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Chapter 3

Japanese Guidelines for Intussusceptions and Current Management

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Abstract

The Japanese Society of Emergency Pediatrics published clinical guidelines for the management of intussusceptions in children in 2012. The guidelines aimed to guide clinicians in order to diagnose intussusceptions as early as possible, to initiate appropriate treatment promptly, and to protect intussuscepted children from bowel necrosis, perforation, and shock. Three criteria of "diagnostic criteria," "severity assessment criteria," and "criteria for patient transfer" were proposed for these purposes.

The guidelines consisted of 50 clinical questions and the answers. Grades of recommendation were added to the procedures on the basis of the strength of evidence levels. Barium was no longer recommended for enema reduction, because the patient becomes severely ill once perforation occurs. Use of other contrast media such as water-soluble

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contrast, normal saline, or air was recommended under either fluoroscopic or sonographic guidance.

Liquid enema using water-soluble contrast was suggested to start with caution at a pressure of 100 cmH_2O and gradually increased to a maximum limit of 120 cmH_2O. With gas reduction, gas was suggested to inflate into the rectum at the initial pressure of 80 mmHg which may be increased up to 120 mmHg. Infants under 6 months of age were warned for a higher risk of perforation. The starting pressure of liquid and gas enemas in infants under 6 months of age was suggested to suppressed as low as 80 cmH_2O and 60 mmHg respectively, with special caution in increasing the pressure. Delayed repeat enema was recommended for improvement of reduction success rate, if the initial enema partially reduced the intussusception and if the patient condition is stable.

Before publication of the guidelines, a survey of the current management of intussusception in Japan was performed in 2011. A postal questionnaire was sent to members of the Japanese Society of Emergency Pediatrics, and the response rate was 41%. The results are shown under the "current management in Japan" at the end of each section.

Introduction

Intussusception is one of the most common causes of pediatric emergencies. Delay in diagnosis and treatment may result in bowel necrosis or even death of infants and children.

However, there had been no evidence-based guidelines for the management of intussusception in children neither in Japan nor in other countries until the Japanese Society of Emergency Pediatrics published clinical guidelines for the condition in 2012 [1, 2]. The guidelines were completed with the consensus of the Japan Pediatric Society, the Japanese Society of Pediatric Surgeons, and the Japanese Society of Pediatric Radiology, as well as the Japanese Society of Emergency Pediatrics.

The guidelines aimed to guide clinicians in order to diagnose intussusceptions as early as possible, to initiate appropriate treatment promptly, and to protect intussuscepted children from bowel necrosis, perforation, shock, and death.

The main recommendations of these guidelines are introduced as well as the current management of intussussception by a postal survey of the members of the Japanese Society of Emergency Pediatrics [3].

Methods of Formulatibg the Guidelines

The guidelines were prepared using the technique of evidence-based medicine. Literature was collected from PubMed (Ovid; 1966 to September 2009) and using the key words "intussusception" and "child" or "children," with limiting words of "human" and "English" and the internet version of the Japana Centra Revuo Medicina (Nippon Igaku Chuuou Zasshi; Ovid; 1983 to September 2009) with the equivalent key words of Japanese. Two thousands thirty three papers were collected (1275 English and 758 Japanese) including papers selected from references. The evidence level of each paper was rated in accordance with the Oxford Center for Evidence-Based Medicine Levels of Evidence (March 2009) [2].

The guidelines consisted of 50 clinical questions and the answers related to epidemiology, diagnosis, assessment of severity, and treatment. Grades of recommendation [2] were decide to the procedures of managements on the basis of the strength of evidence levels (Table 1) in principle, but social factors such as medical environment, cost performance, and the Japanese Health Insurance System were also considered.

Table 1. Grading system for rating recommendations [2]

Grade	Type of recommendation
A	Strong recommendation to perform this procedure There is good evidence to support its clinical effects.
B	Fair recommendation to perform this procedure There is fair evidence to support its clinical effects.
C1	Poor recommendation to perform this procedure The existing evidence is poor, but there is a possibility of favorable effects.
C2	Recommendation undetermined The existing evidence is poor or conflicting, and does not allow for making a clear recommendation.
D	Recommendation not to perform this procedure There is evidence to deny its usefulness, or to show its adverse effects.

Survey of Current Management in Japan

Before publication of the guidelines, a survey of the current management of intussusceptions [3] was performed in October 2011. A postal questionnaire was sent to 1783 members of the Japanese Society of Emergency Pediatrics, and 735 replies (response rate 41%) were received. Respondents were 542 pediatricians, 139 pediatric surgeons, 30 emergency room (ER) doctors, 1 general surgeon, and others (23), working in teaching hospitals (183), children's hospitals (86), district general hospitals (403), private clinic (58), and others (5). There was no radiologist member in the Society.

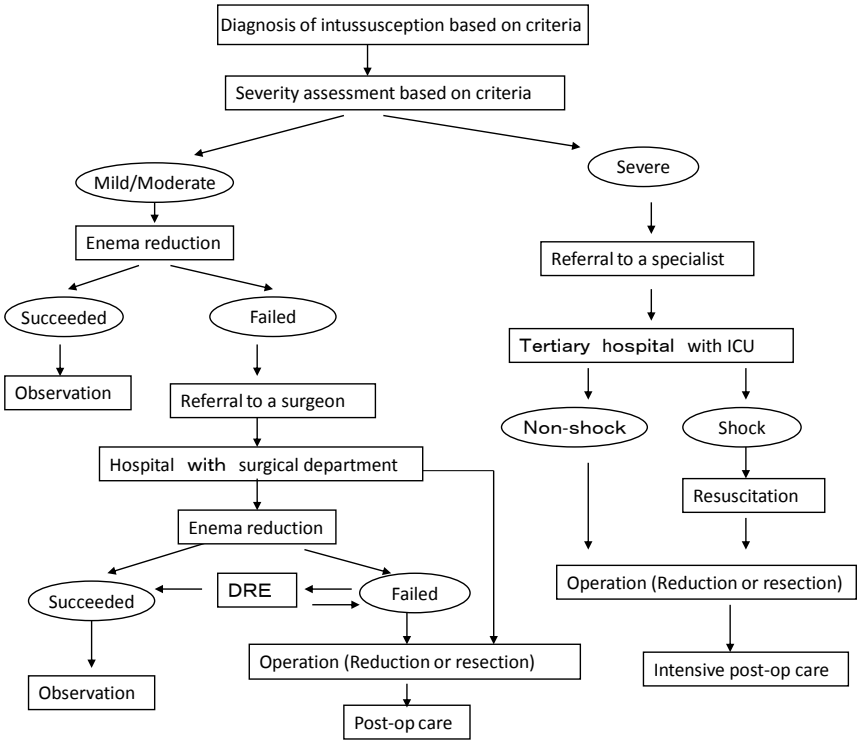

Figure 1. A flowchart for the management of intussusception in children [2] DRE: delayed repeat enema; ICU, Intensive care unit.

The draft of these guidelines had been presented in the annual meetings of the Japanese Society of Emergency Pediatrics since 2 years prior to the

publication to reach a consensus, so that society members were thought to be influenced by the discussion to some extent at the time of the survey.

Flowchart for Management

A flowchart for the management of intussusception in children [2] is presented in Figure 1. The details of diagnostic criteria for early detection, severity criteria for severity assessment, and criteria for patient transfer for referral are described in each section. In these guidelines, the term "enema reduction" is used to represent hydrostatic and pneumatic reduction.

Incidence and Mortality in Japan

There are no national statistics regarding the incidence of intussusception in Japan. There are, however, a statistics of admitted intussusceptions registered at Diagnosis Procedure Combination / Per Diem Payment System (DPC/PDPS) of the Ministry of Health, Labour and Welfare [4]. During 6 months (from July to December) in 2010, enema reduction was undertaken in 2854 patients under 15 years old. Two hundred sixty intussusceptions were reduced by operation and 33 were operated otherwise.

