

REVIEW ARTICLE

Inflammatory Bowel Disease in Childhood and Adolescence

Diagnosis and Treatment

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SUMMARY

Background: The incidence of inflammatory bowel disease (IBD) in childhood and adolescence is 5–11 cases per 100 000 persons per year, corresponding to a new diagnosis of IBD in 800–1470 patients in Germany each year.

Methods: This review is based on pertinent publications retrieved by a selective search in PubMed, including guidelines from Germany and abroad.

Results: Children and adolescents with IBD often have extensive involvement and an aggressive course of disease. Nonetheless, infliximab and adalimumab are the only biological agents that have been approved for this group of patients. In Crohn's disease, exclusive enteral nutrition is the treatment of first choice for inducing a remission. Patients with (peri-)anal fistulae are treated primarily with infliximab. Corticosteroids and aminosalicylates should be used with caution. In contrast, children and adolescents with ulcerative colitis are treated with either aminosalicylates or prednisolone to induce a remission. As a rule, maintenance pharmacotherapy with thiopurines in Crohn's disease and severe ulcerative colitis, or with aminosalicylates in mild to moderate ulcerative colitis, is indicated for several years, at least until the end of puberty. Patients with refractory disease courses are treated with methylprednisolone, anti-TNF- α -antibodies, and/or calcineurin inhibitors. The spectrum of surgical interventions is the same as for adults. Specific aspects of the treatment of children and adolescents with IBD include adverse drug effects, the areas of nutrition, growth, and development, and the structured transition to adult medicine.

Conclusion: Children and adolescents with IBD or suspected IBD should be cared for by pediatric gastroenterologists in a center where such care is provided. Individualized treatment with multidisciplinary, family-oriented long-term care is particularly important. Drug trials in children and adolescents are needed so that the off-label use of drugs to patients in this age group can be reduced.

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The incidence of Crohn's disease in Germany is up to 6.6 per 100 000 population. Its prevalence is approximately 100 to 200 per 100 000 population (1). For ulcerative colitis, the incidence in Germany is 3.0 to 3.9 per 100 000 population, and its prevalence approximately 160 to 250 per 100 000 population (2). Inflammatory bowel disease (IBD) is diagnosed before the age of 18 years in approximately 25% of all patients; approximately one-quarter of all affected children and adolescents are under the age of 10 years at diagnosis (3). Children and adolescents with IBD are more likely to have more severe intestinal involvement at diagnosis and faster disease progression than adults (4). Treatment recommendations for children and adolescents are different than those for adults (5–13, e1). The treatment of children and adolescents with suspected or confirmed IBD should comply with these recommendations and be performed by pediatric gastroenterologists (1, 2). Multidisciplinary treatment of children and adolescents with IBD is complex, especially because it requires the availability of numerous subdisciplines (e2). Data on children and adolescents with IBD in Germany is recorded in the CEDATA-GPGE registry of the German-speaking Society for Pediatric Gastroenterology and Nutrition (GPGE, *Gesellschaft für Pädiatrische Gastroenterologie und Ernährung*) (14, 15). This paper addresses the increasingly important subject of medical care for children and adolescents with IBD in the context of aspects specific to ages at which development is ongoing.

Methods

This article is based on a selective search of the literature in PubMed. Both German (1, 2) and European (11–13) guidelines for both the above-mentioned diseases are available and were consulted. For the diagnosis of IBD, the available data is mostly limited to case series, but treatment recommendations are usually based on controlled trials or meta-analyses of controlled trials.

Diagnosis

As with adults, IBD is suspected in children and adolescents when initial diagnostic examination reveals a combination of symptoms and abnormal laboratory

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TABLE

Inflammatory bowel disease symptoms and differential diagnoses in childhood and adolescence

Symptoms	Extraintestinal manifestations	Differential diagnoses
<ul style="list-style-type: none"> ● Fever ● Fatigue ● Pale skin and mucous membranes ● Loose stools ● Occult/visible blood in stool ● Bloody diarrhea ● Abdominal pain ● Abdominal tenderness on palpation ● Resistance (particularly in lower right abdomen) ● Tenesmus ● Developmental delay ● Perianal fistulae, fissures, abscesses 	<ul style="list-style-type: none"> ● Impaired growth/growth retardation ● Aphthous stomatitis ● Erythema nodosum ● Scleritis, episcleritis ● Arthritis, arthropathy ● Primary sclerosing cholangitis ● Gallstones ● Autoimmune hepatitis ● Venous thromboembolism ● Nephrolithiasis ● Pancreatitis 	<ul style="list-style-type: none"> ● Carbohydrate malabsorption ● Infectious colitis, enterocolitis ● Cow's milk protein allergy ● Celiac disease ● Henoch–Schönlein purpura ● Appendicitis ● Anal fissures ● Intestinal polyps ● Hemorrhoids ● Intussusception ● Meckel diverticulum ● Immunological diseases ● Functional diseases ● Intestinal tuberculosis ● Adverse drug reactions

findings (including fecal inflammatory markers). It is diagnosed if there are abnormal findings in clinical history and on physical examination using endoscopy and radiology, including histopathological evaluation of stepwise biopsies from the upper and lower gastrointestinal tract (16).

Symptoms

Although the clinical presentation of IBD in children and adolescents can be similar to that found in adults, some of the disease phenotype is substantially different. This can be caused by, for example, specific complications, sometimes age-specific, such as growth retardation or delayed puberty (*Table*). For Crohn's disease in particular, variability between individuals is particularly great in childhood and adolescence. It is not uncommon for symptom onset to be very hard to notice. Because symptoms differ in degree of severity and intensity, in individual cases they can be confused with nonspecific or functional complaints (17, 18). The most common extraintestinal manifestation of IBD in children and adolescents is impaired growth/growth retardation; this is particularly true of Crohn's disease, in which impaired growth/growth retardation occurs in 10 to 30% of cases. Approximately 10% of children and adolescents have other extraintestinal manifestations of IBD at diagnosis; these can also occur in adults (19) (*Table*).

