medical management of pediatric Crohn's disease

Dr mahnaz sadeghian

Pediatric gastroenterologist

Assistant professor

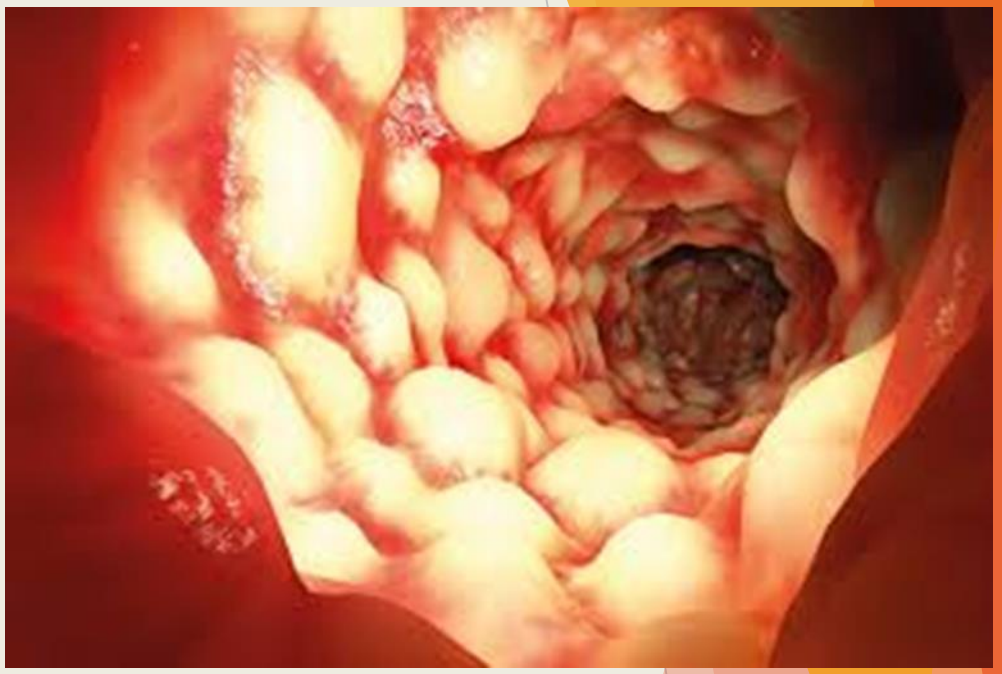
IUMS

- Approximately 10% of patients with Crohn’s disease [CD] are diagnosed before their 17th birthday.
- The past decade has seen significant advances in the care of children with CD.
- With an expanding therapeutic armamentarium, there has been a shift of therapeutic goals from symptom control alone towards mucosal and transmural healing with consequent reduction of bowel damage.

- There is increasing evidence that the treatment plan for a pediatric patient with CD should be individualized.

- The plan should consider factors such as age, disease location, disease behavior, presence of growth delay, potential side effects of medications, and quality of life.

Treatment goals



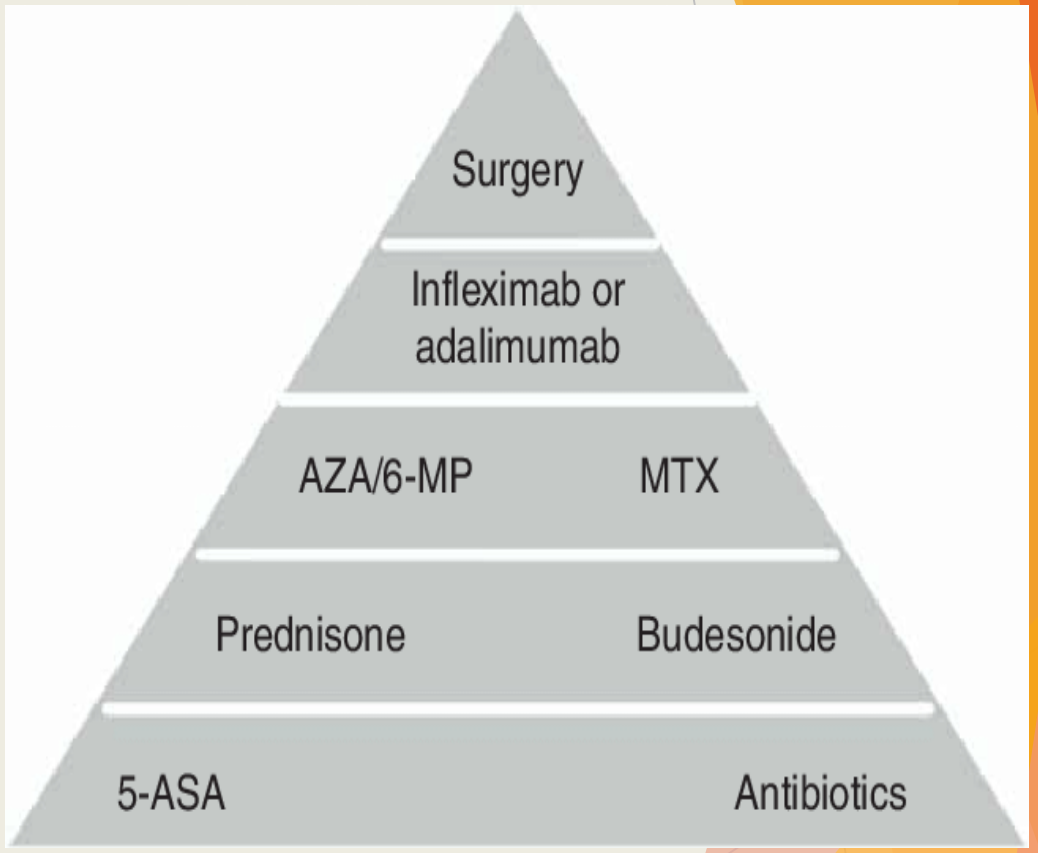
- Clinical remission
- Optimize growth
- Improve quality of life
- Minimizing drug toxicity
- Para clinical remission
- Endoscopic remission
- Mucosal remission(treat-to-target) “deep remission”
- Bone density restoration

components for management

- Medications
- Surgery
- Nutritional rehabilitation
- Psychosocial support
- Colorectal cancer screening for older patients
- granulocyte monocyte apheresis
- stem cell transplantation

Medical therapy

- *5-Aminosalicylic Acid Derivatives
- * Corticosteroids
- * Immunosuppressant's
- * Monoclonal Antibodies
- * Alpha 4 Integrin Inhibitors
- Thalidomide
- Antibiotics
- Antidiarrheal
- Bile Acid Sequestrates
- Anticholinergic Agents
- probiotics



Systems for scoring disease activity

- The Pediatric CD Activity Index (PCDAI)
  - Inactive:0-10
  - Mild :11-30
  - Moderate to severe >30
- Endoscopic scoring systems
- Patient self-report systems

Standard risk

High risk

- Standard-risk patients: mild, moderate , sever (without risk factors for complicated disease)

- High-risk patients:
  - Fistulizing disease
  - Abdominal abscess
  - Refractory disease
  - sever perianal disease
  - severe growth retardation
- early-onset inflammatory bowel disease

Table 1. Predictors of poor outcome in paediatric Crohn's disease and suggested induction therapy.

Paris classification [at diagnosis]		Additional risk factors	Risk stratification	Suggested induction therapy
B1	Inflammatory	None	Low	Exclusive enteral nutrition; corticosteroids
B1	[non-stricturing, non-penetrating]	No clinical and biochemical remission 12 weeks after start induction therapy	Medium	Consider accelerated step-up to anti-TNF therapy
B1 + G1		Growth delay	Medium	Exclusive enteral nutrition; consider up-front anti-TNF therapy
B1 [L3 + L4]		Extensive disease[a] or deep colonic ulcers	High	Up-front anti-TNF therapy
B1 + p		Perianal disease	High	Up-front anti-TNF therapy in combination with antibiotic therapy, surgery, or both
B2	Stricturing disease[b]	None	High	Up-front anti-TNF therapy
		Prestenotic dilatation, obstructive signs or symptoms, or both	High	Bowel resection in combination with postoperative anti-TNF therapy
B3	Penetrating disease[c]		High	Surgery in combination with postoperative anti-TNF therapy

TREATMENT STRATEGIES

- Step-up" therapy – Initiate treatment with a less potent immunosuppressive drug that may be effective in treating the patient's disease activity, and promptly step up therapy to a more potent drug if response is incomplete

- "Top-down" therapy – Initiate treatment with a potent immunosuppressant (anti-TNF antibody) early in the course of the disease.

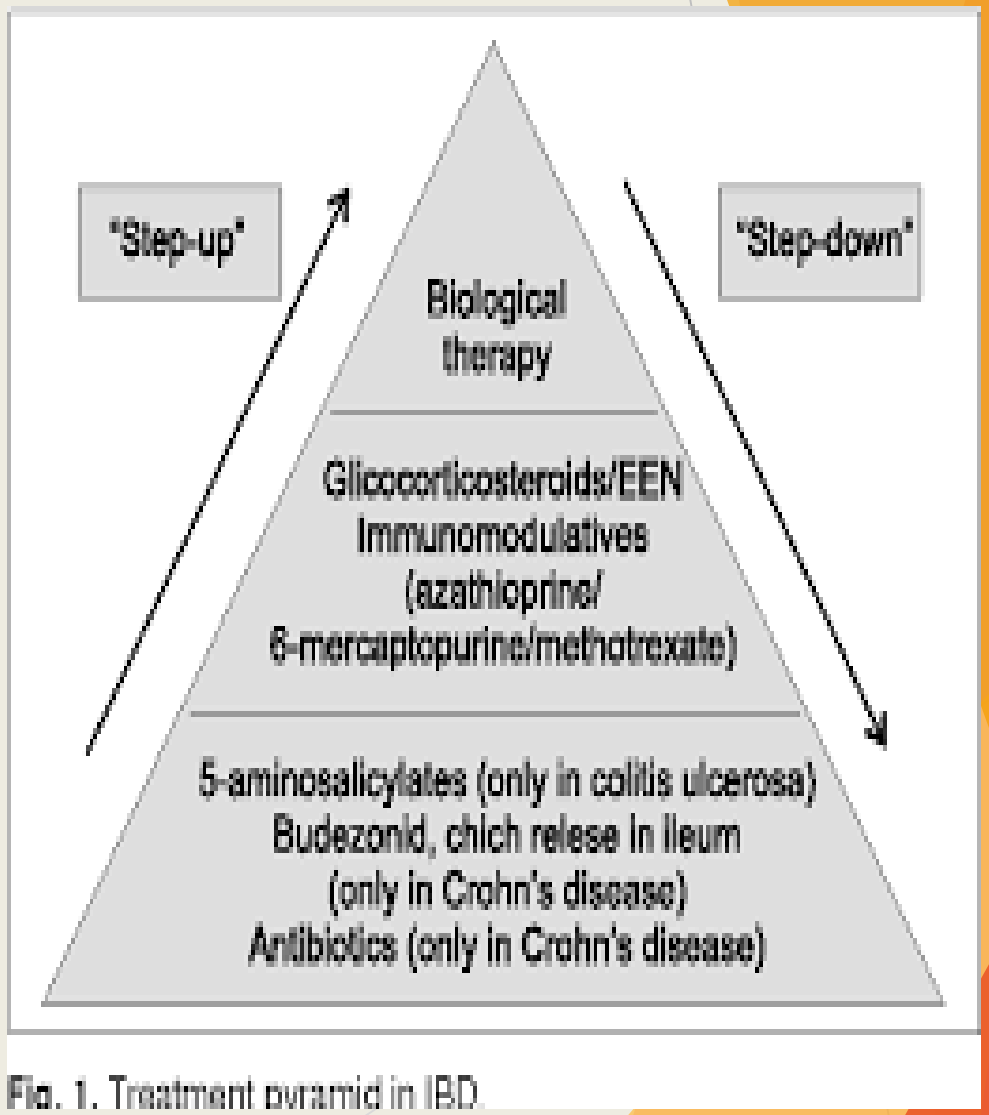
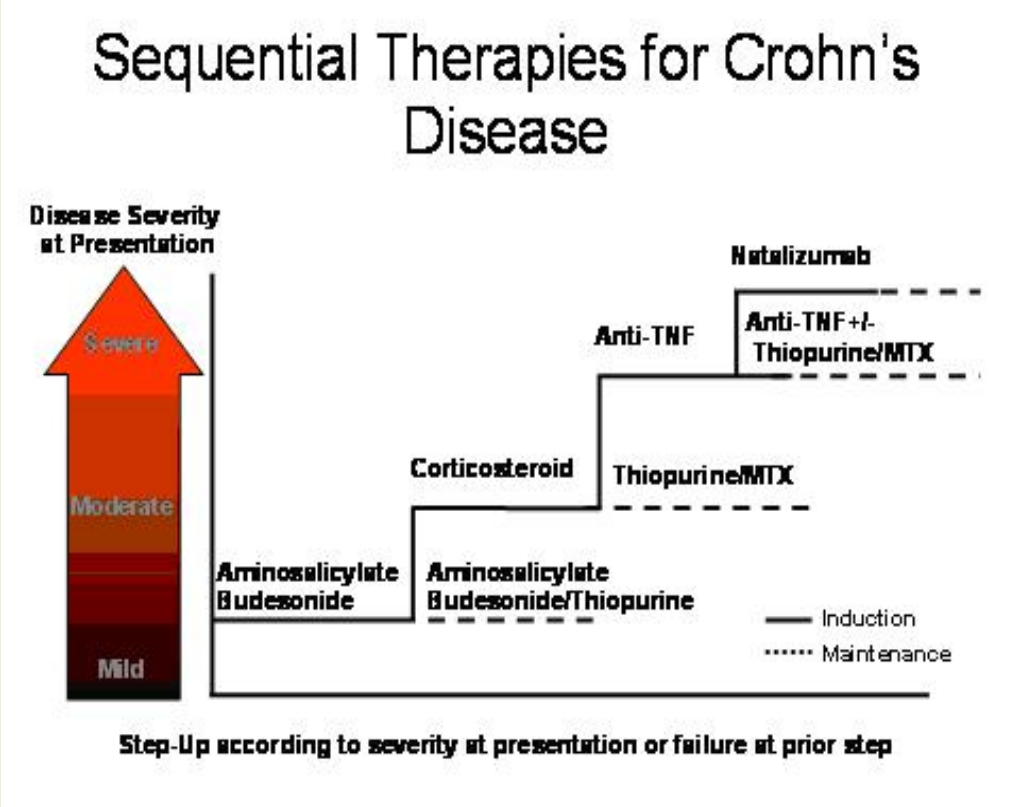


