Acute Severe Ulcerative Colitis with Multiple GI Infections

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Case 1.

- Male, 62 yo.
- Admitted with unstable hemodynamic status and bloody diarrhea, stabilized in ICU.
- Recently hospitalized in another hospital, no progression hence referred to our IBD Centre.
- Chronic frequent fever, abdominal pain, bloody diarrhea on and off for several months, colonoscopy January 2023: pancolonic UC, Mesalamine 3x1 tab, Meropenem
- Physical exam in Wards after being stabilized in ICU: anemic and malnourished

Further exams

07/04/23 CRP: 160, hypoalbuminemia (1.8 g/dL)

08/04/23 Panel GI: *Entamoeba histolytica*

08/04/23 **Calprotectin: 395**, M2PK 16

03/05/23 Anti Amoeba +, Faeces parasitology –

01/05/23 Panel GI: -

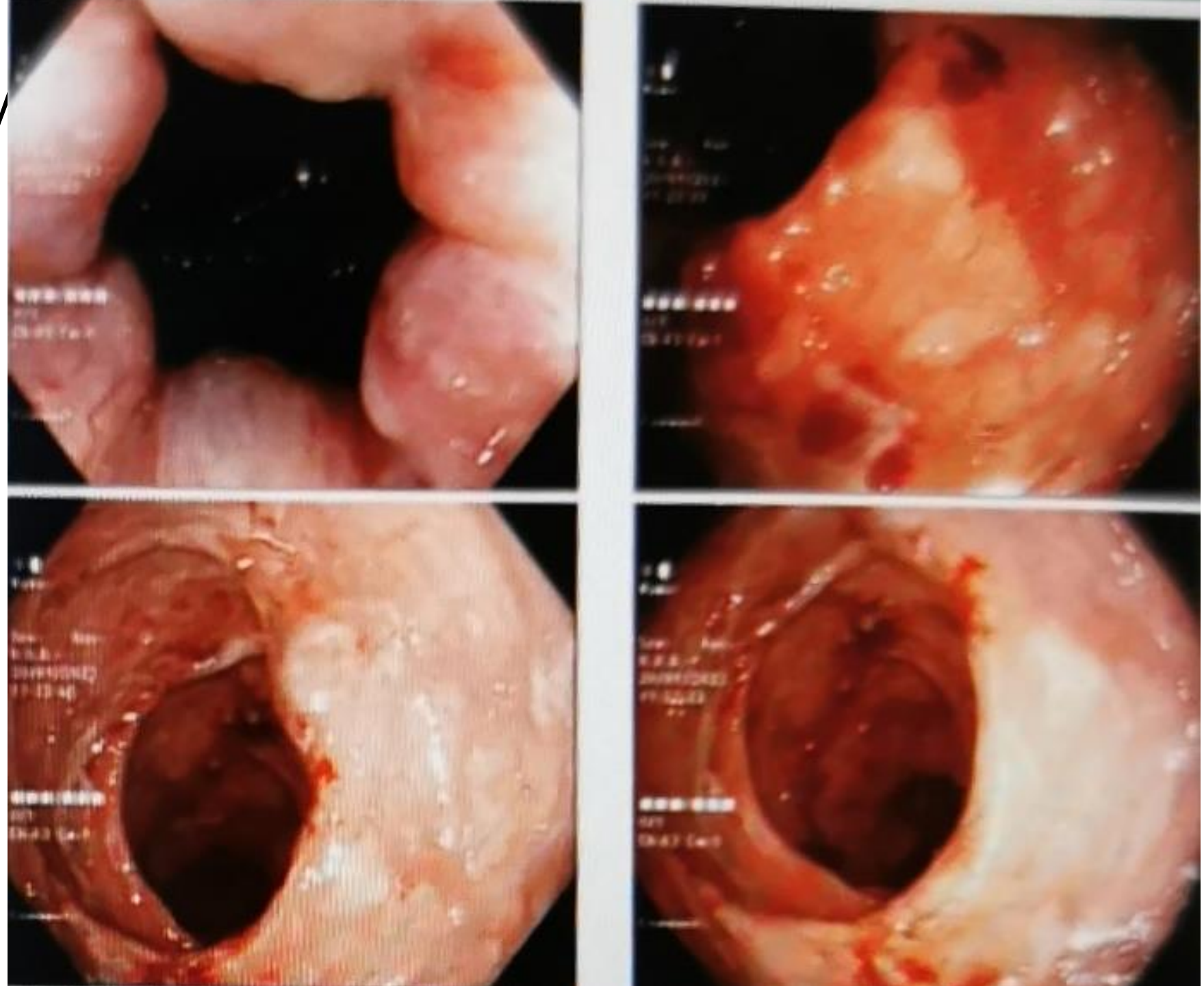
08/05/23 CRP 157 PCT 0,25, Calprotectin: 1044, M2PK 16

12/05/23 Kultur Darah *Stenotrophomonas maltophilia, MDR (Amikacin sensitive)*

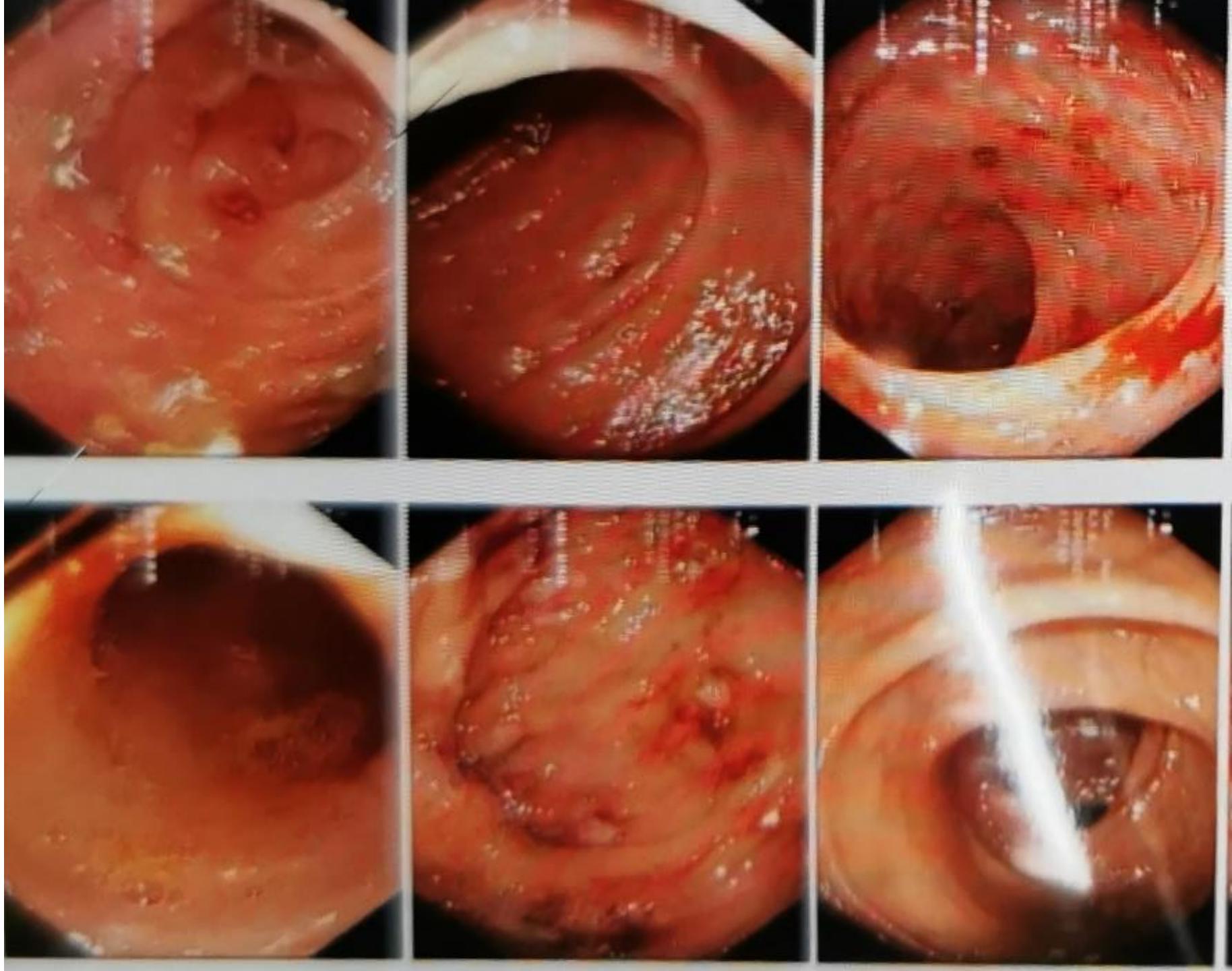
17/05/23 PCR Toxoplasma –, EBV nuclear Ag > 600, Anti EBV VCA IgG +376/IgM -

