Intussusception in preterm neonates: A systematic review of a rare condition

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Abstract

Background: While necrotizing enterocolitis (NEC) is a prevalent condition in preterm neonates admitted to neonatal intensive care unit (NICU), intussusception is exceedingly uncommon and often overlooked. This is due to the fact that they share many clinical characteristics. The initial misdiagnosis of intussusception in preterm neonates (IPN) especially has led to a delay in their management, which increases the risk of developing compromised bowel. Additionally, it is difficult to reach a diagnosis as neonatal intussusception does not have any classical radiological signs even when contrast enema is used. This systematic review is based on the published literature including case reports and case series to review the clinical features of IPN and how to differentiate it from NEC in order to shed the light on this rare disease and how having a high index of suspicion would help practitioners to make an early and accurate diagnosis.

Methods: A systematic literature search to report all cases of relevant articles that reported IPN till date. All cases that were born before 37 weeks gestational age, presented within the neonatal period and having well established documentation were included in the study. Any case that did not have these criteria was excluded from our study.

Results: Only 52 cases met these criteria during the period from 1963 till date. An average of 10 days had elapsed before the cases were confirmed to have IPN either clinically or intraoperatively. The most frequent manifestations were abdominal distension and bilious gastric residuals, occurring in 85% and 77% of the cases respectively, followed by bloody stools in 43% of cases. However, this triad was present only in approximately one-third of the cases. Only 13 cases were diagnosed as having intussusception preoperatively. About two thirds of the intussusception were located in the ileum. Pathological lead point was present in 7 cases only; 4 of them were due to Meckel’s diverticulum. Nine cases only out of the 52 cases with IPN died.

Conclusion: It is crucial to detect the clues for diagnosis of intussusception because in contrast to NEC, it is unresponsive to conservative management, affects the viability of the bowel and surgery is essential.

Key Words: intussusception, preterm, necrotizing enterocolitis

Background

Although intussusception is the commonest etiology of bowel obstruction in infants, it is uncommonly encountered in neonates. Moreover, it is extremely uncommon in preterms [1]. Clinically, it could be commonly confused with the more common disorder in neonates, necrotizing enterocolitis (NEC), as both share common symptomatology. This includes abdominal distension, bilious emesis, bloody stools and feeding difficulties [2].

The initial misdiagnosis of intussusception in neonates especially preterms has led to a delay in their management, which increases the risk of developing compromised bowel. In addition, it is difficult to reach a diagnosis as neonatal intussusception does not reveal any classical radiological signs even when contrast enema is used.
used. Moreover, contrast enemas may even be hazardous as it may increase the risk of bowel perforation as in most cases the bowel is already compromised at the time of investigation. However, in order to reach a successful management of intussusception in preterm neonates (IPN), a timely and accurate diagnosis is required [3].

Therefore, we conducted the current study based on the systematic review of the published literature including case reports and case series to review the clinical features of IPN and how to differentiate it from NEC in order to shed the light on this rare disease and how having a high index of suspicion would help practitioners to make an early and accurate diagnosis. Although case reports are usually not an integral component of systematic reviews, in rare diseases they should be included to attain a comprehensive overview of the state of research and provide useful information especially when other types of studies are not available.

Methods
An extensive systematic literature search was done to identify relevant articles that reported intussusception in preterm neonates (IPN). MEDLINE/PubMed, Google Scholar and Science direct databases were searched using key words: “preterm, newborn(s), and intussusception” with no restriction on publication language and date. Literature review was completed on 4 February 2021. To determine their relevance, the title and abstract of all potentially relevant papers were read. Full articles were also scrutinized should the title and abstract were unclear. All cases included in the analysis met the following criteria:

(a) Gestational age <37 weeks,
(b) Onset of symptoms within the neonatal period,
(c) Well established documentation as regards patients’ demography, clinical presentation and intraoperative confirmation of intussusception.

We excluded reports discussing intussusception in full-term neonates, antenatal intussusception and those who are lacking clinically relevant data. Moreover, reviews of previously published papers were excluded to prevent case duplication. The majority of articles were individual case reports, whilst the remaining were case series. All the studies obtained from the search were sent to EndNote X9 software to sum up all studies and track potential duplications and remove these duplicates.

There are challenges to research on rare and heterogeneous conditions. However, case reports and case series occupy an important role as the preliminary data source for such conditions, and when carefully performed, systematic reviews of case reports and case series can provide a useful addition to evidence-based medicine.