Fig. 1. Treatment pyramid in IBD

The selection of drugs for induction and maintenance depend on:

- age
- disease severity and location
- clinical course

- **Remission regimen:** potent therapy with a rapid onset of action.
- **maintenance regimen:** medications that are appropriate for long-term use.



Induction duration

- EEN :8 to 12wk
- Corticosteroid? 1-3 wk full dose and 7 wk tapering
- Anti-TNF agents: 0- 2- 6 wk

Maintenance treatment duration

- moderate to sever: unclear probably life long
- High risk group: unclear probably life long
- Mild : 2 years??

A-Standard risk(mild ,moderate ,sever)

Induction:

- Glucocorticoids
- EEN
- Anti-TNF biologics
- Aminosalicylates(mild)

Maintenance:

- Anti-TNF biologic
- thiopurine
- MTX
- Aminosalicylates (MILD)

B-High risk

- Fistulizing disease
  - bowel rest and TPN for severely ill patients
  - Anti-TNF biologics
  - Antibiotics
  - surgery
- Abdominal abscess
  - percutaneous drainage and systemic antibiotics
  - surgical resection
- Refractory disease
  - infliximab or adalimumab
  - ustekinumab, vedolizumab,

Standard risk
Ileocolonic disease

- **Mild** :"Step-up" therapy
  - Induce remission :aminosalicylates; with or without antibiotics/prednisolon?/EEN?
  - Maintenance therapy:aminosalicylates alone
- **Moderate or severe** :
- induction therapy:
  - Early use of an anti-TNF agent, either infliximab or adalimumab
  - Glucocorticoids
  - EEN
- maintenance therapy :immunomodulator, based on patient preference or if infliximab or adalimumab are not available

Steroid dependent Crohn's disease:

- Patients who respond to steroids but who's disease flares on tapering (precluding steroid withdrawal) are classified as being steroid dependent.

The use of corticosteroids at baseline is not equal to steroid-dependency, unless previous attempts to taper steroid use have proved unsuccessful.

Tapering schedules must be standardized and too rapid tapering avoided.

	Body weight		
Week	10–20 kg	20–30 kg	> 30 kg
1–3	20 mg	30 mg	40 mg
4	15 mg	25 mg	35 mg
5	15 mg	20 mg	30 mg
6	12.5 mg	15 mg	25 mg
7	10 mg	15 mg	20 mg
8	7.5 mg	10 mg	15 mg
9	5 mg	10 mg	10 mg
10	2.5 mg	5 mg	5 mg

Refractory Crohn’s disease:%30

Patients who have active disease despite the use of corticosteroids in an adequate dose and for an adequate time period are defined as being steroid refractory.

Patients are refractory to azathioprine/6-mercaptopurine if they do not respond to a sufficient dose within 3 to 6 months.

Patients are refractory to anti (TNF) therapy if they make no initial response to two appropriate doses of anti-TNF therapy.

Fistulizing disease

- infliximab or adalimumab is the treatment of choice, sometimes initially combined with bowel rest and TPN for severely ill patients.
- thiopurine or methotrexate may be helpful
- Antibiotics are sometimes used
- Glucocorticoids and aminosalicylates are not beneficial for fistulizing disease.

Abdominal abscess

- combination of percutaneous drainage and systemic antibiotics
- Percutaneous drainage promotes healing and should be performed for abscesses larger than 2 cm.
- patients should be NPO and supported with TPN, and the drain should be left in place until the output is low (<10 mL/day).
- Appropriate intravenous systemic antibiotics regimens include imipenem, piperacillin-tazobactam, or the combination of ceftazidime with metronidazole .
- Patients with persistent or recurrent abscesses are candidates for percutaneous drainage, followed by surgical resection of the affected intestinal segment.

STRICTURES

Other disease locations

- Oral lesions: Topical prednisolone syrup-0.1% triamcinolone
- Gastroduodenal disease: induced with glucocorticoids mercaptopurine/azathioprine or methotrexate for maintenance therapy.ppI.

  sulfasalazins are ineffective
- Active ileitis: glucocorticoids, aminosalicylates, immunomodulators, or anti-TNF antibodies
- Proctitis: rectally administered glucocorticoids or aminosalicylate preparations
- Perianal disease: antibiotics-surgery- Mercaptopurine or azathioprine-anti-TNF agent- Glucocorticoids should generally be avoided.

Monitoring Response

- CLINICAL RESSPONSE
- LAB RESPONSE
- ENDOSCOPIC RESPONSE
- RADIOLOGIC RESPONSE
- HISTOLOGICAL RESPONSE

TREATMENT GOAL :

- "treat-to-target" therapy:
  - Achieve mucosal healing rather than resolution of clinical symptoms and laboratory abnormalities.
  - (MH)mucosal healing (based on objective measures such as serial magnetic resonance imaging [MRI], upper endoscopy, or colonoscopy with biopsies).
  - endoscopic healing is poorly correlated with clinical symptoms and/or laboratory values.
- Achieving mucosal healing typically requires long-term immunosuppressive therapy, so the goal of improved mucosal healing must be balanced against the potential risks of the specific medication.

response monitoring in induction remission phase

- Clinical remission ↓ PCDAI
- (Treatment response)

Early remission — Proxy marker of treatment success

- Lab remission:
- Calprotectin - CRP

Early remission — Proxy marker of treatment success

- Radiologic remission
- MRE ? IUS

MH ? Deep remission

- Endoscopic response

MH

- Histological remission

deeper remission

ASSESSMENT OF DISEASE ACTIVITY

- The response to therapy is based upon the clinician's evaluation of clinical disease **activity and supporting laboratory data**, assessed during clinical visits approximately every three to four months. Very stable patients can be assessed twice a year.

- follow-up magnetic resonance imaging (MRI), upper endoscopy, or colonoscopy, are increasingly used to monitor disease progression and guide treatment decisions.?

- contrast-enhanced ultrasound has the benefit of being less invasive and easier for the patient but provides less information than MRI.

-

ASSESSMENT OF DISEASE ACTIVITY

- Because the treatment goal is typically to achieve mucosal healing (the "treat-to-target" approach endoscopy and colonoscopy with biopsies should be performed 6 to 12 months after initiation of any therapy to determine whether the therapy was successful. ?

Monitoring treatment Response

- There is no evidence-based consensus of **when** best to re-evaluate disease activity after initiation of induction therapy; repeat endoscopies to evaluate resolution of inflammation are impractical.
- The frequency of re-evaluation depends on the severity and activity of their disease.

- There is an increasing demand to replace invasive procedures with surrogate non-invasive markers.
- High-quality evidence for serial measurement of fecal calprotectin as a non-invasive diagnostic strategy to determine resolution of inflammation.
- There is no linear correlation between calprotectin levels and the severity or extent of mucosal inflammation. Although a decrease of calprotectin during induction therapy [eg, from 2000 to 1000 µg/g] may be statistically significant, the latter result is still indicative of active disease.
- Treatment success is defined as a calprotectin result <250 µg/g in combination with absence of symptoms.

Monitoring treatment Response

- Repeat fecal calprotectin measurements in patients in clinical remission [tight control] makes it possible to identify a disease flare early.
- Increase in fecal calprotectin precedes the recurrence of symptoms by 2 to 3 months.
- pre-emptive treatment escalation based solely on fecal calprotectin results is currently not recommended.
- The combination of fecal calprotectin with CRP is superior to fecal calprotectin alone for treatment escalation.

Monitoring treatment Response

- calprotectin handling is refrigeration of the filled stool container until delivery to the laboratory.
- Measuring calprotectin in patients with inflammation localized to the colon is well recognized, but the marker was thought to be less sensitive in isolated small-bowel disease?.
- To minimize misinterpretation of calprotectin changes over time, it is prudent to use calprotectin assays from the same manufacturer

Treatment success

- defined as a calprotectin result <250 µg/g in combination with absence of symptoms.
- Patients who achieved this target within 12 weeks had a higher probability of sustained remission during the first year.
- The closer the calprotectin value gets to 50 µg/g, the higher the likelihood for complete endoscopic healing.
- calprotectin <100 means inactive CD.

Relapse risk

- ⇓ [PCDAI]??
- C-reactive protein [CRP] >20 mg/L
- fecal calprotectin > 400 µg/g

at Week 12 after starting induction therapy were at higher risk of relapse at the end of the observation period.

Monitoring treatment Response

endoscopic or mucosal healing [MH] :

Endoscopic response is commonly defined by a decrease in Simple Endoscopic Score for Crohn's Disease [SES-CD] or Crohn's Disease Endoscopic Index of severity [CDEIS] of at least 50% from baseline.

MH is usually defined as the absence of macroscopic inflammation or an SES-CD .

Normal histology has been gaining increasing attention as a possible treatment target, but there is no evidence that histological remission is superior to MH in achieving long-term clinically important outcomes.

Although histological remission is considered a 'deeper' remission than merely mucosal healing, it is currently still controversial as a treatment target in CD.

Monitoring treatment Response

Table 4. Rutgeerts scoring system for endoscopic recurrence [158] of Crohn's Disease.

Endoscopic remission	i_0 No lesions in neo-terminal ileum
	i_1 ≤5 aphthous ulcers
Endoscopic recurrence	i_2 >5 aphthous ulcers with normal intervening mucosa, skip areas of larger lesions confined to ileocolonic anastomosis
	i_3 Diffuse aphthous ileitis with diffusely inflamed mucosa
	i_4 Diffuse inflammation with large ulcers, nodules, and/or stenosis

Monitoring treatment Response

- Both MRE and IUS are non-invasive imaging techniques without ionizing radiation; IUS has the additional advantages of low costs and easier access.

- Among the features that can be evaluated during IUS, parietal thickness <3 mm better predicts transmural healing than color Doppler grade and the percent increase of parietal enhancement.

- A composite score of faecal calprotectin, CRP, and clinical score is currently considered to be the best suitable non-invasive test to evaluate MH in pediatric CD.

