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Determining factors of clinical outcomes in paediatric intussusception at Johannesburg hospital

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1. Literature Review

1.1 Introduction

Intussusception is the commonest cause of intestinal obstruction in infants [1]. The morbidity and mortality attributed to intussusception have decreased markedly in developed countries, with the rate of successful pneumatic reduction approaching well above ninety percent and overall mortality approaching zero percent [2,3]. This conflicts with experience in developing countries, where the rate of successful pneumatic reduction varies from 0-40% and mortality from 3-54% respectively [1]. A review of all South African case series on intussusception noted a successful nonoperative management rate between 0 – 53 % and mortality of 2 – 12 % (4,5,6,7,8,9, 10,11). The aim of this research report is to assess which local epidemiological and clinical factors impact on the higher morbidity and mortality in our setting expressed as defined clinical outcomes.

1.2 Epidemiology & Pathophysiology

In South Africa intussusception has an incidence of 32 cases per 100,000 children per year, corresponding with figures from surrounding African countries, and comparing favourably with an Asian experience reporting in excess of 400 cases per 100,000. The North American and European incidence of intussusception varies from 20 to 200 cases per 100,000 [4,12,13]. Socioeconomic factors and indigenous clinical factors impact

significantly on outcome of disease in our setting: poor access and large distances to medical facilities as well as failure to present or refer timeously result in delays in instituting appropriate management [14].

Intussusception is the pathological process whereby a proximal segment of intestine (intussusceptum) invaginates into a distal segment of intestine (intussuscepiens). Retrograde intussusception which is the reverse process, when a distal segment invaginates into a proximal segment, is described but rare. The occurrence of prograde together with retrograde components is termed a compound intussusception, and is extremely rare [15]. An intraluminal or extraluminal mass arising from or adjacent to the intestinal wall acts as a lead point for the development of intussusception. If intussusception is not reversed, congestion and subsequent ischaemia of the bowel wall will result in necrosis, perforation and death as possible outcomes.

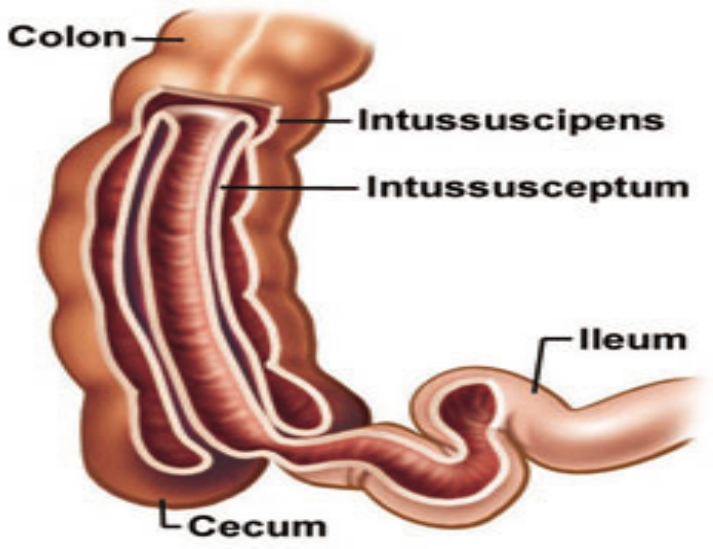


Diagram 1: Ileocolic intussusception demonstrating proximal intussusceptum (ileum) invaginating into distal intussuscepiens (ascending colon).

Intussusception can occur at any point along the intestinal tract, with ileocolic intussusception the most commonly occurring variant. Rogers has reported a 81% incidence of ileocolic intussusception in Johannesburg, South Africa [10]. Other variants include colocolic, ileoileal and jejuno-jejunal.

Moore, Mayell, Davies and Postma reported high rates of colocolic intussusception 9 - 29 % of all cases, in comparision to international reports of only 5% [4,5,6,9,16]. Cases of colocolic intussusception occurred in an older population compared to the common ileocolic intussusception. The constellation of clinical features of colocolic intussusception, an older age group, delayed presentation as well as a lower incidence of bowel pathology has become known as “tropical intussusception”[17]. Seventy eight percent of all colocolic intussusception is described to be presigmoid [6].

There is a male preponderance for all types of intussusception of between 52 and 72 percent, but there is no clear hypothesis explaining the gender difference [16].

Geographic variations in the incidence of intussusception have also been noted globally, with a higher incidence noted in the developing compared to the developed world, as well as a higher occurrence of colocolic intussusception, 17% vs. 5% in tropical compared to temperate regions [1].

It is traditionally thought that the incidence of intussusception is seasonal, with peaks corresponding to peaks in diarrhoeal and respiratory tract infections, usually during summer and spring months. However a recent case series inclusive of patients from four countries disputes this well held belief, showing that though diarrhoeal episodes peaked during spring (March in the northern hemisphere and October in the southern

hemisphere), no relationship was demonstrated with the occurrences of intussusception [18].

Intussusception is classically divided into idiopathic and pathological causes, with idiopathic intussusception more common between the ages of 6 months and 3 years [20]. Even though the term idiopathic intussusception has been used for these cases, viral infections, abnormal embryological intestinal rotation, exclusive breastfeeding and rotavirus immunization have all been implicated as predisposing factors [20,21,22,23,24]. The association of abnormal embryological intestinal rotation and intussusception is known as Waugh's syndrome [19].

Over the age of 3 years, pathological aetiologies predominate, with Meckel's diverticulum, intestinal duplication cysts, polyps and intestinal malignancy the most commonly occurring lead points [25]. Rare lead points include ectopic pancreatic tissue, vascular malformations and lipoma of the bowel wall [26,27,28]. Postoperative intussusception is a well known entity and described after various intraabdominal surgeries [29,30,31]. Possible causative factors for postoperative intussusception are intramural haematomas, adhesive bands, intraluminal foreign material and surgical anastomosis acting as lead points.

Acquired Immunodeficiency Syndrome-associated Kaposi Sarcoma has been identified as an important regional pathological cause of paediatric intussusception. A South African case series reporting on six children, with five of the six children been diagnosed with HIV for the first time. Poor outcomes were reported, with five of the six dying due to extensive haemorrhage due to anorectal involvement [32].