The total number of intussusceptions for half a year will be 3147. But there is a possibility that all patients who underwent enema reduction did not necessarily had intussusceptions, because the diagnosis is made for the reimbursement of medical fees to hospitals. But the number of operated patients is assumed to be accurate. As the recent average reduction success rate in Japan is approximately 87% (87.3% by water-soluble contrast media, 90.2% by air, see Figure 5), total number of non-operatively reduced intussusceptions will be at about 2250 for half a year and 4500 for a year. As the number of live birth in 2010 in Japan was 1,071,000 [5], the incidence of intussusceptions was about 45 per annual 10,000 live birth. As the review of 14 Japanese papers showed that infants under 1 year old comprised 58.0% of 5279 intussusceptions [2], the annual incidence of 26 cases per 10,000 children under 1 year old was 6.7 times higher in comparison with 3.9 per 10,000 in New York States [6]. Japan had to wait until 2013 for the introduction of Rotavirus vaccination in infants. Mortality from intussusception is considered very rare in Japan, but there were 51

intussusception-associated autopsies of children younger than 14 years old reported to registry of the Japan Pathology Association between 1989 and 2008 [2, 7]. Forty of these deaths were infants younger than 1 year old. This is an average of at least 2.5 child or 2.0 infant deaths annually in Japan. There were 5 intussusception-related deaths for all ages registered at the DPC/PDPS [4] in 2010.

Standardized Diagnostic Criteria for Early Detection

The classic triad of abdominal pain, vomiting, and bloody stool were manifested in only 21-36% of cases at presentation [8-10]. In general, the earlier a child visits a clinic, the lesser the degree or severity of the symptoms. If the diagnosis is made promptly, most intussusceptions can be reduced successfully without operation. In addition, deaths from intussusceptions are avoidable. The diagnostic criteria were proposed in the guidelines [2] aiming at early detection of the condition and prompt initiation of the treatment (Table 2).

Criteria A consist of the three most specific symptoms and signs, and criteria B consist of less specific symptoms and signs. Definitive diagnosis is defined as characteristic findings of intussusceptions by imaging (criteria C). These diagnostic criteria are modifications of the case definition developed by the Brighton Collaboration Intussusceptions Working Group to investigate the association between vaccination and intussusceptions [11].

Abdominal pain including irritability is the most frequent presenting symptom of intussusceptions [8-10]. Intermittent and crampy pain is characteristic to this condition.

Bloody stool is also characteristic to intussusceptions, but is a late finding [8, 9]. Spontaneous passage of bloody stools is not commonly present at the initial stage of intussusceptions. Therefore diagnostic enema is helpful when intussusceptions is suspected. The presence of blood in stools increased from 40% to 97% [12] after diagnostic enema and from 53% to 71% by testing stools obtained by rectal examination for occult blood [13]. However negative bloody stools do not necessarily rule out the possibility of intussusceptions. Bloody stools were detectable only in 16% of cases with duration of symptoms less than 12 hours, and rectal bleeding was the primary sign in only 8% of cases [8].

Table 2. Diagnostic criteria for intussusception in children [2]

Criteria A

Abdominal pain or irritability
Bloody stool (including blood detected by enema）
Abdominal mass or distension

Criteria B

Vomiting
Pallor
Lethargy
Shock
Abnormal bowel gas pattern on plain abdominal radiograph

Criteria C

Characteristic image of intussusceptions by contrast enema, ultrasound, computed tomography or magnetic resonance imaging

"Suspicious diagnosis" is defined as when any of the following criteria are met:
One criterion A (abdominal pain or irritability) when it is intermittent
Two criteria A
One criterion A plus one criterion B
Three criteria B

"**Definitive diagnosis**": 'Suspicious diagnosis' plus one of the criteria C.

A tender "sausage-shaped" mass in the right upper quadrant of the abdomen is palpable in 30-85% of cases [8-10, 12, 14], depending upon the skill of the clinician. Emptiness of the ileocecal region (Dance sign) was observed in only 5% of cases, and was not diagnostic [8]. Abdominal distention appears at high frequency as a late sign after 24 hour duration [10].

Vomiting has a high incidence next to abdominal pain [8-10], but it lacks in sensitivity. The presence of the classic triad of abdominal pain, vomiting, and bloody stool is generally associated with long-standing duration of symptoms [8, 9]. Abdominal distension and fever occur more frequently in cases after 24 hours from the onset [10]. As a late sign, some infants present

with profound listlessness and apathy [15]. Clinicians must also suspect intussusceptions in cases in which lethargy or septic shock is the first presenting symptom [14, 15].

There is no specific finding in blood tests to diagnose intussusception. However, if a patient is in severe condition due to bowel necrosis, leucocytosis is seen [16]. If the duration of symptoms is long, metabolic acidosis is expected. There is one report demonstrating that plasma C-reactive protein (CRP) was a useful marker to predict the clinical outcome of intussusceptions [17]. Abdominal radiographs are often unhelpful in diagnosing intussusception. Sargent, M,A.; et al. [18] reported limited agreement between three observers of radiographs and the diagnostic accuracy of abdominal radiographs was only 40% including equivocals. The best positive predictors of intussusception were opacity of soft tissue mass along the course of the colon and sparse large bowel gas in the right iliac fossa [18]. Lee, J.M.; et al. [19] reported radiolucencies in the soft tissue mass (crescent and target lucencies) as characteristic signs of intussusception on radiographs.

An ileocolic intussusception can be excluded by the presence of gas and feces in the cecum. Small bowel obstruction is a late sign and free peritoneal air is a contraindication of enema reduction [20].

Recommendations

1. If we include irritability and crying of unknown origin in infants in abdominal pain, abdominal pain is the most common clinical presentation, which is usually followed by refractory vomiting. Intussusception should be suspected at this early stage (recommendation A).
2. Confirmation of macroscopic bloody stools or occult blood by enema or rectal examination is helpful for diagnosis, when clinical symptoms are obscure (recommendation B).
3. A sausage-shaped mass is palpated in the right hypochondrium. The incidence of “Dance sign,” emptiness of right lower quadrant, is low. Abdominal distension increases with time. Palpation of the abdomen is highly recommended (recommendation A).
4. Blood tests do not have a diagnostic value for intussusception, but they are useful to evaluate the general condition of the patients (recommendation B).

5. Plain abdominal radiographs have a limited diagnostic value, but they are useful to detect free peritoneal air or small bowel obstruction (recommendation B).

Current Management in Japan

According to the postal survey, diagnostic enema was performed almost always in 73.8% (537/728) of respondents, occasionally in 14.3% (104/728), and never in 11.9% (87/728).

Imaging for Definitive Diagnosis

Sonography is used as the modality of choice for screening intussusception at many institutions. It has great merit in that it requires no radiation. It has high sensitivity of almost 100% and specificity of 88-100% [21-23]. Intussusceptions can usually be found with sonography on the right side of the abdomen as a “target” [22], “doughnut” [22], or “crescent-in-doughnut” [24] sign in the transverse plane, and as “pseudokidney” sign [22] on longitudinal section.

Occasional false-positive examination includes any cause of bowel wall thickening, such as enterocolitis and hematoma. Therefore, scanning of both the transverse and the longitudinal plane is important for the diagnosis of intussusception [21, 23]. The disadvantage of sonography is that the accuracy of diagnosis depends on the experience of the operators, who may have insufficient training. If one does not have confidence in utilizing sonography, or sonography is not available in an emergency situation, contrast study is helpful to confirm the diagnosis [25]. Contrast enema has several merits, although it has the disadvantage of radiation exposure. The technique of contrast enema is easy to learn, well known to almost all clinicians, and is less likely to miss the diagnosis of intussusception than sonography.

Once the diagnosis of intussusceptions is made, the clinician can proceed to the reduction with the same modality [20].

