

The Brighton Collaboration

Clinical Case Definition for Acute Intussusception in Infants and Children

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1. Preamble

Intussusception is the most common cause of acute intestinal obstruction in infants and young children. Intussusception occurs when one segment of intestine invaginates in a segment of distal intestine. As the intussusceptum is propagated distally along the intestine it draws with it the blood vessels. Initially compression of the blood vessels causes venous congestion and bowel wall edema, but, as the obstruction progresses, the arterial supply may be compromised resulting in intestinal ischemia. If the intussusception is not recognized and reduced, intestinal infarction and perforation may occur. Untreated intussusception is a potentially life threatening condition.

Since the first anatomical description of intussusception by John Hunter in 1793, the management of intussusception has been refined. Early diagnosis and non-surgical reduction has resulted in a significant reduction in the morbidity and mortality previously associated with this condition. However, in many developing countries where access to pediatric radiological and surgical expertise is limited, mortality remains high (>20%) (1).

As a consequence of the reported association between receipt of the rotavirus vaccine and intussusception there has been renewed interest in intussusception. Rotavirus is the most common causes of dehydrating gastroenteritis worldwide resulting in over 600,000 deaths annually. There is an urgent need to develop a safe and effective rotavirus vaccine to prevent the significant morbidity and mortality associated with rotavirus infection, particularly in developing countries.

In August 1998, the first rotavirus vaccine was licensed in the United States (RRV-TV, Rotashield®, Wyeth Lederle Laboratories, Philadelphia). Rotashield® was recommended for all US infants as part of the routine immunization schedule (2). However, in July 1999 fifteen cases of intussusception were reported in recipients of the vaccine (Centers for Disease Control and Prevention, 1999). The peak incidence of episodes of intussusception occurred at day 3 to 14 following the first dose of Rotashield® (adjusted odds ratio 21.7) (3). The attributable risk was estimated to be between 1 in 4670 and 1 in 9474 infants vaccinated (3). In response to this report, the recommendation for routine use of Rotashield® was suspended by the US Advisory Committee on Immunization Practice and the vaccine was withdrawn in October 2001 (4). These events have had a major impact on future clinical trials of other oral vaccines.

To assist in the development of future clinical trials and the prompt recognition and reporting of any association between vaccination and the development of intussusception a universally accepted and validated clinical case definition for the diagnosis of acute intussusception in infants and children is needed.

The diagnosis of acute intussusception is not difficult or controversial based on surgical criteria or with liquid contrast enema. However, in clinical vaccine trials it may be inappropriate to perform invasive investigations on all vaccination recipients who may present with non-specific symptoms that can occur with intussusception but also may be explained by another condition. Also in countries where access to radiological facilities and expertise is limited, a clinical alternative to a radiological diagnosis is needed. The aim of a clinical case definition is to identify the majority of patients presenting with intussusception to a range of health care settings. However, no single symptom or sign can accurately distinguish intussusception from other possible surgical or non-surgical conditions. In addition, a range of atypical symptoms are reported to occur with intussusception.

The Brighton Collaboration Intussusception Working Group has developed a clinical case definition for the diagnosis of acute intussusception in infants and children following vaccination. The clinical case definition is based on a combination of clinical symptoms and signs, and radiological investigations. This definition was developed on the basis of a report prepared for The Steering Committee on Diarrhoeal Disease Vaccines, Vaccine Development, World Health Organization (WHO), Geneva (1) and through group consensus of the Brighton Collaboration Intussusception Working Group. The WHO report is a comprehensive description of the incidence, clinical presentation and management of acute intussusception in infants and children, based on a thorough review of the published literature from 70 developing and developed countries. The literature review was based on a 2 phase search strategy using an electronic database search, references sourced from the bibliographies of identified articles and WHO reports. The phase 1 search resulted in the identification of over 3200 references from Medline and Pubmed between 1966 and February 2001. The search was then limited to reflect the epidemiology and clinical presentation of intussusception within the pediatric age group (0-18 years). This search strategy resulted in the identification of 330 publications for review of which 269 publications were selected and summarized in the WHO report.