Based on ROBINS-I (“Risk Of Bias In Non-randomized Studies - of Interventions), reports were assessed according to the following domains: bias in confounding, participants’ selection, classification of intervention, deviation from intended intervention, missing data, outcomes’ measurement and selection of the reported result. It was interpreted as low, moderate, serious and critical risk of bias [4]. The quality of evidence of each citation was rated using a conceptual scheme for evaluating the quality of a case report designed by Pierson [5]. This scheme evaluates the validity of a case report based on five components: documentation, uniqueness, educational value, objectivity, and interpretation, yielding a score with a maximum of 10 (> 5 suggests a valid case report) [5].

Next, two reviewers independently extracted data from each study using a standardized form that highlight data regarding patient clinical features, investigations, intraoperative findings, co-morbidities and outcome. A third author managed to resolve any inconsistencies between both reviewers. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Categorical variables of those patients were expressed as frequencies and numeric ones as mean ± standard deviation, median and range.

Results
The literature search yielded 91 citations related to our topic. After applying inclusion and exclusion criteria, 39 reports were excluded for the following reasons: Three had scanty patients’ data, 3 cases presented after the neonatal period. In addition, 20 were excluded because the cases were full-term, 12 because they were intra-uterine intussusceptions and one was a review article (Figure 1). According to the evaluation criteria cited by Pierson, 44 case reports (85%) scored >5, indicating an overall fair quality of evidence from those cited reports.

Based on the previously mentioned strict criteria, only 52 cases met these criteria during the period from 1963 till date [6–48] (Table 1 and Table 2). Gender was mentioned in all cases. Of these, 38 patients (approximately 73%) were males, whilst 14 (27%) were females, i.e. male-to-female ratio 2.7:1. The mean age of presentation was 10.6 days, while the median was 9.5 days. An average of 9.8 ± 7.5 days for the diagnosis to be confirmed was noted.

Abdominal distension and bilious gastric residuals were the most common symptoms, occurring in 85 percent and 75 percent of cases, respectively, followed by bloody stools in 44 percent of cases. This triad, however, was only seen in about one-third of the cases. The existence
of an abdominal mass on palpation was uncommon, with only 8 instances displaying this symptom. All of the infants had necrotizing enterocolitis (NEC) prior to surgery, with the exception of 13 who were identified with intussusception prior to surgery, either clinically by feeling the sausage-shaped mass or radiologically by demonstrating the characteristic target sign on ultrasonography. The latter accurately diagnosed intussusception in 11 patients only in a total of 17 patients underwent an ultrasound (US) examination yielding a sensitivity of 65%. The remaining cases did not undergo US examination either due to the presence of pneumo-peritoneum dictating immediate exploration [43], or the strong belief that the diagnosis was NEC at the time of examination where US would not be needed [47].

The most common location of IPN was the small bowel, where ileo-ileal intussusception was present in 32 cases (61%). Next in frequency was jejuno-jejunal in 9 cases, ileo-colic in 4 and colo-colic in two cases only. Multiple intussusceptions were reported in 5 cases only. In 53% of the cases, perforation was evident including two cases having the perforation following contrast enema. While the majority of the cases did not show a primary cause, pathological lead point was present in 8 cases only; 4 of them were due to Meckel’s diverticulum, 2 due to meconium plugs and only a case had postoperative intussusception following sigmoid colostomy for imperforate anus and another one due to abdominal lymphangioma. Nine out of the 52 cases (17%) with IPN died; sepsis was the cause of death in 6 cases, whilst the cause of death was not clearly reported in the remaining 3 cases.

Fig. 1 PRISMA IPD Flow Diagram: Flow chart of literature search
Table 1  Studies describing the patients of IPN