18/05/23 PCR CMV +, Galaktomanan -

Colonoscopy 20/01/23

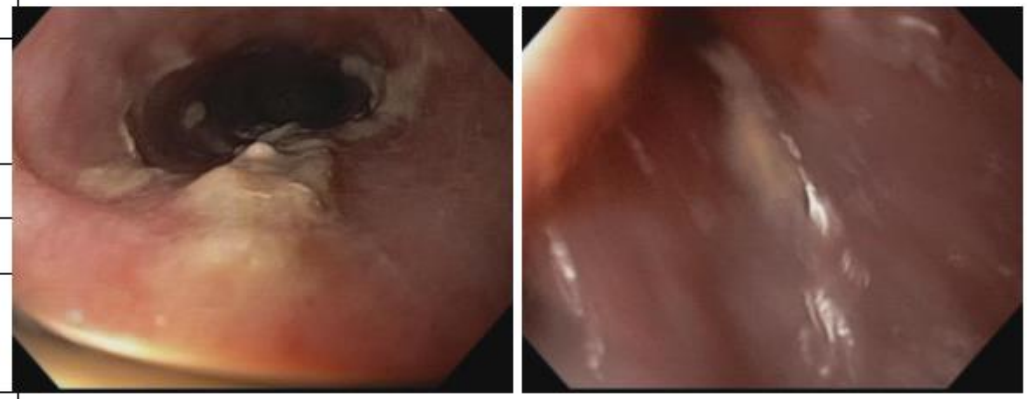


Colonoscopy 20/01/23

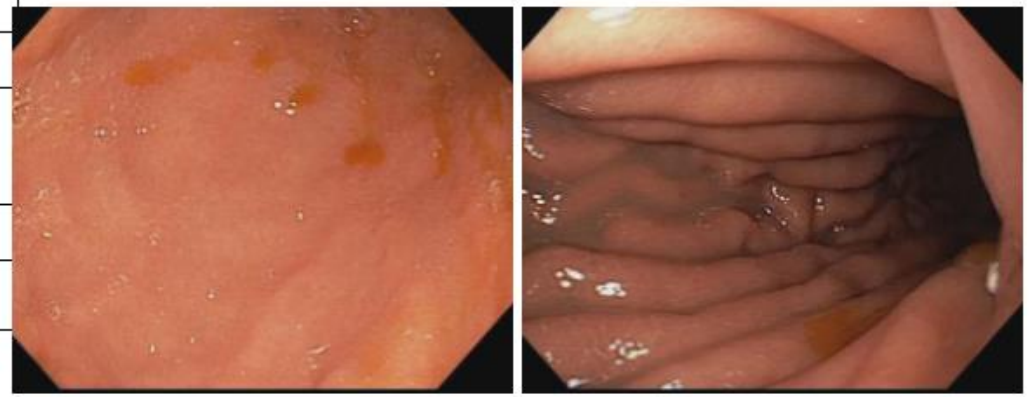


OGD 24/04/23

Obat Premedikasi	propofol
ESOPHAGUS	
Upper third	Normal
Middle third	Hiperemis ringan-sedang, erosi 8 bh
Lower third	Hiperemis ringan, erosi 8 bh
STOMACH	
Cardia	Normal
Fundus	Normal
Corpus	Hiperemis sedang
Antrum	Hiperemis sedang, erosi 8 bh biopsi 1
Pylorus	Normal
DUODENUM	
1st part	Normal
2nd part	Normal

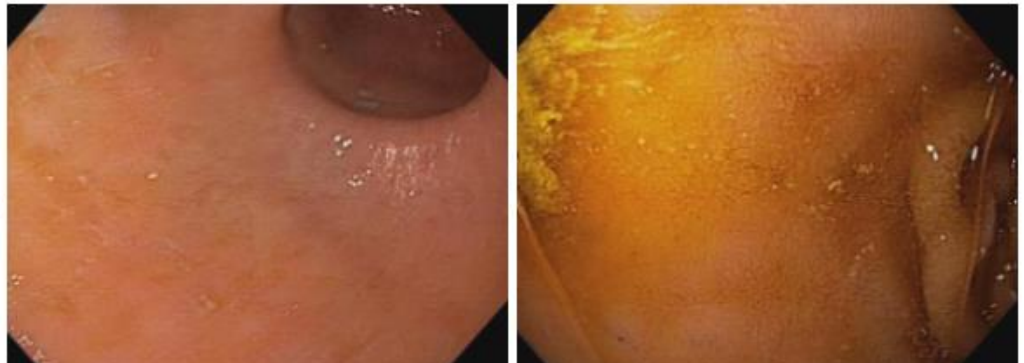


Info. Tamb.



KESIMPULAN

Esofagitis reflux grade A
Suspect candidiasis esofagus DD/ esofagitis erosif ec obat
Gastritis erosif sedang

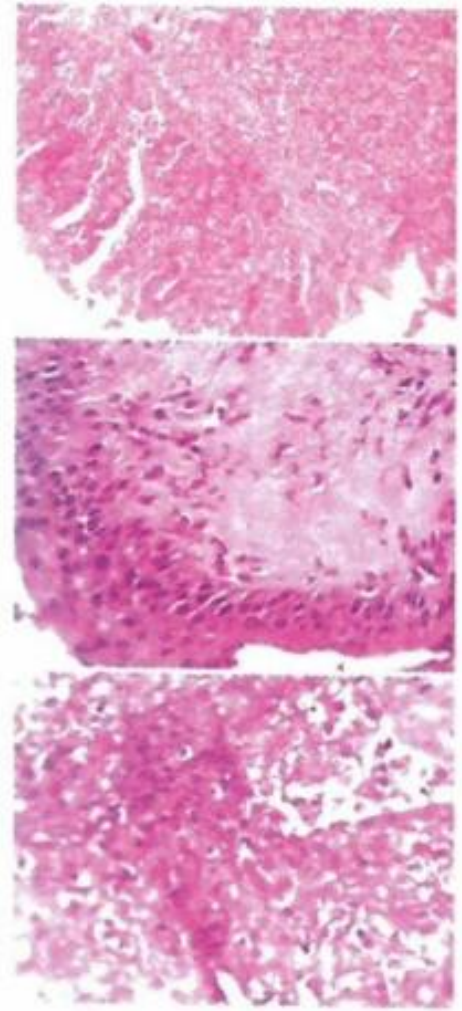


Radiology

- 08/04/23 CT Whole Abdomen: Pancolitis, multiple cholelithiasis, suspected pancreatic head mass, Cystitis

- CT enterography was not feasible to be done due to patient's condition on admission.

I. Sediaan biopsi terdiri atas mukosa lambung
tipe fundal yang menunjukkan:
- Kelenjar atrofik ringan
- Sebukan sel mononukleus ringan
- Tidak ditemukan sel polimorfonukleus
- Tidak tampak metaplasia intestinal/ displasia
- H pylori negatif



II. Sediaan biopsi esofagus dilapisi epitel skuamosa tanpa kelainan.
Lamina propria fibrotik, bersebukan ringan sel radang kronik.
Tampak keping jaringan nekrotik yang terpisah.
Tidak ditemukan spora/ hifa jamur.

I. Gastritis kronik, atrofik, non aktif
Tidak ditemukan metaplasia intestinal/ displasia dan H pylori.

II. Esofagitis kronik, non spesifik dengan keping nekrotik agaknya dari bagian ulserasi.
Tidak ditemukan tanda khas/ ganas/ spora dan hifa jamur pada sediaan ini.

Histopathology from Colonoscopy (26/01/23)

6 biopsy sites

No dysplasis, ulcerative-like lesion. Lamina propria is containing chronic inflammatory cells in all layers of mucosa with some eosinophils, and few PMNs. No basal plasmasitosis nor granuloma. Crypt distorsion exists with varied crypt sizes, uneven distribution, and branch-like appearance with neutrophilic cryptitis.