1.3 Clinical Presentation

The usual presentation is that of inconsolable crying, fever 12 - 54%, paroxysmal cramping abdominal pain 58 - 88%, associated nausea and vomiting 80 - 88% or bloody mucoid stools 50 - 82% [10,16]. Atypical presentations include syncope, seizures, hypotonia, lethargy and fluctuating levels of consciousness [33,34]. A sausage shaped mass may be evident on abdominal palpation as well as on digital rectal examination. Mayell in her South African series reported 26% of all cases having a palpable rectal mass on examination and 4% with a clinically evident prolapsed intussusceptum [5]. In another South African series, Grant noted that cases of colocolic intussusception had a higher rate of a palpable mass per rectum when compared to ileocolic intussusception at 38% vs. 21% respectively [7]. An "empty" right iliac fossa on palpation, known as Dance's sign, is also a feature of intussusception. Cases of neglected intussusception can present with established intestinal obstruction, severe hypovolaemic or septic shock, necessitating aggressive resuscitation and subsequent operative intervention [35].

1.4 Diagnosis

The majority of cases with intussusception are suspected clinically and confirmed radiologically before implementation of management.

1.4.1 Clinical

Weihmiller in an attempt to develop a predictive diagnostic model for intussusception based on clinical factors, in a series of 310 paediatric patients , in whom 38 had

intussusception, identified age older than 6 months (p = 0.04), male gender (p = 0.007), history of lethargy (p = 0.001) and an abnormal abdominal x-ray (p = 0.0001) as univariate predictors of intussusception. Combining all four variables into a diagnostic model a sensitivity of 97% and negative predictive value of 99% was noted [36].

1.4.2 Radiological

Important to note is that all cases of intussusception need to be adequately resuscitated before any diagnostic imaging is performed.

Ultrasonography is the gold standard method of diagnosis, it is the least invasive, with no radiation exposure, as compared to enema fluoroscopy. One paper reports ultrasonography having a sensitivity and specificity of 97.9% and 97.8% respectively, with a positive predictive value of 86.6% and a negative predictive value of 99.7%. Ultrasonography as compared to enema fluoroscopy has also been shown to decrease 79.3 and 59.7 cases of radiation-induced malignancy per 100,000 male and female children respectively [37,38,40]. Ultrasound findings of a “donut”, “target” or “pseudokidney” sign are all suggestive of intussusception – with each sign indicative of multiple bowel layers [39].

Plain radiography as reported by Sargent et al can assist in the diagnosis in 45% of cases of intussusception [41]. Guo et al have gone further to describe a “coffee bean” and “banana” (dilated small bowel loop patterns,) signs that correlate clinically with intussuception associated with vascular compromise [42].

The benefit of enema fluoroscopy is that it may be a therapeutic as well as a diagnostic procedure, by exerting direct pressure via an air or water based medium onto the intussusceptum and assisting in its reduction out of the intussuscepiens.

Computed tomography [CT] imaging is rarely employed in the emergency setting due to cost, radiation exposure and the requirement for sedation in infants/children. CT may be utilized in the further work up for pathological intussusception. Incidental findings of small bowel intussusception are occasionally described during evaluation of the abdomen with CT. This category of intussusception tends to be described involving a short segment of small bowel less than 2cm in length, transient in nature and not associated with proximal bowel dilatation [40].

Radiological investigations can determine management options, either non-operative or operative. Massively distended intestinal loops and pneumoperitoneum on plain radiography are indications for operative intervention.

Ultrasound features associated with operative management would include free intraabdominal fluid, fluid within the intussusceptum, absent Doppler flow of bowel wall or mesenteric vessels and peripheral echogenic foci (air) in the intestinal wall of the intussusceptum, implying bowel wall ischemia or necrosis [43,44,45,46].

An intussusceptum located in the descending colon or rectum on contrast enema, ultrasound or rectal examination is associated with a lower successful reduction rate quoted at 25% [40]. Two further features associated with nonreducibility of an ileocolic intussusception are contrast tracking between the intussusceptum and intussuscepiens known as the “dissection sign” and radiographic visualisations of the lumen of the appendix without air or contrast entering the small bowel is known as the appendix sign [47,48,49].

1.5 Management

Management may be either non-operative or operative. The challenge is in triaging patients into the two management groups which is dependent on epidemiological, clinical and radiological factors.

Non-operative management is suggested for cases that are less than three years of age; systemically well with an ileocolic or colocolic intussusception, early presentation, and a non distended abdomen. Presence of a pathological lead point although having higher rates of failed non-operative management should not be considered a contraindication to non-operative reduction [50]. Operative intervention is suggested for cases where the patient is systemically ill, or presents with an acute abdomen, pneumoperitoneum, or a palpable mass on rectal examination.

Initial management in all cases includes assessment of hydration and haemodynamic status. Establishment of intravenous access and intravenous fluid administration as deemed necessary is vital in all cases. Nasogastric tube insertion is needed when abdominal distension is present. No clear guidelines are available with regards to antibiotic usage, however in our environment an initial dose of broad spectrum antibiotics on presentation is considered prudent.

1.5.1 Nonoperative Management

1.5.1.1 Medical

Though rarely described steroid admininstration can be used in cases of recurrent intussusception due to lymphoid hyperplasia [51]. Steroid administration has also

assisted in cases of small bowel intussusception in the setting of Henoch-Schonlein purpura (HSP). Sonmez et al reported their experience of 6 cases of ileal-ileal and one of ileal caecal intussusception due to HSP – 3 of the seven were treated succesfully with prednisolone administration for 24 hours. Strict repeat abdominal examinations and monitoring was strongly advised by Sonmez if one is to embark on a course of steroid treatment [52].

1.5.1.2 Radiological

Nonoperative management entails a fluoroscopically or sonographically guided pneumatic (air) or hydrostatic (water, saline or barium) reduction, whereby the selected medium is introduced per rectum under pressure, thereby reducing the intussusceptum out of the intussuscepiens. Pneumatic reduction was re-introduced into the western world towards the end of the twentieth century, after extensive use in China [53].

Hippocrates is quoted as recommending a treatment for "ileus" by "connecting a bellows to the anus and inflating the bowel with air". Pneumatic reduction was extensively described during the late 19th century in Europe with the use of hands bellows as a source of air for pneumatic reduction [54,55].

The choice of pneumatic or hydrostatic medium is based on local experience. As per local protocol the diagnostic modality of choice is ultrasound, with barium enema reserved for equivocal cases. Pneumatic reduction is utilised for nonoperative management for the idiopathic age group (3 months to 3 years). With the surgeon in attendance, pneumatic reduction is performed by the radiologists under fluoroscopic guidance. The device used for the pneumatic reduction is a Foley catheter connected by

a three way stop-cock to an aneroid sphygmomanometer with an insufflation bulb. This device can be easily constructed at any health care facility. Sedation is not routinely used. Laparotomy is performed in all cases that have a failed pneumatic reduction or where it is contraindicated. Contraindications include: peritonitis, free intraabdominal air, established small bowel obstruction with abdominal distension, haemodynamic instability and multiorgan dysfunction.

