Journal of Gastroenterology and Hepatology
JGHF
doi:10.1111/jgh.16084

REVIEW ARTICLE

Management and monitoring of pediatric inflammatory bowel disease in the Asia-Pacific region: A position paper by the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN) PIBD Working Group: Surgical management, disease monitoring, and special considerations

Way Seah Lee,[*,†] Katsuhiro Arai,[‡] George Alex,[§] Suporn Treepongkaruna,[¶] Kyung Mo Kim,[**] Chee Liang Choong,[*] Karen Calixto Mercado,[††] Andy Darma,[‡‡] Anshu Srivastava,[§§] Marion M. Aw[¶¶] and on behalf of APPSPGHAN PIBD Working Group

*Department of Paediatrics, Faculty of Medicine, University Malaya, Kuala Lumpur, †Department of Population Medicine, Faculty of Medicine and Health Sciences, University Tunku Abdul Rahman, 59100, Kajang, Selangor, Malaysia; ‡Center for Pediatric Inflammatory Bowel Disease, National Center for Child Health and Development, Tokyo, Japan; §Department of Gastroenterology and Nutrition, Royal Children's Hospital, Melbourne, Victoria, Australia; ¶Division of Gastroenterology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; **Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, South Korea; ††Makati Medical Center and The Medical City, Philippine Society for Pediatric Gastroenterology, Hepatology and Nutrition, Manila, Philippines; ‡‡Department of Child Health, Dr. Soetomo General Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia; §§Department of Paediatric Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India; ¶¶Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Key words
Asia-Pacific region, complications, differentiating intestinal tuberculosis from Crohn's disease, monitoring, pediatric inflammatory bowel disease, surgery.

Accepted for publication 29 November 2022.

Correspondence
Way Seah Lee, Department of Population Medicine, Faculty of Medicine and Health Sciences, University Tunku Abdul Rahman, 59100 Kajang, Selangor, Malaysia.
Email: leewayseah@utar.edu.my

The position paper is supported by APPSPGHAN. All authors contributed equally to the paper.
Conflict of interest: None of the authors have any conflict of interest to declare.
Statement of ethics: The preparation of the manuscript strictly adheres to the ethics and integrity policies of the *Journal of Gastroenterology and Hepatology*.

Abstract

Disease phenotype of pediatric inflammatory bowel disease (PIBD) in children from the Asia-Pacific region differs from that of children from the West. Many parts of Asia are endemic for tuberculosis, making diagnosis and management of pediatric Crohn's disease a challenge. Current available guidelines, mainly from Europe and North America, may not be completely applicable to clinicians caring for children with PIBD in Asia due to differences in disease characteristics and regional resource constraints. This position paper is an initiative from the Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology and Nutrition (APPSPGHAN) that aims to provide an up-to-date, evidence-based approach to PIBD in the Asia-Pacific region. A group of pediatric gastroenterologists with a special interest in PIBD performed an extensive literature search covering epidemiology, disease characteristics and natural history, management, and monitoring. Attention was paid to publications from the region with special consideration to a resource-limited setting. This current position paper deals with surgical management, disease monitoring, immunization, bone health, and nutritional issues of PIBD in Asia. A special section on differentiating pediatric Crohn's disease from tuberculosis in children is included. This position paper provides a useful guide to clinicians in the surgical management, disease monitoring, and various health issues in children with IBD in Asia-Pacific region.

Funding sources: No external source of funding received in the preparation of this work.

Introduction

The incidence of inflammatory bowel disease (IBD) is rapidly rising in many newly industrialized countries in the Asia-Pacific region.[1] Disease phenotype of pediatric IBD (PIBD) from the Asia-Pacific region differs from that seen in Caucasian children.[2] In Asia, ileocolonic disease and inflammatory phenotype is the most common phenotype observed in children with Crohn's disease (CD).[2] In addition, a high incidence of stricturing disease has also been reported in Asia. Stricture at diagnosis was reported

in 46% and 34% of children with CD in Shanghai, China, and Taiwan, respectively,[3,4] as compared with 14% in Caucasian children in the EUROKIDS registry.[5] Tuberculosis (TB) is highly endemic in many regions in Asia.[6] Differentiating intestinal tuberculosis (ITB) from pediatric CD in areas endemic for TB is a challenge to clinicians in the developing world where the disease burden of IBD is also on the rise.[6]

The Asia Pan-Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN) Working Group on PIBD was established with a goal of establishing best management practices of PIBD in the Asia-Pacific region. The current position paper addresses disease complications, surgical management, and monitoring of PIBD in the region. A section focusing on differentiating pediatric CD from ITB as well as management of latent TB infection (LTBI) in PIBD is also included. It complements the position paper by APPSPGHAN PIBD Working Group on the medical management of PIBD in the Asia-Pacific region.

Methods

A group of pediatric gastroenterologists with special interest in PIBD performed literature search on epidemiology, disease characteristics, natural history, management, and disease monitoring on PIBD, including published data from the Asia-Pacific region with special consideration in resource-limited setting. A list of statements were formulated, discussed, revised, and agreed by members of the group. Statements which at initial voting did not reach consensus agreement were discussed and modified until a consensus was reached. All statements mentioned in this position paper are in 100% agreement.

Scope. This position paper deals with surgical management, disease monitoring, and other aspects of management of PIBD, such as nutrition, immunization, bone health, and transition to adult care. There is also a section on managing of PIBD in areas endemic for TB.

Table 1 Surgical management, monitoring, and special consideration in managing pediatric inflammatory bowel disease (PIBD) in Asia—a summary of recommendations by PIBD Working Group of Asian Pan Pacific Society for Pediatric Gastroenterology, Hepatology, and Nutrition (APPSPGHAN)

1. Surgical management
   - 1.1 In pediatric CD, surgical management should be considered in chronic active disease limited to a short segment despite optimal medical therapy and in prepubertal or pubertal children with reduced growth velocity lasting more than 6–12 months
   - 1.2 Surgery for perianal disease in CD such as placement of seton and fistulectomy should be performed in combination with a biologic. All decisions should be made by a multidisciplinary team
   - 1.3 Temporary diversion surgery can be considered in refractory perianal disease, but bowel restoration is only successful in a limited number of patients
   - 1.4 In pediatric UC, colectomy should be considered in children with active or steroid-dependent disease despite maximal medical therapy, or in the presence of colonic dysplasia, toxic megacolon, life-threatening bleeding, perforation, or in ASC refractory to adequate medical therapy
2. Disease monitoring—clinical assessment
   - 2.1 In resource-limited setting, regular clinical assessment in addition to serial assessment of PCDAI/wPCDAI can help prioritize patients needing further endoscopic assessment
   - 2.2 Both PCDAI and wPCDAI scores are useful in predicting clinical remission in pediatric CD but are poor predictors of mucosal healing
   - 2.3 PUCAI correlates well with endoscopic severity in pediatric UC and predicts mucosal healing
3. Disease monitoring—biologic markers
   - 3.1 In pediatric CD, FC level <250 μg/g correlates with mucosal healing and level <100 μg/g identifies deep healing
   - 3.2 In pediatric UC, FC levels >250 μg/g indicates a need for further endoscopic evaluation or possible treatment intensification while level between 100 and 250 μg/g indicates a need for closer monitoring
4. Imaging studies and endoscopy
   - 4.1 Using SBFT to exclude internal fistula, narrowing or stenosis of small or large intestine should only be considered if other imaging options are not available
   - 4.2 MRE is the imaging of choice for monitoring children with CD
   - 4.3 In resource-limited settings, CTE is a useful alternative to MRE
   - 4.4 The usefulness of IUS in pediatric IBD needs further research
   - 4.5 After initial diagnosis, endoscopy is recommended before any major changes in treatment strategy, for cancer surveillance, and to exclude other gastrointestinal complications such as stricture or infections like CMV colitis
5. Nutrition, growth, bone health, immunization, and transition to adult care
   - 5.1 Nutrition status should be monitored regularly using standard anthropometric measurements. Dietary intake should also be assessed regularly in children and adolescents with IBD, and more frequently if there is growth faltering
   - 5.2 DXA is recommended in children with newly diagnosed PIBD as part of initial assessment
   - 5.3 In resource-limited settings, DXA may be prioritized in newly diagnosed PIBD with risk factors such as low BMI and growth faltering at diagnosis, history of repeated use of steroids, history of bone fractures, or chronically active disease
   - 5.4 All children with IBD should receive age-appropriate vaccination according to the national recommendations. Live-attenuated vaccines should be administered before the start of immunosuppressive medication in non-immune children, wherever possible
   - 5.5 A properly planned transitional care is recommended for older children and adolescents before being transferred to adult care
6. Differentiating Crohn's disease from intestinal tuberculosis
   - 6.1 All efforts should be made to differentiate ITB from CD at presentation and to make a correct diagnosis
   - 6.2 Screening for latent or active TB should be performed before commencing steroids, IM, or biologic therapy for pediatric IBD
7. Initiating treatment for Crohn's disease with immunomodulators or antitumor necrosis factor (TNF)
   - 7.1 In children with newly diagnosed CD with a concomitant LTBI, a 3-week course of chemoprophylaxis for TB is recommended before starting anti-TNF. However, the simultaneous initiation of both anti-TNF and treatment for LTBI may be considered in urgent cases
   - 7.2 Screening for active TB using suggestive clinical symptom and or chest radiograph for household contacts are recommended
   - 7.3 Necessity of regular TB infection tests for children with IBD receiving anti-TNF has not been universally recommended, but patient and caregiver education regarding symptoms suggestive of TB is recommended