Clinical history and physical examination

Children and adolescents with IBD are more likely than adults to have a positive family history of IBD. This indicates that genetic factors play a greater role in IBD when initial manifestation occurs during childhood or adolescence (20, e3). Intestinal inflammation in infants and young children can be caused by a number of genetic defects that can lead to involvement of the immune system and the intestinal epithelium (this is known as monogenic IBD). Approximately 1% of children and adolescents with IBD are less than 1 year

old; around 15% are younger than 6 years (21). Full physical examination must include oral and perianal inspection (rectal examination if necessary) and evaluation of height and weight using age- and sex-specific percentile curves and pubertal development (Tanner stages). A height *z*-score of less than -2.5 indicates significant impaired growth/growth retardation. Body mass index (BMI) and rate of growth (in centimeters per year) are also calculated, on the basis of anthropometric data. BMI below the 10th percentile and/or rate of growth less than 5 cm per year (in children older than 2 years) indicates significant impaired growth/growth retardation.

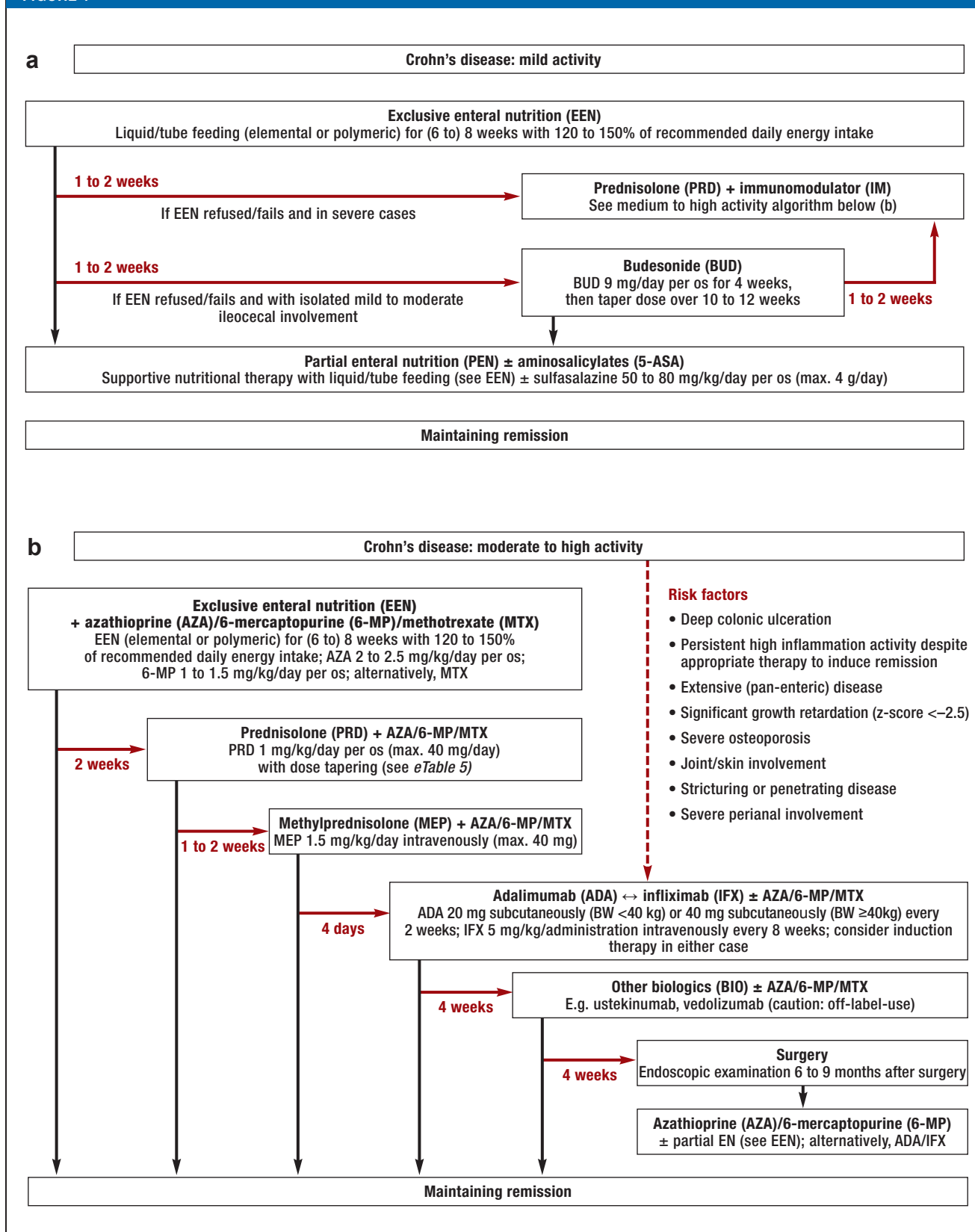
Laboratory diagnostics

As in adults, diagnosis of IBD requires blood and stool tests (1, 2, 16) (*eTable 1*). Diagnostic procedures for celiac disease must be performed in children and adolescents with growth retardation and/or nonbloody diarrhea (22). In children with suspected IBD before the age of 2 years, primary immunodeficiency must also be ruled out (21). Disease onset before the age of 6 years is probably caused by a genetic, possibly monogenic, immunodeficiency with intestinal inflammation typical of IBD. The incidence of very early disease onset is approximately 4.37 per 100 000; its prevalence is 14 per 100 000 (21). The possibility of an underlying food allergy must also be considered (23, e4).