Hadidi compared pneumatic, barium enema and ultrasound guided saline reduction in a randomised controlled trial and described the success rates of 90% vs. 70% vs. 67% respectively. A statistical difference was noted between pneumatic vs. barium enema reduction ($p < 0.01$) however none was noted when comparing barium enema and ultrasound guided saline reduction ($p > 0.05$) [56]. Meyer has previously reported no statistical difference between the success rates between the two modes of reduction, pneumatic vs. hydrostatic 76% vs. 63% ($p = 0.31$) [57]. A literature review by Appelgate reported that 32 studies used pneumatic reduction vs. 39 studies used hydrostatic reduction with average successful rates of reduction of all studies at 82% vs. 68% respectively. No statistical analysis was undertaken [40].

The average perforation rate for both pneumatic and hydrostatic reduction is quoted as being less than 1%. There is a perceived benefit of pneumatic over hydrostatic reduction with regards to the extent of peritoneal cavity contamination if perforation had to occur [35]. Shiels et al reporting on their porcine model where they compared various modes of reduction with and without a Valsalva manouever, concluded that pneumatic reduction is safer than hydrostatic reduction. Mean intracolic pressures at which perforation occurred for pneumatic reduction during Valsalva manouvers was 145mmHg compared to 121mmHg during hydrostatic reduction without Valsalva

manouvers ($p < 0.05$). The Valsalva manouver results in a decreased colonic transmural pressure , thereby “strengthening “ the colonic wall. Laparotomy findings after reduction attempts complicated by perforation demonstrated greater peritoneal contamination after hydrostatic reduction as compared to that after pneumatic reduction. No statistical difference was noted in the number and size of perforation between hydrostatic and pneumatic reduction with or without Valsalva manouver [58].

Perforation resulting in pneumoperitonoeum is a significant complication with acute abdominal compartment syndrome and death as possible outcomes [59,60]. In a series of 9028 examinations, Guo reported on 14 cases of pneumoperitoneum after pneumatic reduction with two episodes of tension pneumoperitoneum. Both cases resulted in a mortality [61]. Perforation during pneumatic reduction has been noted to occur in a lower age group. Daneman reported on fourteen infants who sustained intestinal perforations during barium and pneumatic reduction. All except one case were less than 6 months of age. Transmural necrosis was only identified in six cases suggesting that excessive pressure resulted in colonic perforation [62].

Wiersma has recommended general anaesthesia for the pneumatic reduction procedure, particularly those who have had a failed primary non operative attempt as well as for cases who have significantly delayed presentation. After instituting this practice they have noticed an increase in the success of non operative management from 22% – 53% ($p = 0.02$) [11]. Wiersma attributes this improvement to the fact that the patient is relaxed and pain free during the reduction attempt and therefore counterproductive abdominal straining is abated, improving the chances of a successful reduction. This is contrary to Shiels experimental evidence.

Two mechanisms explain pneumoperitoneum during pneumatic reduction. The first is known as a "lead point perforation", which is perforation through a weakened intestinal wall, usually at a site of transmural necrosis due to pressure exerted by the apex of the intussusceptum; the second is a perforation through normal intestinal wall due to excessive air pressures at reduction [62,63].

A standardised protocol for pneumatic reduction is the application of air pressure initially at 80mm HG for three minutes. If the reduction attempt is not successful the pressure is increased in 20mm HG increments every three minute session to a maximum of 120mm HG. A rule of "threes" applies for the technique of hydrostatic reduction – three attempts of three minutes duration with the liquid enema bag three feet above the fluoroscopy table.

As mortality is a real risk of pneumatic reduction the surgeon is advised to ensure adequate resuscitation before a reduction attempt as well as being prepared to perform an urgent needle decompression in an event of pneumoperitoneum development [60,62]. Rogers et al reported a 20% complication rate associated with non operative management of intussusception. This high morbidity was attributed to non standardisation of reduction protocols and inexperience of the radiologist in performing the technique [10]. If non operative management is not initially successful and no complications have arisen, a repeat session can be undertaken after at least 15 minutes of inactivity, with successful reductions described after such a period [65,66]. A recurrence rate of 10% has been noted after both pneumatic and hydrostatic reductions [40].

Vazquez et al have recently described a novel technique of external manual reduction for intussusception in 13 paediatric patients [67]. The procedure was performed under

sedation with ultrasonic guidance and the intussusceptum is reduced by palpation and manipulation transabdominally. A successful reduction rate of 80 percent was achieved. The mean duration of the procedure was 14 minutes with 11 of the 13 cases having duration of symptoms for less than 24hrs.

Numerous clinical factors including age, sex, weight, temperature, duration of symptoms, rectal bleeding, white cell count, neutrophil count, rectal prolapse of the intussusceptum, small bowel obstruction and dehydration have been analysed as predictors for pneumatic reduction failure. Only duration of symptoms, rectal bleeding, rectal prolapse of intussusceptum, small bowel obstruction, high neutrophil count and C-reactive protein have been to shown to be statistically significant with regards to pneumatic reduction failure [13,68,69,70,71].

Much has been reported with regards to duration of symptoms related to the success of pneumatic or hydrostatic reduction with conflicting conclusions. Many reports note that duration of symptoms longer than 24hrs is an absolute contraindication to non operative management, although there is no supporting evidence for this. Tareen et al reported on their experience on 256 children presenting with intussusception undergoing pneumatic reduction with a 91.5 % success rate, and compared reduction rates in three categories of symptom duration, these being less than 24 hours, between 24 - 48hours and greater than 48 hours. Reduction rates in all three groups were in the vicinity of 90% and they concluded that duration of symptoms does not influence outcome of pneumatic reduction [72]. Mensiah et al reported that the majority of cases in their series with symptoms of at least two days had a failed pneumatic reduction [73]. Ramachandran on reporting on a series of 179 patients concluded after logistic regression that only prolapsed intussusceptum ($p < 0.05$) and small bowel obstruction

($p < 0.001$) affected pneumatic reduction success rates and not duration of symptoms [70].

Katz et al on reporting on a series of 282 patients concluded after multivariate analysis that dehydration, small bowel obstruction and duration of symptoms greater than 12 hours were predictors for an unsuccesful pneumatic reduction [74].