ASC, acute severe colitis; BMI, body mass index; CD, Crohn's disease; CMV, cytomegalovirus; CTE, computer tomographic enterography; DXA, dual-energy X-ray absorptiometry; FC, fecal calprotectin; IBD, inflammatory bowel disease; ITB, intestinal tuberculosis; IUS, intestinal ultrasound; LTBI, latent tuberculosis infection; MRE, magnetic resonance enterography; PCDAI, pediatric Crohn's disease activity index; PUCAI, pediatric ulcerative colitis activity index; SBFT, small bowel follow-through; TB, tuberculosis; TNF, tumor necrosis factor; UC, ulcerative colitis; wPCDAI, weighted pediatric Crohn's disease activity index.

A summary on the recommendations on the management of PIBD in Asia by the Working Group is shown in Table 1.

Surgical management

Surgery in CD. Indications for surgery in pediatric CD include surgical resection in patients with active disease limited to a short segment(s) despite optimal medical therapy,[7] stricture with pre-stenotic dilatation and/or obstructive symptoms as well as penetrating disease such as intra-abdominal or perianal fistulas.[8] Surgery should also be considered in children going through puberty if growth velocity for bone age is reduced over a period of 6–12 months despite optimal medical and nutritional therapy.[8]

Perianal fistula is present in a significant proportion of children with CD. The management of perianal disease in pediatric CD is highly variable. Despite a lack of evidence on their use in pediatric perianal CD, the use of antibiotics has been promoted as a first-line treatment. However, management of complex perianal CD usually includes medical, surgical, or a combination of both.[9] A study in children with perianal fistula showed a healing rate of 28.6% after seton placement for 1 year[10] and 28.5% in children undergoing fecal diversion.[11] A systematic review involving four studies in children with perianal CD treated with IFX showed a complete resolution of perianal disease in 55% of children, with another 17% showing partial response.[9] A combination of surgery and biologics showed a combined healing rate of 68.5%.[9]

Some children who have adequate healing of the perianal fistula after temporary fecal diversion surgery by means of an ileostomy or colostomy may have the stoma reversed.[11] However, the risk of the ostomy becoming permanent is significant. In a systematic review, temporary fecal diversion improved symptoms in approximately two-thirds of adult patients with refractory perianal CD, but bowel restoration was only successful in only 17% of patients.[12]

Currently, examination under anesthesia, drainage, fistulectomy, and placement of seton is recommended as first-line surgical treatment for perianal disease in children with CD in conjunction with antibiotics and biologics.[9] Because the presence of perianal disease can be devastating in children, and placement of seton alone showed a low healing rate, combination of seton with a biologic (infliximab [IFX] or adalimumab [ADA]) should be considered even in resource-limited setting.

Early elective surgery for CD in resource-limited setting. Stenosis is a common complication in Asian children with CD.[3] Stricturing disease at diagnosis has been reported in 34%–45% of children with CD in some parts of Asia[3,4] as compared with the 14% reported in the EUROKIDS registry.[5] Initial biologics therapy is recommended in children who present with stenosis without pre-stenotic dilatation at diagnosis.[8] However, in resource-limited setting where biologics are not easily available, endoscopic dilatation or surgical management should be considered.[13] Endoscopic dilatation is most suitable for endoscopically accessible short segment stenosis without sharp angulation or penetrating disease.[8] Stricture connected to the fistula or abscess, however, is a contraindication for endoscopic dilatation.[14] Bowel resection should be performed in stenosis with phlegmon.[14] Stricturoplasty, which preserves bowel length, is preferred over intestinal resection in fibrostenotic strictures with no active inflammation.

Surgery in ulcerative colitis. In children with active or steroid-dependent ulcerative colitis (UC) despite maximal treatment with 5-ASA, thiopurine, and biologics therapy, or the finding of colonic dysplasia, elective total colectomy may be indicated.[15] Presence of toxic megacolon, refractory or life-threatening bleeding, and perforation (iatrogenic or spontaneous) are also indications for urgent surgery.[15] Subtotal colectomy and ileostomy are usually performed initially with proctectomy and ileal pouch anal anastomosis (IPAA) at a later stage.[16] Decision of IPAA should be individualized in adolescent/young females and patients of UC with primary sclerosing cholangitis (PSC).[14] Colectomy should also be considered in any child with acute severe colitis (ASC) refractory to adequate medical therapy (including intravenous corticosteroids and other second-line therapy such as IFX, tacrolimus, or cyclosporin).[15] However, cytomegalovirus colitis needs to be excluded before surgery.

Disease monitoring

Clinical assessment. Mucosal healing in IBD has been associated with reduced risks of surgery, hospitalizations, treatment escalation, and complicated disease behavior, particularly in the adult setting.[17,18] However, prospective studies to confirm the long-term advantages of achieving mucosal healing as a treat-to-target strategy in childhood IBD is still lacking.[18,19] In active disease, clinical assessment every 4–6 weeks is recommended, whereas assessment every 3–6 months is recommended during clinical remission.[15]

Disease activity score. Clinical disease activity scores are commonly used to predict clinical remission (Table 2). However, when escalation of therapy is being considered, clinical disease assessment alone is inadequate because clinical activity scores do not always correlate accurately with intestinal inflammation or mucosal healing, especially in CD.[20] Both the pediatric CD activity index (PCDAI) and the weighted PCDAI (wPCDAI) were found to be accurate in predicting clinical remission in children with CD.[21–27] However, neither index can give a valid assessment of mucosal healing.[23] Endoscopic assessment may be necessary if escalation of therapy is considered. In resource-limited settings, serial assessment of PUCAI in UC or wPCDAI in CD, in combination with regular clinical assessments and biomarkers such as fecal calprotectin (FC), could help to prioritize patients needing further endoscopic evaluation.[23]

Unlike PCDAI, which has a poor correlation with mucosal healing, pediatric UC activity index (PUCAI) has been shown to correlate well with the Mayo score for UC and predicts mucosal healing.[28] A PUCAI <10 correlates well with endoscopy in detecting mucosal healing.[29,30] In addition, PUCAI is also superior to both C-reactive protein (CRP) and erythrocytic sedimentation rate (ESR) in predicting long-term outcomes such as 1-year steroid-free sustained remission and colectomy by 2 years.[31,32] In a systematic review on adult-onset UC, there was a moderate-to-strong correlation between clinical activity, particularly the

Table 2 Pediatric Crohn's disease and ulcerative colitis disease activity indices commonly used in children

	Strength	Potential disadvantages
PCDAI	Score ≥30 indicates moderate/severe disease activity in children with CD[24] Accurately reflect disease activity as assessed by physician global assessment in pediatric CD[24] Accurate in predicting clinical remission in pediatric CD[17,18]	Not valid for assessing/predicting mucosal healing[23] Poor correlation with fecal calprotectin[21,27]
wPCDAI	Accurate in predicting clinical remission in children[17,18] Compared with PCDAI, wPCDAI had better discrimination between the disease activity categories. It is also more feasible, reliable, valid, and responsive index as compared to PCDAI[25]	Not valid for assessing/predicting for mucosal healing[23] Correlates poorly with endoscopic activity[22] Poor correlation with fecal calprotectin[21]
PUCAI	Correlates well with the Mayo score for UC and predicts mucosal healing[28] PUCAI <10 correlates well with endoscopy in detecting mucosal healing[29,30] Superior to both C-reactive protein (CRP) and erythrocytic sedimentation rate (ESR) in predicting long-term outcomes such as 1-year steroid-free sustained remission and colectomy by 2 years[30,31]	Underperform in the setting of UC with PSC[26]

CD, Crohn's disease; PCDAI, pediatric Crohn's disease activity index; PSC, primary sclerosing cholangitis; PUCAI, pediatric ulcerative colitis activity index; UC, ulcerative colitis; wPCDAI, weighted pediatric Crohn's disease activity index.

combination of rectal bleeding and stool frequency, and endoscopic activity in patients with UC.[32] But it underperforms in the setting of UC with PSC.[26]

Biologic markers. In childhood IBD, repeated endoscopy in monitoring disease activity may not be practical, including in resource-limited settings in Asia. Biologic markers (biomarkers) such as FC and CRP have been used widely as biomarkers of inflammation.