Monitoring treatment Response

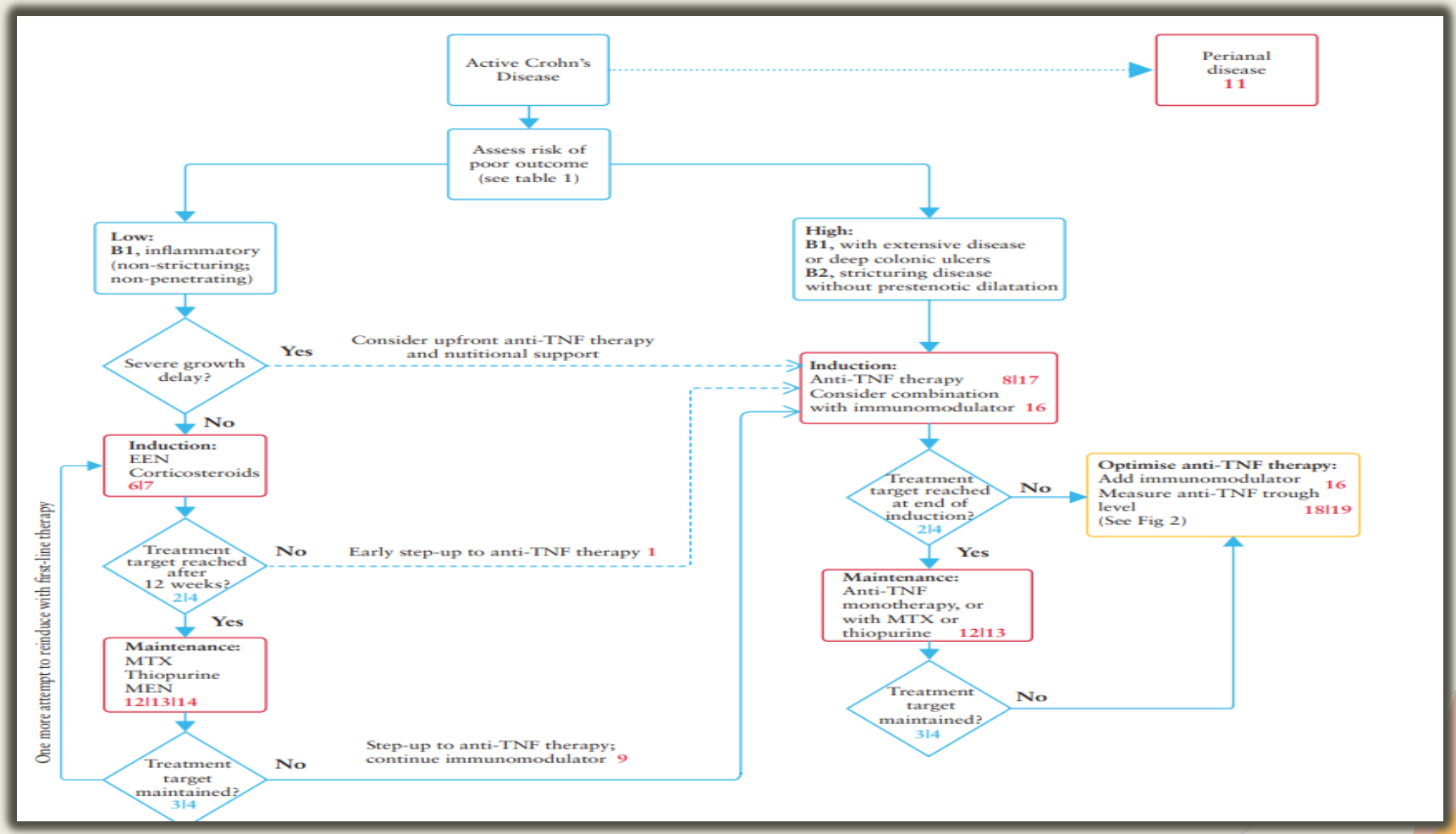
- MRE:
- There have been recent reports of gadolinium deposits in the human body, particularly in the brain, especially after repeated intravenous administration.
- The use of gadolinium-based MRI contrast agents should therefore be carefully individualised, especially when future repetition of small-bowel imaging is anticipated.

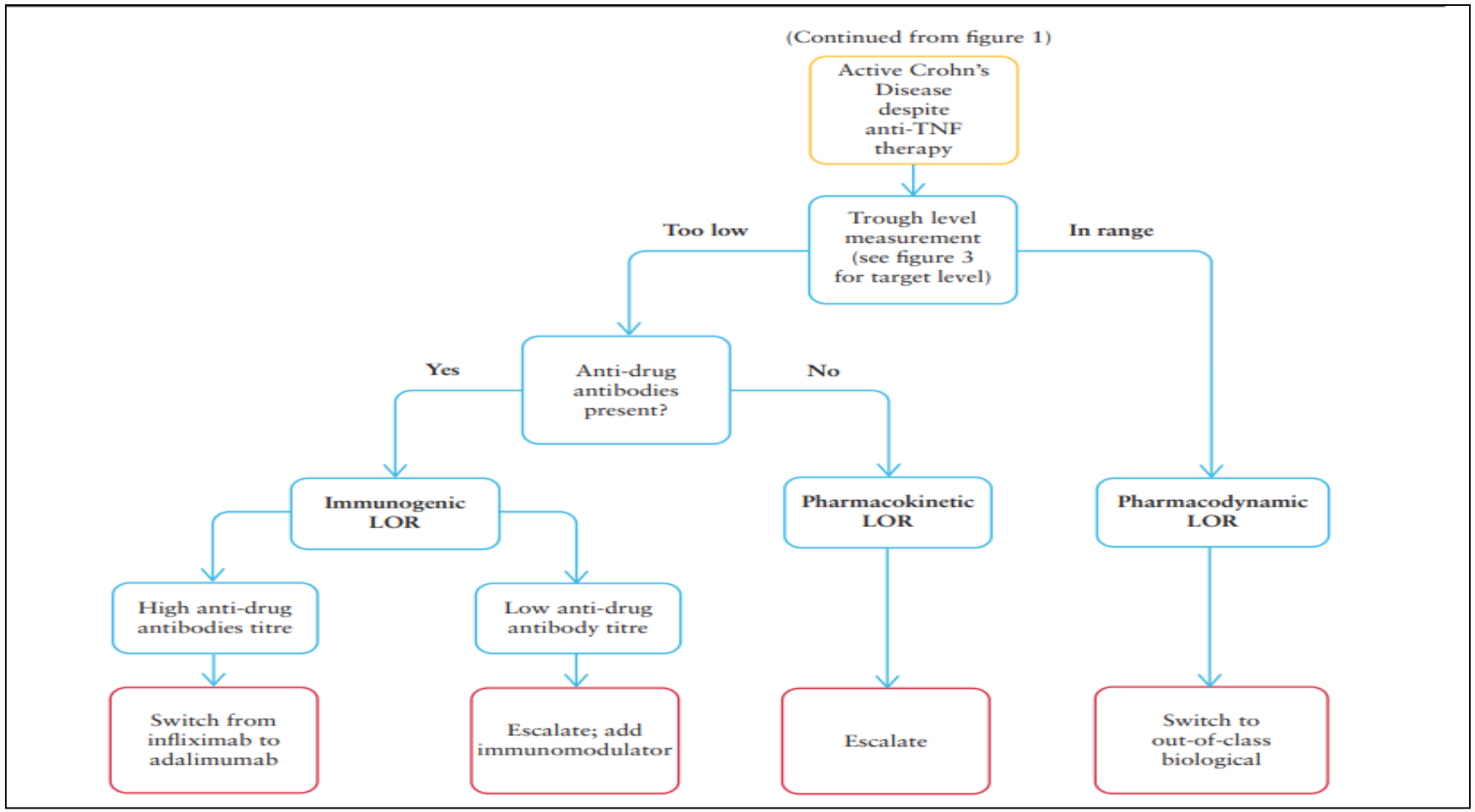
Table 2. The MINI Index

Item	Points
1. Stool	
0–1 Normal or liquid stools, no blood	0
≤2 Semiformed with small blood, or 2–5 liquid	4
Gross bleeding, or ≥6 liquid, or nocturnal diarrhea	8
2. Fecal calprotectin	
<50 μg/g	−3
50–99.9 μg/g	0
100–299.9 μg/g	5
300–599.9 μg/g	7
600–899.9 μg/g	9
≥900 μg/g	12
3. ESR and CRP	
ESR < 10 mm/h and CRP <5 mg/L	0
30 > ESR ≥10 mm/h or 10 > CRP ≥5 mg/L	1
50 > ESR ≥30 mm/h or 30 > CRP ≥10 mg/L	2
ESR ≥50 mm/h or CRP ≥30 mg/L	5
Sum of MINI	−3 to 25

IMPORTANT HEALTH MAINTENANCE ISSUES

- ●Monitoring nutritional status
- ●Bone health
- ●Infection risk
- ●Immunizations
- ●Eye examinations
- ●Psychological issues
- ●Transition to adult health care
- ●Cancer surveillance


Active Crohn's Disease
Perianal disease 11
Assess risk of poor outcome (see table 1)
Low: B1, inflammatory (non-stricturing; non-penetrating)
High: B1, with extensive disease or deep colonic ulcers B2, stricturing disease without prestenotic dilatation
Severe growth delay?
Yes
Consider upfront anti-TNF therapy and nutritional support
No
Induction: EEN Corticosteroids 6|7
Induction: Anti-TNF therapy 8|17 Consider combination with immunomodulator 16
Treatment target reached after 12 weeks? 2|4
No
Early step-up to anti-TNF therapy 1
Yes
Maintenance: MTX Thiopurine MEN 12|13|14
Treatment target maintained? 3|4
No
Step-up to anti-TNF therapy; continue immunomodulator 9
One more attempt to reinduce with first-line therapy
Treatment target reached at end of induction? 2|4
No
Optimise anti-TNF therapy: Add immunomodulator 16 Measure anti-TNF trough level 18|19 (See Fig 2)
Yes
Maintenance: Anti-TNF monotherapy, or with MTX or thiopurine 12|13
Treatment target maintained? 3|4
No


(Continued from figure 1)
Active Crohn's Disease despite anti-TNF therapy
Trough level measurement (see figure 3 for target level)
Too low
In range
Anti-drug antibodies present?
Yes
No
Immunogenic LOR
Pharmacokinetic LOR
Pharmacodynamic LOR
High anti-drug antibodies titre
Low anti-drug antibody titre
Switch from infliximab to adalimumab
Escalate; add immunomodulator
Escalate
Switch to out-of-class biological

ECCO-ESPGHAN Guideline

- Patients with newly diagnosed Crohn's disease [CD] who do not achieve clinical and biochemical remission after induction therapy are at risk of a more complicated disease course.

- In patients with luminal CD following induction therapy, a decrease of **fecal calprotectin** in the context of clinical improvement can be used as a marker of **treatment response.**

- In patients with luminal CD in clinical remission, a significant **rise of fecal calprotectin** should trigger **further investigations** and consideration of treatment escalation.

ECCO-ESPGHAN Guideline

- In patients with luminal CD, assessment of transmural involvement by bowel **ultrasound or MRI** can be used as a marker of treatment response.

- In patients with luminal CD, clinical scores alone [PCDAI] do not adequately reflect mucosal healing.

- In children with active luminal CD, dietary therapy with exclusive enteral nutrition [EEN] is recommended as first line for induction of remission.

- In children with active luminal CD, when EEN is not an option, corticosteroids may be considered for inducing remission.

ECCO-ESPGHAN Guideline

- In new-onset patients with high risk for a complicated disease course, anti-TNF therapy is recommended for inducing remission.
- In patients with active CD who fail to achieve or maintain remission with an immunomodulator, anti-TNF agents are recommended for induction and maintenance of remission.
- In children with active CD, thiopurine monotherapy should not be used to induce remission.
- Methotrexate can be used to maintain clinical remission as a first-choice immunomodulator, or after thiopurine failure or intolerance.

ECCO-ESPGHAN Guideline

- In patients who have reached remission, thiopurines [azathioprine or 6-mercaptopurine] can be used to maintain remission.
- In children with low-risk CD who achieved clinical remission, monotherapy with maintenance enteral nutrition [at least 50% of daily energy requirements] can prolong remission.
- Following ileocaecal resection, patients should be monitored by endoscopy 6–12 months post-resection. In patients with high risk of recurrence, it is recommend postoperative use of anti-TNF agents.
- In patients starting with infliximab, it is recommend combination therapy with an immunomodulator.