Computed tomography (CT) has high resolution in the diagnosis of intussusceptions, but it is not practically used because of the larger dose of radiation required and the necessity for sedation. The use of CT should be reserved for delineation of small-bowel intussusceptions and/or a pathological lead point (PLP) in older children with atypical symptoms [26].

Recommendations

6. Sonography has nearly 100% sensitivity and specificity in diagnosis of intussusception, and is useful for screening the condition (recommendation A).
7. Sonography has priority for diagnosis, but if the diagnosis is uncertain, or when sonographic expertise is not available in an emergency situation, contrast enema study is necessary (recommendation A).
8. Considering radiation exposure, CT is not the first choice for diagnosis of intussusception. But it is useful when intussusception cannot be ruled out, or in rare cases of small-bowel intussusception (recommendation B).

Current Management in Japan

Sonography was selected for diagnosis almost always in 84% (615/730) of respondants, and fluoroscopy was preferred in only 9% (67/730). The rest used either of them depending on the situation (Figure 2).

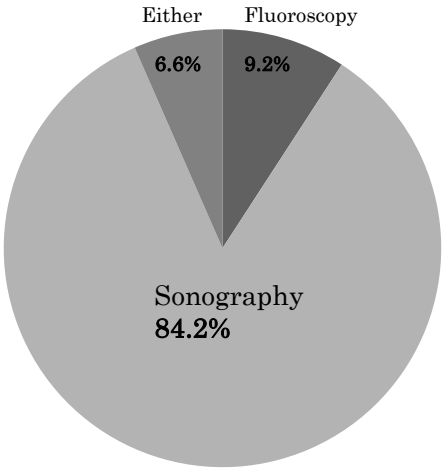

Figure 2. Replies to the question, “What modality do you use for diagnosis in suspected cases?” (n = 730).

Severity Assessment Criteria for Saving Severely Ill Patients

Intussusceptions is a strangulation obstruction, leading to bowel ischemia, necrosis, sepsis, and eventually death. There are a variety of degrees of severity from mild to severe in the pathophysiology of intussusceptions. The severity assessment criteria [2] were proposed in the guidelines aiming at selection of the appropriate procedures for diagnosis, treatment, or prompt referral to a tertiary hospital according to the severity of the intussusceptions (Table 3).

Table 3. Severity assessment criteria for intussusception in children [2]

Severe	Poor general condition or one of the following conditions indicating bowel necrosis 1) Septic shock 2) Peritonitis 3) Free peritoneal air on a plain abdominal radiograph
Moderate	Stable general condition, but one of the following conditions indicating possible ischemia of the bowel 1) Duration of symptoms beyond 48 h 2) Infants of 3 months of age and younger 3) The apex located beyond the splenic flexure 4) Ileoileocolic type 5) White blood cells > 20,000/μL, elevated CRP > 10mg/dL 6) Small bowel obstruction on a plain abdominal radiograph 7) Ultrasound findings of lack of blood flow, trapped fluid between intussuscepted bowl walls, and presence of pathological lead point
Mild	Stable general condition in which criteria of "severe" or "moderate" are excluded.

"Severe" intussusception is a state of poor general condition from its basic disease or suspected bowel necrosis. Poor general condition suggests

gangrenous intussusceptions. Severe dehydration, septic shock, and signs of peritonitis are suggestive of a “severe” state of intussusception. After adequate resuscitation by intensive care, surgery is the treatment of choice. Contrast enema reduction is contraindicated, [27, 28] and sonography is preferable as a diagnostic modality.

“Moderate” intussusceptions is a state of stable general condition, but is accompanied by symptoms and signs of possible bowel ischemia. Enema reduction is not contraindicated but because of the possibility of perforation or unsuccessful reduction, cautious selections of contrast media, reducing pressure, reduction time, and reduction attempts are necessary.

Duration of symptoms of more than 48 hours was significantly correlated with failure of enema reduction and with a high rate of bowel resection [16]. The longer the duration of symptoms, the lower the likelihood of successful enema reduction and the higher the rate of bowel perforation [29]. However, a long duration of symptoms itself is not a contraindication for attempted enema reduction. For infants, age of 3 months and younger was associated with a low success rate of reduction [30], and younger age was a predictor of perforation [29]. The location of the apex has also been correlated with severity. Reduction success rate was low when the intussusception was encountered beyond the splenic flexure [31]. Successful enema reduction is less likely especially once the apex reaches the rectosigmoid region [32].

Among types of intussusceptions, the ileoileocolic type is also significantly correlated with low enema reduction rate [29, 33] and bowel necrosis [29].

Leucocytosis is more frequently seen in moderate-to-severe cases. In one study, the incidence of white blood cell count greater than 20,000/μL was significantly higher in the bowel-resection group compared with those of the operative-reduction group and the enema-reduction group [16]. Elevated CRP > 10mg/dL also reflects the degree of severity of the condition. The incidence of CRP > 10mg/dL was significantly higher in the bowel-resection group compared with those of the operative-reduction group and the enema-reduction group [17].

The presence of small-bowel obstruction is a risk factor for failure of enema reduction and for bowel resection [34], but it is not a contraindication to performing the enema. Free intraperitoneal air is said to be a contraindication for enema reduction, but there were no relevant cases documented in literature after 1966.

Absence of blood flow by Color Doppler sonography has been shown to be predictive of bowel necrosis and the need for bowel resection [35-37].

Detection of blood flow was associated with successful enema reduction, and lack of flow is suggestive of failure of enema reduction [36, 38, 39]. However, nonvisualization of blood flow by color Doppler sonography was not a contraindication for attempted air enema reduction [38]. These different results may be influenced by the sensitivity of the equipment used and the technique of the examiners.

Trapped peritoneal fluid between two limbs of the intussuscepted was also shown to be associated with a significantly lower reduction success rate and higher degree of bowel ischemia [40, 41]. Although trapped fluid is not a contraindication for attempting air enema reduction, vigorous, high-pressure enema reduction should not be attempted [40]. The presence of free intraperitoneal fluid in small or moderate amount does not predict a lower enema success rate, but a large amount of intraperitoneal fluid is predictive of surgery [21, 23]. The presence of a PLP is a risk factor for irreducible intussusceptions and surgery [9, 31, 42], but it does not necessarily mean that enema reduction is impossible [23].

There are no reports demonstrating a sufficient evidence level that discuss the correlation between CT findings and the severity of the intussusceptions. Sonography has priority in the assessment of severity. The use of CT should be reserved for special cases, in which sonography is of no use.

“Mild” intussusceptions is a state which does not fulfill the above mentioned conditions of “severe” or “moderate” intussusceptions. Patients with this condition are good candidates for enema reduction.

As predictors of bowel necrosis, duration of symptoms beyond 48 hours, ileoileocolic type, and lack of blood flow by color Doppler have been considered in previous clinical discussions. But none of these features, in isolation, is an absolute contraindication to enema reduction. However, a combination of these factors will significantly increase the risk of bowel necrosis, the possibility of bowel resection, and incidence of complications.

Recommendations

9. Shock, peritonitis, duration of symptoms, age, location of the apex, and invagination type do correlate with severity. Therefore, a detailed history of clinical symptoms and physical examination are important (recommendation A).
10. Leucocytosis of white blood cell counts > 20,000/μL and elevated CRP > 10mg/dL are often observed in moderate to severe

intussusceptions. White blood cell count and CRP are useful for severity assessment (recommendation B).

11. Free peritoneal air and small bowel obstruction on plain abdominal radiographs are useful for severity assessment (recommendation B).
12. Lack of blood flow, trapped fluid between intussuscepted bowl walls, and presence of PLP correlate with severity of intussusception. Sonography is useful for severity assessment (recommendation B).
13. Location of the apex and invagination type correlate with severity of intussusception. Contrast enema is useful for severity assessment (recommendation B).
14. There are a few case reports on CT findings demonstrating bowel necrosis. However, evidence levels are low and moreover there is a concern of radiation exposure in CT. CT is not useful for severity assessment (recommendation C2).