Conclusion: Active chronic colitis suspectedly caused by IBD

Assessment

- ASUC (History of hemodynamic shock) pancolonic triggered by multiple infections (CMV, EBV, Bacteria, Amoeba)
- Oral candidosis
- DM, ADHF, HHD, multiple cholelithiasis, suspected pancreatic head mass, cystitis
- Electrolyte imbalance, hypoalbuminemia

Therapies

Steroid MP 1x62.5 mg IV -> 2x62.5 mg-> no response
Metformin 3x1 tab PO
Budesonide 2x3 mg PO
Mesalamine granule 2x1.5 g PO
Albumin 3x1 tab PO
Sucralfat 4x15 cc PO
Rebamipide 3x100 mg PO
Esomeprazole 2x1 amp IV
Albuminar 25% 100 cc Iv
Meropenem 2x1 g IV

Ondansetron 3x4 mg IV
Otilinium bromide 3x1 PO
Trud enema 2x/day
Lacidofil 3x2tab
Normagut 2x1
Parenteral nutrition 500cc/24 h
Gancyclovir 2x250 mg iv
Hidrasec 3x1
Duspatalin 1x1
Fluconazole 1x200 mg
Ciprofloxacin -> Levofloxacin -> Meropenem

Questions

Diagnostic aspects:

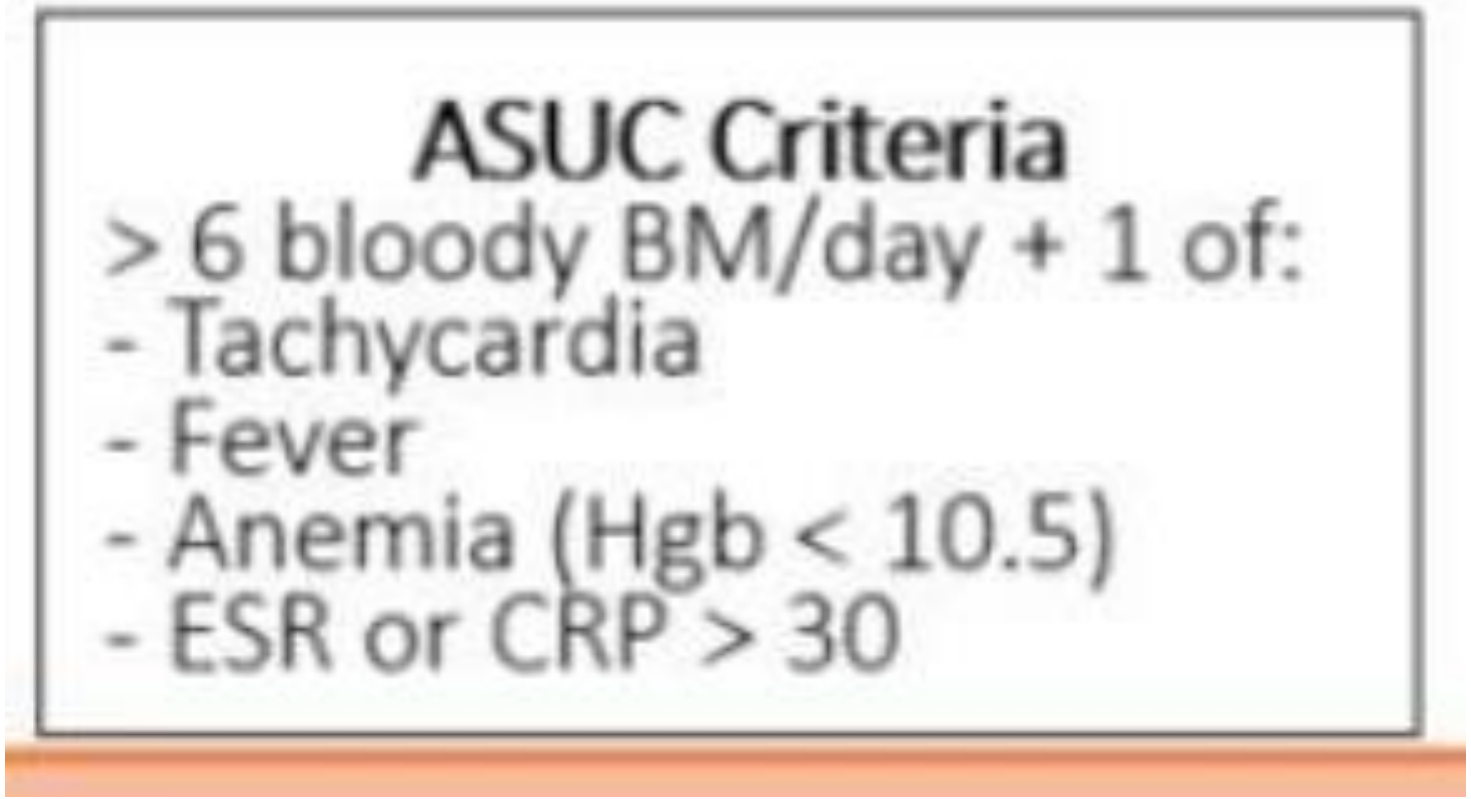
How to compile all Clinical, Lab, Endoscopy, Radiology, Histopathology as the background for his IBD diagnosis?

Risk of a Severe Attack in Patients With UC

- **Progression of UC studied in 624 patients over 24 years**
  - 18.8% of first attacks were severe
  - 17.6% of all attacks were severe
  - 3-fold higher mortality rate if first attack is severe vs mild-moderate

Edwards FC, Truelove SC. *Gut.* 1963;4:299-315.

What and When is ASUC indicated?



DEFINITION OF ASUC

Go to:

Conventional diagnosis of ASUC is historically based on the Truelove and Witts' criteria (Table 1),[13] which consist of the presence of bloody stools ≥6 times a day and at least one of the following signs of systemic toxicity: pulse rate >90 beats/min, temperature >37.8°C, hemoglobin <10.5 g/dL, or erythrocyte sedimentation rate >30 mm/hr. These still remain the most sensitive criteria for defining ASUC, although they must always be applied and considered owing to individual circumstances and settings.[14] Other indices, such as the clinical partial Mayo score and the Montreal classification, are less frequently used in clinical practice; however, comparative studies for the diagnosis of ASUC are not available.[15,16]

Table 1

Disease Activity in Ulcerative Colitis

Variable	Mild	Moderate in "between mild and severe"	Severe
Bloody stools, times/day	<4	4 or more if	≥6 and
Pulse, beats/min	<90	≤90	>90 or
Temperature, °C	<37.5	≤37.8	>37.8 or
Hemoglobin, g/L	>115	≥105	<105 or
ESR, mm/hr	<20	≤30	>30
CRP, mg/L	Normal	≤30	>30

- Truelove SC *et al*. Br Med J 1955;2:1041-1048

ASUC CRITERIA

Disease Activity in Ulcerative Colitis

Variable	Mild	Moderate in "between mild and severe"	Severe
Bloody stools, times/day	<4	4 or more if	≥6 and
Pulse, beats/min	<90	≤90	>90 or
Temperature, °C	<37.5	≤37.8	>37.8 or
Hemoglobin, g/L	>115	≥105	<105 or
ESR, mm/hr	<20	≤30	>30
CRP, mg/L	Normal	≤30	>30

Open in a separate window

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Adapted from Truelove SC *et al*. Br Med J 1955;2:1041-1048.[13]

AMERICAN COLLEGE OF GASTROENTEROLOGY
Advancing Gastroenterology, Improving Patient Care

Defining Disease Activity – ACG Definition

	Remission	Mild	Moderate-Severe	Fulminant
Stools (#/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (µg/g)	<150-200	>150-200	>150-200	>150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

Rubin DT, et al. Am J Gastroenterol. 2019 Mar;114(3):384-413.

Therapies in UC: New and Notable

- Questions:

What’s the best possible treatment and why?

ACG Guidelines: Current Treatments for UC

Mild-Moderate Extensive UC[a]

Topical 5-ASA/steroids[b]	Varies by delivery method
Oral 5-ASA[b]	Titrated up to 4.8 g QD
Oral steroids[b]	20-60 mg QD
AZA/6-MP[b]	1.5-2.5 mg/kg QD

Severe UC

IV steroids[b]	300 mg hydrocortisone 60 mg methylprednisolone
CsA (+/-6-MP)	
Colectomy	

[a] Extensive UC refers to disease extending proximal to the splenic flexure and that requires systemic medication.
[b] FDA- and EU-approved treatments.

Kornbluth A, Sachar DB. *Am J Gastroenterol*. 2004;99(7):1371-1385.
Cima RR, Pemberton JH. *Arch Surg*. 2005;140(3):300-310.

First Line Therapy in ASUC

IV Corticosteroids (CS)

Truelove and Witts did study of the use of CS as first line medical therapy in ASUC -> remission in 73% of patients at Day 5, improved endoscopic profile, lowered mortality rates

No additional benefit for higher doses than methylprednisolone 60 mg/day after 7-10 days of therapy (complications will increase!)