CRP and erythrocyte sedimentation rate. In children with CD, elevation of CRP (>0.8 mg/dL) has been associated with active mucosal inflammation on colonoscopy, active transmural inflammation, and moderate-to-severe clinical activity.[32] In pediatric UC, CRP has a fair correlation with colonoscopic inflammation.[33] Changes in the values of CRP when monitored over time has been found to be useful in reflecting disease activity at the more severe end of the spectrum. However, up to one-third of children may have normal CRP and ESR even in the presence of active intestinal inflammation, more so if the initial levels were normal, which could be due to individual genetic trait.[34]

FC. When used in conjunction with clinical symptoms, serial monitoring of FC is useful in assessing therapeutic response in PIBD. In a prospective study of newly diagnosed PIBD, CD patients who reached the target FC of ≤250 μg/g quickly within 12 weeks after induction therapy had a more favorable disease course in the first year.[35] This was however not applicable in children with newly diagnosed UC.[35]

Monitoring of FC has also been used as a surrogate marker for mucosal healing. In pediatric CD, FC level of <250 μg/g correlates well with mucosal healing but a lower level at <100 μg/g was needed to identify deep healing.[36] Conversely, persistently high FC levels corresponded well with persistent intestinal inflammation.[35,37–39]

For pediatric UC, FC > 250 μg/g has been found to be an indicator for further endoscopic evaluation and possible treatment intensification.[40] On the other hand, FC levels between 100 and 250 μg/g indicate the need for closer monitoring.[40] A small pediatric study on UC found that a FC > 298.5 μg/g predicted endoscopic activity by a Mayo Endoscopic Score with a 92.3% sensitivity and 95.2% specificity.[41]

It should be emphasized that when monitoring disease course of a child with IBD, serial monitoring of FC in conjunction with repeated assessment and PCDAI/PUCAI score is preferred over one isolated score of PCDAI or PUCAI.

Although the utility of FC in the monitoring of childhood IBD is well described, more robust evidence is needed. In Asia, the use of FC is impacted by regional differences including cost as well as the availability of quantitative versus qualitative testing, variation in the method of assay used, and different cutoffs. Interpretation should be correlated with clinical and other biologic markers such as CRP, if relevant.

False elevation of FC can be seen in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors. In addition, FC values in infants younger than 6 months varies widely.[42] Thereafter, in young children aged between 6 and 48 months, FC levels show a steady downward trend with age but are still higher than the normal levels observed in healthy adults and children.[42] A Korean study showed an average FC level of ~50 μg/g around the age of 2 years.[43] The FC values should be interpreted as per the appropriate age-dependent cutoff values and serial measurements may be more valid to see the trend.

Imaging studies

Plain radiographs. Plain abdominal radiograph is useful for detecting urgent complications of IBD such as intestinal obstruction, free intraperitoneal air in bowel perforation, and marked colon dilatation in toxic megacolon[44–46] (Table 3).

Table 3 Imaging modalities in inflammatory bowel disease in children

Mode of imaging	Sedation requirements	Exposure to radiation	Advantages	Disadvantages
Plain abdominal radiograph[44,46]	No sedation	Yes	Readily available; cheap; useful in detecting urgent complications	Many bowel features are not specific
Small bowel follow through[45]	No sedation	Yes	Readily available; cheap; well tolerated	Relatively long examination time; interpretation is operator dependent; unable to detect extramural/extra-intestinal involvement; large volume of oral contrast involved
Computerized tomographic enterography[47,48]	No sedation	Yes	Bowel wall can be clearly visualized, extraintestinal involvement like lymph nodes, collection etc., quick, easily available	More expensive than conventional x-ray or barium studies; younger children may have difficulty in drinking enough oral contrast for small bowel distension
Magnetic resonance enterography[47–50]	General anesthesia may be required	No	Good assessment of bowel wall; differentiates between inflammatory and fibrotic stricture	Expensive, not readily available in many resource-limited settings; prone to motion artifact, radiological expertise needed for interpretation, younger children may have difficulty in drinking enough oral contrast for small bowel distension
Intestinal ultrasound[51,52]	No sedation	No	Cheap; free of radiation; well tolerated	Operator dependent, less reproducible; no consensus on definition "what is abnormal," pediatric data lacking
Capsule endoscopy[53–55]	Sedation may be required in young children who are unable to swallow the capsule	No	Useful in evaluating small bowel involvement in suspected CD	Expensive, not readily available in many resource-limited settings, contraindicated in children with a known stenosis of the gastrointestinal tract, may lead to retained capsule; image in some cases may not be very clear

Barium studies. Small bowel follow through (SBFT) can demonstrate internal fistula, narrowing, and stenosis of small and large intestine. Its limitations include exposure to ionizing radiation, inability to detect extramural and extra-intestinal disease, and difficulties for young children to ingest large volume of oral contrast.[45] SBFT is contraindicated if obstruction or perforation are suspected. Radiation exposure is a major concern; repeated fluoroscopic exposure and abdominal radiographs can result in radiation dose equivalent to that of an abdominal CT scan.[56] SBFT should only be used if other imaging options are not available.

Computer tomographic enterography. Computer tomographic enterography (CTE) is indicated as initial cross-sectional enterographic examination when magnetic resonance enterography (MRE) is not available or there is a history of allergy to gadolinium-based contrast media.[56] It is also useful when intra-abdominal complications such as abdominal sepsis, abscess, or complex intra-abdominal disease such as fistulas, sinus tracts, and phlegmons are suspected.[47] Compared with SBFT, CTE and MRE are less operator-= dependent and allow better visualization of extraintestinal manifestations and complications of IBD stated above and a better delineation of bowel loops.[48] Advantages of CTE over MRE include better spatial resolution, fewer motion artifacts, wider availability of CT scanners, and shorter examination times.[49] However, exposure to ionizing radiation makes it less than ideal for disease monitoring if repeated imaging is necessary.

MRE. MRE and CTE are similar imaging tests although follow-up MRE has now been accepted as a marker of treatment response.[7] The advantages of MRE are no radiation exposure, high-contrast resolution, multiplanar ability, and cine imaging.[50] Diffusion-weighted imaging (DWI) is a useful MRI sequence for assessment of disease activity in CD.[57] In addition, MRE can help define disease activity that is important in the management of CD. For instance, MRE allows differentiation between a fibrotic and inflammatory stricture and guides the subsequent therapeutic decision (surgery *vs*. biologics). MRE also helps in distinguishing between inflammatory, stricturing, and penetrating disease[50]; however, the high cost of MRI scan, its limited availability in many resource-limited settings, and the requirement of general anesthesia in young children limit the use of serial MRE to monitor disease activity. Dedicated pelvic magnetic resonance (perianal fistula magnetic resonance imaging protocol) is recommended for evaluation of perianal CD and its complications.

Intestinal ultrasound. Intestinal ultrasound (IUS) has been used as a diagnostic and monitoring tool in IBD.[51] A recent study identified bowel wall thickness and mesenteric inflammatory fat as two important sonographic parameters for predicting disease activity.[52] The main disadvantage, however, is that it remains an indirect measure of transmural inflammation, its diagnostic accuracy in detecting intestinal inflammation in PIBD is inconclusive, and currently, there is no consensus on defining what is abnormal.[51] Thus, although more research is needed before IUS can be recommended for routine use in the monitoring of disease activity in PIBD, this would be an area of expertise that could be developed particularly in resource limited settings.

Endoscopy. Endoscopy plays an important role in assessing treatment response and achievement of treatment target and should be performed 6–12 months after the initial diagnosis of IBD or before a major therapeutic change (escalation or de-escalation).[7] Endoscopy should also be considered in the following scenarios: to diagnose complications such as dysplasia and to exclude infections such as cytomegalovirus colitis.[7]

In CD, endoscopic healing is associated with improved long-term outcomes.[17,58] In children with CD, persistent mucosal inflammation is associated with more common long-term disease-related complications, disease flares, and surgeries.[11] The International Organization for the Study of Inflammatory Bowel Diseases[17] defined complete mucosal healing as the ideal treatment target and endoscopic remission as a more practical target. A Simple Endoscopic Score for Crohn's disease (SES-CD) < 3 or absence of ulcerations (e.g., SES-CD ulceration subscore = 0) or Crohn's Disease Endoscopic Index of Severity (CDEIS) < 3 (no ulcers) indicates endoscopic remission.[17] Endoscopic response is improvement of >50% from baseline SES-CD or >50% from baseline CDEIS score.[17]

For pediatric UC, endoscopic healing should be measured by Mayo endoscopic subscore of 0 points, or Ulcerative Colitis Endoscopic Index of Severity (UCEIS) ≤ 1.