ECCO-ESPGHAN Guideline

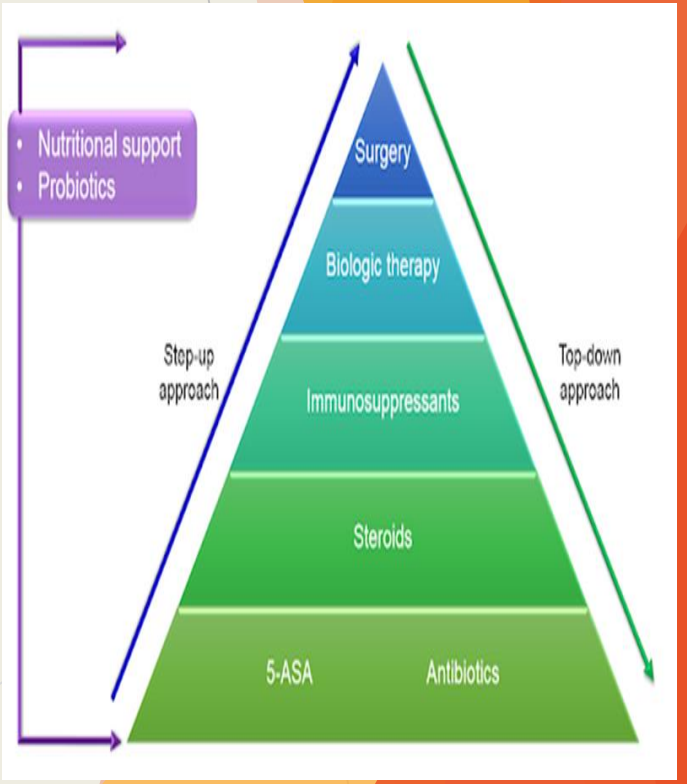
- In patients naïve to anti-TNF agents, adalimumab monotherapy is an alternative to adalimumab combination therapy.
- In patients on anti-TNF agents, early proactive therapeutic drug monitoring [TDM] followed by dose optimization is recommended.
- In patients with active CD who are treated with anti-TNF agents, it is recommended to use TDM to guide treatment changes over empirically escalating the dose or switching therapies.
- In patients who fail to achieve or maintain clinical remission on anti-TNF agents, despite anti-TNF dose optimization and immunomodulator use, ustekinumab or vedolizumab can be considered.

ECCO-ESPGHAN Guideline

- In patients with CD, probiotics should not be used to induce or maintain remission.
- In patients with CD, fecal microbiota transplantation should not be used to induce or maintain remission.
- In children with active CD, thiopurine monotherapy should not be used to induce remission.

NUTRITIONAL THERAPY

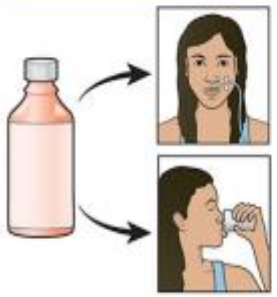
- Exclusive enteral nutrition (EEN) – Providing all nutritional needs through a liquid formula (EEN or primary nutritional therapy) can promote mucosal healing in a patient with active disease and suppress intestinal inflammation.
- supplemental enteral nutrition – Enteral nutrition can also be used as a supplement to increase energy and nutrient intake and promote growth in a patient with growth failure while the patient continues to take food orally.
- Micronutrient deficiencies – Children with CD are at risk for micronutrient deficiencies due to inadequate food intake and malabsorption, including deficiencies of iron, vitamin B12, and zinc. Optimal care includes routine monitoring for these deficiencies and replacement as needed.



EN — Enteral Nutrition

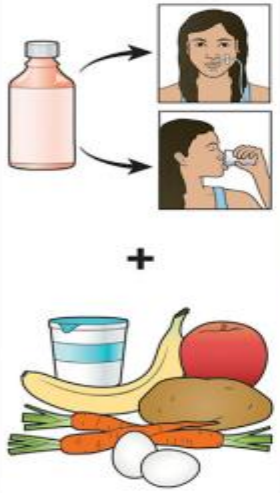
- Term used when describing use of enteral nutrition through an enteric access device (feeding tube)
- Common access devices used: nasojejunal, gastrostomy tube, jejunostomy tube
- Generally used for those where adequate nutrition is not possible via oral means
- Can provide any amount of caloric intake depending on oral intake adequacy
- There is no sufficient evidence to support the use of disease specific formulations for IBD

EEN — Exclusive Enteral Nutrition (by mouth or feeding tube)



- Generally prescribed via oral route but can be offered via feeding tube
- No other food via oral means is allowed
- 100% caloric intake is consumed via oral supplement and/or polymeric enteral support product
- Oral nutrition supplements should be calorically appropriate and meet estimated needs for protein
- Does not need to be an elemental formula, okay to use intact protein formulas

PEN — Partial Enteral Nutrition (by mouth or feeding tube)



- Generally prescribed via oral route but can be offered via feeding tube
- Total of 50%—80% calorie goal
- Products are consumed in combination with food (either ad libitum or modified diet as in CDED)

CDED

Phase 1 (week 1–6)	Phase 2 (week 7–12)	Phase 3 (week 13+)
• 50% calories via oral supplements • 1 serving fresh chicken, 2 eggs • 2 potatoes (peeled, cooked, cooled) • 2 bananas, 1 apple (peeled) • Additional allowed foods: rice & small amounts of low taurine fish • Restricted foods: red meat, high taurine seafood, alcohol	• 25% calories via oral supplements • 1 serving fresh chicken, 2 eggs • 2 potatoes (peeled, cooked, cooled) • 2 bananas, 1 apple • Additional allowed foods: rice & small amounts of low taurine fish, gradually increased variety of fruits, starches, vegetables in Phases 2 and 3 • Restricted foods: red meat, high taurine seafood, alcohol	• 25% calories via oral supplements • No required foods • Encouraged to follow Phase 2 on weekdays and liberalize diet on weekends • Advances to full fat yogurt • Permanent restrictions: soft drinks, processed meats, emulsifiers, gums

surgery

Surgical therapy should be reserved for very specific indications

- Recurrence rate after bowel resection is high (>50% by 5 yr); the risk of requiring additional surgery increases with each operation.

Surgery is the treatment of choice for :

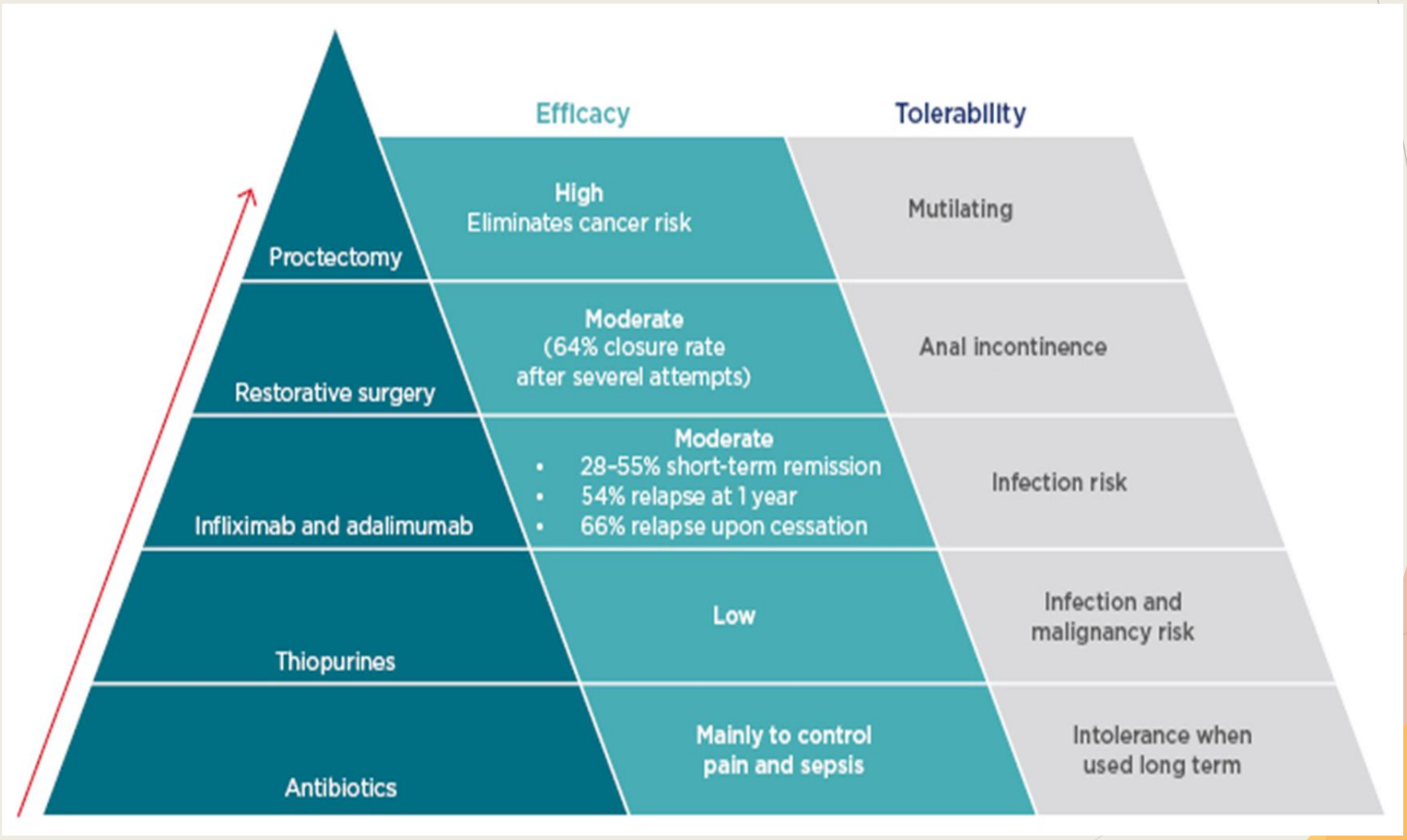
-Localized disease of small bowel or colon that is unresponsive to medical treatment

-Bowel perforation

- Fibrosed stricture with symptomatic partial small bowel obstruction

- Intractable bleeding

Thanks for your attention


Efficacy
Tolerability
Proctectomy
High
Eliminates cancer risk
Mutilating
Restorative surgery
Moderate
(64% closure rate
after severel attempts)
Anal incontinence
Infliximab and adalimumab
Moderate
• 28–55% short-term remission
• 54% relapse at 1 year
• 66% relapse upon cessation
Infection risk
Thiopurines
Low
Infection and
malignancy risk
Antibiotics
Mainly to control
pain and sepsis
Intolerance when
used long term