Endoscopy and histopathology

If suspected IBD is confirmed on the basis of clinical history, physical examination, and laboratory findings, the patient requires treatment by an experienced pediatric gastroenterologist. Upper gastrointestinal endoscopy and ileocolonoscopy are usually performed under sedation (or general anesthesia). During endoscopy stepwise biopsies are taken from all sections of the gastrointestinal tract, including those which are endoscopically normal. These then undergo histopathological evaluation (e5–e7).

FIGURE 1



Treatment algorithms for children and adolescents with Crohn's disease: a) mild activity; b) moderate to high activity

Black arrows: clinical response to treatment; red arrows: no response to treatment within the stated time period or treatment refused; ±: administer if required; ↔: equally valid treatment options; BW: body weight.

The procedure outlined here is closely based on the consensus recommendations of international specialized societies (ECCO, ESPGHAN) (11).

Imaging diagnostics

Involvement of the small intestine is assessed using either magnetic resonance (MR) enterography with oral contrast only (administered per os or via nasogastric tube) or video capsule endoscopy (16). MR enterography can be performed from the age of 3 or 4 years. In addition, high-resolution transabdominal Doppler ultrasound is highly suitable as a screening or monitoring examination in children. Conventional X-ray is used if ileus, subileus, or toxic megacolon is suspected, and to determine bone age (left hand). Computed tomography is used only in emergencies or where other diagnostic procedures have failed, due to the radiation burden it entails. MR cholangiopancreatography (MRCP) is used in children and adolescents for certain specific issues (e.g. suspected liver/bile duct involvement).

Differential diagnoses

The main differential diagnoses for IBD in children and adolescents are summarized in the *Table* (17, 18, 22, 24, 25).

Classification

The Paris classification for inflammatory bowel disease in children and adolescents is closely based on the Montreal classification for IBD in adults. Among other issues, it stratifies risk before the beginning of treatment (16, 28, e8). Clinical indices are of proven value in assessing disease activity, particularly within studies. They were developed specifically for children and adolescents with Crohn's disease (*eTable 2*) and ulcerative colitis (*eTable 3*) (8, 9, e1). However, because of the increasing importance of specific biomarkers (particularly fecal calprotectin), these indices require revision (e9, e10).

Treatment

Specific features of IBD in children and adolescents

Treatment for IBD in patients under the age of 18 years differs from treatment recommendations for adults, sometimes substantially (1, 2, 27, 28). Two examples of this are intensiveness of treatment and drug authorization. *eTable 4* details randomized clinical trials in children and adolescents with IBD (e11–e22). The main differences between treatment algorithms for children and adolescents and those for adults are shown in the *eBox* (11, 12, 27, e17, e23). Detailed written information on all aspects of IBD written specifically for children, adolescents, parents, schoolteachers, and kindergarten teachers is available, as are apps for smartphones and tablets and an IBD booklet specifically for children and adolescents. The treatment concept also includes seminars for physicians, patients, and parents and IBD training programs for children and adolescents. Children from the age of approximately 4 years must be either supervised when they take tablets or trained in doing so; alternatively, medication can be provided in alternative pharmaceutical forms. Treatment algorithms for children and adolescents with IBD are summarized in *Figures 1* and *2*.

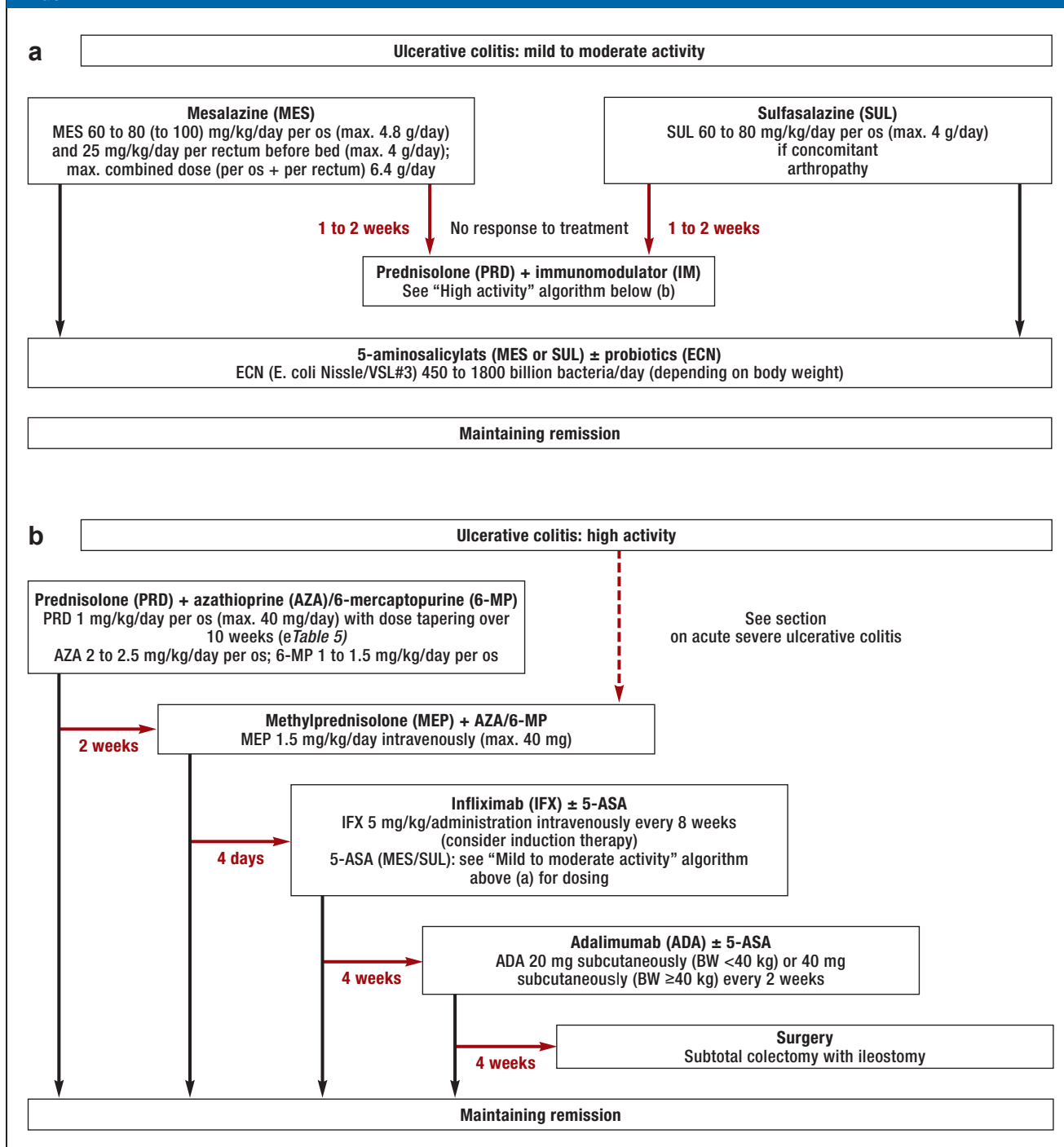
Preparation for immunosuppressant therapy