Criteria for Patient Transfer

Criteria for patient transfer [2] is proposed in the following "Recommendations."

Severely ill patients with peritonitis or in shock are contraindicated for enema reduction, and it is recommended to transfer these patients immediately to tertiary hospitals, including children's hospitals, where intensive preoperative care is possible and surgeons (ideally pediatric surgeons) are available. Enema reduction rate was higher, and hospital stay was shorter when patients were treated at children's hospitals in comparison with those treated at non-children's hospitals, owing to a positive volume-outcomes relationship [43, 44]. If an attempted enema reduction is a failure in mild-to-moderate cases, it is also necessary to refer these patients to a hospital where surgeons are available. Prompt transfer of patients is important for improvement in case management. Delay of transfer of more than 24 hours from a non-teaching hospital to a teaching hospital increased the incidence of operation significantly [43, 45].

Recommendations

15. Patients with severe intussusception should not undergo enema reduction, but should be transferred immediately to a tertiary hospital

where intensive care, including surgery, is possible (recommendation A).

16. Patients with moderate intussusceptions need careful attempt at enema reduction. If the attempt is in failure, the patient should be transferred to surgical facilities as soon as possible (recommendation A).
17. Patients with mild intussusception are good candidates for enema reduction. If the reduction fails, the patient should be transferred to surgical facilities as soon as possible (recommendation A).

Management for Non-Operaive Reduction

It is now generally accepted that non-operative reduction should be attempted in most patients with acute idiopathic intussusception. The apex of the intussusceptum is pushed back by hydrostatic or pneumatic enema. Different types of contrast media (including negative contrast of air) are used under the guidance of fluoroscopy or sonography. Various combinations of contrast media and monitoring modalities are possible.

Based on the reduction success rates published in the recent literature, one should aim to achieve at least an 85% success rate, and even as high as 95%. However, these rates will be influenced by the specific patient population one sees.

Fluid

In cases deemed moderate-to-severe by severity assessment, it is important to correct the child's hypovolemia and dehydration with adequate fluid replacement intravenously prior to surgery or enema reduction [27, 46, 47]. Dehydration is observed about in 50% of cases of intussusception [46].

In mild cases with good hydration, intravenous resuscitation is not necessary. However, placement of venous line is desired for safety to cope with complications that may arise during enema reduction.

Recommendations

18. In cases of severe and moderate intussusceptions, circulatory insufficiency and dehydration should be treated with extracellular fluid replacement (recommendation A).

19. In cases of mild dehydration, intravenous fluid is not necessarily required, but it is desirable to maintain the venous route to handle complications expected by enema reduction (recommendation B).

Current Management in Japan

Venous route was maintained almost always in 86.8% (592/682) of respondents, occasionally in 8.5% (58/682), and never in 4.7% (32/682) according to the postal survey.

Use of Anesthesia

Some authors, in the past, have recommended routine use of general anesthesia including gas [48], thiopenthal [49], and ketamine [50, 51], which they believed improved enema reduction rate. However no differences have been demonstrated in reduction rates between two groups with and without anesthesia [52, 53]. There are also papers recommending the use of general anesthesia in the second attempt in the operating room with improvement of reduction rates [54-56]. However, in these cases, improvement of reduction rates may possibly be attributed to the effect of delayed repeat enema (see the section of "delayed repeat enema"), not of general anesthesia.

Recommendation

20. There is no significant difference between enema reductions with and without general anesthesia. General anesthesia is not necessary for reduction (recommendation C2).

Current Management in Japan

General anesthesia for reduction was performed almost always in 17.5% (119/681) of respondents, occasionally in 17.5% (119/681), and never in 65.0% (443/681).

Use of Sedation and/or Antispasmodics

Various kinds of sedation such as diazepam [30, 50, 55, 57, 58], chloral hydrate [55, 59], pentazocine [60, 61], meperidine [15, 62], morphine sulfate

[15, 63, 64], etc. have been customarily used. There is a comparative study of analgesic premedication, which improved the reduction rate [62]. However the conclusion is of this study is questionable, because the reduction rate of the sedation group was 68%, while that of the non-sedation group was only 36%, which is extremely low. Therefore, there is little evidence to support or condemn the use of sedation. The use of sedation depends on the clinician's preference at present. Butylscopolamine (Buscopan®) has been used customarily as an antispasmodic agent, to irrigate the colon smoothly with contrast media [57, 65, 66]. However, there are no controlled studies evaluating its effectiveness. The use of Buscopan® is left to the clinician's preference at present. Glucagon has muscle relaxant effects as well as Buscopan®, and has been used for enema reduction. In earlier reports, the reduction rate was higher when Glucagon was used [60, 63]. However, more recent randomized controlled studies have shown that glucagon is of no benefit [67, 68]. The use of glucagon is not recommended as it is an expensive drug in comparison to Buscopan®, and health insurance in Japan may not cover the fee.

Recommendations

21. There are few papers discussing the effectiveness of sedation. The use of sedation is left to the physician's choice (recommendation C1).
22. There is no comparative study on the effectiveness of Buscopan® in enema reduction. The use of Buscopan® is left to the physician's preference (recommendation C1).
23. The effectiveness of glucagon in the improvement of reduction rate is inconsistent. Glucagon is not recommended for reduction (recommendation C2).

Current Management in Japan

Sedation and/or antispasmodics were used almost always in 21.0% (145/674) of respondents, occasionally in 15.9% (107/674), and never in 62.6% (422/674).

Selection of Imazging

There are many reports of enema reduction under sonography [33, 55, 61, 69-78] since Bolia's report [79] in 1985. The greatest advantage of sonography is that it does not involve radiation exposure to children, and therefore reduction can be attempted repeatedly without concern for time [55]. The modality of sonography has another advantage in that it is able to detect PLPs on reduction such as Meckel diverticulum or duplication cysts [80, 81]. The main disadvantage of sonography is the need for training of a clinician, because it is an extremely operator-dependent modality [70, 81].

There is no study on the direct comparison of reduction with fluoroscopy versus reduction with sonography, Considering the differences of medical environments and expertise of clinicians, the choice of either fluoroscopy or sonography depends on a clinician's favor.

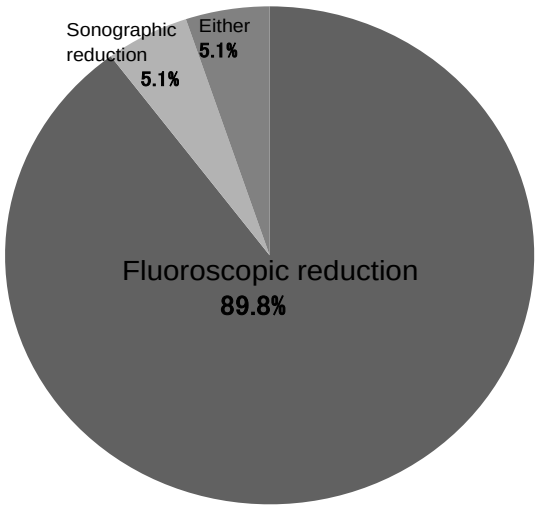

Figure 3. Replies to the question, "What modality do you use for non-operative reduction?" (n = 683).

Current Management in Japan

Fluoroscopic reduction was preferred in 89.8% (613/683) of respondents and sonographic reduction was selected in only 5% (35/683). The rest used either of them depending on the situation (Figure 3).

Selection of Contrast Media

After Ravitch's report [82] in 1948, the use of barium for enema reduction has become the definitive non-operative management throughout the world. However, the major disadvantage of barium enema reduction is the complication of barium peritonitis when perforation occurs during the enema [83-87].