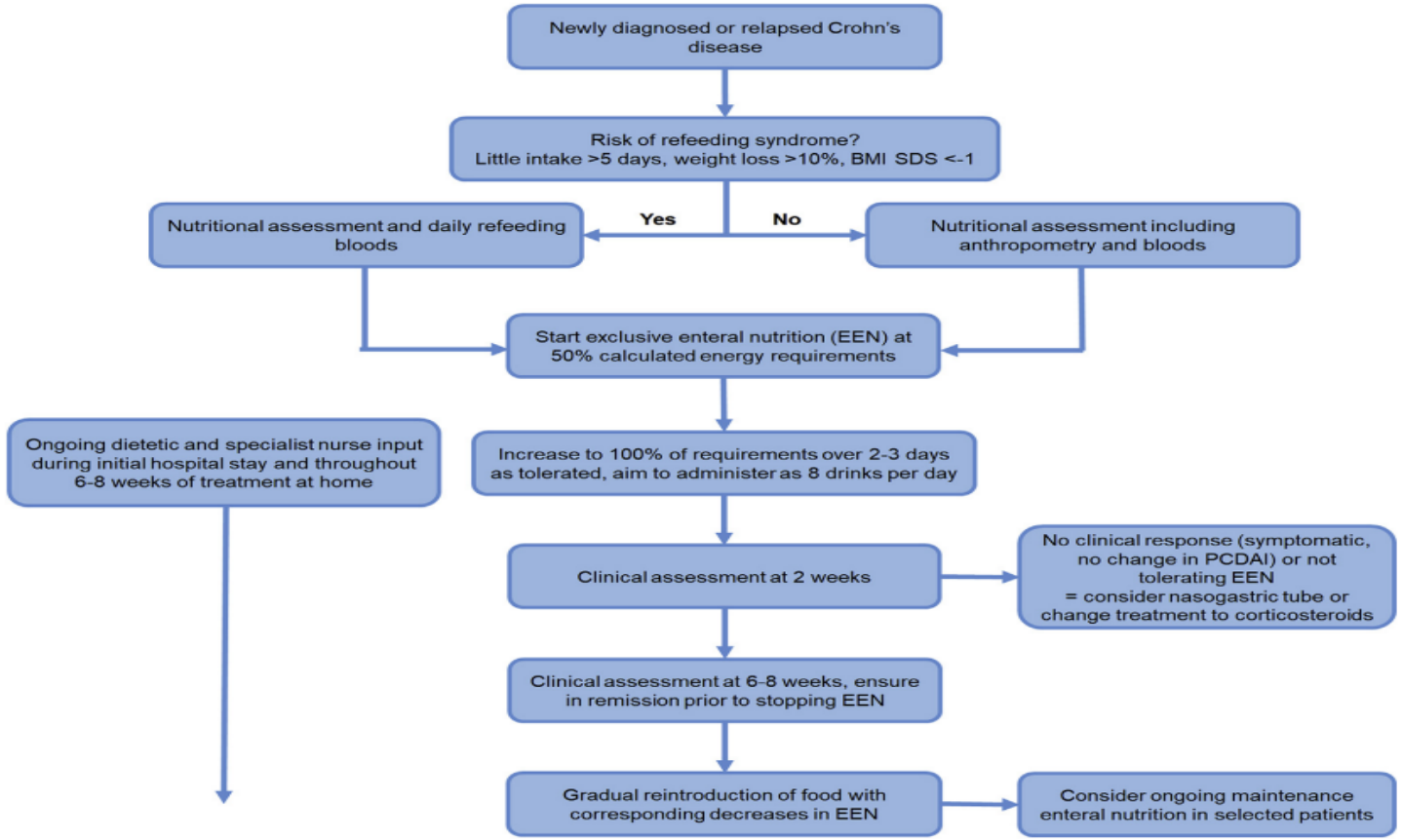
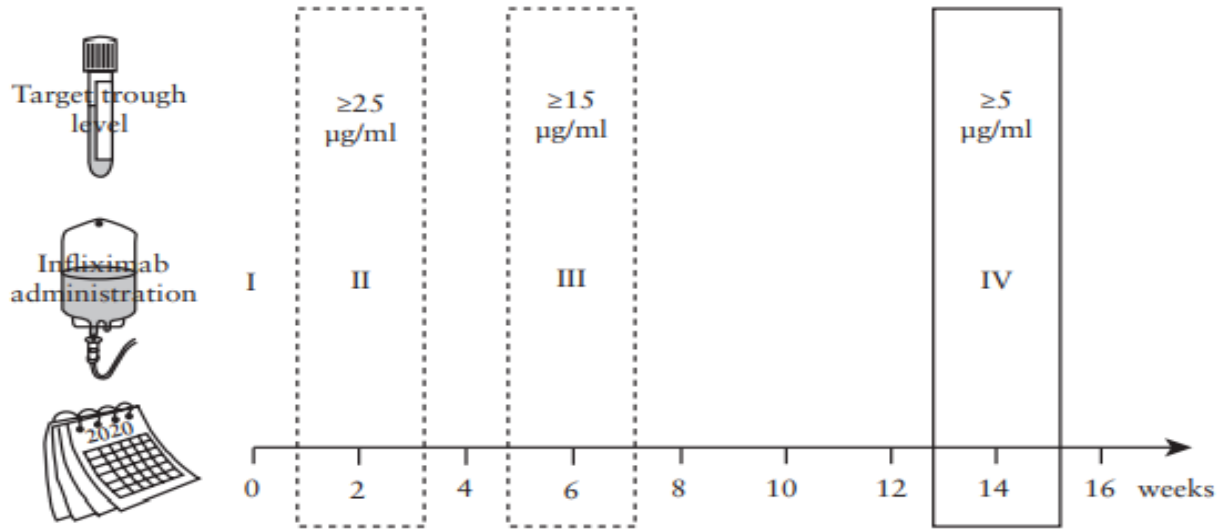
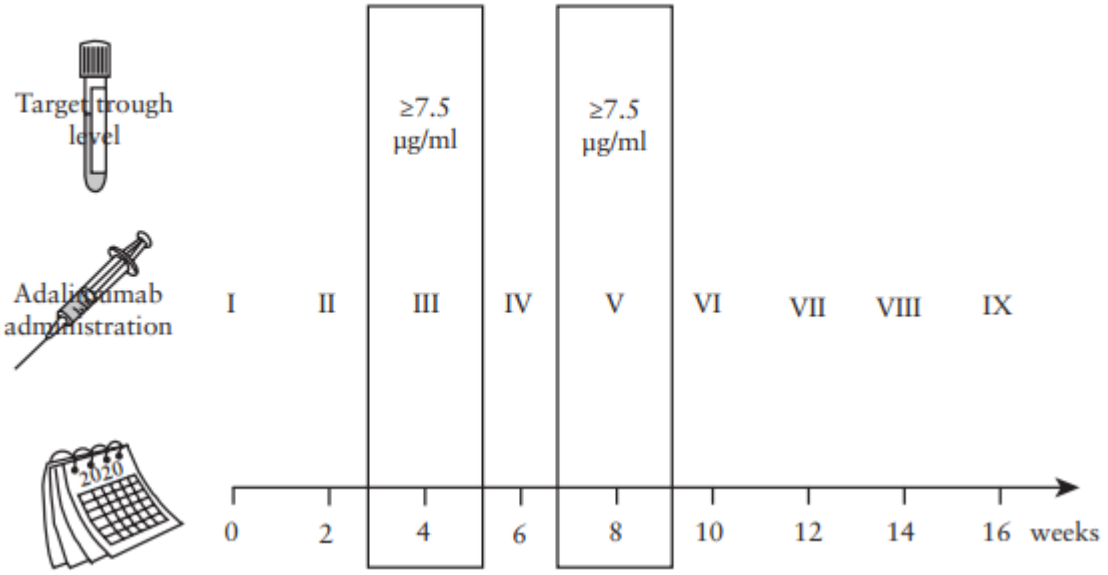


Fig. 2. Treatment algorithm for use of exclusive enteral nutrition as induction therapy in paediatric Crohn's disease.

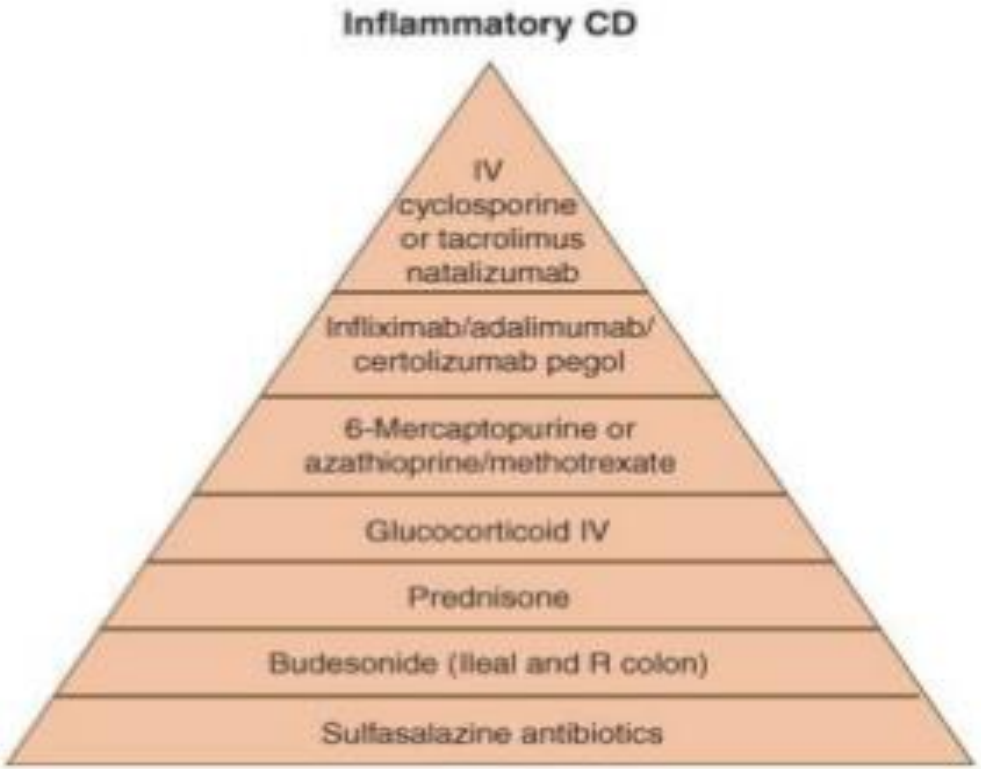
Table 1. Target Thiopurine Metabolite Levels and Biologic Trough Concentrations

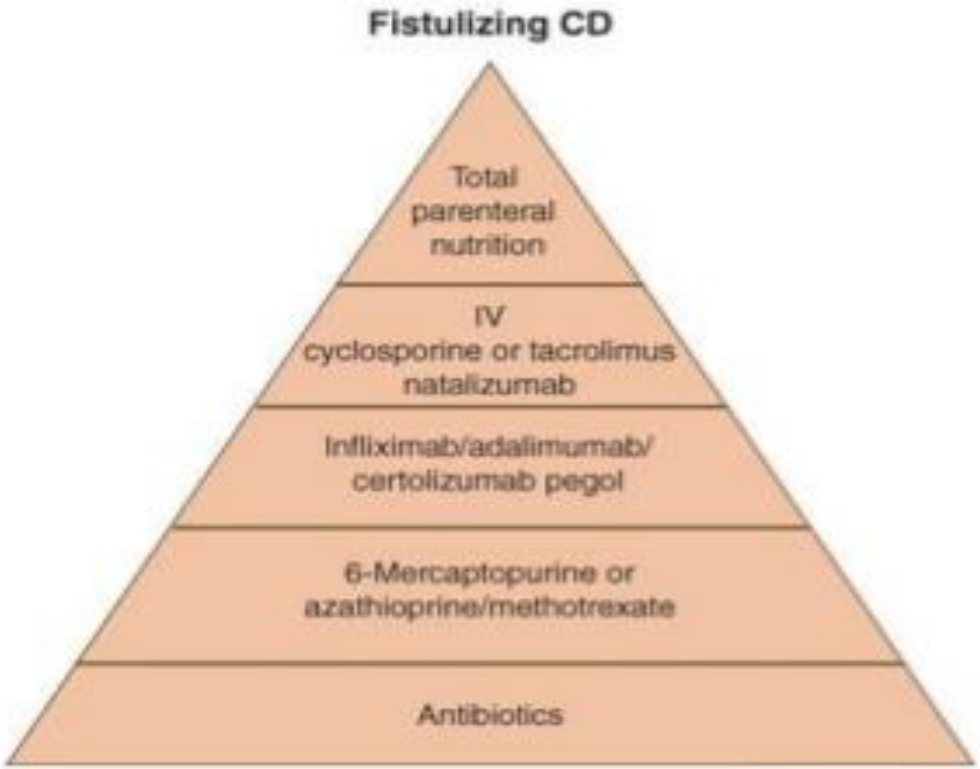
Drug	Target	BRIDGe[141]	AGA Guideline[121]
Thiopurine monotherapy	Clinical remission	—	6-TGN 230–450 pmol/8 × 10^8
Infliximab (and biosimilars)	Clinical remission Endoscopic healing	wk 14 and beyond: ≥3 μg/mL[a] ≥7 μg/mL	≥5 μg/mL
Adalimumab[b]	Clinical remission Endoscopic healing	wk 4 and beyond: ≥5 μg/mL[a] ≥7 μg/mL	≥7.5 μg/mL
Certolizumab	Clinical remission	wk 6: ≥32 μg/mL Remission: ≥15 μg/mL	≥20 μg/mL
Golimumab	Clinical remission	wk 6: ≥2.5 μg/mL Remission: ≥1 μg/mL	No recommendation
VDZ[c] and UST[d]		No recommendation	No recommendation