Hydrocortisone 4x100 mg -> higher rates of hypokalemia

- Approximately 30% patients with ASUC may **become corticosteroid-refractory** and require medical or surgical rescue therapy. Short-term colectomy rate in these patients is ~25–30%.[4] Based on evidence presented above, infliximab is probably effective and cyclosporine may be effective in decreasing short-term risk of colectomy in corticosteroid-refractory patients with ASUC.

Second Line or Rescue Therapies in ASUC

Second line therapies for ASUC:

1. Calcineurin inhibitor: cyclosporine A and tacrolimus

Oral tacrolimus, targeting a trough concentration of 10–15ng/ml, may also be effective in inducing clinical response in the short-term, which probably translates into lower risk of colectomy.

1. Infliximab

Third line therapy

CsA to IFX -> avoid

IFX to CsA -> better

Weisshof et al. assessed 40 steroid and IFX-refractory ASUC patients receiving sequential therapy with CsA; 60% achieved clinical remission within 2 weeks, and 42% had colectomy-free survival at 1 year, with no increased in adverse events, which suggest CsA therapy following rescue therapy failure with IFX can be effective and safe in ASUC [56]. A recent publication in a mixed cohort of steroid and/or anti-TNF refractory UC +/- ASUC (*n* = 39) has shown safety and efficacy of bridging patients from third line CsA to VDZ, with **68% colectomy-free rate** at 12 months follow-up

A systematic review of ten studies, or 314 participants, showed sequential treatment with combinations of **steroids, CsA or TAC, and IFX**, led to ASUC patients achieving a response in 62% of cases and remission in 39%; colectomy rates were 28% at 3 months.

Questions

Therapeutic aspects: Vedolizumab use in this ASUC case? Anticoagulants?

Other Therapeutic Options:

1. Tofacitinib
2. Vedolizumab
3. Ustekinumab

1. Tofacitinib

Post-hoc analysis of pivotal phase III trials of tofacitinib in outpatients with **moderate-severe UC** suggest that 29–32% patients may experience decrease in stool frequency and rectal bleeding within 3 days of initiation of therapy.[125]

Other biologics have not been specifically evaluated in the setting of ASUC.

Vedolizumab (VDZ)

VDZ is a selective antibody against alpha4beta7- integrin, which targets leukocyte trafficking in the GI tract.

Efficacy of VDZ in induction and maintenance of moderate-to-severe UC was demonstrated in phase III GEMINI 1 trial.

At week 52, 42% of patients achieved clinical remission on 8-weekly VDZ infusions.

Moreover, VDZ has a safer adverse event profile than other molecule

There is no data evaluating VDZ in ASUC in cohort methodology.

Verdon C. J Clin Med. 2019.

Data

Vedolizumab, an anti-integrin agent, has a relatively slower onset of action particularly in patients with prior exposure to other biologics, and may not be effective by itself in hospitalized patients with ASUC.[126]

More data are needed on the use of VDZ in ASUC.

Ustekinumab

- The recent UNIFI trials show that ustekinumab, an anti-IL12/23 antagonist, induces clinical remission in moderate-to-severe colitis more often than placebo (respectively 15% vs 5%).[72] Despite the rapid onset of remission, no trials are specifically investigating the use of ustekinumab in ASUC.

Holvoet T, Lobaton T, Hindryckx P. Optimal Management of Acute Severe Ulcerative Colitis (ASUC): Challenges and Solutions. *Clin Exp Gastroenterol*. 2021;14:71-81
https://doi.org/10.2147/CEG.S197719

Last Frontier: Surgery

- **Emergency Indications**
  - Free perforation
  - Hemorrhage
  - Systemic instability
- **Urgent Indication**
  - Severe attack unresponsive to medical therapy after 2-5 days

Urgent indications for surgery are severe colitis with or without toxic megacolon that is unresponsive to conventional maximal medical therapy, and less severe colitis with medically intractable symptoms or complications related to adverse effects of chronic medical therapy.

References

- 1. Cima RR, Pemberton JH. *Arch Surg.* 2005;140(3):300-310.
- 2. Kornbluth A, Sachar DB. *Am J Gastroenterol*. 2004;99(7):1371-1385.

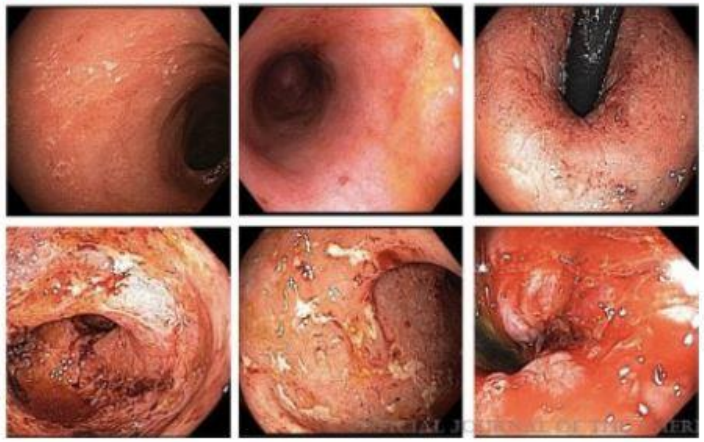
Acute Severe Ulcerative Colitis (ASUC)

#MondayNightIBD
@JPAchkarMD
@DCharabaty
#IBDAlgorithm
@wabillin

Sept 17, 2021

Background

- Life-threatening medical emergency
- 1/3 of patients do not respond to steroids
- Initial presentation of 1/3 of UC patients



Mayo 2
UCEIS 4-6

Mayo 3
UCEIS 7-8

ASUC Suspected

Truelove & Witts Criteria
≥6 🩸 💩 /day + 1 of:
- HR>90
- T>37.8
- Hgb<10.5
- ESR>30 or ⬆️CRP

ACG UC Severity
≥6 💩 /day +/- 🩸
- urgency
- FCP>150-200
- Mayo 2-3
- Hgb<75% normal
- ESR>30 or ⬆️CRP
- UCEIS 5-8

→ **Inpatient Admission**

Labs
- CBC
- ESR
- HBV
- Lipids
- CDI Algo
- Stool Cx
- CMP
- CRP
- IGRA
- FCP
- TPMT

Imaging
- KUB
- +/- CT

Flex Sig Bx
- Assess severity w/i 24-72 hrs
- R/o CMV

Treatment

🚫NSAIDs
🚫Opioids
🚫Anticholinergics

Supportive
- IVF, PRBC prn
- PO as tolerated
- 💡 repletion
- DVT prophylaxis

IV Steroids
60 mg methylpred /day equivalent

✂️ Surgery Consult

Treat infectious triggers (CDI, CMV, etc.)

Monitoring

- Vitals
- Stool frequency
- Serial exams
- CRP
- KUB

Improvement in ≤3 days?

No

✂️Indications
Refractory to 💉💊
Toxic Megacolon
Perforation
Severe hematochezia
Multiorgan dysfunction

Salvage Therapy
- IFX 5-10 mg/kg +/- Redose in 3-5 days
- IF hx IFX failure, ⬇️ albumin: IV steroids + CysA induction ➡️ VDZ or thiopurines maintenance (PJP ppx while on pred+CysA+AZA)
- Tofa 10mg TID

Yes

- Transition to PO steroids + start maintenance therapy*
- ⬇️ risk of ✂️ at follow-up if response to steroid vs need salvage therapy in ASUC

Outcomes

- Early prediction of steroid non-response is a challenge and limited prospective research exists
- Mayo 3 / UCEIS ≥ 7 predictive of ✂️ need
- ⬇️albumin, ⬆️ CRP, ⬆️ FCP predictive of steroid and IFX non-response and ✂️ need
- IFX clearance may predict response and ✂️ need
- Delay in ✂️ a/w ⬆️ post-op complications
- Shared decision making with early surgical involvement is important

🔑
FCP: fecal calprotectin
IGRA: TSPOT or Quantiferon gold
CDI: c. diff infection
💡: electrolytes
PRBC: Packed red blood cell transfusion
*: dependent on prior exposures/failures