| Author            | sex | Gest. age | Weight | Age at onset | Age at surgery | Abd. distension | Gastric residue | Bloody stools | Abd. Mass | Location | Perforation | Outcome |
|-------------------|-----|-----------|--------|--------------|----------------|------------------|----------------|--------------|-----------|----------|------------|----------|---------|
| Spencer et al [3] | F   | 28        | Not given | Not given    | Died preop     | Yes              | No             | No           | No        | Ileum    | Yes        | Died     |
| Yoo et al [4]     | M   | 34        | 2140    | 2            | 2              | Yes              | Yes            | No           | No        | Ileocolic| Yes        | Survived |
| Stine et al [5]   | F   | 28        | 970     | 6            | 33             | Yes              | Yes            | Yes          | No        | Ileum    | No         | Survived |
| Smith et al [6]   | F   | 29        | 910     | 21           | 43             | Yes              | Yes            | Yes          | No        | Ileum    | No         | Survived |
| Glick et al [7]   | M   | 28        | 1070    | 14           | 17             | Yes              | No             | Yes          | Yes       | Ileum    | Yes        | Survived |
| Carman et al [8]  | M   | 25        | 740     | 9            | 15             | Yes              | No             | No           | No        | Ileum    | No         | Survived |
| Blair et al [9]   | M   | 26        | 720     | 8            | 11             | Yes              | Yes            | No           | No        | Ileoecolic| Yes        | Survived |
| Rausin et al [10] | F   | 5         | 1080    | 5            | 8              | No               | Yes            | Yes          | No        | ileum    | Yes        | Survived |
| Farstad et al [11]| M   | 27        | 1160    | 4            | 14             | Yes              | No             | No           | No        | Ileum    | No         | Survived |
| M               | 24   | 720     | 14        | 28             | Yes            | Yes              | No             | No           | No        | Ileum    | Yes        | Died     |
| Price et al [12]  | M   | 26        | 765     | 15            | 54             | Yes              | Yes            | Yes          | Yes       | Jejunum  | Yes        | Survived |
| M               | 30   | 1240    | 4        | 6             | Yes            | Yes              | No             | Yes          | No        | Ileum    | Yes        | Survived |
| Iuchtmann et al [13]| F | 26   | 970      | 15            | 20             | Yes              | No             | Yes          | Yes       | Ileum    | No         | Survived |
| M               | 28   | 820     | 16        | 18             | Yes            | No               | No            | Yes          | No        | Jejunum  | No         | Survived |
| Puvabanditsuin et al [14]| M | 26  | 690      | 18            | 35             | No               | Yes            | Yes          | No        | ileum    | Yes        | Survived |
| Mooney et al [15] | M   | 27        | 893     | 11            | 27             | Yes              | Yes            | No           | No        | Ileum    | No         | Survived |
| Reguerre et al [16]| M | 29   | 1300    | 15            | 28             | No               | Yes            | No           | No        | Ileum    | Yes        | Survived |
| Wang et al [17]   | M   | 32        | 2328    | 6            | 21             | Yes              | Yes            | Yes          | Yes       | Ileum    | Yes        | Survived |
| M               | 27   | 950     | 10        | 22             | Yes            | Yes              | Yes          | No           | No        | Ileum    | No         | Survived |
| F               | 30   | 1500    | 14        | 21             | Yes            | Yes              | Yes          | No           | No        | Ileum    | Yes        | Died     |
| Stanely et al [18]| M   | 32        | 1205    | 9            | Not given      | Yes              | Yes            | No           | No        | Ileum    | Yes        | Survived |
| Gorgen-Pauly et al [19]| M | 29  | 995      | 6            | 13             | Yes              | Yes            | Yes          | Yes       | Ileum    | Yes        | Survived |
| Hirokawa et al [20]| M | 23   | 630     | 9            | 14             | Yes              | No             | No           | No        | Ileum    | Yes        | Died     |
| Woo Goo et al [21]| M   | 27        | 1185    | 15            | 21             | No               | Yes            | No           | No        | Ileum    | Yes        | Survived |
| Margentha et al [22]| M | 28   | 1200    | 3            | 10             | No               | Yes            | No           | No        | Jejunum  | No         | Survived |
| Nock et al [23]   | M   | 24        | 649     | 9            | Not given      | Yes              | Yes            | Yes          | No        | Ileum    | Yes        | Survived |
| Avansino et al [24]| M | 24  | 608      | 14            | 34             | Yes              | Yes            | Yes          | No        | Jejunum  | yes        | Survived |
| M               | 30   | 1130    | 3        | 5             | Yes            | No               | No            | No           | No        | Ileum    | Yes        | Survive |
| Biarge et al [25] | F   | 26        | 610     | 30            | 31             | Yes              | Yes            | No           | Yes       | Jejunum  | No         | Survived |
| Ueki et al [26]   | M   | 34        | 1940    | 1            | 1              | No               | No            | No           | No        | Ileum    | No         | Survived |
| Slam et al [27]   | M   | 25        | 690     | 18            | 53             | Yes              | No             | No           | No        | Multiple | No         | Died     |
| Loukas et al [28] | F   | 34        | 2120    | 7            | 10             | Yes              | Yes            | No           | No        | Ileum    | Yes        | Survived |
Table 1 (continued)