Patients' vaccination status and infectious disease history should be ascertained before beginning treatment. If a patient is not sufficiently protected by prior vaccinations, the necessary vaccinations—in line with the patient's age and with current vaccination recommendations—should be administered before immunosuppressant treatment is begun. This is particularly important for live vaccines, as these are usually contraindicated later, i.e. during immunosuppressant treatment (e24, e25). Inactivated vaccines can and should be used even in immunosuppressed children and adolescents (ideally, for optimal efficacy, at least 2 weeks before the beginning of immunosuppressant treatment or during stable disease phases). In addition, latent tuberculosis must be ruled out using clinical history, chest X-ray, and a tuberculosis blood test (γ -interferon assay) before immunosuppressant treatment is begun (particularly before anti-TNF- α antibody therapy). The genotype (or activity) of thiopurine methyltransferase (TPMT) should be determined before thiopurine therapy is administered; this is because hereditary low or absent TPMT activity entails an increased risk of severe thiopurine-induced bone marrow toxicity (11, 29, e26).

Inducing remission

First-line treatment to induce remission in children and adolescents with Crohn's disease, regardless of severity, is exclusive enteral nutrition (EEN) via liquid or tube feeding (11, 30–32). Exceptions to this are children and adolescents who present risk factors (particularly anal fistulae): for this group, primary treatment is infliximab therapy (11). Formula feeding can be administered orally, via a nasogastric tube, or via a percutaneous endoscopic gastrostomy (PEG) tube as part of EEN. Regarding PEGs, caution is required in cases of isolated involvement of the upper gastrointestinal tract proximal to the Treitz ligament (e27). If therapy has had no effect after 1 to 2 weeks or if treatment is refused by the patient or the patient's family, glucocorticoid treatment is administered instead. TNF- α blockers (adalimumab, infliximab) are authorized for the treatment of Crohn's disease in patients over the age of 6 years. If any risk factors are present, TNF- α blockers should be used as initial remission induction therapy (11). Prognostic risk factors for severe disease progression in children and adolescents with Crohn's disease are listed in *Figure 1b* (11). In children and adolescents with mild to moderate ulcerative colitis, remission is induced using 5-aminosalicylates; corticosteroids are used if disease activity is high or the disease is severe (12). Long-term and/or frequent use of corticosteroids in children and adolescents is no longer current practice, among other reasons because of their severe side effects for growth and physical development (11). *eTable 5* states the recommendations for tapering prednisone or prednisolone dosing (11, 13).

FIGURE 2



Treatment algorithms for children and adolescents with ulcerative colitis: a) mild to moderate activity; b) high activity

Black arrows: clinical response to treatment; red arrows: no response to treatment within the stated time period or treatment refused; ±: administer if required; BW: body weight

Adalimumab has not been formally authorized in Germany for the treatment of ulcerative colitis in children or adolescents (off-label use).

The procedure outlined here is closely based on the consensus recommendations of international specialized societies (ECCO, ESPGHAN) (12, 13).

Maintaining remission

Immunosuppressants (thiopurines, methotrexate) and/or biologics (adalimumab, infliximab) are generally used to maintain remission in children and adolescents with Crohn's disease (11). Because of the high relapse rate after cessation of EEN, in moderate to severe Crohn's disease immunomodulators (i.e. thiopurines, or methotrexate if thiopurines are not tolerated) should be used to maintain remission at the same time as EEN is begun to induce it. Partial enteral nutrition (PEN), if appropriate in combination with 5-aminosalicylates (if there is only colonic involvement), can be used as maintenance therapy if the patient responds well to EEN and Crohn's disease activity is initially mild (11). Even when Crohn's disease activity is initially moderate or severe, PEN can be used as supportive therapy in addition to pharmacological maintenance therapy. Budesonide is used rarely and only for selected Crohn's disease patients under the age of 18 years with mild to moderate ileocecal involvement (11). In children and adolescents with ulcerative colitis, 5-aminosalicylates are used to maintain remission, in combination with thiopurines or biologics (infliximab) if involvement is extensive or severe (12). Surgery is an established part of therapy for serious or complicated progression in the long term. Indications for surgery in children and adolescents with IBD are *de facto* the same as for adults; as it is known to have the potential for complications, it should be performed only by surgeons experienced in IBD surgery (e28). Finally, due to the trials conducted to date and drug authorizations for children and adolescents with IBD, off-label drug use or individualized treatment approaches such as other biologics (e.g. vedolizumab, ustekinumab, or golimumab in children under the age of 6 years) are often required (27).