- Rubin AJG 2019
- Laharie Gut 2017
- Choy IBD 2019
- Truelove BMJ 1955

Relapsing Acute Severe Ulcerative Colitis

#IBDAlgorithm @Waseem_AhmedMD
#MondayNightIBD @fudmanMD

7-10-2020

IFX +/- Pred

- If Prior Steroid Responsive → Lowest Effective Dose
- If 1°LOR → ↑ IFX dose, CNI, Tofa (!! Systemic IS/ Infectious Risk)
- If 2°LOR → Optimize Tx +/- Dual Biologic/Small Mol.
- Serial FCP/CRP q4-8wks & Flex Sig @3mo

Response

- Wean Steroids
- Serial FC/CRP
- If in Steroid-Free Endo Remission @ 6-12mo:
  - Consider Monotherapy Based on DAEs and SDM
  - Cont. Dual Therapy with Close Monitoring for DAEs

Declines Surgery

LOR

- **(Re)consult Colorectal Surgery**
- Assess Adherence
- Assess Disease Activity: Flex Sig, FCP, CRP
- Rule Out C. Diff. & CMV (& COVID)
- TDM: IFX/CNI/VDZ Trough
- If c/f Complication: Cross-Sectional Imaging
- **Urgent Surgery :**
  - ✓ **Fulminant UC**
  - ✓ **Toxic Megacolon**
  - ✓ **Systemic Toxicity**
  - ✓ **Patient Preference**

LOR

CNI +/- Pred + IMM or VDZ

- If Prior Steroid Responsive → Lowest Effective Dose
- If 1°LOR → ↑ CNI Dose, Tofa, IFX (if naïve) (!! Systemic IS /Infectious Risk)
- If 2°LOR → Optimize Tx +/- Dual Biologic/Small Mol.
- Serial FCP/CRP q4-8wks & Flex Sig @3mo

Response

- Wean Steroids
- Serial FC/CRP
- If in Steroid-Free Endo Remission @ 6-12mo:
  - Consider Monotherapy Based on DAEs and SDM
  - Cont. Dual Therapy with Close Monitoring for DAEs

Declines Surgery

No Response

Colectomy

Or

No Response

LOR

- Alternative/Dual Therapy Above
- Clinical Trial
- FMT ?
- Hyperbaric Oxygen ?
- Apheresis ?
- Combination antibiotics

LOR

Key Points

- Consult Colorectal Surgery ASAP with Regular Follow up
- Surgery ≠ Treatment Failure
- If Hesitant for Surgery → Multidisciplinary Meeting with Patient and Family
- RD Referral to Optimize Nutrition
- CNI + Steroid + IS → PJP Prophylaxis

DAE: Drug Adverse Effects
SDM: Shared-Decision Making

Acute Severe Ulcerative Colitis (ASUC)

ASUC Criteria
> 6 bloody BM/day + 1 of:
- Tachycardia
- Fever
- Anemia (Hgb < 10.5)
- ESR or CRP > 30

#MondayNightIBD @IBD_Houston
#IBDAlgorithm @joshsteinbergMD

Inpatient Admission

- **Labs**: CBC, CMP, CRP, +/- FCP
- **Stool Studies**: Cdiff, Stool Cx → + Abx
- **Abd Imaging**: X-ray, CT
- **Supportive Care**: IVFs, Nutrition, Electrolytes, DVT PPX
- **Serial Abd Exam**
- **Flex Sig + Bx**: Assess Dz; R/O CMV → + ID c/s + Antivirals

IV Steroids
3 Days

Improvement

Transition to PO Steroids

Start Effective Maintenance Rx

Choice based on shared decision & prior h/o Rx exposure/failure

No Improvement

Surgery Consult

Shared Decision Making

Refractory to meds
Toxic megacolon
Perforation
Severe hematochezia
Multiorgan Dysfunction