Fike et al have recently shown in their 10 year retrospective review that bloody diarrhoea ($p <0.001$) duration of symptoms > 24hrs ($p = 0.05$), lethargy ($p < 0.001$) and distal position of the apex of the intussusceptum within the intussuscepiens ($p < 0,001$) are all associated with failed pneumatic reduction [75].

Clinical Scoring Cards have been retrospectively evaluated in 200 patients with intussusception. Depending on presenting clinical features, points are allocated per severity or characteristic of each feature. Clinical features included were duration of symptoms, age, duration before appearance of bloody stools, nature and colour of stools, presence of diarrhoea, extent of abdominal distension and dehydration. As concluded by the authors, scores of greater than 15 out of a possible 25 were associated with near impossible reduction. No statistical analysis was undertaken to verify accuracy or credibility of such scoring cards [13].

1.5.2 Operative Management

Before operative management, all cases undergo appropriate fluid resuscitation.

Traditional operative management includes a laparotomy through a transverse skin incision with either manual reduction of the intussusception or intestinal resection,

primary anastomosis or gastrointestinal diversion, specifically ileostomy. Ileostomy is rarely described in the management of intussusception, and reserved for cases who are metabolically unwell and where it is deemed safer to divert rather than to risk an anastomotic leak or in those cases where an ileorectal anastomosis would be necessary to establish bowel continuity in an emergency setting. Manual reduction is described as a gentle action compressing the distal tip of the intussusceptum within the intussuscepiens in a retrograde direction, similar to squeezing tooth paste out of a toothpaste tube.

With the advent of laparoscopy, minimally invasive techniques can be used in the management of intussusception. Laparoscopy was initially used as an aid in evaluating those cases of intussusception taken to theatre after a failed radiological reduction, where on the operating table examination were found to have spontaneously reduced hence avoiding an unnecessary laparotomy [76]. It has now progressed to being used in assisting in reduction of the intussusception, with hospital expenditure and length of stay shown to be less than an open procedure, 8171 +/- 2595 US dollars vs 11 672 +/- 5466 US dollars ($p = 0.088$) and 3.00 +/- 1.31 days vs 4.52 +/- 1.98 days ($p = 0.005$) respectively [77,78].

A French study group retrospectively assessed a multi-institutional experience with laparoscopy in management of intussusception and noted a 31.9% conversion rate to an open procedure. Risk factors that were noted to be associated with conversion were duration of symptoms 1.6 vs 3.1 days ($p = 0.048$), peritonitis on clinical examination 10.6 % vs 41% ($p = 0.003$) and presence of a pathological lead point 17% vs 50% ($p=0.004$) [79].

1.6 Inflammatory Biomarkers

C-reactive protein (CRP) an acute phase reactant produced by the liver, has been shown to be a marker of severity in intussusception by Willets. Willets assessed serum values of malondialdehyde, CRP, interleukin 6, neopterin, tumour necrosis factor alpha, endotoxin and IgG and IgM antiendotoxin core antibody in 32 consecutive cases of intusussception [72]. All cases were divided into three groups. Those who underwent a successful pneumatic reduction, those who required open reduction and those in whom a bowel resection was necessary. By stepwise discriminate analysis CRP was identified as the best marker to distinguish between all three groups ($p < 0.001$). CRP is also described as a marker of bacterial translocation, bacterial translocation density and vascular compromise in an intestinal obstruction mouse model described by El-Awady et al [80]. El-Awady went further to show that intestinal obstruction results in cytoskeleton disruption, neutrophil priming and mechanical gut barrier disruption. Cevikel et al also demonstrated that increases in CRP corresponded with increases in bacteria identified in mesenteric lymph node and liver tissue cultures in an intestinal obstruction rat model ($p < 0.01$) [81].

Intussusception results in congestion and ischemia of the intestine. Intestinal ischemia triggers a marked response in proinflammatory cytokine production within the intestinal wall, as well as decreasing the intestinal barrier to bacterial and endotoxin translocation. Bacteria and endotoxins stimulate further proinflammatory cytokine production. These cytokines disseminate systemically via the lymphatic system and directly result in the systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS) and the multiple organ dysfunction syndrome (MODS) [82]. SIRS, ARDS and MODS are noticed in those cases with a significant

duration of symptoms in our experience. Though CRP could be used as a predictor of outcome, its clinical application in choosing a management option in intussusception is not well defined [71]. A raised neutrophil count was associated with failed pneumatic reduction (multivariant analysis odds ratio 11.52) by Fragoso; however it does not have a significant predictive value [69]. Procalcitonin has been shown to be useful in diagnosing necrotic bowel in intestinal obstruction in adults, however no current study has evaluated procalcitonin's usefulness in the paediatric population [83].

1.7 Long Term Outcomes

The literature is sparse with regards to long term outcomes of pediatric intussusception. Daneman in a 17 year review of 763 children with 876 episodes of intussusception revealed a recurrence rate of 9%. Of these cases 68% experienced a single recurrence episode. Only 14% of those cases with more than one recurrence had a pathological lead point. Recurrences were noted until the age of 8 years [84].

1.8 South African Experience

The South African paediatric intussusception experience is described in the literature by seven retrospective case series: Moore 2010 (423 cases), Rogers 2007 (39 cases), Wiersma 2004 (106 cases), Grant 1996 (192 cases), Isdale 1986 (81 cases), Postma 1985 (76 cases) and Mayell 1972 (223 cases) [4,5,6,7,8,9,10]. Comparison between these to our series are discussed during the discussion as per Table 1.

	MAYELL 1972	POSTMA 1985	ISDALE 1986	GRANT 1996	WIERSMA 2004	ROGERS 2007	MOORE 2010
NO. CASES	223	76	81	192	106	39	423
MALE PERCENTAGE	63%	62%	49%	56%	*	*	57%
ATTEMPTED NON OPERATIVE MANAGEMENT	7/223 (3.1%)	12/76 (15.8%)	43/81 (53.0%)	138/192 (72.0%)	59%	24/39 (61%)	*
NONOPERATIVE MANAGEMENT SUCCESS RATE	3/7 (43.0%)	0/12 (0%)	6/43 (14.0%)	32/138 (23.2%)	22% (53%)**	6/24 25%	*
MORTALITY	6/223 2.7%	5/76 6.5%	3/81 3.7%	8/192 4.2%	9%	2/39 5.1%	9/423 2.1%
INTESTINAL RESECTION RATE	50/220 (22.7%)	24/76 (31.6%)	30/75 (40.0%)	71/158 (44,9%)	(45.0%)	16/33 (48.4%)	100/247 (40.4%)

Table 1: Comparison of South African Case Series on Paediatric Intussusception [4,5,6,7,8,9,10].