Barium spilled into the abdominal cavity and mixed with feces cannot be removed completely. Barium adhered to the peritoneum and omentum remains radiologically for years and can cause intestinal obstruction later. Once perforation has occurred, patients with barium enema have been shown to require bowel resection more often, longer hospital stays, and increased morbidity rates compared to those with air [84, 88] or water-soluble contrast enema [87, 88]. Because of this risk, water-soluble iodinated contrast media such as diatrizoate meglumine (Gastrografin®) [85, 88 -91] or air [29, 46, 47, 49, 50, 59, 64] is preferred over barium as an alternative contrast media for enema reduction under fluoroscopy.

The advantage of the use of the barium enema reduction technique has been claimed to be its clear delineation of the reducing process of intussusception, but water-soluble agents diluted to iso-osmolar concentrations still allow appropriate anatomical delineation under fluoroscopy [85, 91]. Water-soluble iodinated contrast media is recommended instead of barium if one chooses hydrostatic reduction under fluoroscopic guidance. On the other hand, air is preferred outside of Japan, because it is considered cheaper and safer when perforation occurs. The disadvantage of the air enema technique under fluoroscopy is that the delineation of the intussusception image is less clear, and clinicians who are accustomed to positive contrast media may need to get used to it. Especially, it may be more difficult to visualize both the intussusception and reduction in patients with marked amounts of gas in the small bowel [50]. As for the contrast media under sonographic guidance, there are several series studies that have achieved equally high reduction rates using air [38, 41, 71, 73, 75, 76] or liquid [33, 55, 61, 69, 70, 72, 74], but no comparative study of air and liquid has been carried out. Either air or normal saline can be used according to the preference of the physician.

Recommendtion

24. Barium has traditionally been used as a contrast media, which most physicians are accustomed to. However, once perforation occurs

during the enema, the patient becomes severely ill. Barium is no longer recommended (recommendation D). Use of contrast media other than barium is recommended.

Current Management in Japan

Gastrografin® was preferred for fluoroscopic reduction in 67% (433) over air 23% (150) of 646 respondents. Barium which is not recommended in the guidelines any more was used only in 6% (40/646) (Figure 4). For sonographic reduction, normal saline was preferred in 73% (49) over air 15%(19) of 67 respondents.

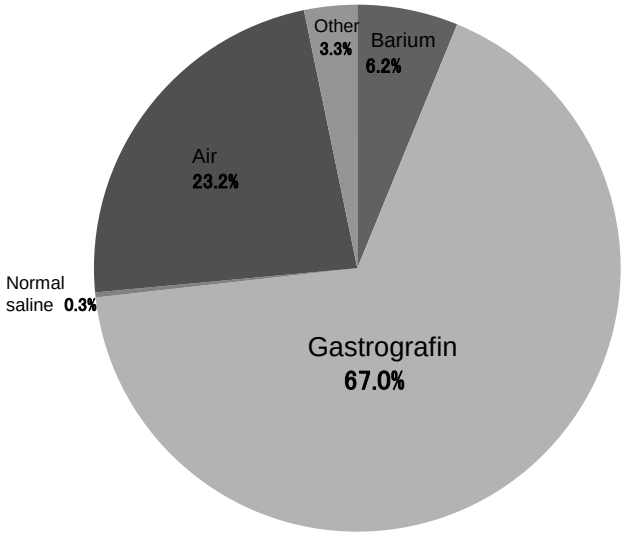

Figure 4. Replies to the question, "What contrast media do you use for fluoroscopic reduction?" (n = 646).

Comparison of Reduction Success Rate between Japan and Other Countries

Surveys [92-94] of pediatric radiology departments in North America and Europe have shown a trend among pediatric radiologists to change from hydrostatic reduction to pneumatic reduction techniques under either fluoroscopy or sonography. This change may be due to the lower reduction success rate in barium than in air or oxygen in comparative studies (53-85%

versus 73-100% [95-98]. This relatively low reduction success rate in barium enema may be explained by relatively low reduction pressure in the "Rules of Threes" (three attempts of 3 minutes each, with enema bag 3 feet (91 cm) above the fluoroscopy table) [99], to which pediatric radiologists have been strictly adhered.

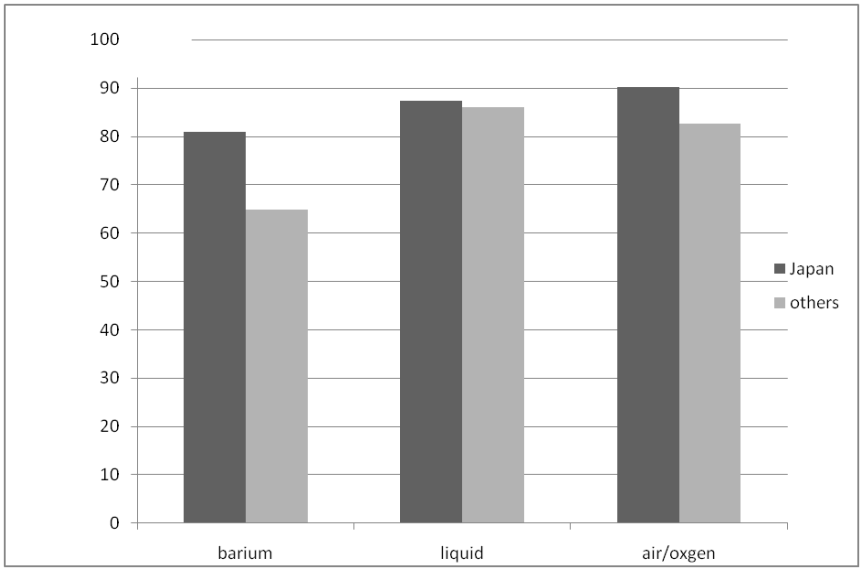

Figure 5. Comparison of reduction success rates of different contrast media in Japan and other countries.

Different from North America and Europe, the health insurance system in Japan allows patients free access to hospitals. The majority of patients with intussusceptions visit clinics or hospitals in a timely fashion and are seen primarily by pediatricians with a surgeon in attendance or by pediatric surgeons. Average reduction success rate of 81.0% (3088/3811) in barium enema under fluoroscopy in Japan [48, 52, 53, 56, 60, 66, 100-104] is much higher than 64.8% (2601/4013) in other countries [9, 14, 16, 30, 57, 61-63, 65, 67, 68, 86, 95, 96, 98, 105-114] (Figure 5). This difference may be due to higher pressure (100~120 cmH_2O) applied in reduction in Japan. On the other hand, average reduction success rates in the Japanese literature was 87.3% (1319/1511) in liquid (water-soluble contrast media) [39, 51, 56, 58, 89, 91, 115-119] enama, and 90.2% (707/784) in air enama [12, 49, 50, 56, 71, 120]. In comparison, average reduction success rates in other countries were, 86.0%

(1579/1836) in liquid enema (normal saline, Hartman's solution, tap water, and water-soluble contrast media) [33, 40, 54, 55, 61, 69, 70, 72, 74, 77, 78, 112, 113, 121] and 82.7% (3496/4226) in air or oxygen enama [10, 29, 36, 38, 41, 46, 47, 64, 73, 75, 76, 86, 95-98, 106, 112, 122-134] (Figure 5). In Japanese institutions, therefore, either Gastrografin® (diluted 1:5 [115]) or air is chosen as a contrast media.

The reduction rates of these two contrast media are comparable, leaving the selection to the clinician's favor.

Recently, Beres, A.L. and Baird, R. [135] reported systematic review with meta-analysis of pneumatic versus hydrostatic reduction, and concluded that pneumatic reduction should be the method of choice. But comparison was made mostly between air reduction and barium reduction in this review. Comparative studies of gas (air and oxygen gas) versus liquid (water-soluble contrast media, normal saline, and Hartman's solution) would be necessary.

Pressure for Enema

Traditional practice in Japan dictates a barium column of 100 cm to a maximum of 120 cm if the intussusception is static [51, 102-104]. Same rule is applied in liquid enema reduction under fluoroscopy [115,118] and sonography [51, 117].