Endoscopy is also important in cancer surveillance in children with UC. Annual ileocolonoscopic surveillance for adenocarcinoma is recommended in children with a disease duration of >10 years or with a duration of disease of >8 years in adolescents older than >16 years, or in those with risk factors such as extensive colitis, high burden (severe and chronic) of the colitis over time, and a family history of colorectal cancer in a first-degree relative.[29,59] When PSC coexists with IBD, cancer surveillance is recommended every 1–2 years from the time of the diagnosis of PSC for children ≥12 years.[59] In children <12 years of age, cancer surveillance may be delayed if the risk factors described above are absent.[59] Surveillance colonoscopy should preferably be done in the quiescent phase of disease.

Video capsule endoscopy. Video capsule endoscopy (VCE) can detect mucosal lesions in the small bowel and is useful in evaluating small bowel involvement in suspected CD.[53–55] Its use has also resulted in a change in diagnosis from previously diagnosed UC to CD[53] or reclassification of the phenotype in confirmed CD cases.[60] However, the role of VCE in monitoring disease activity in small bowel CD has not been fully established.[61]

Limitations of VCE include its high cost, inability to take biopsy, and the risk of retention in small bowel in the presence of narrowing. Sometimes the images may not be very clear. In patients with symptoms of GI obstruction, a small bowel imaging or testing with patency capsule should be done before VCE to avoid retention. Currently, there is no prospective study to define the role of using VCE to monitor small bowel CD in children.

The advantages and disadvantages of various imaging modalities used in children with IBD are shown in Table 3.

Nutrition and growth. Nutritional status at every follow-up should be monitored using standard anthropometric measurements (weight, height, and BMI z-scores), which should be plotted in growth charts and tracked longitudinally.[62] Dietary intake should be monitored in all children regularly, more frequently if there is evidence of growth faltering. The vitamin and mineral status should be closely and regularly monitored.[63,64] Monitoring should be done more frequently if there is growth faltering, in which case nutritional intervention is required. In addition, children older than 10 years should have pubertal stage assessed annually until puberty is completed.[63]

Bone health. In human beings, maximum bone mass is usually achieved in the first two decades of life. PIBD poses a significant threat to bone health in children and adolescents, especially in children with prolonged exposure to CS or those who are undernourished.[65] Both decreased bone mineral density (BMD) and osteoporosis are recognized extraintestinal complications of PIBD.[66] Children with IBD may have an increased risk for fractures, especially vertebral fractures.[67]

Currently, there is no systematic review on the prevalence of osteopenia and osteoporosis in children with IBD.[68–72] However, various studies in children have shown that low BMD is common in children and adolescents with IBD (Table 4).[69] Risk factors for low BMD in PIBD includes growth impairment or low body weight-for-age at initial presentation,[72] whereas a higher cumulative dose of CS is a risk factor at follow-up after diagnosis.[69]

Monitoring of markers of bone health in PIBD have been recommended.[72] Dual-energy X-ray absorptiometry (DXA) should be considered if available.[72,73] It should be considered in newly diagnosed PIBD, especially in adolescents and children with growth impairment.[69,70]

Measurement of vitamin D levels is also recommended in children with newly diagnosed IBD. If serum vitamin D level is deficient or the intake of calcium is inadequate, supplemental vitamin D and calcium are recommended.[63] Subjects with osteopenia should preferably be given biologics to control bowel inflammation, along with nutritional rehabilitation, in addition to avoiding steroids.

Immunization. As soon as a diagnosis of PIBD is made, a review of the vaccination history of the child is important.[74,75] All children with IBD should receive age-appropriate vaccination according to the national recommendations. Live-attenuated vaccines such as measles, mumps, rubella and varicella should be administered before the start of immunosuppressive medication in non-immune children, wherever possible. It is important to establish the hepatitis B immune status and administer primary immunization or booster dose as indicated. Oher non-live or inactivated vaccines such as influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines can be given even during therapy.[76,77] However, in sick children requiring urgent immunosuppressive medications, delaying treatment in favor of completing vaccination is not recommended.

Transition to adult care. Diagnosis of IBD has major implications in education, physical growth, and psychological well-being, especially in older children and adolescents.[78] It is estimated that approximately 25% of all IBD are diagnosed before 16 years of age.[79]

Table 4 Bone density studies in using dual-energy X-ray absorptiometry in children with inflammatory bowel disease

Author/ area or country/ year	Number	Age at the time of diagnosis of IBD	Nature	Definition	Time of assessment after diagnosis of IBD	Main findings	Comments/recommendation
Rozes *et al.*[69] Paris, France; 2021	*N* = 193; all CD	Median 11.7; range 3.6–16.9 y	Retrospective longitudinal	Osteopenia: $z \leq -2.0$ adjusted for age, body size, and gender	At diagnosis and at end of follow-up	Osteopenia at diagnosis: 18.7%; at end of follow-up: 16% BMD values lower in lumbar spine and in total body	Risk factors: • At diagnosis: low BMI or growth impairment • At end of follow-up: cumulative dose of corticosteroids
Ronel *et al.*[72] Israel; 2021	*N* = 116; all CD	Mean age 13 ± 3.1 y	Retrospective inception cohort; all newly diagnosed CD	Osteopenia: $z < -2.0$ Borderline osteopenia: between −1 and −2.0	At diagnosis	Normal: 23% Borderline osteopenia: 31% Osteopenia: 46%	Risk factor: • Osteopenia associated with lower BMI z-score • Low BMI z-score was the only risk factor
Saadah *et al.*[70] Saudi Arabia; 2021	*N* = 64; all CD	Median: 16 y Range 8–19 y	Retrospective	Normal: ≥ -1.0 Osteopenia: $-2.0 < z < -1.0$ Osteoporosis: $z \leq -2.0$	Not described	Total body: Osteoporosis: 39% Osteopenia: 31.3% Normal: 29.7% Lumbar: Osteoporosis: 39.1% Osteopenia: 28.1% Normal: 32.8%	Risk factors: • Low WFA and HFA z-scores • Low vitamin D level • More frequent use of steroids • Older age at presentation
Mosli *et al.*[71] Saudi Arabia; 2021	*N* = 37; all UC	Mean 13.4 ± 3.9 y	Retrospective	Normal: ≥ -1.0 Osteopenia: $-2.0 < z < -1.0$ Osteoporosis: $z \leq -2.0$	Mean duration of illness at assessment after diagnosis 2.1 ± 2.4 y	Lumbar: Osteoporosis: 29.7% Osteopenia: 40.5% Normal: 35%	More common in females and in children with extra-intestinal manifestations
Schmidt *et al.*[68] Sweden; 2012	*N* = 144 CD = 45, UC = 83	Mean 14.2 y; range 6–19 y	Prospective longitudinal, population-based		At diagnosis and at follow-up 2 y later	Lumbar (mean BMD z-score ± SD): At diagnosis: −0.8 ± (2.9) At follow-up: −0.7 ± (2.9)	Persistent decrease in BMD z-scores over the follow-up period
Levy-Sharga *et al.*[66] Israel; 2019	*N* = 41 CD = 30, UC = 9, IBD-U = 2	Mean 12.1 ± 3.2 y First scan: 14.3 ± 3.2 y Second scan: 17.7 ± 3.1 y	Retrospective longitudinal		First scan 2.2 ± 0.9 y from diagnosis Second scan 5.6 ± 3.3 y after first scan	First scan: Lumbar: −1.64 ± 1.02 Total body: −1.42 ± 0.83 Second scan: Lumbar: −1.62 ± 1.03 Total body: −1.28 ± 0.88	Improvement in BMD was possible and more pronounced in children who gained weight or whose BMD was low at the first scan

Anti-TNF, antitumor necrosis factor; BMD, bone mineral density; BMI, body mass index; CD, Crohn's disease; DXA, dual-energy X-ray absorptiometry; HFA, height-for-age; UC, ulcerative colitis; WFA, weight-for-age; y, year; z-score, standard deviation score.

Lumbar: lumbar spine L1–L4; total body: total body bone mineral density excluding the head.

Source: Bishop N, et al. Fracture prediction and the definition of osteoporosis in children and adolescents: The ISCD 2013 Pediatric Official Positions. *J Clin Densitom* 2014;17:275–280.

Transition in care is generally defined as a set of purposeful, planned movements of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented healthcare systems.[80] The main aims are to promote continuity of care, improve treatment adherence and disease knowledge, encourage independent disease management, and build confidence in the new adult healthcare team among the patients and their families.[81] A well-planned, successfully implemented transitional process results in better disease control in terms of higher remission rate and lower rates of active disease, acute flare, emergency admission, and emergency surgery.[82]

Currently, few formal studies on the policy or implementation of transitional care for PIBD in Asian patients have been conducted.[83,84] Generally, a properly planned transitional care is recommended for older children and adolescents with IBD before being transferred to adult care.