The clinical case definition for the diagnosis of intussusception is based on levels of evidence and a combination of major and minor criteria. As this model is also used in the clinical diagnosis of other diseases, including rheumatic fever and bacterial endocarditis, the format will be familiar to healthcare workers (5).

Due to the range of atypical symptoms reported to be associated with intussusception, no clinical case definition can be expected to identify all patients presenting with this condition. In addition, as experience with the definition broadens and developments in methods of diagnosis occur, the definition may need to be refined accordingly in the future. One area currently under evolution is the role of ultrasound in the diagnosis of intussusception. In centers with specific expertise in pediatric ultrasound, the sensitivity and specificity of this technique is equivalent to contrast enema. However, even in published studies the specificity of ultrasound in the diagnosis of intussusception ranges from 78 to 100% (6). In the Brighton Collaboration Clinical Case Definition, the role of ultrasound in the definite diagnosis category is qualified by the presence of characteristic features of ultrasound which resolve following hydrostatic enema reduction. The presence of an abdominal mass with features characteristic of intussusception but not seen to resolve following enema reduction is included as a major criterion with the category of probable intussusception. The minor criteria defined in the Clinical Case Definition are a group of non-specific features which, in combination with major criteria, improve the sensitivity of the definition, however, when assessed alone have poor predictive power. For example, male sex and age less than 1 year has been defined within this group. A male predominance has been observed in almost all studies on intussusception however the reason for this is not yet known. Similarly a peak age of acute intussusception was reported as between 4 and 8 months in most studies (1). A further discussion on the rationale for the selection each clinical criterion is available in the following publication (6).

2. Clinical case definition for the diagnosis of Acute Intussusception in infants and young children

Level 1 of Evidence (*Definite*) Intussusception

Surgical criteria

The demonstration of invagination of the intestine at surgery,

and/or

Radiological criteria

The demonstration of invagination of the intestine by either gas or liquid contrast enema,

Or

The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features¹ that is proven to be reduced by hydrostatic enema on post-reduction ultrasound

and/or

Autopsy criteria

The demonstration of invagination of the intestine.

Level 2 of Evidence (*Probable*) Intussusception

Clinical criteria

Using specific definitions listed in below

2 major criteria

or

1 major criterion² and 3 minor criteria

Level 3 of Evidence (*Possible*) Intussusception

Clinical criteria

4 or more minor criteria

Footnotes

¹ target sign or doughnut sign on transverse section and a pseudo-kidney or sandwich sign on longitudinal section.

² If 1 major criterion is rectal bleeding in the form of bloody diarrhoea then consideration should be given to infectious causes, such as *E.coli*, *shigella* or *amoebiasis*. In such cases 2 major criteria should be met.

Definitions of Terminology used in the Clinical Case Definition

Major Criteria

1. Evidence of intestinal obstruction

- I. History of bile-stained vomiting
and either
- II. Examination findings of abdominal distension and abnormal or absent bowel sounds,
or
- III. Plain abdominal radiograph showing fluid levels **AND** dilated bowel loops

2. Features of intestinal invagination

One or more of the following:

- I. abdominal mass
- II. rectal mass
- III. rectal prolapse
- IV. plain abdominal radiograph showing a visible intussusceptum or soft tissue mass
- V. abdominal ultrasound showing a visible intussusceptum or soft tissue mass
- VI. abdominal CT scan showing a visible intussusceptum or soft tissue mass

3. Evidence of intestinal vascular compromise or venous congestion

- I. rectal bleeding, *or*
- II. “red currant jelly” stool, *or*
- III. blood on rectal examination

Minor criteria

- Predisposing factors: age < 1 year and male sex
- Abdominal pain
- Vomiting¹
- Lethargy²
- Pallor²
- Hypovolemic shock
- Plain abdominal radiograph showing non-specific abnormal

Footnotes

¹ *If the vomiting is bile-stained, it cannot be counted twice as a major and minor criterion*

² *Lethargy and pallor typically occur intermittently although in some patients particularly those with an increased severity of intussusception these symptoms may persist until the intussusception has been successfully treated*

3. Guidelines for Determination, Recording and Presentation of Intussusception as an AEFI

It was the consensus of the Intussusception Brighton Collaboration Working Group to recommend the following guidelines to enable meaningful and standardized determination, recording, analysis and reporting of information collected about intussusception. It is understood that levels of reporting detail may vary depending upon available resources and whether the source of information is a prospectively designed clinical trial, a post-marketing surveillance study, or an individual report of an adverse reaction following immunization.