*No data available.

** After general anaesthesia added to reduction protocol

2. Methods

A retrospective hospital record review of paediatric intussusception admitted to Chris Hani Baragwanath Academic (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospitals (CMJAH) for the period of January 2007 to April 2010 was undertaken. CHBAH and CMJAH are the largest academic and tertiary hospitals affiliated to the University of the Witwatersrand. Each hospital has a dedicated Paediatric Surgical unit. On avearge 180 cases are operated at CHBAH per month and 120 cases at CMJAH. Combined outpatient attendance approaches 1000 patients per month.

Records were reviewed of all known paediatric cases of intussusception for the following data: age, sex, weight on admission, referral status, duration of symptoms, palpable intussusceptum on rectal examination, radiological investigation and management results, serological and haematological results, surgical findings and procedure, histological reports, ICU admission and discharge summary, general ward admission and discharge summary.

The following determining factors were assessed against clinical outcomes: Duration of symptoms, weight, palpable rectal intussusceptum and admission C reactive protein results.

The seven clinical outcomes were: failed pneumatic reduction, perforation during attempted reduction, intestinal resection, ileostomy, ICU admission, relook laparotomy and death.

Subgroup analysis was undertaken on those patients presenting primarily to CHBAH or CMJAH (walk-in) and those referred from other health care facilities.

Only data of patients between 3 months and 3 years were submitted for analysis.

C-reactive protein levels were measured by the latex immunoassay method by the National Health Labarotory Service. All histological reports of cases that underwent resection were assessed for comment as to whether transmural necrosis of the intestinal wall was present.

Results were analyzed with the Mann-Whitney U and student t-test for variables with a skewed or normal distribution respectively. Chi square/Fisher exact test were used for categorical variables. Correlation between CRP and Duration of symptoms [DOS] was analyzed by the Pearson's product-moment coefficient. Univariate logistic regression was used to quantify the association between determining factors and clinical outcomes. Statistica © Version 9.0, Statsoft Inc software was employed for statistical analysis. A calculated P value of less than 0.05 was considered as significant.

The Human Research Ethics Committee of the University of the Witwatersrand granted ethics approval for this study. Protocol number M080206

3. Results

A total of 108 cases of paediatric intussusception were found of which 11 were excluded, therefore 97 cases were submitted for analysis. Of these cases excluded, 8 were older than 3 years and underwent primary surgical intervention as dictated by local protocol, and one case was an infant who underwent a laparotomy for an unknown cause of intestinal obstruction, where a jejunojejunal intussusception was discovered. Two cases died before any intervention was undertaken.

The mean (SD) age of all cases was 7.0 (4.3) months and 53% of the cases were male. Sixty eight percent of cases were from CHBAH. Fifty seven percent of all cases were referred from surrounding medical facilities. Forty two percent of all cases were below the 25th weight for age centile, twenty three percent between the 25th and 50th, eighteen percent between the 50th and 75th and only seventeen percent above the 75th wieght for age centile. On reviewing the admission dates of all cases of intussusception for a possible seasonal variation no pattern was noted.

Sixty two of 97 cases had an attempted pneumatic reduction with a 51.6% success rate and an overall success rate of 33% (Figure 1). Seven cases developed pneumoperitoneum during pneumatic reduction, with all cases having transmural necrosis at the perforation site. Thus a total of 65 cases underwent surgical management. Of those 81.5% (53/65) underwent intestinal resection, with right hemicolectomy resection predominating. In addition 16.7% (12/65) either had a spontaneous (7/65) or a manual reduction (5/65).

Ileostomy diversion was necessary in 13.8% (9/65) of operative cases and 11% (7/65) needed a second surgical procedure during the initial presenting admission, all seven underwent intestinal resection at the primary procedure.

All intensive care unit admissions were in cases that underwent definitive primary operative management, resulting in a 20.7 % (20/97) and 30.3% (20/65) admission rate for all and primary operative cases respectively.

There was an overall mortality rate of 9.3% (9/97). Two (ileocolic) of the nine mortalities occurred preoperatively from multiple comorbidities, one four month old with Acquired Immune Deficiency Syndrome, pneumocystis jarvovicii pneumonia and sepsis and a three month old with acute lymphoblastic leukaemia, tumour lysis syndrome and acute renal failure. Five cases died after prolonged ICU admission from nosocomial sepsis and multiple organ dysfunction. Of these cases, four had a relook procedure. An infant also died from severe gastroenteritis and septic shock one week after hospital discharge. Another death occurred when an infant developed seizures of an unknown aetiology, one week after discharge and presented dead on arrival. This infant had undergone a manual reduction of an ileocolic intussusception.

Seven relook procedures were necessary. The most common indication for a relook procedure was abdominal compartment syndrome. Sheath dehiscence was an indication in two cases and an anastomotic leak in one case after right hemicolectomy and ileocolic anastomosis. One case needed a relook laparotomy due to a jejunal perforation arising from a serosal tear sustained at initial laparotomy.