Management of pediatric IBD in areas with high endemicity of TB. TB is highly endemic in the Asia-Pacific region.[85] With the emergence of multidrug-resistant TB, TB has become a major threat worldwide over the past two decades. Almost one-third of the global population has LTBI. In Asia, countries with an estimated population prevalence of LTBI of ≥40% are Bhutan, Cambodia, Indonesia, Laos, Myanmar, the Philippines, and South Korea.[86] It was estimated that both China and India each have 350 million people with LTBI.[86] TB can involve any part of the intestine, from the esophagus to the rectum. The clinical features of intestinal TB (ITB) in children are nonspecific, often resulting in diagnostic delays. Abdominal pain, fever, and weight loss are the most frequent findings of ITB in children at presentation.[87] ITB can mimic any of the diseases affecting the gastrointestinal tract, especially CD.[88]

Initiating immunosuppressants or biologics after a presumptive diagnosis of IBD in a child with LTBI can lead to reactivation of LTBI with severe and sometimes fatal complications, such as the systemic dissemination of the infection.[85] The misdiagnosis of a case of CD as ITB with subsequent unnecessary anti-TB treatment can also lead to potential drug toxicity, drug resistance, and a delay in the treatment of IBD. Therefore, all efforts should be made to differentiate ITB from IBD, especially CD, and to make a correct diagnosis. Screening for latent or active TB should always be performed before commencing IM or anti-TNF treatment to avoid disease flare.

Table 5 Differentiating Crohn's disease from intestinal tuberculosis in children

	Suggestive of Crohn's disease	Suggestive of intestinal tuberculosis
Clinical features[†87,89]	*Chronic diarrhea* *Hematochezia*[85,89] Perianal disease *Extraintestinal manifestations*[85]	History of TB exposure Fever Weight loss Abdominal pain or symptoms of *intestinal obstruction*[85,89] *Ascites*[89] Extraintestinal involvement; e.g., lung
Serology and microbiology	ASCA[91] Diagnosis accuracy: 57% Pooled sensitivity and specificity of ASCA for diagnosis of CD was 33% and 83% respectively in a meta-analysis[91]	Intestinal biopsy or fecal specimen's polymerase chain reaction for acid-fast bacilli[92] Sensitivity: 44% Specificity: 95% Diagnostic yield: Acid-fast staining Sensitivity: 2.7–37.5% Mycobacterial culture 19–70% GeneXpert MTB/RIF assay 8.1% Demonstration of AFB is uncommon as ITB is a paucibacillary disease[7]
Imaging[93,94]	Long segment involvement Comb sign Skip lesions Higher visceral-to-subcutaneous fat ratio	Shorter (<5 cm) strictures Enlarged (>1 cm) and necrotic lymph nodes Isolated ileocecal involvement Ascites
Endoscopic findings[85]	*Longitudinal*/aphthous ulcers Skip lesions Cobblestone appearance[81] *Left colon involvement (rectosigmoid)*	Transverse ulcers Gaping ileocecal valve *Isolated involvement of ileocecal area*
Histology of intestinal biopsy[‡85,87]	Small and sparse granuloma Architectural crypt distortion Focal enhanced colitis	Large granuloma (>200 μm), confluent granulomas in submucosa caseous necrosis in granuloma

[†]Most data are derived from adult studies except those marked in *italics*, which are from comparative study in children.[87]
[‡]Except for necrotic lymph nodes and demonstration of AFB (on smear/culture/GeneXpert) that are typical of TB, the remaining findings are relative and cannot be considered in isolation for making a diagnosis.
AFB, acid-fast bacilli; ASCA, anti-*Saccharomyces cerevisiae* antibody; CD, Crohn's disease; ITB, intestinal tuberculosis; TB, *Mycobacterium tuberculosis*; TB, tuberculosis.

In areas endemic for TB, it is imperative that a complete work-up is done to exclude ITB before making a definite diagnosis of CD and starting immunosuppressive therapy. The diagnostic work-up should include (i) a detailed history such as previous diagnosis of TB or contact with someone with TB, (ii) chest X-ray or chest CT scan, (iii) LTBI screening with tuberculin skin test (TST) or with interferon-γ release assay (IGRA), (iv) upper GI endoscopy and colonoscopy with biopsies for histology, nucleic acid amplification test (GeneXpert) and mycobacterial culture and (v) cross-sectional imaging (CTE) of the abdomen looking for features suggestive of TB.[89,90] It is imperative to be aware that in places where *Bacillus Calmette-Guerin* (BCG) vaccine is given, TST could have false results.[44] All attempts should be made to take tissue biopsy from multiple sites such as enlarged lymph nodes, intestinal ulcers, ascitic fluid, and sputum for appropriate microbiological testing which include Ziehl–Neelsen stain, GeneXpert and culture for *Mycobacterium tuberculosis*. Presence of caseating granuloma on histology, and/or positive sputum smear of acid-fast bacillus (AFB) on Ziehl Nielsen stain, positive culture for *M. tuberculosis*, or GeneXpert positive for *M. tuberculosis* confirms ITB (Table 5).[7]

Differentiating CD from ITB. Pediatric CD differs from adult CD in several aspects (Table 6).[7,85,87,89–92,95,96] Most of the current guidelines differentiating CD from ITB are based on adult data.[89,91] There is a dearth of pediatric data differentiating ITB from CD.[87,97]

History of exposure to TB. In areas where incidence of TB is low, LTBI should be suspected if there is a history of TB exposure. However, a history of exposure to TB is of little values in areas endemic for TB. Lal *et al*. from India, where TB is highly endemic, observed that only 32.5% of the 218 children with ITB had a positive history of TB contact.[87]

TST and laboratory tests. TST, IGRA test, and chest radiograph and abdominal CT scan have all been used to diagnose ITB.[85] Lal *et al*. found that of the 218 cases with ITB, 25% also had evidence of pulmonary disease whereas TST was positive in only 38% of the patients.[87]

Endoscopy. Endoscopically, the presence of longitudinal or aphthous ulcers, skip lesions, and cobblestone appearance are commonly seen in CD, whereas transverse ulcers, gaping ileocecal valve, and isolated involvement of ileocecal area suggests TB. On cross-sectional imaging, the presence of necrotic lymph nodes, ascites, and shorter (<5 cm) strictures favor TB, whereas long segment involvement, comb sign (engorgement of mesenteric vessels with vascular dilatation and tortuosity, and prominence of surrounding mesenteric fat resembling as comb),[94] skip lesions and higher visceral-to-subcutaneous fat ratio are common in CD. In a systematic review, necrotic lymph nodes and comb sign had the best diagnostic accuracy in differentiating CD and ITB on abdominal CT.[93]

In pediatric CD, Singh *et al*. evaluated 20 children with ITB and 23 children with CD and noted that chronic diarrhea and bloody stools favored CD whereas symptoms of subacute intestinal obstruction and presence of ascites favored ITB.[97] Endoscopically, isolated ileocecal involvement was a feature in ITB, whereas longitudinal ulcers involving multiple colonic segments, left-sided involvement, and extraintestinal manifestations favored CD.[97]

Initiating treatment for CD with immunomodulators (IM) or anti-TNF. In children with luminal CD without high-risk behavior, EEN is the ideal choice of therapy in the initial few weeks in the event of any uncertainty about the diagnosis of CD. Once a diagnosis is confirmed, definitive therapy needs to be instituted. Children with CD requiring high-dose steroids, IM, or biologics are at risk of reactivation of LTBI or developing disseminated TB.[98] Most cases of active TB occurred within 3–4 months after initiating anti-TNF therapy, mainly caused by reactivation of LTBI.[100]

In children with CD presenting with severe luminal disease or active perianal disease when anti-TNF is considered, the initial approach depends the endemicity of TB where the patient resides. A proposed approach to the treatment of PIBD in areas with different population prevalence of LTBI is shown in Table 6.

Table 6 Proposed treatment scheme of Crohn's disease in areas with different endemicity for latent tuberculosis infection

	Low endemic area	High endemic area
Negative TST/IGRA[44,85,87]	Proceed with immunosuppressant/anti-TNF as clinically indicated[44]	Detailed work-up to exclude LTBI is recommended. In cases with diagnostic dilemma between CD and ITB a therapeutic trial with anti-TB drugs for 2–3 months and follow-up to assess response to therapy is recommended. Further course of therapy depends on the response to anti-TB therapy[85,89,90]
Positive TST/IGRA	Treat LTBI according to local TB preventive guidelines Delay immunosuppressant/anti-TNF for 3 weeks[98] In urgent cases Initiation of both anti-TNF and treatment for LTBI may be considered together[85,98]	Treat as TB and subsequent therapy is guided by the clinical response and endoscopic reassessment after anti-TB therapy[98] Regular screening for TB infection, TST or chest x-ray should be considered[99]

Anti-TNF, antitumor necrosis factor; IGRA, interferon gamma release assay; ITB, intestinal tuberculosis; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test.