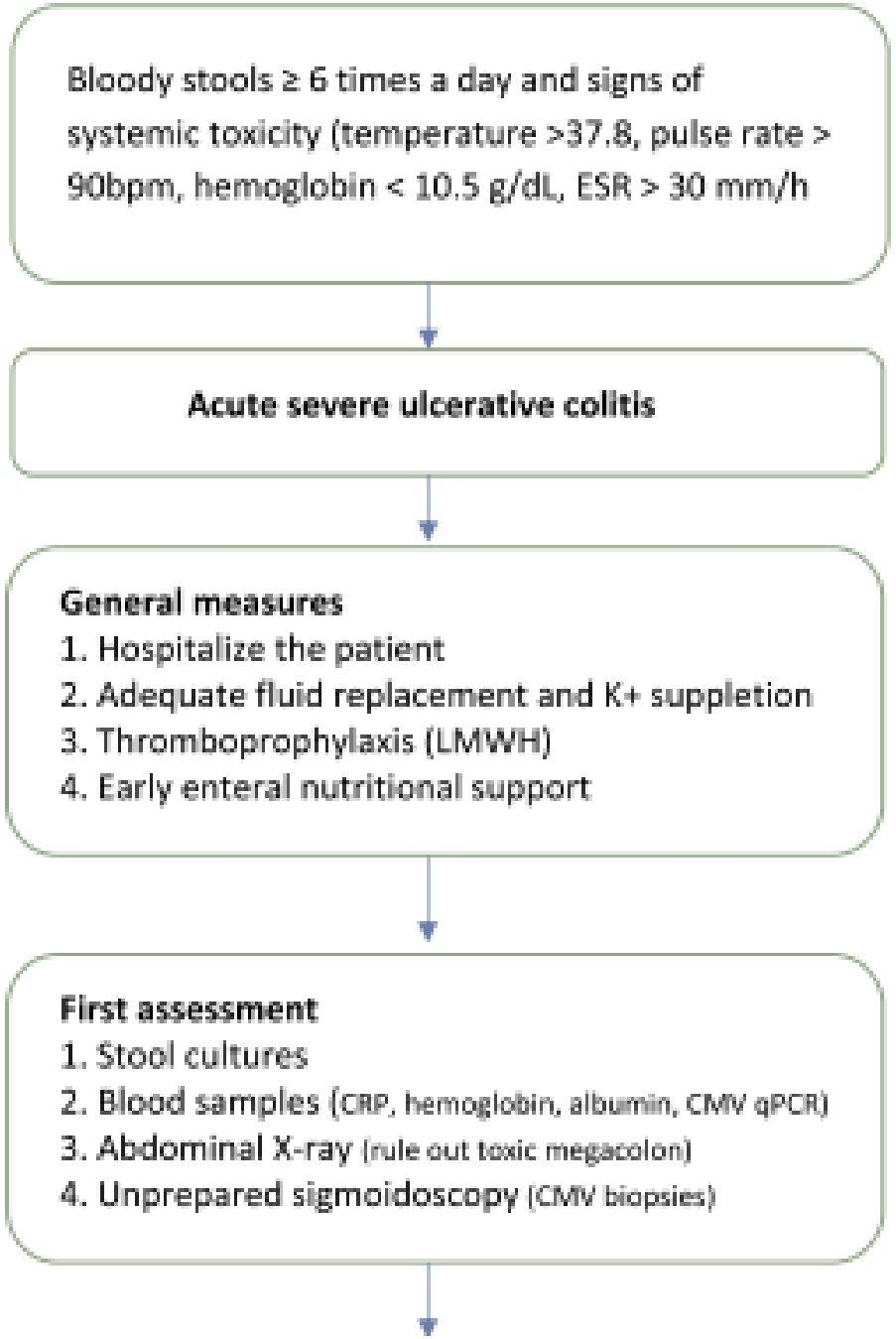
Colectomy

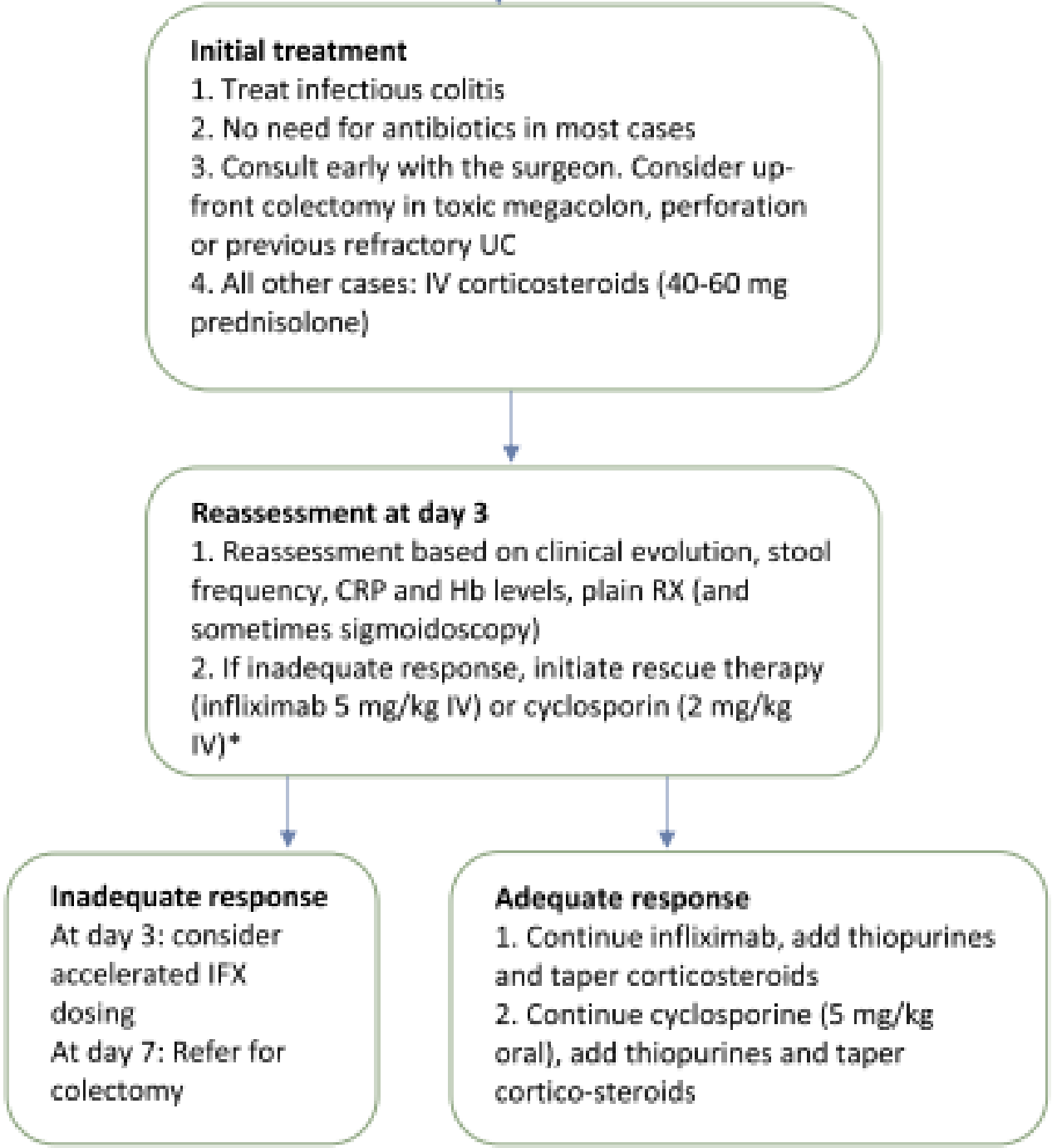
Salvage Tx

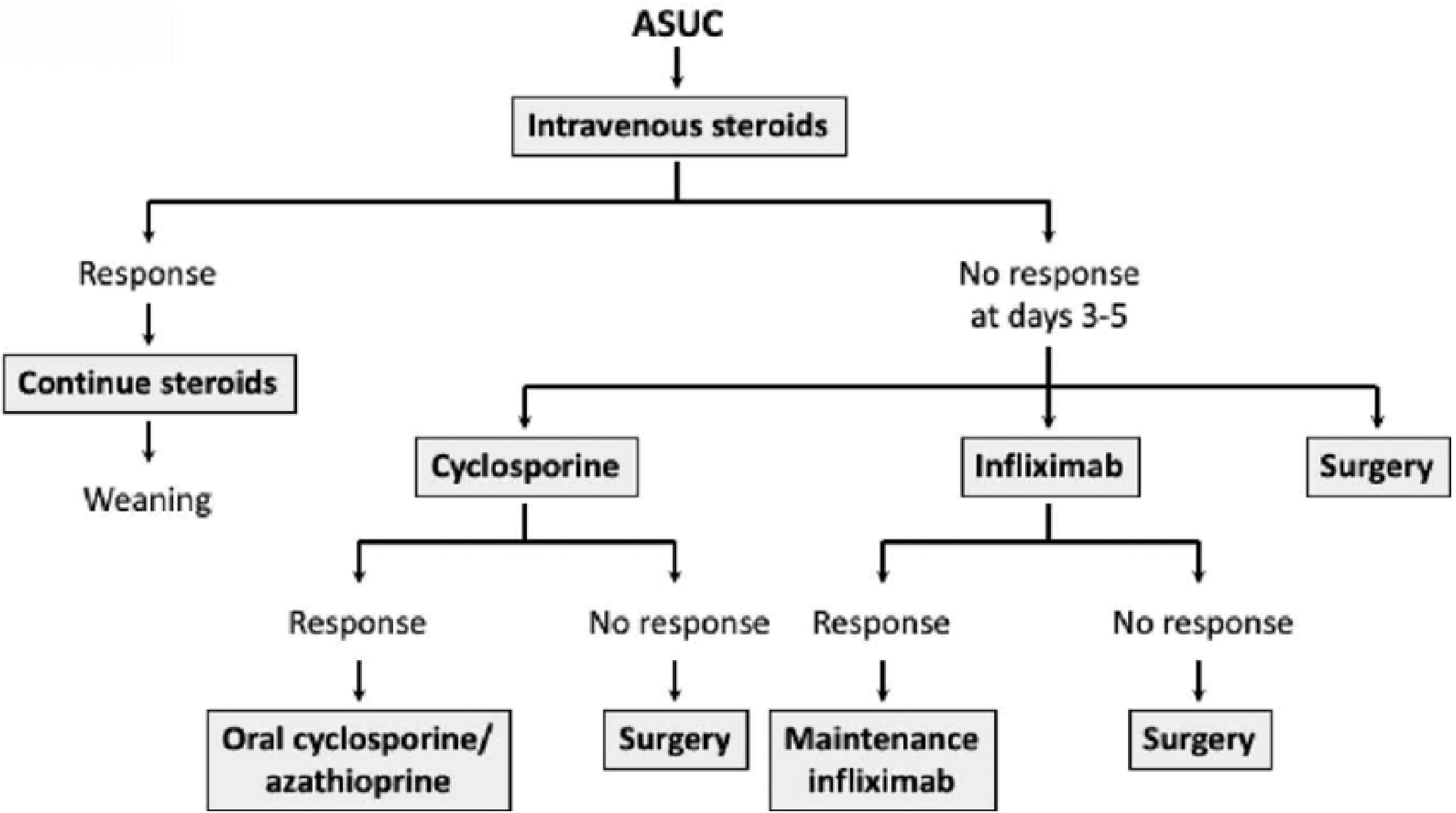
h/o IFX failure
Low albumin

- **IFX**
  - +Response → **Maintenance with IFX**
  - No Improvement → **Refractory UC**
- **Cyclosporine**
  - +Response → **Maintenance with VDZ or Thiopurine** [if no prior failure]
  - No Improvement → **Refractory UC**
- **JAK-i ?**
  15mg BID or 10 TID
  [small case series]

Refractory UC → **Colectomy**


Bloody stools ≥ 6 times a day and signs of systemic toxicity (temperature >37.8, pulse rate > 90bpm, hemoglobin < 10.5 g/dL, ESR > 30 mm/h
Acute severe ulcerative colitis
General measures
1. Hospitalize the patient
2. Adequate fluid replacement and K+ suppletion
3. Thromboprophylaxis (LMWH)
4. Early enteral nutritional support
First assessment
1. Stool cultures
2. Blood samples (CRP, hemoglobin, albumin, CMV qPCR)
3. Abdominal X-ray (rule out toxic megacolon)
4. Unprepared sigmoidoscopy (CMV biopsies)


Initial treatment
1. Treat infectious colitis
2. No need for antibiotics in most cases
3. Consult early with the surgeon. Consider up-front colectomy in toxic megacolon, perforation or previous refractory UC
4. All other cases: IV corticosteroids (40-60 mg prednisolone)
Reassessment at day 3
1. Reassessment based on clinical evolution, stool frequency, CRP and Hb levels, plain RX (and sometimes sigmoidoscopy)
2. If inadequate response, initiate rescue therapy (infliximab 5 mg/kg IV) or cyclosporin (2 mg/kg IV)*
Inadequate response
At day 3: consider accelerated IFX dosing
At day 7: Refer for colectomy
Adequate response
1. Continue infliximab, add thiopurines and taper corticosteroids
2. Continue cyclosporine (5 mg/kg oral), add thiopurines and taper cortico-steroids


ASUC
Intravenous steroids
Response
Continue steroids
Weaning
No response at days 3-5
Cyclosporine
Infliximab
Surgery
Response
No response
Response
No response
Oral cyclosporine/ azathioprine
Surgery
Maintenance infliximab
Surgery