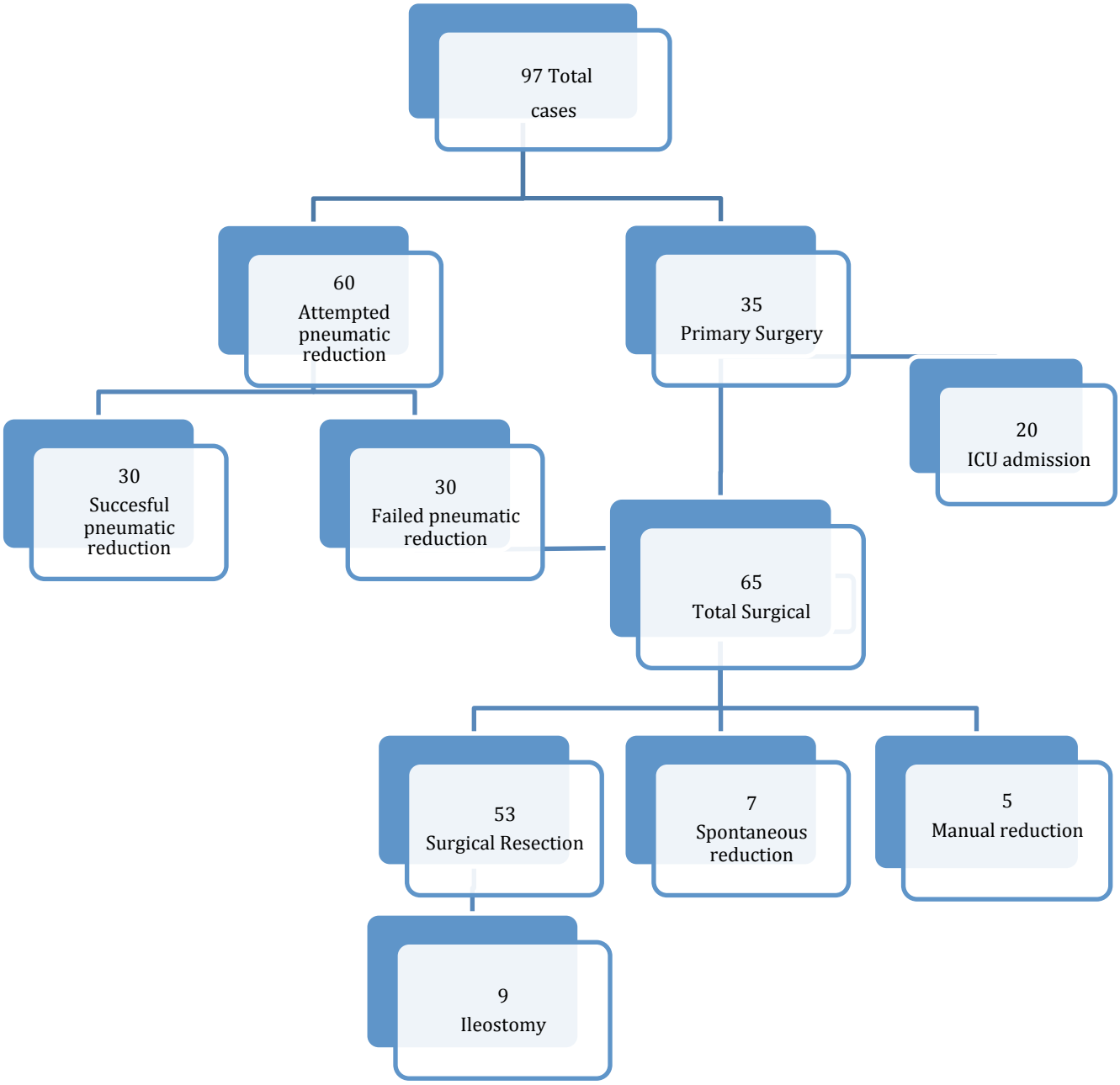


Figure 1. Flow Diagram of intussusception management outcomes.

*Relook laparotomy and mortality not included

Averages of the determining factors are tabulated in Table 2.

Results of determining factors reaching statistical significance per clinical outcome are tabulated in Table 3.

Predictive determining factors per clinical outcome are listed in Table 4, as per univariant logistic regression modelling.

Pearson's coefficient for DOS and CRP is 0.4 .

Further analysis identified ICU admission and Relook laparotomy having odds ratios (95% CI) of 6.1 (1.46 – 25.35) and 44.2 (5.92 – 329.78) respectively in predicting mortality.

In the subgroup analysis of the referred patients, no difference was noted in the duration of symptoms, admission CRP level and weight between those cases presenting initially to CHBAH or CMJAH. The referred group had a less successful pneumatic reduction rate of 41.9% (18/30) vs. 60% (13/31) (p = 0.16) though not statistically significant. Mortality rate was nearly three times higher in the referred group 12.7% (7/55) vs. 4.7% (2/42) (p= 0.18), however differences were not statistically significant, Table 5.

In the subgroup analysis of operated cases that underwent intestinal resection. CRP levels were compared with histological reports noting transmural necrosis and those without. Though a difference is noted in the CRP levels between the two groups statistical significance was not reached. 108 [11.8-229.9] vs. 39.2 [6 -245.4] (p = 0.057)

Determining Factors	Mean (SD) /Frequency / Median [Range]
Weight (kg)	7.4 +/- 4.3
Duration of symptoms (days)	3.0 +/- 2.2
Palpable Rectal Intussusceptum	22% 21/97
Admission CRP level (mg/l)	50.9 {1-249.3]

Table 2: All four determining factors.

	CRP g/ml median [Range]	P value	WT Kg Mean (SD)	P value	DOS Days Mean (SD)	P value	PRI Frequency	P value
Failed pneumatic reduction	34.5 [4-249.3]	0.004			3.1 (1.8)	0.005	4/32	0.17
Successful pneumatic reduction	7 [1-249.3]				1.9 (1.3)		8/30	
Perforation			6.3 (1.2)	0.04				
No Perforation			7.6 (1.3)					
Resection								
Manual reduction								
Ileostomy								
No ileostomy								
Relook	197.7 [88.8-237.2]	0.02			7.2 (3.8)	<0.001		
No relook	79.5 [1-249.3]				3.1 (1.4)			
ICU admission								
No ICU admission								
Mortality					5.1 (4.4)	0.004		
No Mortality					2 (1.7)			

Table 3: Clinical outcomes compared to the determining factors. Only those determining factors that reached statistical significance are shown.

CRP – C-Reactive Protein, WT – Weight , DOS – Duration of symptoms ,PRI – Palpable Rectal Intussusceptum

Clinical Outcome	P value	Odds Ratio (95% CI Interval)
Failed Pneumatic Reduction		
DoS (days)	0.013	2.0 (1.2 – 3.5)
CRP (mg/L)	0.043	1.01 (1.001 – 1.04)
Relook		
DoS (days)	0.005	2.49 (1.3 – 4.7)
CRP (mg/L)	0.025	1.01 (1.001 – 1.027)
Mortality		
DoS (days)	0.02	1.4 (1.06 – 1.85)

Table 4: Univariant logistic regression per clinical outcome, only determining factors with an odd ratio above one are tabulated

CRP – C Reactive Protein, DoS – Duration of Symptoms

Walk-in (n=42) vs. Referred group(n=55)	Mean (SD) /Median [Range] /Frequency	P value
Duration of symptoms	2.8(2.1) vs. 3.2(2.2)	0.40
Weight	7.2(1.4) vs. 7.52(1.5)	0.28
CRP	57.9 [1 – 249.3] vs. 85.3 [1 – 240]	0.12
Successful pneumatic reduction	58,1% (18/31) vs. 41.9% (13/31)	0.16
Mortality	4.7% (2/42) vs. 12.7% (7/55)	0.18

Table 5: Comparison between Walk –in and Referred patients.