Acute severe ulcerative colitis

Acute severe ulcerative colitis in children and adolescents is treated with methylprednisolone (1 to 1.5 mg/kg/day intravenously in 2 divided doses, maximum 60 mg/day) (13, 33). Until thiopurines take effect, second-line treatment involves calcineurin inhibitors (cyclosporine, tacrolimus) or infliximab. TNF- α blockers (infliximab) are an option for maintenance therapy if there is no response to thiopurines, steroids are not tolerated, or if there is increased cyclosporine toxicity (13). Subtotal colectomy with ileostomy should be considered early in cases of acute severe ulcerative colitis or toxic megacolon if there is no response to conservative treatment (13).

Optimizing treatment

Treatment adherence problems are not uncommon, particularly during puberty and among adolescents (e29). Adherence has been found to decrease between the ages of 7 and 17 years (e30). Optimization of existing treatment should be the first step if treatment failure is suspected and before every escalation of therapy. This includes checking medication adherence, dosing, and

efficacy. In addition, therapeutic drug monitoring with testing for thiopurine metabolites (6-TGN and 6-MMP) or for trough levels and antibodies against infliximab and adalimumab (29, 34) and biomarker dynamics (particularly fecal calprotectin) plays an important role in the treatment of children and adolescents with IBD. This is particularly true when thiopurines and/or TNF- α blockers lose clinical efficacy (e9, e10). Testing for thiopurine metabolites is part of checking for adherence.

Long-term treatment

Follow-up

Subsequent checkups performed by a pediatric gastroenterologist are usually required at least every 3 months (more frequently in complicated or treatment-refractory cases). These are particularly important to enable impaired growth, delayed puberty, nutritional deficiencies, drug side effects, opportunistic and other infections, and extraintestinal manifestations to be treated promptly (35, e31). Endoscopic or histological re-evaluation is indicated before major changes to treatment and when response to treatment is uncertain (12). Colitis-associated cancers can occur in IBD patients even before the age of 18 years and necessitate appropriate screening (35, 36).

Growth and nutrition

Impaired growth can be prevented or mitigated through swift diagnosis (calculation of genetic target height, growth prognosis based on bone age), appropriate/intensive treatment with sparing corticosteroid use, and sufficient energy/nutrient intake (36). Children and adolescents with IBD require concomitant treatment by nutritional therapists, as their nutritional status is usually critical (37, e32, e33). Intravenous ferric carboxymaltose is the preferred treatment for iron deficiency, which is common. Vitamin D should be administered at a dose of 600 IU/day in children and adolescents with IBD, as for healthy children and adolescents; the recommended calcium intake is 1000 mg/day for children aged between 4 and 8 years and 1300 mg/day for those aged 9 to 18 years. Children and adolescents with IBD require regular vitamin D and calcium supplementation, as regular family food often fails to comply with these recommendations (35, 36, e34, e35). Alternatively, single oral administration of vitamin D3 may be sufficient (e36). The target serum concentration of 25 hydroxyvitamin D (25-OHD) is above 30 ng/mL (e37).

Psychosocial treatment

Children and adolescents with IBD are at increased risk of psychosocial problems and psychiatric illness (particularly depression). These can have adverse effects on school attendance, education, leisure activities, medication adherence, and quality of life (38, e38–e41). Case studies suggest that 25 to 40% of IBD patients, usually adolescents, show signs of clinical depression (e42, e43). Concomitant treatment in the form

of initial psychological counselling/evaluation and, if necessary, psychotherapy is therefore recommended for children and adolescents with IBD (e44, e45).

Transition

A structured transition program (e.g. the Berlin Transition Program) should provide a comprehensive, accompanied transition from adolescent to adult care, with costs covered. This is because deficiencies in care during this particularly critical phase result in treatment interruptions, insufficient treatment compliance, and increased frequency of complications that are probably avoidable (10, 39, e28, e46, e47).

Additional information on IBD is provided by the German-speaking Society for Pediatric Gastroenterology and Nutrition (GPGE, *Gesellschaft für Pädiatrische Gastroenterologie und Ernährung*) at www.gpge.de and the German Association for Crohn's Disease and Ulcerative Colitis (DCCV, *Deutsche Morbus Crohn/Colitis ulcerosa Vereinigung*) at www.dccv.de.

Conflict of interest statement

Prof. Däbritz has received consultancy and lecture fees and reimbursement of travel expenses from Abbvie, Nestlé, Shire, Humana, and Takeda.

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KEY MESSAGES

- There are differences between the diagnosis and treatment of children and adolescents with inflammatory bowel disease (IBD) and treatment recommendations for adults.
- The most common extraintestinal manifestation of IBD, particularly Crohn's disease, in childhood and adolescence is impaired growth/growth retardation.
- Children and adolescents with IBD are at increased risk of psychosocial problems and psychiatric illness.
- Children and adolescents with IBD require concomitant treatment by nutritional therapists to prevent and treat malnutrition.
- Treatment adherence falls between the ages of 7 and 17 years. It is particularly problematic during puberty and in adolescents.