Target trough level
Infliximab administration
2020
≥25 µg/ml
≥15 µg/ml
≥5 µg/ml
I
II
III
IV
0
2
4
6
8
10
12
14
16
weeks

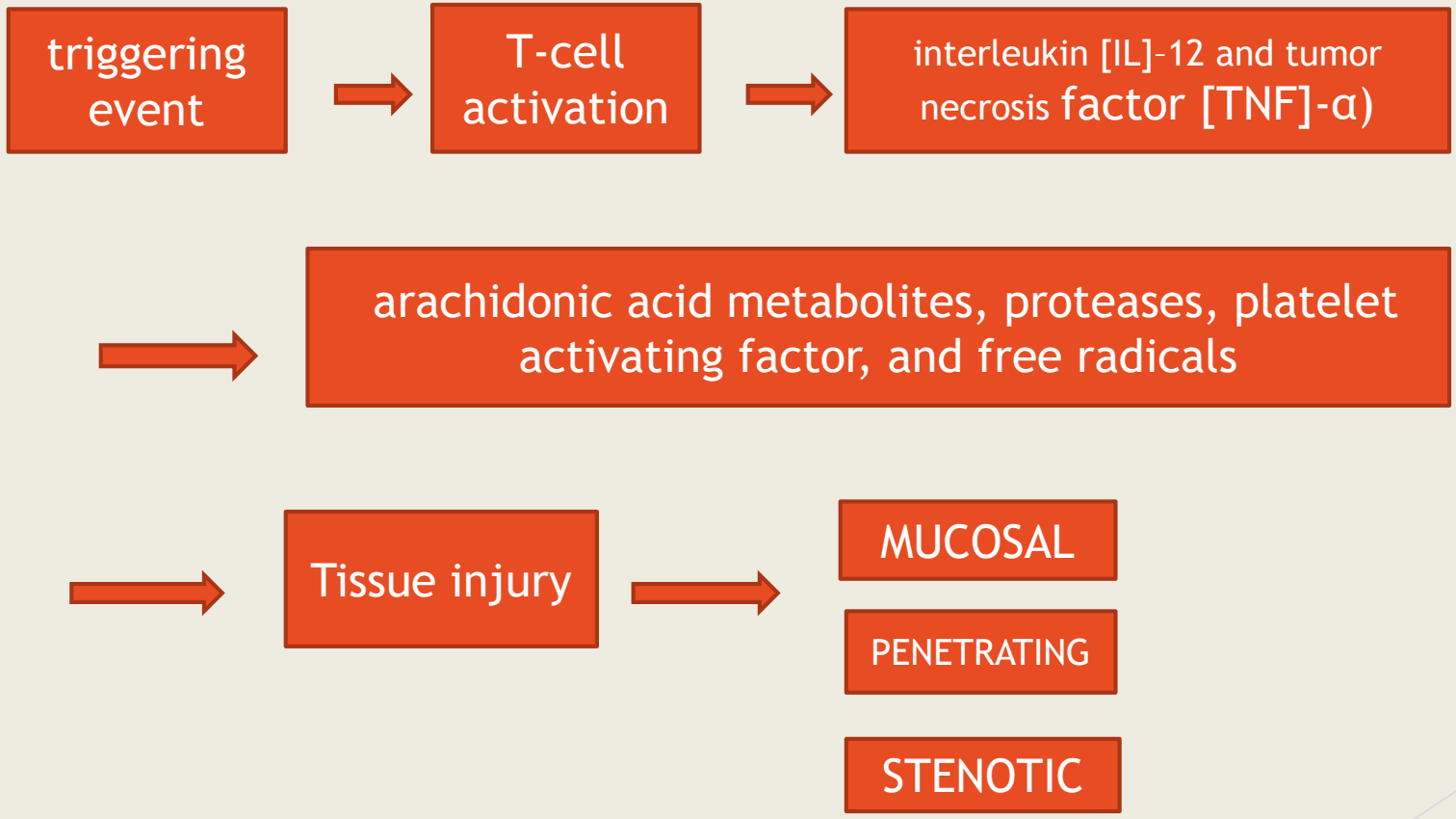

Target trough level
Adalimumab administration
2020
≥7.5 µg/ml
≥7.5 µg/ml
I
II
III
IV
V
VI
VII
VIII
IX
0
2
4
6
8
10
12
14
16
weeks

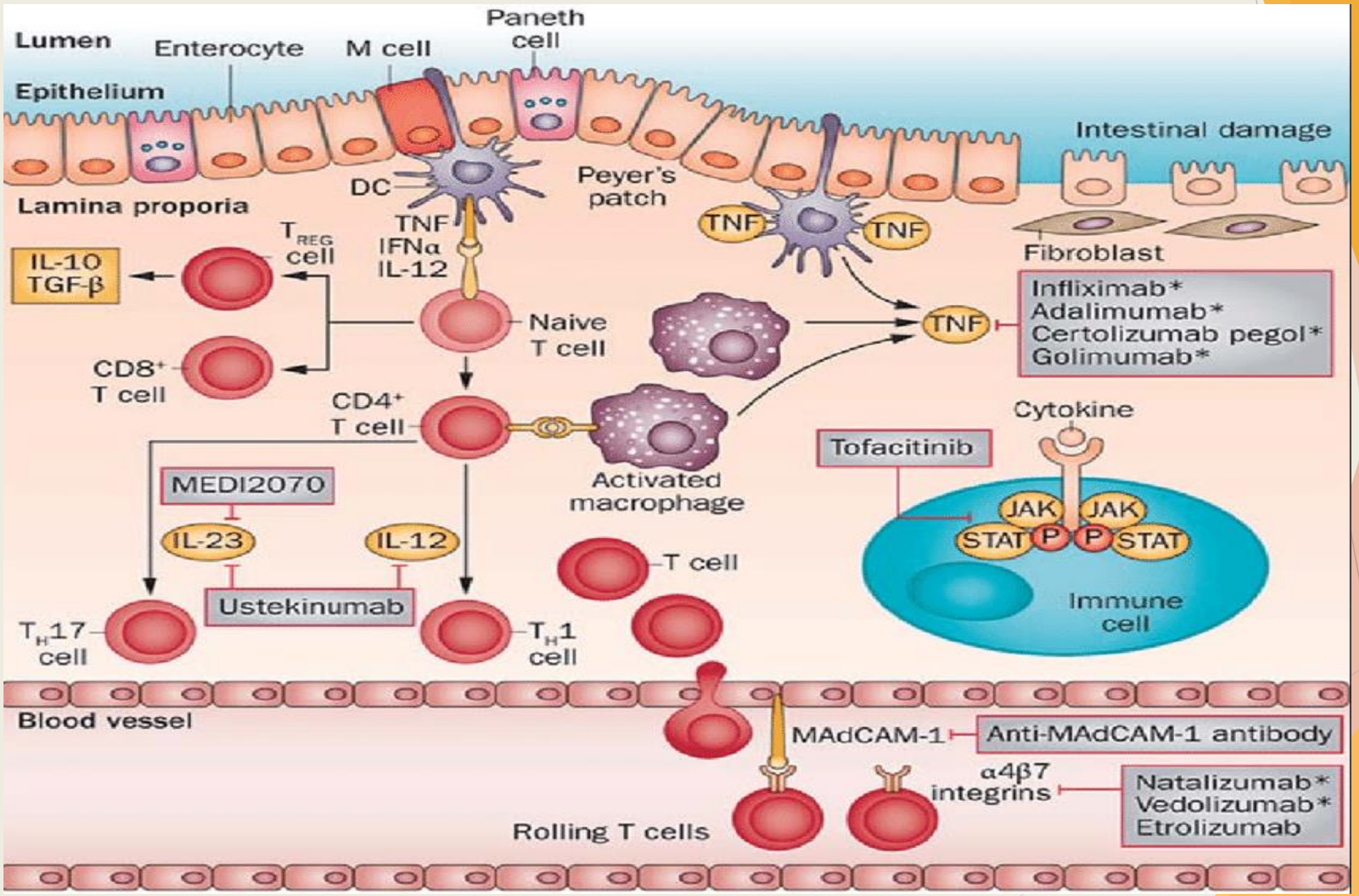
Step up therapy for Crohn's disease





Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com


triggering event
T-cell activation
interleukin [IL]-12 and tumor necrosis factor [TNF]-α)
arachidonic acid metabolites, proteases, platelet activating factor, and free radicals
Tissue injury
MUCOSAL
PENETRATING
STENOTIC

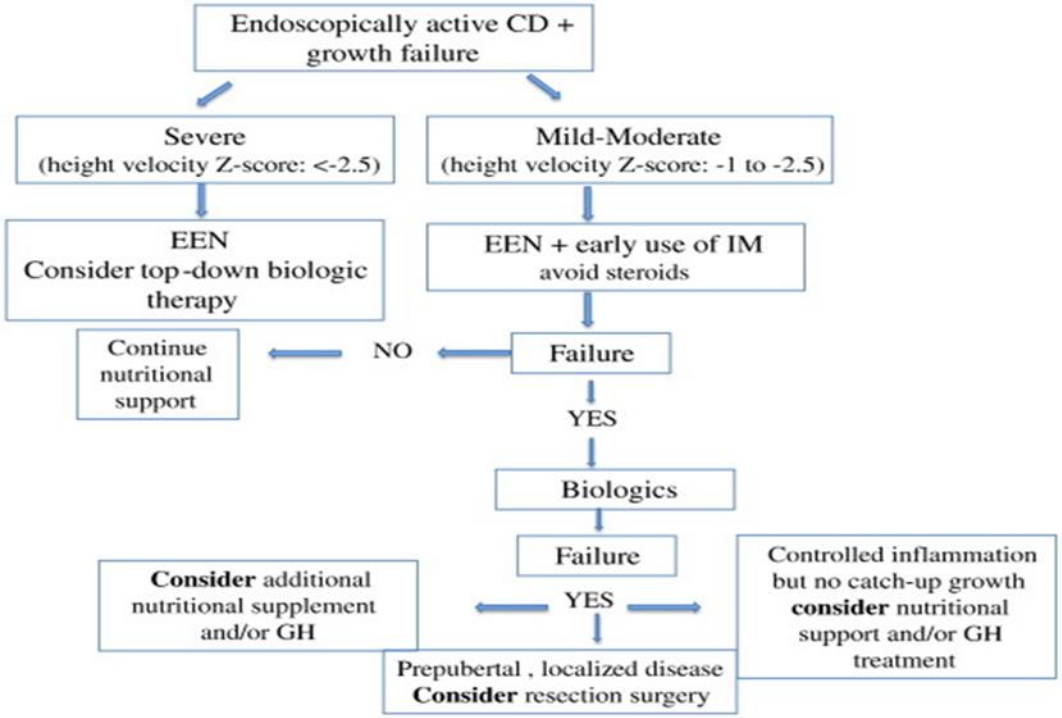

Lumen
Enterocyte
M cell
Paneth cell
Epithelium
Intestinal damage
DC
Peyer's patch
Lamina proporia
TNF
IFNα
IL-12
TNF
TNF
Fibroblast
T REG cell
IL-10
TGF-β
Naive T cell
TNF
Infliximab*
Adalimumab*
Certolizumab pegol*
Golimumab*
CD8+ T cell
CD4+ T cell
Activated macrophage
Cytokine
Tofacitinib
MEDI2070
IL-23
IL-12
JAK
JAK
STAT
P
P
STAT
Immune cell
T cell
Ustekinumab
TH17 cell
TH1 cell
Blood vessel
MAdCAM-1
Anti-MAdCAM-1 antibody
α4β7 integrins
Natalizumab*
Vedolizumab*
Etrolizumab
Rolling T cells

- Crohn disease (CD) is a chronic inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area.
- Children and adolescents with Crohn's disease (CD) present often with a more complicated disease course compared to adult patients.
- Medical therapy is a cornerstone of management in all age groups.
- The choice of therapy varies depending upon the anatomic location and severity of the disease and treatment stage (induction versus maintenance of remission).
- The potential impact of CD on growth, pubertal and emotional development of patients underlines the need for a specific management strategy of pediatric-onset CD.