In air enema reduction under fluoroscopy and sonography, air is carefully pumped into the rectum up to a pressure of 80 mmHg at first, which is equivalent to 1-m column of barium [95, 96]. The pressure may be increased to 100 mmHg [49, 71] and to a maximum limit of 120 mmHg [46, 47, 73, 76], which is equivalent approximately to 1.5-m barium column [47]. Guo, J.B. et al. [59] stated that the maximum pressure in young infants should be limited to 80 mmHg. For air reduction, pressure needs to be carefully monitored by pressure gauge [47, 59, 73, 75], which may require a pressure release device and an experienced operator. Once perforation occurs, an emergent tap of the peritoneal cavity by an 18 gauge needle is necessary for tension pneumoperitoneum [46, 47, 84].

Recommendation

25. Liquid enema using diluted Gastrografin® is started with caution at a pressure of 100 cmH_2O and gradually increased to a maximum limit of 120 cmH_2O (equivalent to 94 mmHg). With gas reduction, gas is inflated into the rectum at the initial pressure of 80 mmHg which may

be increased up to 120 mmHg. In infants under 6 months of age who have a higher risk of perforation, the starting pressure of liquid and gas enemas should be 80 cmH_2O and 60 mmHg, respectively, and great attention should be paid to the increase of pressure (recommendation B). Notwithstanding, there is always a risk of perforation.

Current Management in Japan

The pressure limit for 10 months old infant was 120 cmH_20 for liquid reduction in the majority (93%) (Figure 6), and that for 3 months old infant was 100 cmH_20 in the majority (84%) (Figure 7).

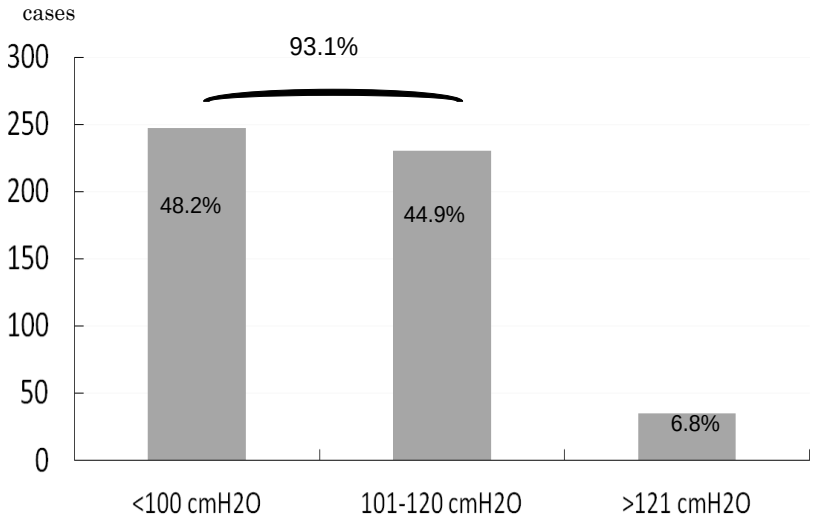

Figure 6. Replies to the question, "If you perform liquid enema what maximum pressure do you apply on a 10 months old infant?" (n = 512).

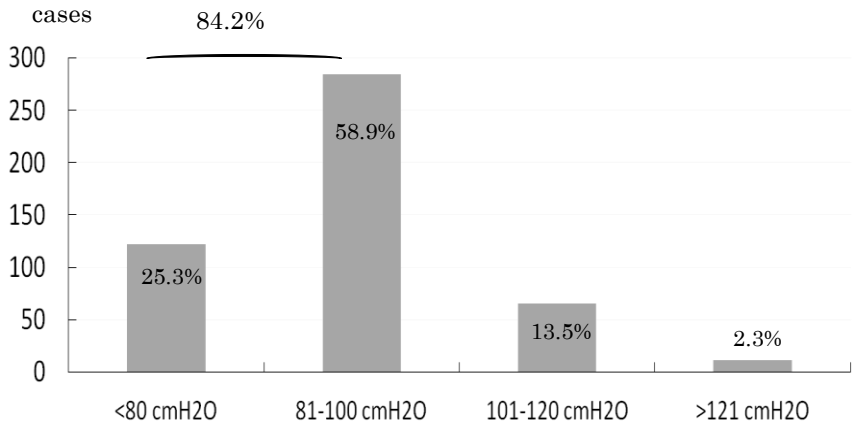

Figure 7. Replies to the question, "If you perform liquid enema what maximum pressure do you apply on a 3 months old infant?" (n = 482).

The pressure limits for 10 months old infant was 120 mmHg for air reduction in the majority (96%) (Figure 8), and that for 3 months old infant was 100 mmHg in the majority (88%) (Figure9).

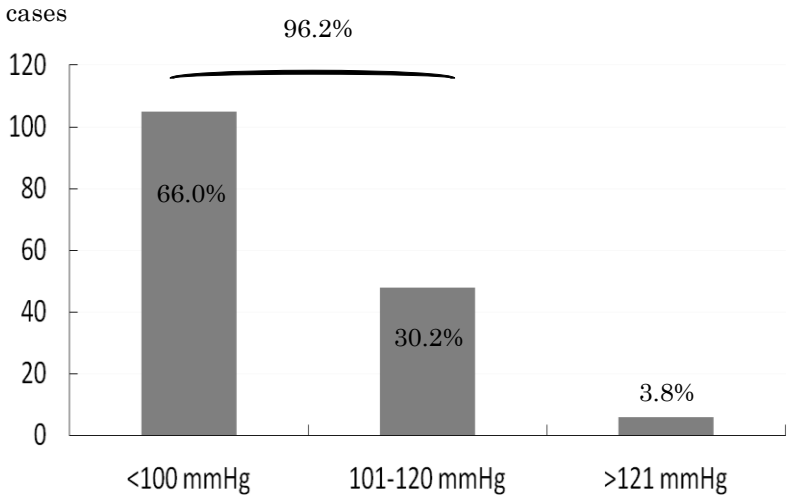

Figure 8. Replies to the question, "If you perform air enema what maximum pressure do you apply on a 10 months old infant?"(n = 159).

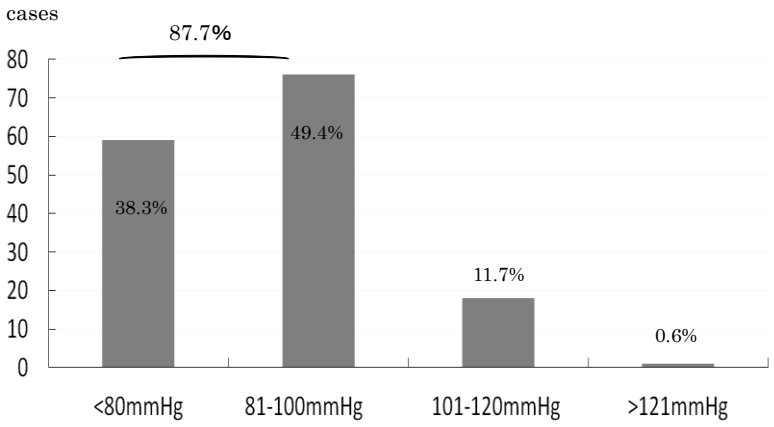

Figure 9. Replies to the question, "If you perform air enema what maximum pressure do you apply on a 3 months old infant?" (n = 154).