CRP – C Reactive Protein

4. Discussion

Paediatric intussusception is associated with significant morbidity and mortality in Johannesburg, with high rates of intestinal resection, ileostomy, relook laparotomy and mortality. With regards to the determining factors; duration of symptoms predicts for failed pneumatic reduction, relook laparotomy and mortality. A raised CRP is associated with failed pneumatic reduction and relook laparotomy. None of the measured determining factors are associated with intestinal resection, ileostomy diversion or intensive care unit admission rates.

Several limitations are evident within this research report. Due to its retrospective nature, data is dependent on the record keeping at both hospitals. It is probable that not all cases of intussusception have been accounted for during the study period. The relatively low numbers obtained (n=97) reduced the power and statistical significance of some of the variables analysed.

A clear distinction could not be made between ileocolic and colocolic intussusception in all cases treated successfully with pneumatic reduction. Review of the radiological reports did not allow for such distinction, therefore this research report is not able to demonstrate whether there is a difference in the rate of nonoperative reduction and operative outcome between these two variants of intussusception.

The degree of dehydration on admission was not taken into account when assessing weight as a determining factor, with those cases presenting with severe dehydration all most likely demonstrating acute weight loss. This limitation should however not affect the analysis of the patients undergoing pneumatic reduction, on the assumption that the

majority of cases with severe dehydration, and noticeable weight loss, would not be candidates for pneumatic reduction in the first instance.

Though the pneumatic reduction protocol is standardized across both hospitals, the level of experience of the radiology consultants and registrars attempting the pneumatic reduction could not be standardized. The same limitation is noted with regards to definitive operative management.

On reviewing the previous South African case series of intussusception , Isdale did not note a male preponderance in her series. Though a difference is noted in our series it is not marked. Grants's series notes the highest attempted nonoperative reduction rate at 72% compared to our rate of 63%. This high attempt rate reported by Grant may be explained by the fact that the majority of cases underwent barium enemas as the method of diagnosis and if intussusception was demonstrable, and unless any notable contraindication, barium enema reduction was presumed to be attempted at the same time.

Nonoperative reduction success rate is varied in South Africa, with our series experiencing the second highest after Wiersma's series. Wiersma achieved this success rate after the introduction of general anaesthesia prior to attempting reduction. The last reported Johannesburg experience, from CMJAH by Rogers, noted a 25% success rate in comparison to the current success rate of 51.6%. Presumably greater experience and standarised protocols since then explain the marked improvement. No information with regards to nonoperative reduction is noted in Moore's national retrospective surveillance study from 1998 - 2003 which would be of interest allowing for comparison to a national average. Of importance no series used pneumatic reduction

exclusively, as in our series, making comparison and interpertation of success rates based on method of reduction cumbersome.

One can only speculate as to why our units have a favourable success rate. Whether this data directly concurs with international experience that pneumatic reduction has an inherent advantage over hydrostatic reduction is probable. Experience has also improved amongst radiologists and surgeons over the years resulting in better patient selection for nonoperative intervention.

There is however a selection bias in our study which is not evident in the other case series. By selecting cases between 3 months and 3 years, there is a process of selecting out the majority of pathological lead point associated intussusception, which is known to be associated with a higher pneumatic reduction failure rate [40].

A far greater surgical resection rate of 81.5% is noted compared to other series. Mayell reports a 22.7% resection rate with the rest of the operative cases undergoing spontaneous or manual reduction. Local surgical policy at the time is suggested to contribute to Mayell's relatively high spontaneous or manual reduction rate. Evaluation of the previous South African case series show a steady decrease in the number of manual reductions over the years, with our experience demonstrating the lowest manual reduction rate, suggesting that local protocols for pneumatic reduction are stringent and reliable.

Our mortality rate is the highest amongst all South African series. Comparison of mortality rates can be misleading with many unaccounted for factors contributing to death. Whether patients presented with more or less physiological derangements in our series compared to others cannot be ascertained, as no series including our own

reported initial physiological and haemodynamic parameters on presentation. Whether regional referral systems work more or less effectively in our environment compared to elsewhere can also not be determined. Another point to consider is whether previous case series reported only admission mortality or whether discharge mortality was considered as well. If we exclude the two cases that died after discharge our mortality rate would be seven percent and if we exclude further the two cases that died before any definitive intervention the mortality rate would drop to 5 %, comparable to the other South African case series.

Our results compared to international data are not favourable. Current international series as mentioned in the literature review are experiencing over 90% success rates in non operative reduction and zero percent mortality associated with intussusception. A better health infrastructure, well informed population, wealthier socioeconomic standards, greater number of specialists (paediatric surgeons, radiologists etc) and easier access to health care all could possibly contribute to the notable difference.

The average duration of symptoms is 3.0 +/- 2.2 days before presentation in our series, which compares poorly to data from the developed world but is a similar experience to other series from third world countries. As mentioned in the literature review, there are different view points with regards to duration of symptoms and outcome , especially in relation to non operative management. Our average DOS is far greater than that reported from first world series, where at times the majority of cases have mere hours of symptomatology. The average duration of symptoms for a succesful pneumatic reduction in our series is 1.9 +/- 1.3 days this would suggest that stringent protocols excluding attempts at pneumtic reduction in cases with symptoms longer than 24 hrs is not founded.

The longer the duration of symptoms the more physiologically unwell the patient will be. This is confirmed by the positive predictive nature of the duration of symptoms for relook laparotomy and mortality.

Why DOS does not have any influence in the resection and ileostomy rate in our series is queried, it is expected the longer the duration the intussusceptum is within the intussuscepiens the greater the chance that ischemia and necrosis would develop and thereby necessitate a resection or ileostomy diversion at laparotomy. One could postulate that though DOS does not impact on the development of ischemia and necrosis, it does allow though for a prolonged opportunity for bacterial translocation thereby resulting in systemic inflammatory response syndrome and multiple organ dysfunction syndrome to develop. Prolonged duration of symptoms would also result in excessive fluid losses due to intestinal obstruction, resulting in metabolic and electrolyte abnormalities. Intussusception can result in localised intra abdominal complications, bowel necrosis and perforation, however it is the systemic effects which are the more concerning, and those that need to be addressed rapidly before definitive management.

It is of interest that DOS and CRP predict for similar clinical outcomes. A positive correlation between DOS and CRP is noted. Though not linear, CRP values increase the longer the child has symptoms. It is important to clarify however, that prolonged DOS results in poor outcome whilst a raised CRP level is a marker of, but not contributory to poor outcome.

A raised CRP predicts for pneumatic reduction failure and relook laparotomy. Our results concur with previous studies indicating an association of failure of pneumatic reduction with a raised CRP [71]. This study did not evaluate at what level a raised CRP

would positively predict failure, however the converse should hold true. A patient with a normal CRP value on presentation should result in a successful pneumatic reduction in the majority of cases. As positive predictors of outcome these two factors in combination with other clinical and radiological factors can assist the clinician in stratifying patients for operative and nonoperative management.