PRESANTATION

- very early-onset inflammatory bowel disease
- Ileocolonic disease
- High-risk patients
- Standard-risk patients
- Fistulizing disease
- Abdominal abscess
- Refractory disease
- Other disease locations
  - Oral lesions
  - Gastroduodenal disease
  - Active ileitis
  - Proctitis
  - Perianal disease

PCDA index


Endoscopically active CD + growth failure
Severe (height velocity Z-score: <-2.5)
Mild-Moderate (height velocity Z-score: -1 to -2.5)
EEN Consider top-down biologic therapy
EEN + early use of IM avoid steroids
Continue nutritional support
NO
Failure
YES
Biologics
Failure
Consider additional nutritional supplement and/or GH
YES
Controlled inflammation but no catch-up growth consider nutritional support and/or GH treatment
Prepubertal , localized disease Consider resection surgery

Pediatric Crohn disease activity index (PCDAI)

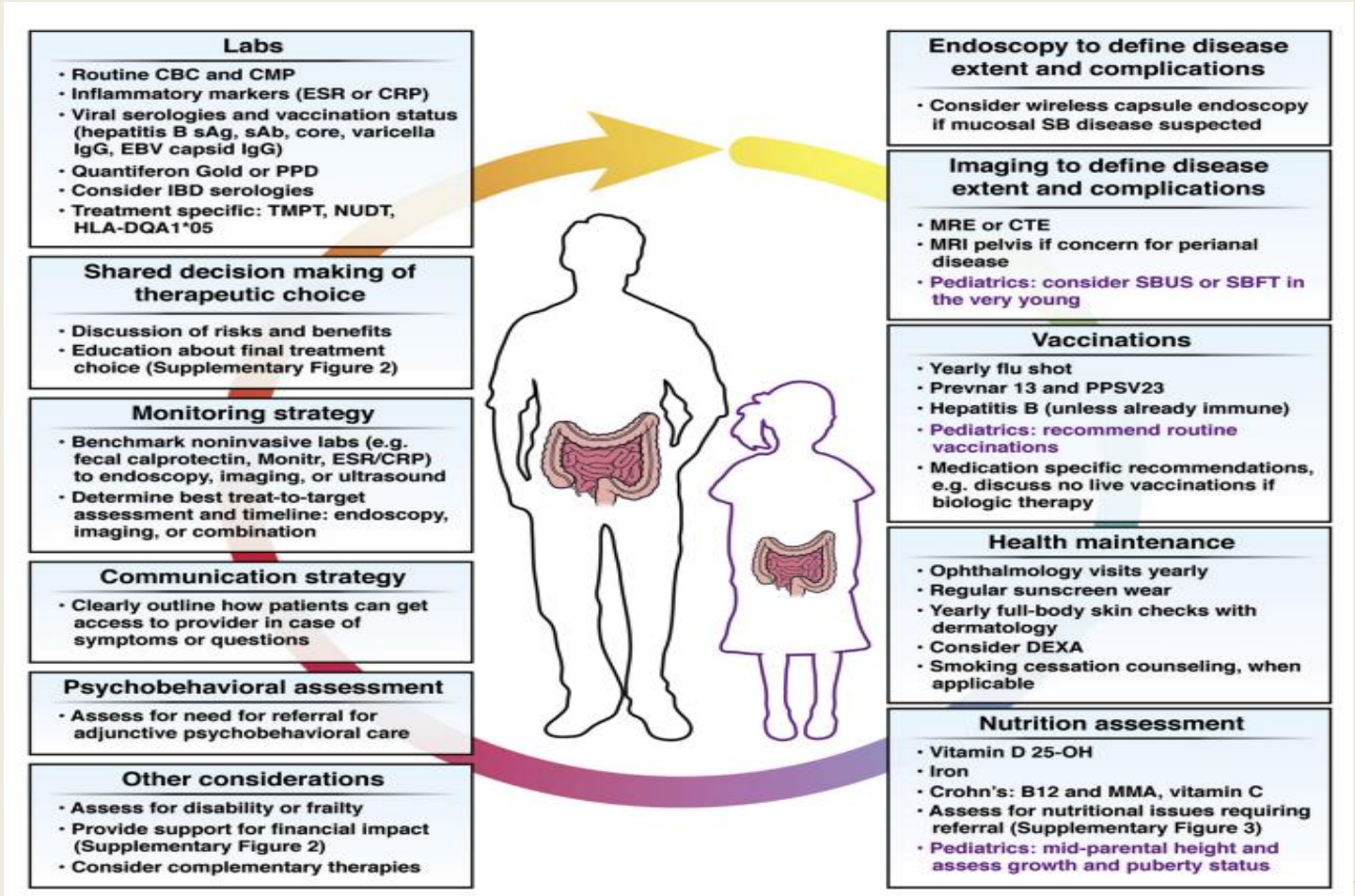
Category	Parameter	Detailed description	Point
History (recall, 1 wk)	Abdominal pain	None	0
		Mild (brief, does not interfere with activities)	5
		Mod/severe (daily, longer lasting, affects activities, nocturnal)	10
	Stools (per day)	0-1 liquid stools, no blood	0
		Up to 2 semi-formed with small blood, or 2-5 liquid	5
		Gross bleeding, or ≥6 liquid, or nocturnal diarrhea	10
Patient functioning, general well-being (recall, 1 wk)	No limitation of activities		0
	Occasional difficulty in maintaining age appropriate activities		5
	Frequent limitation of activity, very poor		10
Laboratory	Hematocrit (%) (use age-specific reference)	Normal	0
		Mild decrease	2.5
		Mod/severe decrease	5
	Erythrocyte sedimentation rate (mm/h)	<20	0
		20-50	2.5
		>50	5
	Albumin (g/dL)	≥3.5	0
		3.1-3.4	5
		≤3.0	10
Examination	Weight	Weight gain or voluntary weight stable/loss	0
		Involuntary weight stable, weight loss 1%-9%	5
		Weight loss ≥10%	10
	Height at diagnosis	<1 channel decrease	0
		≥1, <2 channel decrease	5
		≥2 channel decrease	10
	Height follow-up	Height velocity ≥−1 SD	0
		Height velocity <−1 SD, >−2 SD	5
		Height velocity ≤−2 SD	10
	Abdomen	No tenderness, no mass	0
		Tenderness, or mass without tenderness	5
		Tenderness, involuntary guarding, definite mass	10
	Perirectal disease	None, asymptomatic tags	0
		1-2 Indolent fistula, scant drainage, no tenderness	5
		Active fistula, drainage, tenderness, or abscess	10
	Extraintestinal manifestations (n)	0	0
		1	5
		≥2	10

- Patients with evidence of active inflammation over a period of three to six months despite treatment can be divided into 2 categories:

- Steroid dependent Crohn’s disease
- Refractory Crohn’s disease

PCDAI

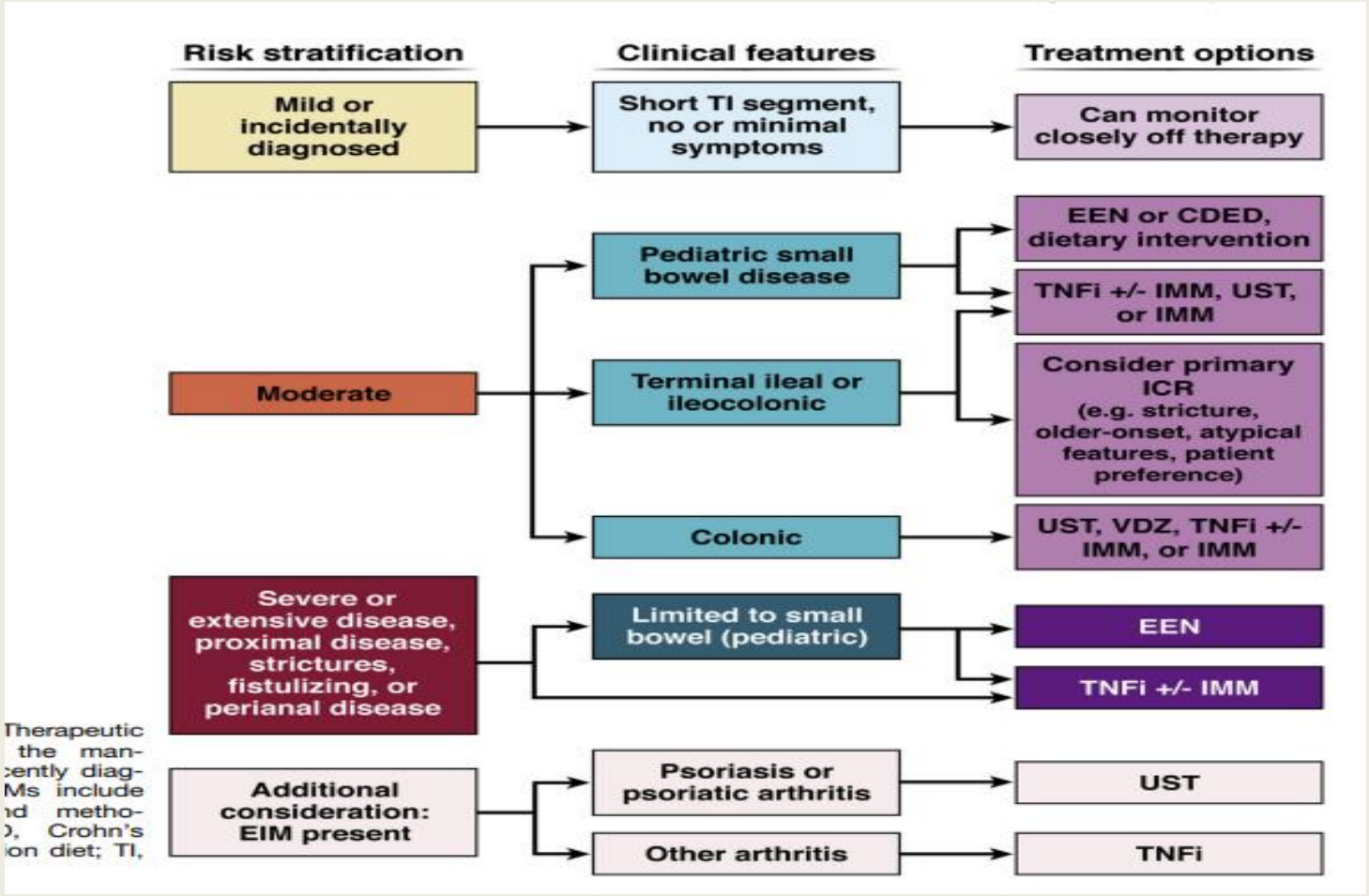
- Inactive:0-10
- Mild :11-30
- Moderate to severe >30


Labs
• Routine CBC and CMP
• Inflammatory markers (ESR or CRP)
• Viral serologies and vaccination status (hepatitis B sAg, sAb, core, varicella IgG, EBV capsid IgG)
• Quantiferon Gold or PPD
• Consider IBD serologies
• Treatment specific: TMPT, NUDT, HLA-DQA1*05
Shared decision making of therapeutic choice
• Discussion of risks and benefits
• Education about final treatment choice (Supplementary Figure 2)
Monitoring strategy
• Benchmark noninvasive labs (e.g. fecal calprotectin, Monitr, ESR/CRP) to endoscopy, imaging, or ultrasound
• Determine best treat-to-target assessment and timeline: endoscopy, imaging, or combination
Communication strategy
• Clearly outline how patients can get access to provider in case of symptoms or questions
Psychobehavioral assessment
• Assess for need for referral for adjunctive psychobehavioral care
Other considerations
• Assess for disability or frailty
• Provide support for financial impact (Supplementary Figure 2)
• Consider complementary therapies
Endoscopy to define disease extent and complications
• Consider wireless capsule endoscopy if mucosal SB disease suspected
Imaging to define disease extent and complications
• MRE or CTE
• MRI pelvis if concern for perianal disease
• Pediatrics: consider SBUS or SBFT in the very young
Vaccinations
• Yearly flu shot
• Prevnar 13 and PPSV23
• Hepatitis B (unless already immune)
• Pediatrics: recommend routine vaccinations
• Medication specific recommendations, e.g. discuss no live vaccinations if biologic therapy
Health maintenance
• Ophthalmology visits yearly
• Regular sunscreen wear
• Yearly full-body skin checks with dermatology
• Consider DEXA
• Smoking cessation counseling, when applicable
Nutrition assessment
• Vitamin D 25-OH
• Iron
• Crohn's: B12 and MMA, vitamin C
• Assess for nutritional issues requiring referral (Supplementary Figure 3)
• Pediatrics: mid-parental height and assess growth and puberty status