Relationship between Maximum Reduction Pressure and Reduction Success Rate

The correlation between maximum reduction pressure and reduction success rate in the different contrast media, including Japanese literatures [2] is illustrated in Figure 10. Reduction success rate correlates well with reduction pressure,

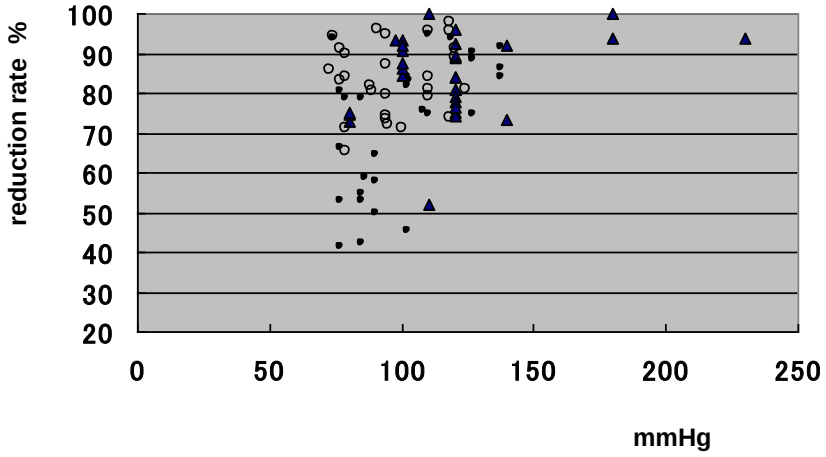

Figure 10. Relationship between maximum reduction pressure and reduction success rate in different contrast media [2] (● Barium, ▲Air, ○Water-soluble contrast).

Complications

The most important potential complication of enema is bowel perforation. There are many reports of high perforation rates by air enema reduction (6.0% [41], 3.9% [76], 2.8% [29]). However, Guo, J.B. et al. [59] reported a very low perforation rate with air enema of 0.141% in 6,396 intussusceptions. Accordingly, the overall mean perforation rate of air enema became extremely low, and perforation rates for air versus liquid enema are reported not to be significantly different in multiple reviews. But Guo's report was excluded from the analysis in the guidelines as the results of critical evaluation [2]. Consequently, perforation rates differed depending on contrast media.

Perforation rates with barium, liquid, and air were 0.14%, 0.37%, and 0.76% respectively [2]. When the perforation rates were confined only in Japanese literatures, they were 0.16% (6/3811) in barium enema [48, 52, 53, 56, 60, 66, 100-104], 0.20% (3/1511) in liquid enema [39, 51, 56, 58, 89, 91, 115-119], and 0.38% (3/784) in air enema [12, 49, 50, 56, 71, 120] (Figure 11). Perforation rate was higher in air than barium or liquid possibly due to the higher pressure applied during pneumatic reduction.

It is clear that the use of excessive pressure during enema reduction is the main cause of perforation [84]. However, perforation does occur at pressures even as low as 60-80 mmHg [84].

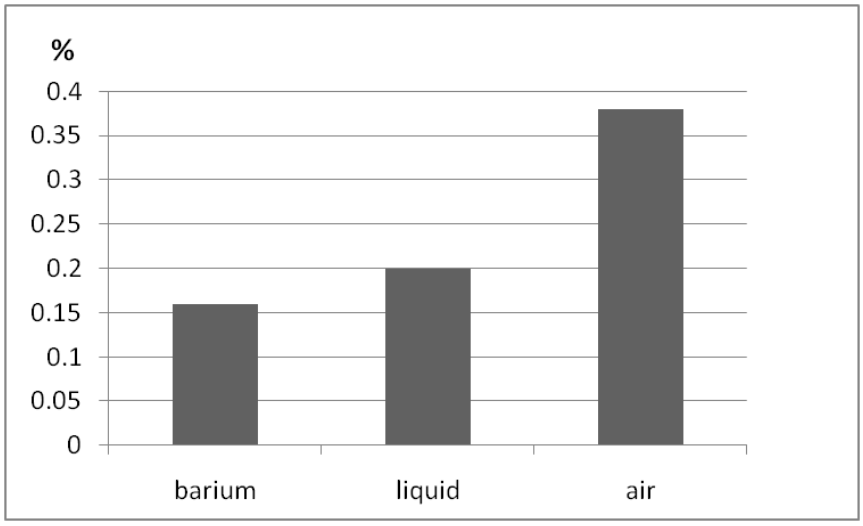

Figure 11. Perforation rates of different contrast media in Japan.

The statistical analysis of perforation shows that more than half of perforations occur in infants less than 6 months of age [2] (Figure 12). Particular care regarding enema reduction should be taken in younger children with a longer duration of symptoms or with evidence of small bowel obstruction on plain radiography [29, 34]. An overly aggressive approach must be condemned in cases with risk factors.

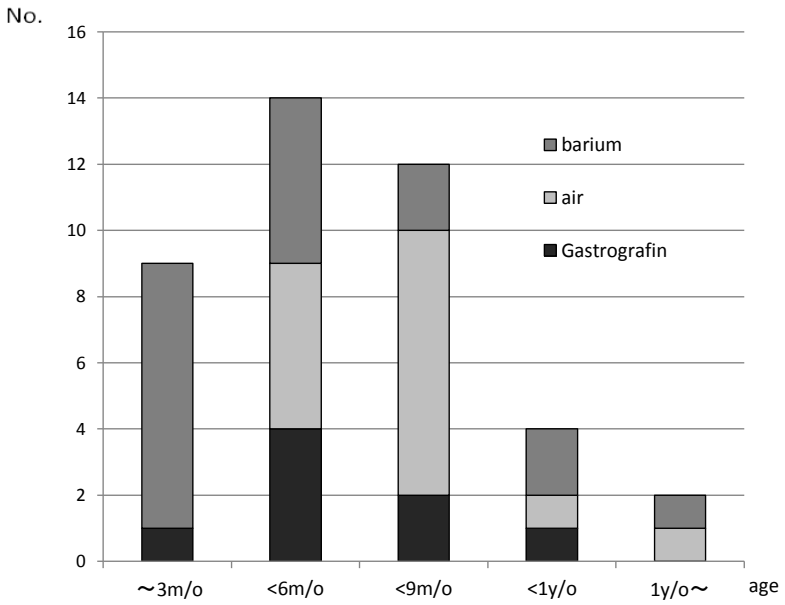

Figure 12. Relationship between age and perforations [2].

Delayed Repeat Enema

Delayed repeat enema refers to reattempt of enema reduction at a certain time interval after the initial attempt at reduction was a failure. It generally refers to reattempt of reduction at the same institution.

Operative reduction is the standard treatment after the failure of enema reduction of intussusceptions. However, 10-14% of intussusceptions have been found to be spontaneously reduced at operation [105, 107]. Hence, enema reduction was repeated at a certain time interval after the first failed attempt. Reduction success rates were improved by 50-86% in DRE cases with failed initial enema reduction [54, 121, 125, 126, 130, 136, 137]. The indications for

DRE are clinically stable infants with no evidence of peritonitis and only when the initial enema achieved a partial reduction [125, 130, 136]. It is believed that partial reduction and the time interval between attempts allow the venous congestion and edema of the bowel wall to decrease and facilitate the reduction of the residual bowel. [54, 125] Optimal timing for the repeat attempt has not been established, but 30 minutes to 4 hours delay after the initial attempt seems to be common [121, 125, 126, 130, 136, 137]. Delayed enema should not be performed if the child is clinically unstable or if the initial enema failed to move the intussusception at all [27, 125, 136].

Recommendation

26. DRE improves reduction success rate. It is useful to attemt DRE, if the initial enema partially reduced the intussusception and if the patient is in stable condition (recommendation B).

Current Management in Japan

DRE (defined as reattempt of reduction at the same institution) was performed mostly after 1 hour (55%, 18 respondents) of those who do DRE (n = 33). DRE was attempted once in 44%, twice in 22%, and 3 times in 33% of respondents who do it with 1 hour intervals (Figure 12).