| Study          | Sex | Age | Weight | Days in Hospital | Type | Surgical Intervention | complication | Location | Outcome |
|----------------|-----|-----|--------|------------------|------|-----------------------|--------------|----------|---------|
| Boubal et al [29] | F   | 35  | 2190   | 2               | No   | Yes                   | No           | Jejunum  | No      | Survived |
| Kim et al [30]   | M   | 25  | Not given | Not given      | Yes  | Yes                   | No           | Multiple | Yes     | Survived |
| Shad et al [31]  | M   | 36  | 1760   | 12              | Yes  | Yes                   | No           | Ileocolic| No      | Survived |
| Shima et al [32] | M   | 24  | 588    | 20              | Died preop | No | Yes                   | Yes          | Ileum    | No      | Died     |
| Altuntas et al [33] | F  | 27  | 1000   | 7               | Yes  | Yes                   | Yes          | Ileum    | Yes     | Survived |
| Kim et al [34]   | F   | 23  | 640    | 12              | Yes  | Yes                   | No           | Multiple | Yes     | Survived |
| Taşkinlar et al [35] | F  | 25  | 725    | 11              | Yes  | Yes                   | No           | Ileum    | Yes     | Survived |
| Prakash et al [36] | M  | 32  | 1300   | 11              | Not given | Yes | Yes                   | Yes          | Ileocolic| No      | Died     |
| Park et al [37]  | M   | 26  | 834    | 23              | Yes  | Yes                   | Yes          | Multiple | Yes     | Died     |
| Patel et al [38] | M   | 35  | 2200   | 21              | Not given | Yes | Yes                   | Yes          | Ileum    | Yes     | Survived |
| Aydin et al [39] | M   | 30  | 2030   | 17              | No   | Yes                   | Yes          | Ileum    | No      | Survived |
| Tempmalai et al [40] | M  | 29  | 1930   | 17              | No   | Yes                   | Yes          | Ileum    | No      | Survived |
| Diwakar et al [41] | M  | 25  | 930    | 6               | Yes  | Yes                   | No           | Multiple | Yes     | Survived |
| Pawar et al [42] | M   | 28  | 1200   | 8               | Yes  | Yes                   | No           | Ileum    | Yes     | Survived |
| Raza et al [43]  | M   | 34  | 2296   | 2               | No   | Yes                   | No           | Colonie | No      | Survived |
| Kott et al [44]  | M   | 33  | 1420   | 21              | Yes  | Yes                   | Yes          | Jejunum  | No      | Survived |
| Hukeri et al [45] | M  | 30  | 1160   | 4               | Yes  | Yes                   | No           | Jejunum  | No      | Died     |
Discussion
Intussusception is the most common cause of intestinal obstruction in infancy; nonetheless, it is an extremely rare in neonates, particularly among premature infants. It comprises for as low as 3% of neonatal intestinal obstruction and 0.3% of all cases of intussusception [49].

IPN could be easily confused with the highly prevalent disease among neonatal age group, necrotizing enterocolitis (NEC), leading to delay in diagnosis with an average of 9.5 ± 7.3 days in most studies [27]. This delay can lead to higher possibility of intestinal necrosis and subsequent perforation in preterm infants with intussusception [22, 28]. Regrettably, the classical presentations of intussusception such as an abdominal mass, vomiting and bloody stools are not commonly encountered in preterm neonates and in the majority of the cases, the definitive diagnosis is confirmed during the exploration. Additionally, the aforementioned signs along with other signs like distended abdomen and increased gastric residues are common symptoms in both pathologies. Moreover, if diagnosis is mistaken for NEC, the treatment of which, at least initially, is conservative, will lead to a further delay of the diagnosis [29, 30, 50]. Inspite of that delay, this premature group showed a lower overall mortality rate (15%), as opposed to the uniformly fatal outcome in children when left untreated for 2-5 days [51]. Infants suffering from intussusception usually have symptoms that are uniquely limited to the abdomen whilst the overall state does not worsen unless there is bowel perforation, compared to NEC in which abdominal manifestations go ahead in tandem with the deterioration of the general condition [46].

There are no specific radiological findings of IPN. Signs of ileus, such as dilatation of bowel loops and occasionally air-fluid levels, are the most prevalent X-ray findings, whereas X-rays of patients with NEC typically show pneumatosis intestinalis or portal venous gas [9]. Contrast enemas can be diagnostic and therapeutic in older infants; nevertheless, they are less effective effective in preterms because the pathology is mainly restricted to the small bowel in this group, whereas it is usually ileocolic in older infants [44]. In older infants, abdominal ultrasonography carries a sensitivity of over 98% and specificity of 100% in diagnosing intussusception [52]. However, in neonatal intussusception in general, there are several factors which can alter the sensitivity of ultrasound in diagnosis. First of all, the sigmoid colon lies superficially on the right side in a considerable number of neonates. Together with the presence of marked abdominal gases, the intussusception and the caecal shadow are obscured. Also, the absence of colonic involvement in preterms is definitely an additional factor [34, 52].