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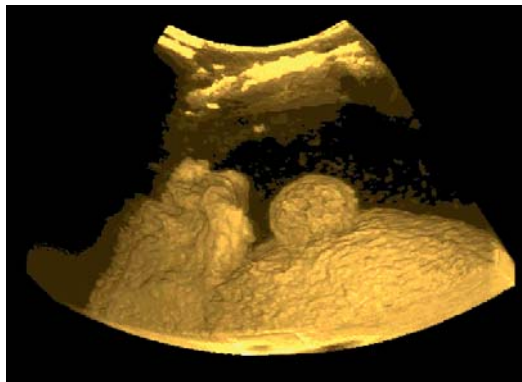
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Supplementary material
 For eReferences please refer to:
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CLINICAL SNAPSHOT

3D Hepatic Ultrasonography—A Detailed Imaging Modality



3D ultrasonographic imaging is widely used in gynecology. The sharp transition between fluid (amniotic fluid) and solid matter (the fetus) allows the creation of very detailed, highly contrasted images of the unborn child. This method, however, has not yet been investigated in imaging of the liver. We used it to create a 3D ultrasonographic image of the liver in a patient who had hepatic cirrhosis as well as a superficially located hepatocellular carcinoma (30 × 27 mm) surrounded by ascites (*Figure*). This technical extension of hepatic ultrasonography allows the creation of novel, detailed images of superficial tumors, and it clearly reveals the uneven surface of the cirrhotic liver. Detailed 3D ultrasonographic images of the liver can be generated without any special ultrasonographic probes or contrast media. It remains to be seen whether this method will have any further practical application in medical practice aside from the visualization of cirrhosis and of superficial tumors.

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 The authors state that they have no conflict of interest.

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Supplementary material to:

Inflammatory Bowel Disease in Childhood and Adolescence

Diagnosis and Treatment

by Jan Däbritz, Patrick Gerner, Axel Enninger, Martin Claßen, and Michael Radke

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eTABLE 1

Blood and stool tests for suspected inflammatory bowel disease in children and adolescents

Blood tests	Stool tests	Additional tests
<ul style="list-style-type: none"> ● Blood count (incl. differential blood count) ● C-reactive protein ● Erythrocyte sedimentation rate ● Creatinine ● Urea ● Electrolytes ● Alanine aminotransferase (ALT) ● Aspartate aminotransferase (AST) ● Gamma-glutamyl transferase (gamma-GT) ● Blood glucose ● Albumin 	<ul style="list-style-type: none"> ● Microbiological tests for the following pathogenic bacteria: <ul style="list-style-type: none"> – Salmonella – Shigella – Yersinia – Campylobacter – Clostridium difficile/Clostridium difficile toxin ● Calprotectin 	<ul style="list-style-type: none"> ● Tissue transglutaminase type 2 IgA and total IgA ● Vitamins A, D, E, and B12 ● Folic acid ● Ferritin ● Zinc ● Fecal occult blood test ● Stool tests for viruses, parasites, and fungi ● Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA)

eTABLE 2

Pediatric Crohn's Disease Activity Index (PCDAI)

Criterion	Characteristics	Score	
Clinical symptoms			
Abdominal pain	<ul style="list-style-type: none"> • None • Mild, brief, does not interfere with activities • Moderate/severe, daily, longer lasting, affects activities, nocturnal 	0 5 10	
Stools	<ul style="list-style-type: none"> • 0–1 liquid stools, no blood • Up to 2 semi-formed with small blood or 2 to 5 liquid stools per day • Gross bleeding or ≥6 liquid stools or nocturnal diarrhea 	0 5 10	
General well-being	<ul style="list-style-type: none"> • Well, no limitation of activities • Below par, occasional difficulties in maintaining age appropriate activities • Very poor, frequent limitation of activities 	0 5 10	
Physical examination			
Changes in body weight over 4 to 6 months	<ul style="list-style-type: none"> • Weight gain, desired stable weight, or voluntary weight loss • Involuntary stable weight or involuntary weight loss of 1 to 9% • Weight loss ≥10% 	0 5 10	
Height at diagnosis	<ul style="list-style-type: none"> • <1 channel decrease • ≥ 1, <2 channel decrease • >2 channel decrease 	0 5 10	
or	or		
Height velocity at follow-up	<ul style="list-style-type: none"> • Height velocity ≥ –1 standard deviation • Height velocity < –1 standard deviation but > –2 standard deviations • Height velocity ≤ –2 standard deviations 	0 5 10	
Abdomen	<ul style="list-style-type: none"> • Normal, no tenderness, no mass • Tenderness, or mass without tenderness • Tenderness, involuntary guarding, definite mass 	0 5 10	
Perineum	<ul style="list-style-type: none"> • None, asymptomatic tags • 1–2 indolent fistula, scant drainage, no tenderness of abscess • Active fistula, drainage, tenderness or abscess 	0 5 10	
Extra-intestinal manifestations: – Fever ≥38.5 °C for 3 days in previous week – Arthritis – Uveitis – Erythema nodosum – Pyoderma gangrenosum	None 1 ≥2	0 5 10	
Laboratory findings			
Hematocrit	≤10 years	>33 28–32 <28	0 2.5 5
	Girls, 11–19 years	≥ 34 29–33 <29	0 2.5 5
	Boys, 11–14 years	≥ 35 30–34 <30	0 2.5 5
	Boys, 15–19 years	≥ 37 32–36 <32	0 2.5 5
Erythrocyte sedimentation rate (ESR) (mm/hr.)	<20 20–50 >50	0 2.5 5	
Albumin level (g/dL)	≥ 3.5 3.1–3.4 ≤ 3.0	0 5 10	
Total score			
≤10 points	Inactive (remission)		
10–30 points	Mild activity		
30–100 points	Moderate to severe activity	

eTABLE 3

Pediatric Ulcerative Colitis Activity Index (PUCAI)