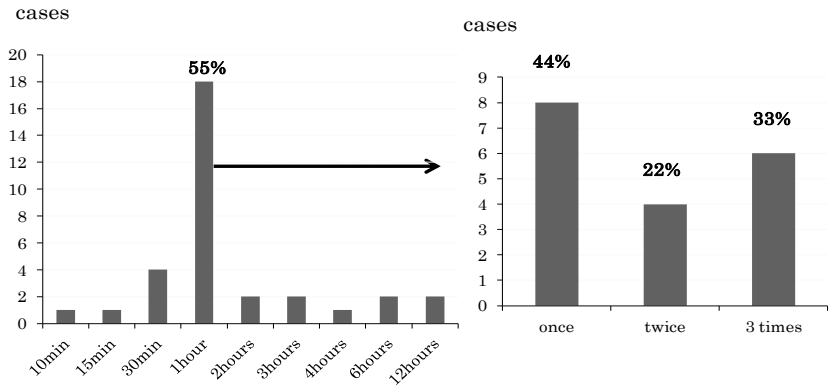

Figure 13. Replies to the questions, “How long is the interval of your delayed repeat enema (n = 33)” and “how many times do you attempt at 1hour interval (n = 18)?”

Admission

Observation under admission is the standard care after a successful enema reduction in Japan. One has to be especially careful in regards to recurrence, because 40% of recurrences take place within 48 hours of the primary reduction of intussusceptions [138]. However, there are several reports in which uncomplicated patients with good hydration, no underlying diseases, and good access to hospitals are able to go home after short-term observation at the outpatient clinic or emergency room [108, 129, 131]. Recurrence of intussusception outside the hospital did not affect clinical outcomes [129].

Recommendation

27. It is allowable to let the patient go home after an appropriate time of observation at an out-patient clinic or emergency room, when the patient is in stable condition and has good access to medical facilities (recommendation C1).

Current Management in Japan

96% (640/669) of respondents replied that they admitted patients almost always for observation after successful reduction.

Antimicrobial Therapy

Serial blood culture studies both pre-enema and post-enema did not justify routine administration of antibiotics after enema reduction [139]. Antibiotics are not routinely used at most institutions [93, 140]. Antimicrobial therapy is justified only in the presence of an underlying sepsis.

Recommendation

28. Routine administration of antimicrobial drugs is not necessary after enema reduction (recommendation C1).

Current Management in Japan

Routine antibiotic cover was denied in 92% (615/667) of respondents.

Confirmation

Reduction is deemed to be satisfactory only if there is free reflux of contrast media into the distal small bowel loops without filling defect under fluoroscopy, together with resolution of symptoms and signs in the patients.

The same thing can be true for air enema [73, 76] or liquid enema [69, 141] under sonography. Sonography is useful to confirm complete reduction repeatedly in uncertain cases without free reflux of contrast media or with persistent filling defect of possible edema, suspected residual bowel or PLP [21, 27, 141]. Edema of the ileocecal valves remains after successful reduction as a post-reduction "donut sign," which is smaller than the target sign and not multi-concentric as is the target sign [27, 142].

Recommendations

29. Sonography is the most effective method to confirm complete reduction and to exclude residual intussusception or recurrence (recommendation B).

Recurrence

In the review of the Japanese literature [2], PLPs were seen in 3.9% (80 PLPs out of 2069 intussusceptions), and the overall recurrence rate of intussusception after enema reduction was an average of 10.3% (392 recurrences out of 3817 intussusceptions) [2].

Daneman, A. et al. [143] found that PLPs were present in 14% of the children who had two or more recurrences compared to 4% of those children who had only one recurrence. More than two recurrences after the initial enema reduction is the predictor of the presence of a PLP.

The age of the patient may be considered a predictor of the presence of PLP, particularly when the intussusception occurs in children older than 4-5 years of age [80, 144], or in recurrent cases in children older than 2 years of age [145]. Lymphoma patients who presented with intussusception ranged in age from 3 to 19 years (median 10 years) [146].

Small intestinal intussusception due to PLP has a high incidence in Peutz-Jehgers syndrome and Henoch-Schonlein purpura. Sonographic findings are of particular value in identifying the rare instances of reduced PLP [80].

Two-thirds of PLPs were identified at ultrasound and 40% of PLPs were diagnosed on barium enema, while air enema had a lower rate of detection of 11% [80]. CT is indicated when sonography fails to identify a suspected PLP [80].

Recommendation

30. In repeated episodes of more than twice or in older children, there is a higher risk of PLPs. Sonography on enema reduction is the most helpful method to detect PLPs (recommendation C1).

Operative Reduction

Operative reduction refers to the Hutchinson procedure by laparotomy in general, but recent laparoscopic reduction is an alternative.

It is important to distinguish between indication and contraindication of enema reduction. Children with evidence of peritonitis, sepsis, or free air on abdominal radiographs are not candidates for enema reduction [27, 147, 148]. These children should be stabilized first and then treated surgically. If a patient is resuscitated from hypovolemic shock and clinically stabilized, enema reduction may be attempted [27, 147, 148]. Operative treatment is also indicated when enema reduction has failed and a PLP was demonstrated or when a PLP is suspected in cases of multiple recurrence [147, 148]. However, multiple recurrences are not a contraindication to attempt enema reduction.

Nonoperative reduction is not expected to be successful in intussusceptions limited to the small bowel.

Indications for bowel resection are perforation of the bowel, necrotic bowel, possibly irreversible ischemia of the bowel, presence of a PLP, and operatively irreducible bowel [147, 148]. Practically, there may be occasions when it is difficult to judge whether the ischemia of the bowel is reversible or not. If there is doubt in regards to the reversibility of the bowel ischemia, it may be safer to resect the bowel and anastomose end-to-end.

Highly mobile cecum has been implicated in the pathogenesis of intussusceptions. Therefore, many surgeons have performed severance of the

ileocecal band, suturing the terminal ileum to the ascending colon (ileopexy) or an appendectomy [147, 148] to encourage fixation of the cecum and to prevent future appendicitis. However, these procedures did not necessarily decrease the recurrence rate [148-150].

There is no significant difference in operation time or complications between laparoscopic procedures and open surgery. There are reports of shorter hospital stay and earlier oral intake in the laparoscopic group compared with the open surgery group [151-153]. Disadvantages of laparoscopic procedures include bowel wall injury and difficulty in identification of PLPs [150]. Conversion to open surgery is seen in about 12.5-32% of cases [150-153]. Laparoscopic reduction of intussusception is not covered by health insurance in Japan at present.

Recommendations

31. Operation is indicated in uncorrectable shock, suspect of bowel necrosis/perforation, peritonitis, irreducible intussusceptions, and the presence of PLPs (recommendation A).
32. Bowel resection is indicated in the presence of bowel necrosis /perforation, PLPs, and operatively irreducible intussusceptions (recommendation A).
33. There is no evidence to support additional procedures of ileopexy, severance of ilececal band, or appendectomy to prevent recurrences (recommendation C2).
34. Earlier start of oral intake and shorter hospitalization can be expected following laparoscopic procedures in comparison with open procedures (recommendation C1).

Current Management in Japan

Additional procedures to prevent recurrence and/or future appendicitis were performed almost always in 9.6% (14/146), occasionally in 13.6% (19/146), and never in 77.4% (113/146).

Laparoscopic reduction was selected almost always in 16.9% (25 /148) of respondents, occasionally in 9.5% (14/148), and never in 73.6% (109/148).

Conclusion

These guidelines are aimed to be used specifically in Japan, but some portions may be of value in other countries as well. However, care must be taken to the fact that these guidelines reflect the Japanese medical environment including the health insurance system.

First, the health insurance system in Japan allows patients free access to hospitals without limitation. The majority of patients with intussusceptions are seen primarily by pediatricians with a surgeon in attendance or by pediatric surgeons from the beginning of their treatment. It is very rare that pediatric radiologists join in the team.

Second, medical expenses of infants and children are covered by health insurance and municipal medical aids, and therefore families do not need to pay fees at all in most cases. It is advised that these guidelines should be modified when they are used in other countries to fit their medical environments. In addition, one should judge each individual clinical situation in accordance with staff numbers, experiences, available devices, and the patient's condition.

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