- I. In order to capture all events suspect of intussusception, it is recommended to report all clinically suspected cases of intussusception irrespective if or if not the Brighton Case Definition is met.
- II. Cases that do not meet any of the three levels of evidence (possible, probable, definite) to make the diagnosis of intussusception, should be reported as “suspected case of intussusception with insufficient evidence”
- III. For all reported cases of any level of evidence and for suspected cases, the criteria fulfilled to meet the definition or suspect intussusception, should be recorded and reported in a table.
- IV. For all cases, the following information should be recorded and reported: Age, gender, and weight & length *at time of diagnosis, if known*. Was the child premature (defined as <37 weeks gestation). If yes indicate the gestational age at birth.
- V. Nutritional intake should be reported, if available in a clinical trial setting (e.g., breastfeeding [yes/no], main food staple [list, _____], malnutrition [yes/no]).
- VI. Any diagnosis of intussusception should be accompanied by information about the following specific predisposing conditions for intussusception and/or predisposing for intestinal obstruction:
 - a. Congenital malformation of the intestine i.e. duplication cyst, malrotation, gastroschisis
 - b. Previous intra-abdominal surgery
 - c. Intestinal polyps
 - d. Meckels diverticulum
 - e. Intestinal vascular malformations
 - f. Cystic Fibrosis
 - g. Hirschsprung disease
 - h. OTHER gastrointestinal malformation, list _____

Equally, prior events of intussusception in the patient should be reported.

- VII. Recording and reporting of concurrent use of medications is essential including prescription and non-prescription medication (e.g., herbal or homeopathic medication), particularly for the day of and the time frame of follow-up since immunization until the diagnosis of intussusception.

VIII. The outcome should be reported:

Treatment received / outcome (circle one):

- a. None - Spontaneously resolved
- b. Resolved by liquid contrast/hydrostatic water/air enema
- c. Required surgical reduction but not resection
Alternatively, intussusception not resolved by liquid contrast/hydrostatic water/air enema, but resolved before abdomen was opened.
- d. Required surgical resection: Specify bowel loss _____ cm.
Record site of bowel loss.

Complications of radiological procedure? If yes, specify _____

Complications of surgery? If yes, specify _____

Did the child survive?

IX. In order to determine the time frame between immunization and intussusception the date of immunization and the date of diagnosis should be used.

The date of onset of symptoms needs to be treated with caution, since the prodromal symptoms are indistinguishable from other gastrointestinal illnesses. If date of onset is used in addition to date of diagnosis, the symptoms and time line should be described.

X. Events of intussusception should be analyzed by day of diagnosis post-immunization with Day of Immunization = Day 1.

XI. Data should be presented with numerator and denominator data (and not percentages only), if available.

Since in surveillance systems denominator data are usually not readily available, attempts should be made to identify approximation denominator data. The source of the denominator data should be reported and calculations of estimates be described (e.g. manufacturer data, reporting through Ministry of Health, coverage / population based data etc).

XII. The full immunization history including dates of other immunization should be recorded.

4. References

1. Bines JE, Ivanoff B. Acute intussusception in infants and young children. Incidence, clinical presentation and management: a global perspective. World Health Organization, Geneva. 2001.
2. Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1999, 48(RR-2): 1-20.
3. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. NEJM 2001, 344:564-572.
4. Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep. 1999;48:1007.
5. Durack DT, Lukes AS, Bright DK, et al. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Am J Med 1994;96:200-209.
6. Bines JE, Ivanoff B. Clinical case definition for the diagnosis in infants and young children. (in press)