Criterion	Characteristics	Score
Abdominal pain	• No pain	0
	• Pain can be ignored	5
	• Pain cannot be ignored	10
Rectal bleeding	• None	0
	• Small amount only, in less than 50% of stools	10
	• Small amounts with most stools	20
	• Large amounts (>50% of stool content)	30
Stool consistency of most stools	• Formed	0
	• Partly formed	5
	• Completely unformed	10
Number of stools per 24 hours	0–2	0
	3–5	5
	6–8	10
	> 8	15
Nocturnal stools (any episode causing waking)	• No	0
	• Yes	10
Activity level	• No limitation of activity	0
	• Occasional limitation of activity	5
	• Severely restricted activity	10
Total (0 to 85 points)	<10: remission 10 to 40: mild activity 40 to 65: moderate activity 65 to 85: high activity

eTABLE 4

Randomized clinical trials in children and adolescents with IBD

Trial	Intervention	Patient cohort	Trial design	Findings	Main ADRs
Griffiths A et al. 1993 (e16)	5-ASA 50 mg/kg BW/day (max. 3 g/day) per os vs. placebo	13 patients with active Crohn's disease of the small intestine; age 5 to 18 years; trial period August 1988 to February 1991	Single-center, double-blind, placebo-controlled, crossover (2 x 8 weeks with 4-week washout phase); 20 weeks' follow-up	43% vs. 0% clinical response in week 8 (5-ASA vs. placebo; $p = 0.130$); clinical response vs. no clinical response in week 20 (5-ASA vs. placebo; $p = 0.03$)	Not observed
Levine A et al. 2003 (e22)	Budesonide 9 mg/day per os vs. prednisone 40 mg/day per os	33 patients with active, mild to moderate Crohn's disease; age 8 to 18 years; trial period not stated	Multicenter ($n = 13$), open-label; 12 weeks' follow-up	47% vs. 50% clinical remission in week 12 (budesonide vs. prednisone; not significant); 32% vs. 71% side effects (budesonide vs. prednisone; $p < 0.05$)	8% vs. 36% muscle involvement; 32% vs. 71% moon facies (budesonide vs. prednisone; $p = 0.07$ and $p < 0.05$)
Escher JC et al. 2004 (e18)	Budesonide 9 mg/day per os vs. prednisolone 1 mg/kg BW/day per os	48 patients with active Crohn's disease of the ileum and/or ascending colon; age 6 to 16 years; trial period April 1998 to December 2000	Multicenter ($n = 36$), double-blind; placebo-controlled; 12 weeks' follow-up	55% vs. 71% clinical remission in week 8 (budesonide vs. prednisolone; $p = 0.25$); higher morning plasma cortisol level (i.e. less adrenal suppression) in budesonide group ($p = 0.003$)	50% vs. 80% glucocorticoid-associated ADRs (budesonide vs. prednisolone; $p = 0.03$); moon facies (23% vs. 60%; $p = 0.01$); acne (5% vs. 28%; $p = 0.03$)
Cezard JP et al. 2009 (e21)	Mesalazine 50 mg/kg BW/day vs. placebo for 12 months	122 patients with active Crohn's disease; age <18 years; trial period 1991 to 1993 and 1996 to 1999	Multicenter ($n = 17$), double-blind, placebo-controlled; 12 months' follow-up	57% vs. 39% relapse after 12 months (mesalazine vs. placebo; not significant)	1% vs. 3% adverse reactions (mesalazine vs. placebo)
Markowitz J et al. 2000 (e17)	6-mercaptopurine (6-MP) 1.5 mg/kg BW/day vs. placebo (plus prednisone 40 mg/day in both groups)	55 patients with moderate to severe Crohn's disease; age 12 to 18 years; trial period not stated	Multicenter ($n = 18$), placebo-controlled, double-blind, 18 months' follow-up	89% clinical remission in week 48 in both groups; shorter concomitant prednisone medication in 6-MP group ($p < 0.001$); lower cumulative prednisone dose in 6-MP group in weeks 24, 48, and 72 ($p < 0.01$); 9% vs. 47% relapse (6-MP vs. placebo; $p = 0.007$)	Mild leukopenia (22%), elevated transaminases (15%)
Hyams J et al. 2012 (e13)	Adalimumab 20 mg vs. 40 mg every 2 weeks subcutaneously (BW ≥ 40 kg) or 10 mg vs. 20 mg every 2 weeks subcutaneously (BW <40 kg)	192 patients with moderate to severe Crohn's disease; age 6 to 17 years; trial period April 2007 to May 2010	Multicenter ($n = 45$), double-blind, open-label induction phase (4 weeks); 48 weeks' follow-up	28% vs. 39% clinical remission in week 26 (adalimumab 10/20 mg vs. 20/40 mg; $p = 0.075$)	Dose-independent: infections (55%), reaction at injection site (10%)
Hyams J et al. 2007 (e11)	Infliximab 5 mg/kg BW every 8 weeks vs. every 12 weeks intravenously	112 patients with moderate to severe Crohn's disease; age 6 to 17 years; trial period February 2003 to March 2004	Multicenter ($n = 34$) open-label, open-label induction phase (10 weeks); crossover (dose/interval modification); 54 weeks' follow-up	88% clinical response vs. 59% clinical remission in week 10; 64% vs. 33% clinical response in week 54 (infliximab every 8 vs. 12 weeks; $p = 0.002$); 56% vs. 24% clinical remission in week 54 (infliximab every 8 vs. 12 weeks; $p < 0.001$)	Independent of interval: infections (56%), infusion reaction (18%)