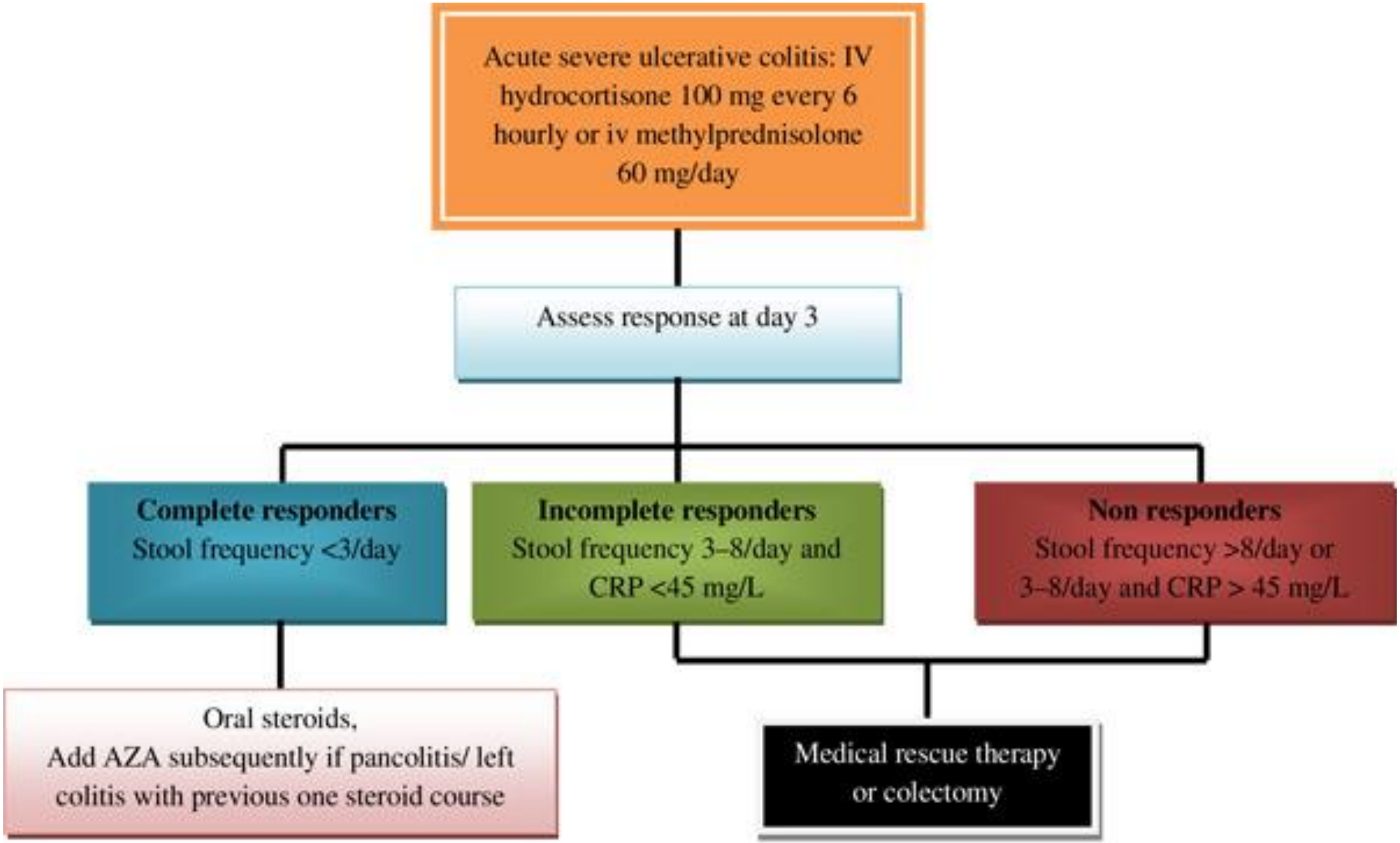


Figure 1: Algorithm for treatment decisions for patients with acute severe UC on intensive steroid therapy

Ahuja V et al.

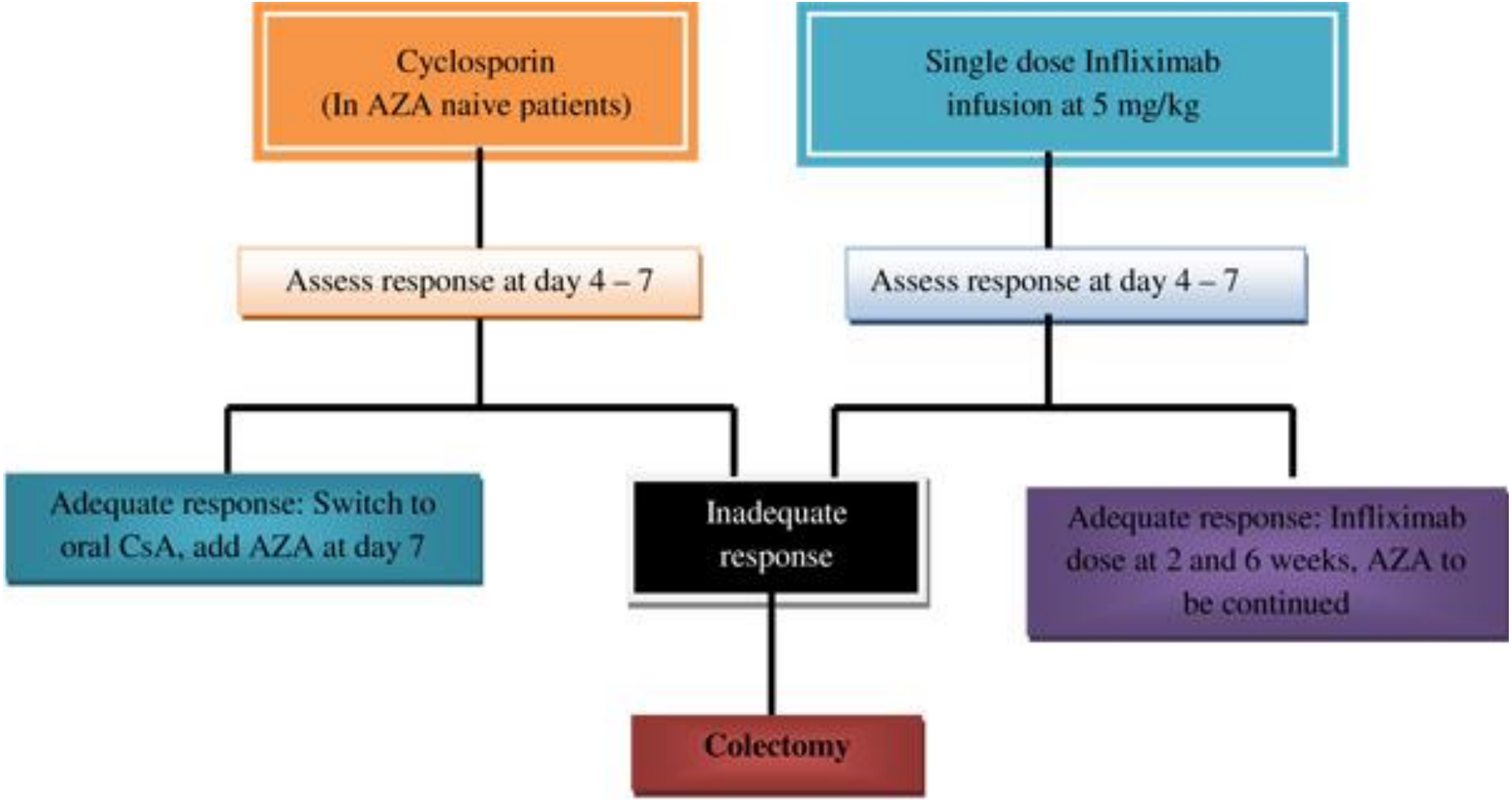
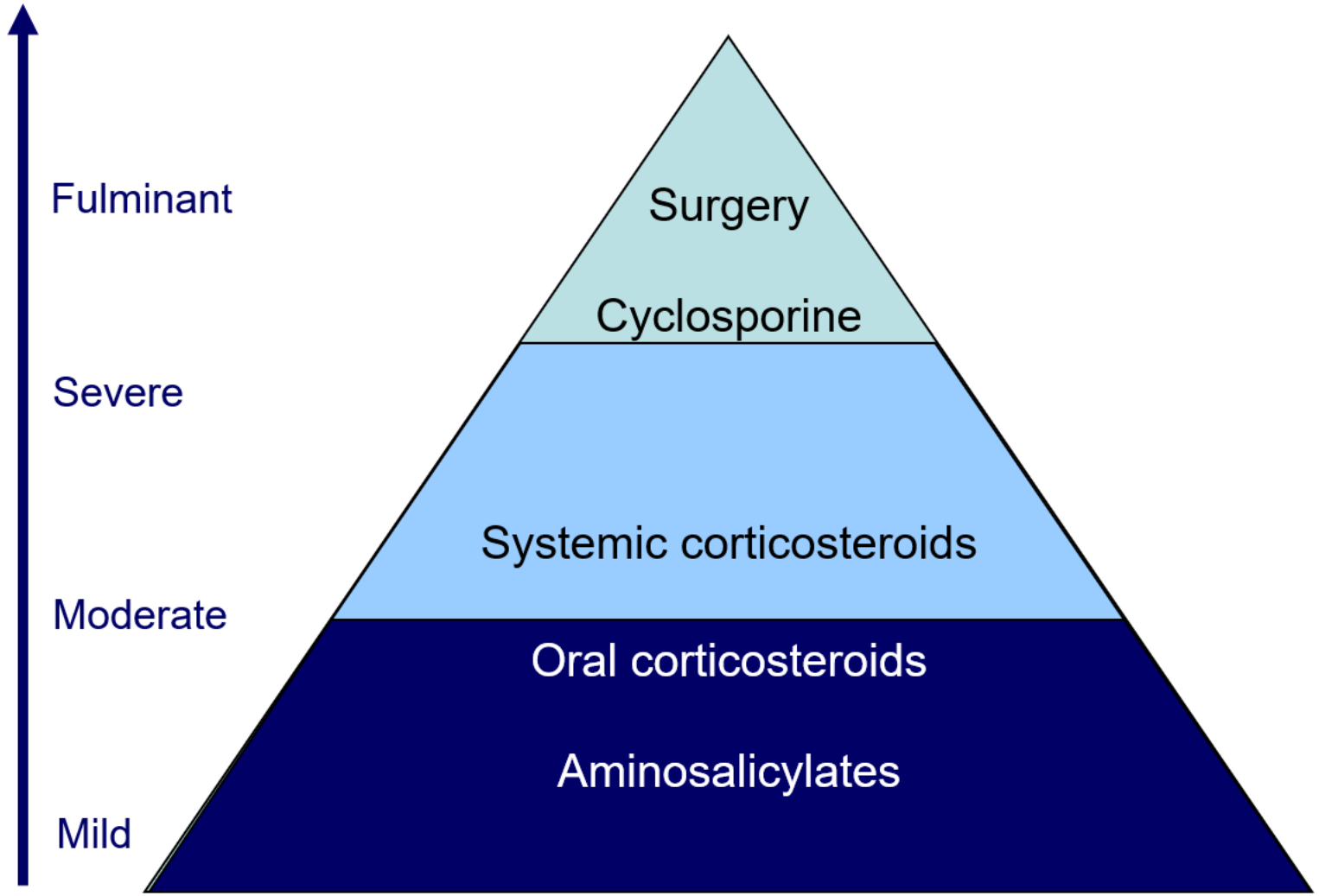