Houben et al.: In the Asia-Pacific region, the following countries have the population prevalence of LTBI of ≥40%: Bhutan, Cambodia, Indonesia, Laos, Myanmar, the Philippines, and South Korea.

Areas of low endemicity. In areas of low endemicity of TB, children with a negative screening result for LTBI using TST and or IGRA can proceed the IM or anti-TNF therapy. On the other hand, children tested positive with TST and/or IGRA should be treated for TB according to local or national guidelines.[100] Treatment options recommended for LTBI include 6–9 months of daily isoniazid, 3 months of weekly rifapentine plus isoniazid, 3–4 months of daily isoniazid plus rifapentine, or 3–4 months of daily rifapentine alone.[100] The recommended treatment regimens for LTBI may vary among different countries. In this situation, a delay of 3 weeks before starting IM or biologics is recommended. Asian guidelines on TB infection in adult patients recommended that in adults with IBD who are planned for anti-TNF therapy but are found to have LTBI, anti-TNF treatment should be postponed for at least 3 weeks after initiating LTBI chemoprophylaxis.[100] However, the simultaneous initiation of both anti-TNF and treatment for LTBI may be considered together in urgent cases.[85,101]

Areas endemic for TB. In areas with high TB prevalence such as the Indian subcontinent, a therapeutic trial of anti-TB therapy for 2–3 months before initiating treatment for CD is suggested if the differentiation between CD and ITB is not possible after appropriate work-up.[85,89,90] Subsequent therapy is guided by the clinical response and endoscopic reassessment after anti-TB therapy.[99]

Follow-up during anti-TNF therapy. In areas of high endemicity of TB, there is always a risk of contact with infectious TB patients. Reactivation of LTBI occurs more commonly and occurred early during biologic therapy in area with high TB burden.[102] Therefore, regular screening for TB infection such as TST or chest X-ray should be considered in patients on anti-TNF therapy in such areas[103] However, currently, there is no universal recommendation on the necessity of regular screening for TB infection.[104] Education of the caregiver about the symptoms suggestive of TB infection in children taking anti-TNF agents is important.

Future research. The main hurdle in formulating PIBD management recommendations in resource-limited countries in Asia is the lack of large-scale population-based epidemiological studies.[105] The limited data available were mostly hospital-based studies, and majority were from developed countries such as Korea,[105] Japan,[106] or Singapore.[107] Children from the Asia-Pacific region have different environmental exposure, genetic background, and gut microbiome compared with children from North America and Europe. Multicenter, prospective studies is urgently needed to provide high-quality data to allow evidence-based management guidelines for PIBD in the Asia-Pacific region.

Acknowledgments

The authors wish to thank the following individuals for the valuable assistance in preparing this position statement: Dr. Lynster Liaw for editing the manuscript, Dr. Daniel Chia, and Dr. Ethan Lim for literature search. No additional data apart from what has been published in the manuscript is available. Further information can be obtained from the corresponding author.

Data availability statement. No additional data apart from what has been published in the manuscript is available. Further information can be obtained from the corresponding author.

References

1 Ng SC, Shi HY, Hamidi N *et al*. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: A systematic review of population-based studies. *Lancet* 2017; **390**: 2769–78.
2 Huang JG, Aw MM. Pediatric inflammatory bowel disease in Asia: Epidemiology and natural history. *Pediatr Neonatol* 2020; **61**: 263–71.
3 Wang XQ, Xiao Y, Xu X *et al*. Study of disease phenotype and its association with prognosis of paediatric inflammatory bowel disease in China. *BMC Pediatr* 2018; **18**: 229. https://doi.org/10.1186/s12887-018-1212-x
4 Tsai CH, Chen HL, Ni YH, Hsu HY, Jeng YM, Chang CJ, Chang MH. Characteristics and trends in incidence of inflammatory bowel disease in Taiwanese children. *J Formos Med Assoc* 2004; **103**: 685–91.
5 de Bie CI, Paerregaard A, Kolacek S, Ruemmele FM, Koletzko S, Fell JME, Escher JC. Disease phenotype at diagnosis in pediatric Crohn's disease: 5-year analyses of the EUROKIDS Registry. *Inflamm Bowel Dis* 2013; **19**: 378–85.
6 Kedia S, Das P, Madhusudhan KS *et al*. Differentiating Crohn's disease from intestinal tuberculosis. *World J Gastroenterol* 2019; **25**: 418–32.
7 van Rheenen PF, Aloi M, Assa A *et al*. The medicalmManagement of paediatric Crohn's disease: An ECCO-ESPGHAN guideline update. *J Crohns Colitis* 2021; **15**: 171–94.
8 Amil-Dias J, Kolacek S, Turner D *et al*. Surgical management of Crohn disease in children: guidelines from the Paediatric IBD Porto Group of ESPGHAN. *J Pediatr Gastroenterol Nutr* 2017; **64**: 818–35.
9 Forsdick VK, Tanny SPT, King SK. Medical and surgical management of pediatric perianal Crohn's disease: A systematic review. *J Pediatr Surg* 2019; **54**: 2554–8.
10 Mattioli G, Pio L, Arrigo S, Pini Prato A, Montobbio G, Massimo Disma N *et al*. Cone-like resection, fistulectomy and mucosal rectal sleeve partial endorectal pull-through in pediatric Crohn's disease with perianal complex fistula. *Dig Liver Dis* 2015; **47**: 658–62.
11 Dharmaraj R, Nugent M, Simpson P, Arca M, Gurram B, Werlin S. Outcomes of fecal diversion for colonic and perianal Crohn's disease in children. *J Pediatr Surg* 2018; **53**: 472–6.
12 Singh S, Ding NS, Mathis KL *et al*. Systematic review with meta-analysis: Faecal diversion for management of perianal Crohn's disease. *Aliment Pharmacol Ther* 2015; **42**: 783–92.
13 Carnovale C, Maffioli A, Zaffaroni G *et al*. Efficacy of tumour necrosis factor-alpha therapy in paediatric Crohn's disease patients with perianal lesions: A systematic review. *Expert Opin Biol Ther* 2020; **20**: 239–51.
14 Kim S. Surgery in pediatric Crohn's disease: Indications, timing and post-operative management. *Pediatr Gastroenterol Hepatol Nutri* 2017; **20**: 14–21.
15 Turner D, Ruemmele FM, Orlanski-Meyer E *et al*. Management of paediatric ulcerative colitis, part 2: Acute severe colitis—An evidence-based consensus guideline from the European Crohn's and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **67**: 292–310.
16 Gonzalez DO, Nwomeh BC. Complications in children with ulcerative colitis undergoing ileal pouch-anal anastomosis. *Semin Podiatry Sure* 2017; **26**: 384–90.