Ruemmele FM et al. 2009 (e14)	Infliximab 5 mg/kg BW every 8 weeks vs. on demand intravenously	40 patients with acute-phase Crohn's disease ; age 7 to 17 years; trial period May 2002 to April 2005	Multicenter (n = 11), open-label, open-label induction phase (10 weeks); crossover (dose/interval modification); 60 weeks' follow-up	85% clinical remission in week 10; 83% vs. 61% clinical response in week 60 (infliximab every 8 weeks vs. on demand; p = 0.011); 23% vs. 92% relapse (infliximab every 8 weeks vs. on demand; p <0.003)	Independent of interval: infections (38%); headache, fever, skin reactions (8% each)
Hyams J et al. 2012 (e12)	Infliximab 5 mg/kg BW every 8 weeks vs. every 12 weeks intravenously	60 patients with moderate to severe ulcerative colitis ; age 6 to 17 years; trial period August 2006 to June 2010	Multicenter (n = 23), open-label, open-label induction phase (10 weeks); 54 weeks' follow-up	73% clinical response in week 8; 38% vs. 18% clinical remission in week 54 (infliximab every 8 vs. 12 weeks; p = 0.146)	Independent of interval: infections (60%); infusion reaction (16%)
Quiros JA et al. 2009 (e15)	5-ASA 2.25 g vs. 6.75 g/day per os	68 patients with mild to moderate ulcerative colitis ; age 5 to 17 years; trial period August 2004 to March 2006	Multicenter (n = 23), double-blind, 8 weeks' follow-up	37% vs. 45% clinical response, 9% vs. 12% clinical remission in week 8 (5-ASA 2.25 g vs. 6.75 g/day; not significant)	Dose-independent: headache (15%), abdominal pain (25%)
Romano C et al. 2010 (e19)	Betamethasone dipropionate (BDP) 5 mg/day per os for 8 weeks followed by 5-ASA 80 mg/kg BW/day per os for 4 weeks vs. 5-ASA 80 mg/kg BW/day per os for 12 weeks	30 patients with mild to moderate ulcerative colitis (pancolitis or left-sided colitis); age <18 years; trial period not stated	Single-center, open-label; 12 months' follow-up	80% vs. 33% clinical remission in week 4 (BDP vs. 5-ASA; p <0.025); better clinical response in BDP group in weeks 8 (p <0.003) and 12 (p <0.015); 73% vs. 27% endoscopic remission in week 12 (BDP vs. 5-ASA; p <0.025)	No significant adverse reactions reported
Ferry GD et al. 1993 (e20)	Olsalazine 30 mg/kg BW/day (max. 2 g/day) per os vs. Sulfasalazine 60 mg/kg BW/day (max. 4 g/day)	56 patients with mild to moderate ulcerative colitis ; aged 2 to 17 years; trial period June 1987 to July 1989	Multicenter (n = 13); double-blind; 12 weeks' follow-up	39% vs. vs. 79% clinical remission in week 12 (olsalazine vs. sulfasalazine; p = 0.006); 36% vs. 4% failure to respond to treatment (olsalazine vs. sulfasalazine; p = 0.005)	39% vs. 46% adverse reactions (olsalazine vs. sulfasalazine): headache, nausea, vomiting, rash, itching, diarrhea, and/or fever

5-ASA, 5-aminosalicylates; BW, Body weight; ADR, Adverse drug reaction

eTABLE 5

Recommended dosing and tapering schedule for prednisone or prednisolone

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11
60 mg	50 mg	40 mg	35 mg	30 mg	25 mg	20 mg	15 mg	10 mg	5 mg	0 mg
50 mg	40 mg	40 mg	35 mg	30 mg	25 mg	20 mg	15 mg	10 mg	5 mg	0 mg
45 mg	40 mg	40 mg	35 mg	30 mg	25 mg	20 mg	15 mg	10 mg	5 mg	0 mg
40 mg	40 mg	30 mg	30 mg	25 mg	25 mg	20 mg	15 mg	10 mg	5 mg	0 mg
35 mg	35 mg	30 mg	30 mg	25 mg	20 mg	15 mg	15 mg	10 mg	5 mg	0 mg
30 mg	30 mg	30 mg	25 mg	20 mg	15 mg	15 mg	10 mg	10 mg	5 mg	0 mg
25 mg	25 mg	25 mg	20 mg	20 mg	15 mg	15 mg	10 mg	5 mg	5 mg	0 mg
20 mg	20 mg	20 mg	15 mg	15 mg	12.5 mg	10 mg	7.5 mg	5 mg	2.5 mg	0 mg
15 mg	15 mg	15 mg	12.5 mg	10 mg	10 mg	7.5 mg	7.5 mg	5 mg	2.5 mg	0 mg

eBOX

Differences between IBD treatment for children and adolescents and for adults

- First-line treatment for children and adolescents with Crohn’s disease, regardless of severity, is exclusive enteral nutrition.
- Pharmacological maintenance therapy lasting several years—usually at least until the end of puberty or transition to adult care—is indicated for patients who have not yet reached adulthood.
- In adults with Crohn’s disease, abstinence from nicotine use is indicated to maintain remission, but pharmacological therapy is not.
- Primary treatment for children and adolescents with Crohn’s disease and anal fistulae is infliximab therapy. This option is not part of adult treatment algorithms.
- Thiopurines are of considerably more benefit in maintaining IBD remission (e.g. to reduce steroid use) in children and adolescents than in adults.