Domain	Response	Score	Response	Score	Response	Score	Response	Score
Abdominal pain	No pain	0	Pain can be ignored	5	Pain cannot be ignored	10		
Rectal bleeding	None	0	Small amount in <50% stools	10	Small amount with most stools	20	Large amount (>50% of stool content)	30
Consistency of most stools	Formed	0	Partially formed	5	Completely unformed	10		
Number of stools per 24 h	0-2	0	3-5	5	6-8	10	>8	15
Nocturnal stools	No	0	Yes	10				
Activity	No limitation	0	Occasional limitation	5	Severe restriction	10		
Sum of PUCAI (0–85)								

Interpretation:
Remission <10
Mild disease ≥10
Moderate disease ≥30
Severe disease ≥65
Change of 20 points defines response

Fig 2 | Pediatric Ulcerative Colitis Activity Index (PUCAI). Adapted from Turner et al[84]



Therapeutic
the man-
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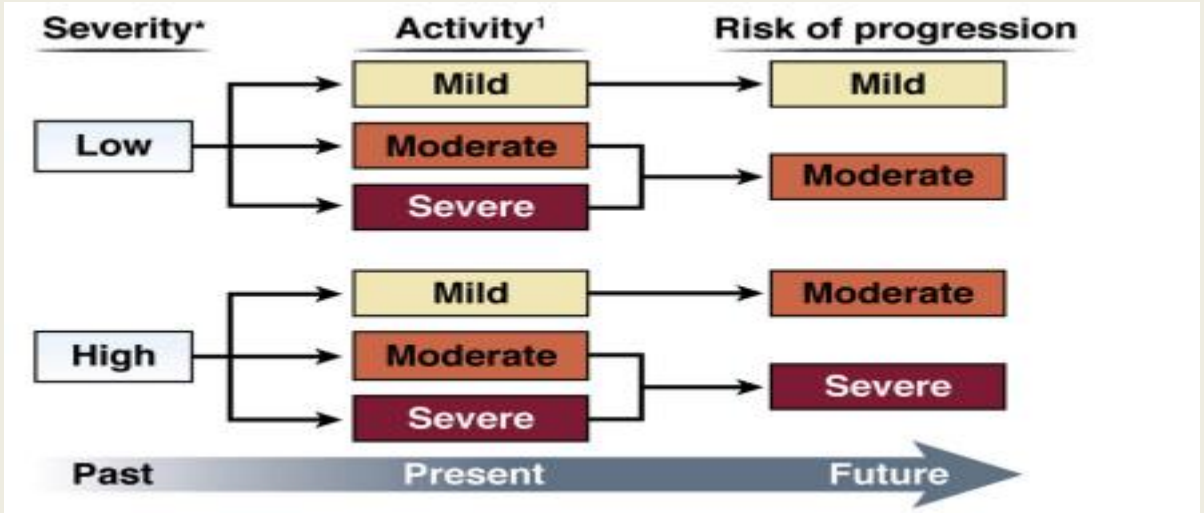

Severity*
Activity¹
Risk of progression
Low
Mild
Moderate
Severe
Mild
Moderate
High
Mild
Moderate
Severe
Moderate
Severe
Past
Present
Future

Standard-risk patients moderate to severe

A:

Induce remission :

Glucocorticoids (PO , IV) or EEN

bowel rest (up to two weeks) +(TPN)

maintenance treatment: 6mp or AZA or MTX

B:

Induce remission :

anti-TNF biologic agent

Maintenance treatment: anti-TNF biologic agent OR 6mp or AZA or MTX

Standard-risk patients
patients with moderate or severe disease but without risk factors for complicated disease

High-risk patients
"Top-down" therapy

- **Induction therapy :**
  - infliximab or adalimumab soon after diagnosis (within the first two to three months)
  - Alternatively: EEN or glucocorticoids
  - **maintenance therapy :**
  - infliximab or adalimumab with or without an immunomodulator

HIGH RISK:
extensive small bowel disease,
severe ulcerating colonic disease,
growth failure in mid- to late puberty,
severe perianal disease,
or steroid-unresponsive disease)

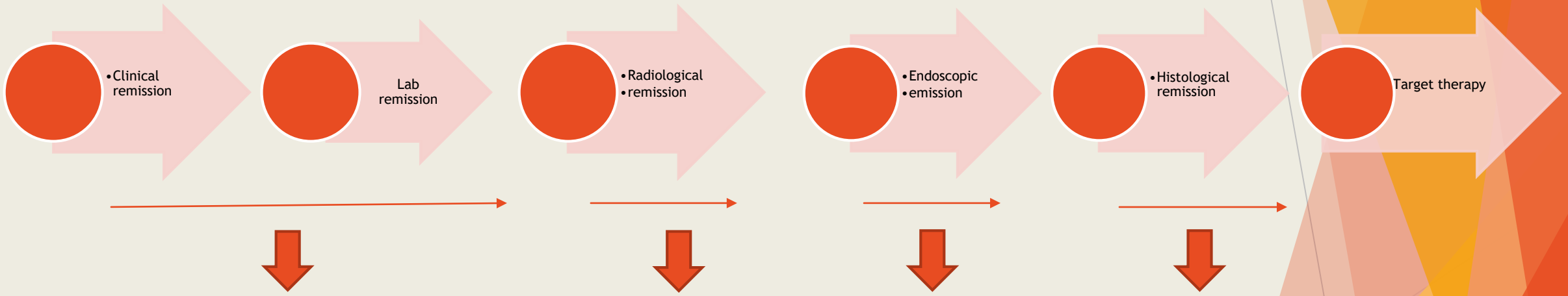
Refractory disease :

In this cases, the first-line treatment options are infliximab or adalimumab.

Patients who do not respond to anti-TNF treatment may benefit from dose adjustment of the anti-TNF, reevaluation to see if there is a surgically resect able segment, or change to another treatment.

Second-line options include ustekinumab, vedolizumab

Refractory disease : Disease refractory to the initial maintenance treatment (whether aminosalicylate, immunomodulator, or biologic) should be reevaluated after three to six months and consideration given to change of therapy



- Initial remission
- Treatment response

MH?

- MH
- Deep remission

Deeper remission

Table2. The MINI Index

Item	Points
1. Stool	
0–1 Normal or liquid stools, no blood	0
≤2 Semiformed with small blood, or 2–5 liquid	4
Gross bleeding, or ≥6 liquid, or nocturnal diarrhea	8
2. Fecal calprotectin	
<50 μg/g	–3
50–99.9 μg/g	0
100–299.9 μg/g	5
300–599.9 μg/g	7
600–899.9 μg/g	9
≥900 μg/g	12
3. ESR and CRP	
ESR < 10 mm/h and CRP <5 mg/L	0
30 > ESR ≥10 mm/h or 10 > CRP ≥5 mg/L	1
50 > ESR ≥30 mm/h or 30 > CRP ≥10 mg/L	2
ESR ≥50 mm/h or CRP ≥30 mg/L	5
Sum of MINI	–3 to 25

Question 1: What are the prognostic factors of surgery?
Statement 1.1. Diagnosis in adolescence (>13 years of age), compared with younger age, may predict increased risk of bowel surgery within 5 years of diagnosis
Statement 1.2. Growth impairment at diagnosis predicts increased risk of bowel surgery
Statement 1.3. Disease location may predict surgery; isolated colonic disease is associated with fewer surgeries
Statement 1.4. Inconclusive evidence exists for sex as a predictor for surgery; presence of NOD2/CARD15 variants, stricturing and/or internal penetrating (B2/B3) phenotype, and positive anti-Saccharomyces cerevisiae antibodies (ASCA) status predict surgery; ethnicity and presence of granulomas at diagnosis do not predict surgery
Question 2: What are the prognostic risk factors of complications?
Stricturing (B2) and/or penetrating (B3) disease
Statement 2.1. Children who develop CD at an older age may be at increased risk of developing internal penetrating (B3) complications, but not stricturing (B2) disease
Statement 2.2. CD patients of Black ethnicity/race are more likely than White patients to develop penetrating (B3) disease
Statement 2.3. CD patients with small bowel disease (ie, L1 or L3 +/− L4b) have an increased risk of developing stricturing complications (B2) and may be at an increased risk of developing penetrating complications (B3)
Statement 2.4. Anti-microbial serologies predict progression to stricturing and/or internal penetrating complications: Statement 2.4.1. Antimicrobial serologies predict progression to stricturing (B2) and/or internal penetrating (B3) complications: ASCA positivity predicts progression to internal penetrating (B3) complications and may predict progression to stricturing (B2) complications; a higher ASCA immunoglobulin (Ig) A titer predicts progression to penetrating (B3) complications ; Statement 2.4.2. Antiflagellin (CBir1) positivity predicts progression to stricturing (B2) and/or internal penetrating (B3) complications; OmpC positivity may predict progression to stricturing (B2) and/or internal penetrating (B3) complications ; Statement 2.4.3. Seropositivity for ≥1 microbial serologies predicts progression to stricturing (B2) and/or internal penetrating (B3) disease; a higher number of positive serologies and higher titers may confer a greater risk
Statement 2.5. Polymorphisms in the NOD2/CARD15 gene predict ileal disease location and may predict stricturing (B2) disease, but location is inadequately controlled for
Statement 2.6. The presence of perianal disease may predict stricturing (B2) and/or internal penetrating (B3) complications
Statement 2.7. Sex, family history of IBD, disease activity at baseline, granulomas, upper GI tract involvement, presence of extraintestinal manifestations, and diagnostic delay do not predict disease location, stricturing (B2) and/or internal penetrating (B3) complications
Perianal disease
Statement 2.8. Older age at CD onset may be associated with an increased risk of developing perianal disease
Statement 2.9. Children and adolescents of Black and South Asian ethnicity with CD are at a greater risk of developing perianal disease
Statement 2.10. Bacterial serology and sex may be associated with the development of perianal disease; genetics, antineutrophil cytoplasmic antibody (ANCA) positivity, anthropometric parameters, disease location, disease behavior, extraintestinal manifestations, diagnostic delay, and disease activity do not predict the development of perianal disease
Linear growth impairment
Statement 2.11. Male sex, younger age at disease onset, and isolated small bowel disease may be associated with a greater risk of linear growth impairment
Statement 2.12. More active disease (assessed at baseline or over time) predicts linear growth impairment
Statement 2.13. Diagnostic delay is a risk factor for linear growth impairment
Statement 2.14. *NOD2/CARD15* polymorphisms may be associated with low weight, and extraintestinal manifestations may be associated with linear growth impairment; pubertal status at disease onset, family history of IBD, ethnicity, gestational age, upper GI tract involvement, oral involvement, granulomas, disease behavior, perianal disease, and presenting symptoms do not predict linear growth impairment
Bone disease
Statement 2.15. Low height, weight, and body mass index predict reduced BMD
Statement 2.16. Higher clinical disease activity (assessed by Pediatric CD Activity Index [PCDAI]) at baseline and over time may predict reduced BMD
Statement 2.17. Sex, disease location, disease behavior, extraintestinal manifestations, granulomas, and perianal disease do not predict BMD
Question 3: What are the prognostic risk factors of chronically active inflammatory disease?
Chronically active inflammatory disease
Statement 3.1. ASCA positivity may predict the need for more intensive therapy
Statement 3.2. Microscopic ileocolonic involvement at diagnosis may be associated with subsequent macroscopic ileocolonic disease
Statement 3.3. Disease activity and disease behavior (ie, B2 and/or B3), but not age and sex, may predict more intensive therapies or a poor response to therapies; there is no strong evidence for a predictive value of ethnicity
Statement 3.4. No strong evidence exists to identify predictive factors of future disease activity or disease severity
Statement 3.5. No strong evidence exists for predictors of disease relapse and the number of relapses
Statement 3.6. Stricturing and/or internal penetrating (B2/B3) phenotype and the presence of granulomas and increased visceral adipose tissue may predict hospitalizations; small bowel involvement, TNF polymorphisms, NOD2 variants, and age do not predict hospitalization

Figure 1. Summary of consensus recommendations for the management of inflammatory disease.