2%)	86.8
Unknown anaesthetic status				
All	9 (0.6%)	1.3	23 (1.3%)	3.9

Figure

Figure 1 – Reduction and closure strategies utilised