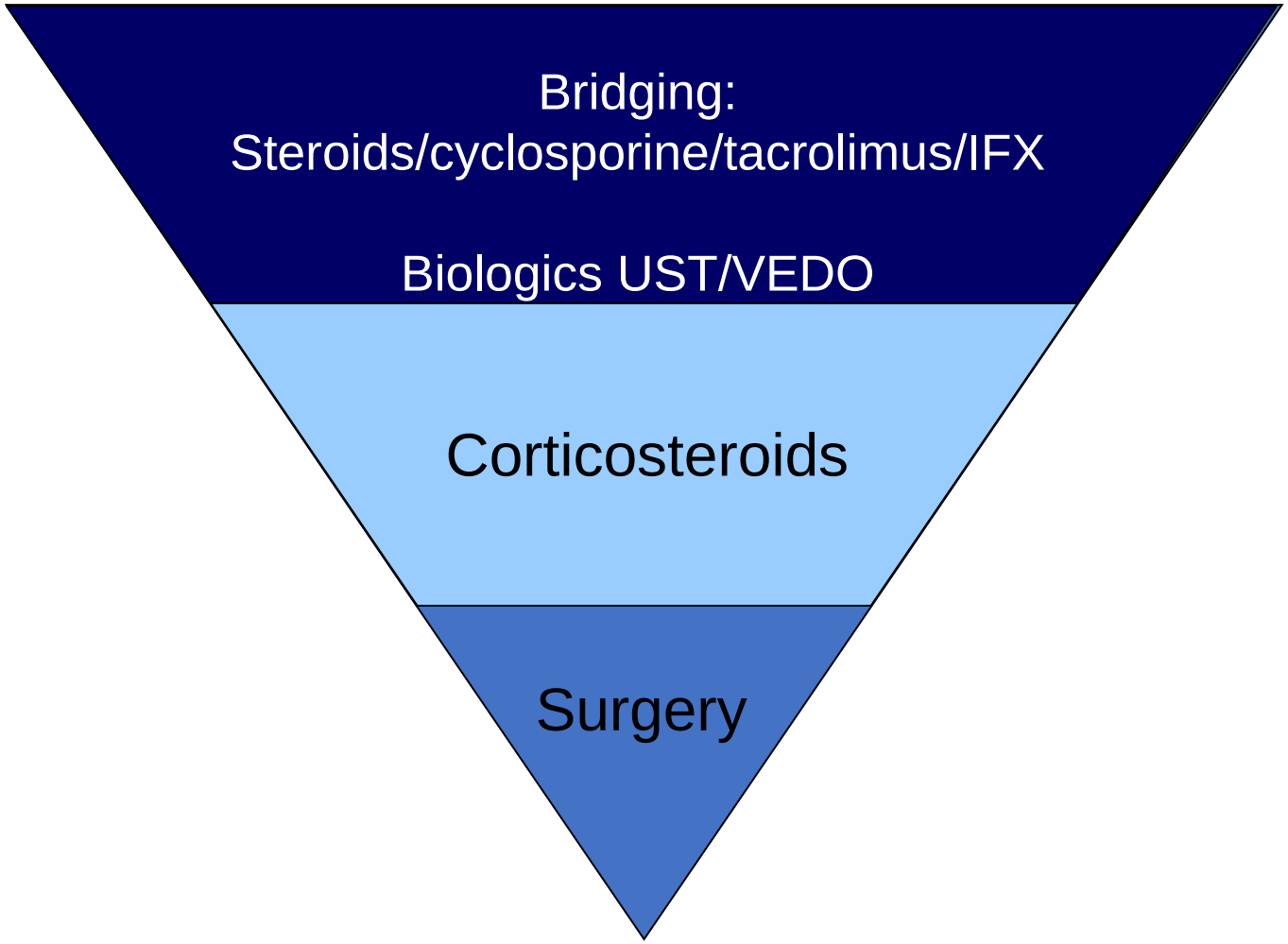
Figure 2: Algorithm for medical rescue therapy after failure of response to intravenous steroids

Evolving "Therapeutic Pyramid" for UC



Hanauer SB. *Nat Clin Pract Gastroenterol Hepatol*. 2005;2(11):493.

Reversing the “Therapeutic Pyramid” for Severe UC: Step Down Approach



Hanauer SB. *Nat Clin Pract Gastroenterol Hepatol*. 2005;2(11):493.

After 3 doses of Vedolizumab, this patient improved clinically

Further evidence of deep remission is about to obtain from second endoscopy, which still being planned for this patient.


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Table 2 Predictive Indices for Corticosteroid Failure in Acute Severe Ulcerative Colitis

Score	**Criteria**	**Probability of IV Corticosteroids Failure**
Travis or Oxford criteria	>8 stools or CRP > 45 mg/L	If any present on day 3 = 85% probability of colectomy
Ho or Scottish index	Colonic dilatation > 5.5 cm = 4 points Albumin < 3 g/dl on admission = 1 point Average daily number of stools over first 3 days: < 4 = 0 points; 4–6 = 1 points, 6–9 = 2 points; ≥ 9 = 4 points	≥ 4 points on day 3 = 85% probability of non-response
Lindgren score	Stool frequency per dag + 0.14 x CRP (mg/L)	>8 points on day 3 = 72% probability of non-response

Note: Data from Gisbert et al. [8]