17 Turner D, Ricciuto A, Lewis A *et al*. STRIDE-II: An update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Oeganization for the Study of IBD (IOIBD): Determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021; **160**: 1570–83.
18 Cucchiara S, D'Arcangelo G, Isoldi S *et al*. Mucosal healing in Crohn's disease: New insights. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 335–45.
19 Le Berre C, Ricciuto A, Peyrin-Birolet L, Turner D. Evolving short- and long-term goals of management of inflammatory bwel disease: Getting it right, making it last. *Gastroenterology* 2022; **162**: 1424–38.
20 Santha SL, Shankar PR, Pan A, Schoen B, Kugathasan S, Sauer CG. Mucosal healing in clinical practice: A single-center pediatric IBD experience. *Inflamm Bowel Dis* 2017; **23**: 1447–53.
21 Zubin G, Peter L. Predicting endoscopic Crohn's disease activity before and after induction therapy in children: a comprehensive assessment of PCDAI, CRP, and fecal calprotectin. *Inflamm Bowel Dis* 2015; **21**: 1386–91.
22 Carmen N, Tomalty D, Church PC *et al*. Clinical disease activity and endoscopic severity correlates poorly in children newly diagnosed with Crohn's disease. *Gastrointest Endoc* 2019; **89**: 364–72.
23 Ziv-Baran T, Hussey S, Sladek M *et al*. Response to treatment is more important than disease severity at diagnosis for prediction of early relapse in new-onset paediatric Crohn's disease. *Aliment Pharmacol Ther* 2018; **48**: 1242–50.
24 Hyams J, Markowitz J, Otley A *et al*. Evaluation of the pediatric Crohn's disease activity index: A prospective multicenter experience. *J Pediatr Gastroenterol Nutr* 2005; **41**: 416–21.
25 Turner D, Griffiths AM, Walters TD *et al*. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. *Inflamm Bowel Dis* 2012; **18**: 55–62.
26 Ricciuto A, Fish J, Carman N *et al*. Symptoms do not correlate with findings from colonoscopy in children with inflammatory bowel disease and primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2018; **16**: 1098–5.e1091.
27 Turner D, Levine A, Walters TD *et al*. Which PCDAI version best reflects intestinal inflammation in pediatric Crohn's disease? *J Pediatr Gastroenterol Nutr* 2017; **64**: 254–60.
28 Turner D, Hyams J, Markowitz J *et al*. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis* 2009; **15**: 1218–23.
29 Schechter A, Griffiths C, Gana JC *et al*. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. *Gut* 2015; **64**: 580–8.
30 Turner D, Griffiths AM, Veerman G, Johanns J, Damaraju L, Blank M, Hyams J. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. *Clin Gastroenterol Hepatol* 2013; **11**: 1460–5.
31 Restellini S, Chao CY, Martel M *et al*. Clinical parameters correlate with endoscopic activity of ulcerative colitis: A systematic review. *Clin Gastroenterol Hepatol* 2019; **17**: 1265–75.
32 Chang S, Malter L, Hudesman D. Disease monitoring in inflammatory bowel disease. *World J Gastroenterol* 2015; **21**: 11246.
33 Turner D, Mack DR, Hyams J *et al*. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or both? A systematic evaluation in pediatric ulcerative colitis. *J Crohns Colitis* 2011; **5**: 423–9.
34 Alper A, Zhang L, Pashankar D *et al*. Correlation of erythrocyte sedimentation rate and C-reactive protein with pediatric inflammatory bowel disease activity. *J Pediatr Gastroenterol Nutr* 2017; **65**: e25–7.
35 Haisma SM, Verkade HJ, Scheenstra R, van der Doef HPJ, Bodewes FAJA, van Rheenen PF. Time-to-reach target calprotectin level in newly diagnosed patients with Inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2019; **69**: 466–73.
36 Weinstein-Nakar I, Focht G, Church P *et al*. Associations among mucosal and transmural healing and fecal level of calprotectin in children with Crohn's disease. *Clin Gastroenterol Hepatol* 2018; **16**: 1089–97.
37 Kolho KL, Sipponen T. The long-term outcome of anti-tumor necrosis factor-α therapy related to fecal calprotectin values during induction therapy in pediatric inflammatory bowel disease. *Scand J Gastroenterol* 2014; **49**: 434–41.
38 Logan M, Clark CM, Ijaz UZ *et al*. The reduction of faecal calprotectin during exclusive enteral nutrition is lost rapidly after food re-introduction. *Aliment Pharmacol Ther* 2019; **50**: 664–74.
39 Foster AJ, Smyth M, Lakhani A, Jung B, Brant RF, Jacobson K. Consecutive fecal calprotectin measurements for predicting relapse in pediatric Crohn's disease patients. *World J Gastroenterol* 2019; **25**: 1266–77.
40 Turner D, Ruemmele FM, Orlanski-Meyer E *et al*. Management of paediatric ulcerative colitis, part 1: Ambulatory care—An evidence-based guideline from European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **67**: 257–91.
41 Shentova R, Baycheva M, Hadjiiski P, Kofinova D, Yaneva P. Role of fecal calprotectin as a predictor of endoscopic activity in paediatric patients with ulcerative colitis. *Gastroenterol Hepatol* 2020; **43**: 57–61.
42 Kapel N, Campeotto F, Kalach N *et al*. Fecal calprotectin in term and preterm neonates. *J Pediatr Gastroenterol Nutr* 2010; **51**: 542–7.
43 Song JY, Lee YM, Choi YJ, Jeong SJ. Fecal calprotectin level in healthy children aged less than 4 years in South Korea. *J Clin Lab Anal* 2017; **31**: e22113.
44 Bernstein C, Eliakim A, Fedail S *et al*. World Gastroenterology Organisation global guidelines inflammatory bowel disease: Update August 2015. *J Clin Gastroenterol* 2016; **50**: 803–18.
45 Anupindi SA, Podberesky DJ, Twobin AJ *et al*. Pediatric inflammatory bowel disease: Imaging issues with targeted solutions. *Abdom Imaging* 2015; **40**: 975–92.
46 Rothrock SG, Green SM, Harding M *et al*. Plain abdominal radiography in the detection of acute medical and surgical disease in children: A retrospective analysis. *Pediatr Emerg Care* 1991; **7**: 281–5.
47 Bruining DH, Zimmermann EM, Loftus EV Jr *et al*. Consensus recommendations for evaluation, interpretation, and utilization of computed tomography and magnetic resonance enterography in patients with small bowel Crohn's disease. *Gastroenterology* 2018; **154**: 1172–94.
48 Siddiki HA, Fidler JL, Fletcher JG *et al*. Prospective comparison of state-of-the-art MR enterography and CT enterography in small-bowel Crohn's disease. *Am J Roentgenol* 2009; **193**: 113–21.
49 Towbin AJ, Sullivan J, Denson LA, Wallihan DB, Podberesky DJ. CT and MR enterography in children and adolescents with inflammatory bowel disease. *Radiographics* 2013; **33**: 1843–60.
50 Varyani F, Samuel S. Can magnetic resonance enterography (MRE) replace ileo-colonoscopy for evaluating disease activity in Crohn's disease? *Best Pract Res Clin Gastroenterol* 2019; **38-39**: 1016–21.
51 van Wassenaer EA, de Voogd FAE, van Rijn RR *et al*. Diagnostic accuracy of transabdominal ultrasound in detecting intestinal inflammation in paediatric IBD patient: A systematic review. *J Crohns Colitis* 2019; **13**: 1501–9.
52 Kellar A, Wilson S, Kaplan G, DeBruyn J, Tanyingoh D, Novak KL. The simple pediatric activity ultrasound score (SPAUSS) for the accurate detection of pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2019; **69**: e1–6.