Contrary to the common description of intussusception occurring in a well nourished infant, 42% of all cases were below the 25th weight for age centile. Low weight was associated with pneumoperitoneum during pneumatic reduction, however not predictive. International reports have noted infants less than 6 months of age are at a greater risk of perforation [62]. Five of the 7 cases in our series who suffered a perforation during pneumatic reduction were less than 6 months of age. As noted previously all cases with perforation during pneumatic reduction had evidence of transmural necrosis at the site of perforation during histological evaluation of the resected specimen, favouring lead point perforation as the pathogenesis above an iatrogenic injury. This conflicts with international data where perforation through an area of transmural necrosis occurred minimally and excessive pressure contributed significantly [62].

Why younger infants are predisposed to perforations is not clarified within the medical literature. One can assume that the bowel anatomy of infants less than 6 months is intrinsically predisposed to transmural necrosis and subsequent perforation. Whether pneumatic reduction protocols should be standardised throughout all age groups or be tailored to age and weight needs to considered as a rational option.

Twenty-two percent of all cases had a palpable rectal intussusceptum. As previously noted a high incidence of rectally palpable intussusceptum occurs in South Africa, and

previous reports suggest greater nonoperative failure rates. Though statistical significance was not reached, twice as many cases with a palpable rectal intussusceptum had a failed pneumatic reduction compared to those with a successful pneumatic reduction. Whether a rectally palpable intussusceptum is a marker of disease progression or a characteristic predominately attributed to colo-colic intussusception could not be concluded in this research report.

A high gastrointestinal diversion, ileostomy, rate is noted in our series. Sparse to no comment is made of ileostomy at the time of surgical management in local and international series of intussusception, so comparison is difficult [85]. One would expect ileostomy diversion to be considered as an indirect marker of severity of illness and disease progression; however as mentioned earlier no association is noted with CRP or duration of symptoms. Whether interpretation of local protocol results in a lower threshold for ileostomy diversion is not known, and whether ileostomy diversion is performed more commonly by junior personnel compared to senior personel has not been assessed. Morbidity associated directly due to ileostomy has not been assessed, during the study period only three cases subsequently underwent ileostomy closure, and outcomes of the remaining cases are not known. None of the operative cases presented after discharge with adhesive bowel obstruction during the study period.

Relook laparotomies are a described but a rare procedure in paediatric surgical practice. However in our series 11% of all operative cases needed a relook laparotomy. Relook laparotomy clearly predicts for mortality and on closer analysis of the cases undergoing relook procedures a common denominator is suspected. Postoperative fluid resuscitation in the face of multiorgan dysfunction and sepsis may contribute to a significant positive fluid balance. This significant positive fluid balance inevitably

results in increased interstitial fluid resulting in generalised oedema, secondary abdominal compartment syndrome, sheath dehiscence and poor anastomotic healing [86, 87]. Abdominal compartment syndrome is an under recognised phenomenon in infants and children [88].

Not unexpectedly ICU admission and relook laparotomy are both predictive for mortality in our group.

In comparison between the walkin and referred group of patients; CRP levels and DOS were similar, leading us to assume similarity of severity of illness. Though no statistical significance is reached with regards to mortality, the referred group's mortality rate was three times higher than in the walk in group. On speculation, the degree of resuscitation or lack thereof on presentation at the first health care facility and during subsequent transportation could be contributive to the higher mortality rate in the referred group, highlighting the importance of resuscitation at the point of first contact.

5. Conclusion

Paediatric intussusception is a significant pathological process in paediatrics. It has been shown that intussusception is not a benign condition but however associated with significant morbidity and mortality. Prolonged duration of symptoms (DOS), inevitably due to socioeconomic, infrastructural and health management factors, and raised C reactive protein (CRP) are predictors for clinical outcomes in intussusception. The use of DOS and CRP in association with other clinical factors may be able to assist local clinicians in making management decisions, specifically with regards to embarking on operative or non operative management.

It appears, though not conclusively proven, that systemic complications related to extended duration of symptoms, as previously mentioned are more contributory to morbidity and mortality rather than intraabdominal effects of intussusception.

Intussusception is a dynamic disease process with yet many unanswered questions. Though it is the commonest cause of small bowel obstruction in children, the exact aetiology or mechanism is not fully understood, and much research into the "basic science" understanding of intussusception is still needed. The question of why intussusception is predominately a paediatric condition is yet to be clarified. Evaluation of the anatomy and physiology of the paediatric intestinal wall merits research. The contribution of immunological and virological factors associated with intussusception still needs to be conclusively clarified.

Public awareness and education are clearly vital in identifying symptoms earlier, allowing for more prompt presentation to health care facilities. Well defined protocols introduced at all points of contact in the health care delivery system would ensure early

recognition and an opportunity to institute aggressive resuscitation as well as definitive management.

INTUSSUSCEPTION DATA COLLECTION FORM

Primary admission		Johannesburg			**Signs and Symptoms**	Duration			
		Baragwanath				Obstruction			
Peripheral referral		Facility				Significant distension			
Presentation	Symptoms	Pain				Respiratory Distress			
		Vomiting				Palpable mass			
		PR bleed				Prolapse			
		Distension				Acute Peritonitis			
		Constipation			**Biochemistry**	HB			
	Signs	Respiratory Distress				WCC			
		Palpable Mass				Urea			
		Acute Abdomen				Creatinine			
		Prolapse				pH			
	Duration					Base Excess			
Radiology	Xray					Lactate			
	Ultrasound					pCO2			
	Contrast Study		Air			pO2			
			Barium		**Radiology**	Xray			
			Other			Ultrasound			
	Other					Contrast Study		Air	
Biochemistry	HB							Barium	
	WCC							Other	
	Urea				**Treatment**	Radiological Reduction	Contraindicated		
	Creatinine						Attempted		
	pH							Pneumatic	
	Base Excess							Hydrostatic	
	Lactate						Result		
	pCO2						Complications		
Treatment	Fluid					Surgery	Open		
	NGT						Laparoscopic		
	Surgery						Findings		
	Other Medical						Reduction		
Transfer	Initial contact	Date					Resection		
		Time			**Complications**	Recurrence			
	Mode of transfer					Wound Complications			
	Arrival	Date				Missed perforation			
		Time				Anastomotic			
Admission Summary						Respiratory			
						Neurological			
						Other			

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