When compared to intussusception in infants and full-term neonates in which the ileo-colic type predominates [14], ileo-ileal intussusception is the most prevalent site in preterms with other locations almost non-existent [28]. Beside the location, another source of difference is an identifiable lead point. Unlike intussusception in full term infants where there is sometimes an identifiable lead point [30], the etiology of neonatal intussusception in premature infants is still unknown. Common prenatal injuries that cause intestinal hypoxia/hypoperfusion, dysmotility, and strictures have been proposed as a possible lead point [27].

Unlike intussusception in full-term babies, bowel resection in preterms was commonly indicated. A primary anastomosis was performed in around 46% of IPN cases. Interestingly, there was no statistically significant difference in death rate between those who underwent a primary anastomosis and those who underwent a stoma

Table 2 Summary of the main features and clinical manifestations of IPN cases

|                           | Mean ± SD | Median | Range |
|---------------------------|-----------|--------|-------|
| Gestational age (weeks)   | 28.5 ±3.49| 28     | 23-36 |
| Birth weight (g)          | 1182 ±526 | 1035   | 588-2328 |
| Age at onset (days)       | 10.6 ±6.57| 9.5    | 1-30  |
| Age at surgery (days)     | 20 ±15.7  | 17     | 1-80  |
| Delay (days)              | 9.8 ±7.5  | 5      | 0-57  |
| Abdominal distention      | 44 (85%)  |        |       |
| Gastric residue           | 40 (77%)  |        |       |
| Bloody stool              | 22 (43%)  |        |       |
| Abdominal mass            | 8 (16%)   |        |       |
| Sex (male:female)         | 38:14     |        |       |
| Mortality                 | 9 (17%)   |        |       |

Table 2 Summary of the main features and clinical manifestations of IPN cases

| Clinical manifestations | Location              | Treatment    |
|-------------------------|-----------------------|--------------|
| Abdominal distention    | Ileoileal             | Anastomosis  |
| Gastric residue         | Jejunoojejunal        | Stoma        |
| Bloody stool            | Ileocolic             | Reduction    |
| Abdominal mass          | Colocolic             | Autopsy      |
| Sex (male:female)       | Perforation           | Full through  |
| Mortality               | Lead point            | Not given    |
and mucous fistula, or those who underwent a primary bowel anastomosis in the setting of a perforated gut. To recap, primary anastomosis could be safely done with no increasing morbidity or mortality; hence, obviating the requirement for a second surgery [27].

This systematic review included 43 studies with a total of 52 cases of IPN reported between 1963 and 2020. Strengths of this report include a thorough search of database, explicit a strict selection criteria for the relevant studies. Furthermore, it summarized a relatively large number of cases of this rare disease, outlined some key features of IPN and how to differentiate it from NEC. However, the main limitation in our study is that it includes only case reports and case series. It is well recognized that case reports remain the lowest rank in the hierarchy of evidence, and though case reports are valuable scoping tools in discovering rare disorders, they have limited strength in the establishment of clear guidelines to differentiate between NEC and IPN. Secondly, the number of cases in our study may not be an accurate one as there are numerous unreported as well as misdiagnosed cases. The latter ones may have been spontaneously reduced or died with their diagnosis being definitely unmasked.

**Conclusion**

IPN is a very rare condition that can be deceiving; thus, necessitating a high index of suspicion in order to avoid confusion with the other causes of neonatal bowel obstruction. From all of those causes, it’s critical to discriminate it from NEC, that may be addressed conservatively in the vast majority of cases

**Acknowledgments**

We thank Dr. Ahmed Madian, Lecturer of Orthodontics, Alexandria Faculty of Dentistry for his continuous and endless support and tips in the process of publication.

**Authors’ contributions**

Study conception and design: HR. Data acquisition: MA, Analysis and data interpretation: MK, YA. Drafting of the manuscript: MA, Critical revision: MK, AE. All authors have read and approved the manuscript.

**Funding**

There was no funding source for this report.

**Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Received:** 24 July 2021  **Accepted:** 9 December 2021  **Published online:** 24 December 2021

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