53 Friedlander JA, Liu QY, Sahn B *et al*. NASPGHAN capsule endoscopy clinical report. *J Pediatr Gastroenterol Nutr* 2017; **64**: 485–94.
54 Nemeth A, Agardh D, Wurm Johansson G *et al*. Video capsule endoscopy in pediatric patients with Crohn's disease: A single-center experience of 180 procedures. *Therap Adv Gastroenterol* 2018; **11**: 1756284818758929.
55 Wu J, Huang Z, Wang Y, Tang Z, Lai L, Xue A, Huang Y. Clinical features of capsule endoscopy in 825 children: A single-center, retrospective cohort study. *Medicine (Baltimore)* 2020; **99**: e22864.
56 Panes J, Bouhnik Y, Reinisch J *et al*. Imaging techiniques for assessment of inflammatory bowel disease: Joint ECCO and ESGAR evidenced-based consensus guidelines. *J Crohns Colitis* 2013; **7**: 556–85.
57 Kedia S, Sharma R, Makharia G *et al*. Indian Guidelines on imaging of the small intestine in Crohn's disease: A Joint Indian Society of Gastroenterology and Indian Radiology and Imaging Association Consensus Statement. *Indian J Radiol Imaging* 2019; **29**: 111–32.
58 Shah SC, Colombel JF, Sands BE, Narula N. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; **43**: 317–33.
59 Oliva S, Thomson M, de Ridder L *et al*. Endoscopy in pediatric inflammatory bowel disease: A position paper on behalf of the porto IBD Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **67**: 414–30.
60 Oliva S, Aloi M, Viola F *et al*. A treat to target strategy using panenteric capsule endoscopy in pediatric patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2019; **17**: 2060–7.
61 Melmed GY, Dubinsky MC, Rubin DT *et al*. Utility of video capsule endoscopy for longitudinal monitoring of Crohn's disease activity in the small bowel: a prospective study. *Gastrointest Endosc* 2018; **88**: 947–55.
62 Miele E, Shamir R, Aloi M *et al*. Nutrition in pediatric inflammatory bowel disease: a position paper on behalf of the Porto Inflammatory Bowel Disease Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; **66**: 687–708.
63 Jin HY, Lim JS, Lee Y *et al*. Growth, puberty, and bone health in children and adolescents with inflammatory bowel disease. *BMC Pediatr* 2021; **21**: 1–9, 35.
64 Song SM, Kim Y, Oh SH, Kim KM. Nutritional status and growth in Korean children with Crohn's disease: A single-center study. *Gut Liver* 2014; **8**: 500.
65 Laakso S, Valta H, Verkasalo M, Toiviainen-Salo S, Makitie O. Compromised peak bone mass in patients with inflammatory bowel disease: A prospective study. *J Pediatr* 2014; **164**: 1436–43.e1.
66 Levy-Sharga Y, Shenkar A, Modan-Moses D *et al*. Longitudinal changes in bone mineral density in children with inflammatory bowel diseases. *Acta Paediatr* 2020; **109**: 1026–32.
67 Wong SC, Catto-Smith AG, Zacharin M. Pathological fractures in paediatric patients with inflammatory bowel disease. *Eur J Pediatr* 2014; **173**: 141–51.
68 Schmidt S, Mellstrom D, Norjavaara E, Sundh V, Saalman R. Longitudinal assessment of bone mineral density in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2012; **55**: 511–8.
69 Rozes S, Guilmin-Crepon S, Alison M *et al*. Bone health in pediatric patients with Crohn disease. *J Pediatr Gastroenterol Nutr* 2021; **73**: 231–5.
70 Saadah OI, Annese V, Mosli MH. Prevalence and predictors of reduced bone density in children and adolescent patients with Crohn's disease. *J Clin Densitom* 2021; **24**: 252–8.
71 Mosli MH, Saadah OI. Metabolic bone disease in children and adolescent patients with ulcerative colitis. *J Pediatr (Rio J)* 2021; **97**: 242–7.
72 Ronel N, Tzion RL, Orlanski-Meyer E *et al*. Clinical criteria can identify children with osteopenia in newly diagnosed Crohn's disease. *J Pediatr Gastroenterol Nutr* 2021; **72**: 270–5.
73 Sigurdsson GV, Schmidt S, Mellstrom S *et al*. Bone mass development from childhood into young adulthood in patients with childhood-onset inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2017; **23**: 2215–26.
74 Dipasquale V, Romano C. Vaccination strategies in pediatric inflammatory bowel disease. *Vaccine* 2017; **35**: 6070–5.
75 Gertosio C, Licari A, De Silvestri A, Rebuffi C, Chiappini E, Marseglia GL. Efficacy, immunogenecity, and safety of available vaccines in children on biologics: A systematic review and metaanalysis. *Vaccine* 2022; **40**: 2679–95.
76 Quan J, Ma C, Panaccione R *et al*. Serological responses to three doses of SARS-CoV-2 vaccination in inflammatory bowel disease. *Gut* 2022: gutjnl-2022-327440. https://doi.org/10.1136/gutjnl-2022-327440
77 Siegel CA, Melmed GY, McGovern DPB *et al*. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: Recommendations from an international consensus meeting. *Gut* 2021; **70**: 635–40.
78 Brooks AJ, Norman P, Peach EJ *et al*. Prospective study of psychological morbidity and illness perceptions in young people with inflammatory bowel disease. *J Crohns Colitis* 2019; **13**: 1003–11.
79 Rosen MJ, Dhawan A, Saeed SA *et al*. Inflammatory bowel disease in children and adolescents. *JAMA Pediatr* 2015; **169**: 1053–60.
80 Blum RW, Garell D, Hodgkin CH *et al*. Transition from child-entered to adult health-care systems for adolescents with chronic conditions: A position paper of the Society for Adolescent Medicine. *J Adolesc* 1993; **14**: 570–6.
81 Fu N, Bollegala N, Jacobson K *et al*. Canadian consensus statements on the transition of adolescents and young adults with inflammatory bowel disease from pediatric to adult care: A collaborative initiative between the Canadian IBD Transition Network and Crohn's and Colitis Canada. *J Can Assoc Gastroenterol* 2022; **26**: 105–15.
82 Mollah T, Lee D, Giles E. Impact of a new young adult inflammatory bowel disease transition clinic on patient satisfaction and clinical outcomes. *J Paediatr Child Health* 2022; **58**: 1053–9.
83 Kumagai H, Shimizu T, Iwama I *et al*. A consensus statement on health-care transition for childhood-onset inflammatory bowel disease patients. *Pediatr Int* 2022; **64**: e15241.
84 van Rheenen PF, Aloi M, Biron IA *et al*. European Crohn's and Colitis Organisation Topical Review on transitional care in inflammatory bowel disease. *J Crohns Colitis* 2017; **11**: 1032–8.
85 Park DI, Hisamatsu T, Chen M *et al*. Asian Organization for Crohn's and Colitis and Asian Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 1: Risk assessment. *J Gastroenterol Hepatol* 2018; **33**: 20–9.
86 Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: A re-estimation using mathematical modelling. *PLoS Med* 2016; **13**: e1002152.
87 Lal SB, Bolia R, Menon JV *et al*. Abdominal tuberculosis in children: A real-world experience of 218 cases from an endemic region. *J Gastroenterol Hepatology Open* 2020; **4**: 215–20.
88 Al Karawi MA, Mohamed AE, Yasawy MI *et al*. Protean manifestation of gastrointestinal tuberculosis: report on 130 patients. *J Clin Gastroenterol* 1995; **20**: 225–32.
89 Banerjee R, Pal P, Mak JWY, Ng SC. Challenges in the diagnosis and management of inflammatory bowel disease in resource-limited settings in Asia. *Lancet Gastroenterol Hepatol* 2020; **5**: 1076–88.

90 World Health Organization. World Health Organization tuberculosis guidelines: recent updates. Available at: who.int/publications/digital/global-tuberculosis-report-2021 (accessed November 10, 2022).
91 Ng SC, Hirai HW, Tsoi KK, Wong SH, Chan FK, Sung JJ, Wu JC. Systematic review with meta-analysis: accuracy of interferon-gamma releasing assay and anti-*Saccharomyces cerevisiae* antibody in differentiating intestinal tuberculosis from Crohn's disease in Asians. *J Gastroenterol Hepatol* 2014; **29**: 1664–70.
92 Ramadass B, Chittaranjan S, Subramanian V, Ramakrishna BS. Fecal polymerase chain reaction for *Mycobacterium tuberculosis* IS6110 to distinguish Crohn's disease from intestinal tuberculosis. *Indian J Gastroenterol* 2010; **29**: 152–6.
93 Kedia S, Sharma R, Sreenivas V *et al*. Accuracy of computed tomographic features in differentiating intestinal tuberculosis from Crohn's disease: A systematic review with meta-analysis. *Intest Res* 2017; **15**: 149–59.
94 Knox C, Almeida J. The comb sign. Clinic. *Gastroenterol Hepatol* 2021; **19**: A29–30.
95 Jin T, Fei B, Zhang Y, He X. The diagnostic value of polymerase chain reaction for Mycobacterium tuberculosis to distinguish intestinal tuberculosis from Crohn's disease: A meta-analysis. *Saudi J Gastroenterol* 2017; **23**: 3–10.
96 Dutta AK, Sahu MK, Gangadharan SK, Chacko A. Distinguishing Crohn's disease from intestinal tuberculosis-A prospective study. *Trop Gastroenterol* 2011; **32**: 204–9.
97 Singh SK, Srivastava A, Kumari N, Poddar U, Yacha SK, Paddy CM. Differentiation between Crohn disease and intestinal tuberculosis in children. *J Pediatr Gastroenterol Nutr* 2018; **66**: e6–11.
98 Park DI, Hisamatsu T, Chen M *et al*. Asian Organization for Crohn's and Colitis and Asian Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: Management. *J Gastroenterol Hepatol* 2018; **33**: 30–6.
99 Lee CK, Wong SHV, Lui G *et al*. A prospective study to monitor for tuberculosis during anti-tumour necrosis factor therapy in patients with inflammatory bowel disease and immune-mediated inflammatory diseases. *J Crohns Colitis* 2018; **12**: 954–62.
100 WHO Operational Handbook on Tuberculosis. *Module 5: Management of Tuberculosis in Children and Adolescents*. Geneva: World Health Organization, 2022 Licence: CC BY-NC-SA 3.0 IGO.
101 Shim TS. Diagnosis and treatment of latent tuberculosis infection due to initiation of anti-TNF therapy. *Tuberc Respir Dis* 2014; **76**: 261–8.
102 Theis VS, Rhodes JM. Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2008; **27**: 19–30.
103 Taxonera C, Ponferrada A, Riesta S *et al*. Serial tuberculin skin tests improve the detection of latent tuberculosis infection in patients with inflammatory bowel disease. *J Crohns Colitis* 2018; **15**: 1270–9.
104 Nakase H, Keum B, Ye BD, Park SJ, Koo HS, Eun CS. Treatment of inflammatory bowel disease in Asia: the results of a multinational web-based survey in the 2nd Asian Organization of Crohn's and Colitis (AOCC) meeting in Seoul. *Intest Res* 2016; **14**: 231.
105 Kim Y. Nationwide population-based epidemiologic study of very-early onset IBD using health-care big data, 2005-2016 Seoul, Korea: University of Ulsan; 2021.
106 Ishige T, Tomomasa T, Hatori R, Tatsuki M, Igarashi Y, Sekine K, Arakawa H. Temporal trend of pediatric inflammatory bowel disease: Analysis of national registry data 2004 to 2013 in Japan. *J Pediatr Gastroenterol Nutr* 2017; **65**: e80–2.
107 Ong C, Aw MM, Liwanag MJ, Quak SH, Phua KB. Rapid rise in the incidence of pediatric inflammatory bowel disease in a South-East Asian cohort in Singapore, 1994-2015. *J Dig Dis* 2018; **19**: 395–403.