Evaluation and Management of Suspected Immune-Mediated Colitis/Diarrhea

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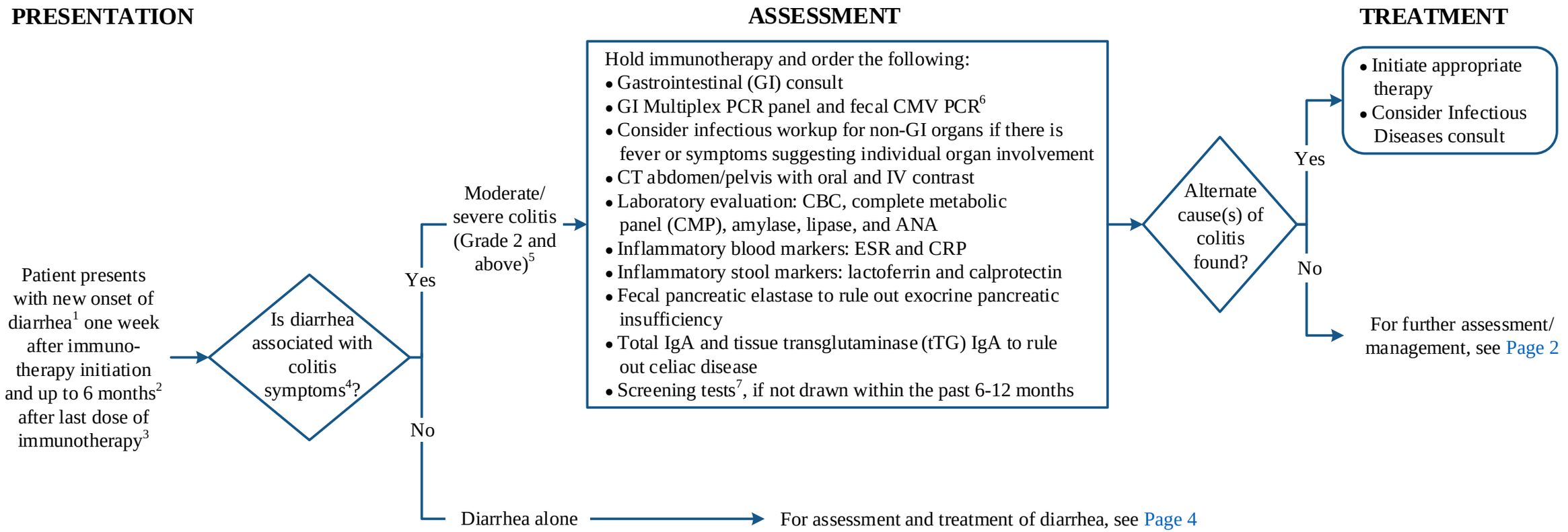
GENERAL EVALUATION



For recurrent colitis/diarrhea assessment and treatment, see Page 5

[1] Diarrhea is defined as the presence of 3 or more unformed stools a day
[2] On rare occasions, GI toxicities may develop beyond the typical 6 month window
[3] PD-1 inhibitors (pembrolizumab, nivolumab), PD-L1 inhibitors (atezolizumab, avelumab, durvalumab), CTLA-4 inhibitor (ipilimumab)
[4] Colitis symptoms include abdominal pain, rectal bleeding, and blood or mucus in stools
[5] Refer to Appendix A for Modified Common Terminology Criteria for Adverse Events (CTCAE)
[6] Fecal CMV PCR has low sensitivity and poor negative predictive value for the diagnosis of CMV colitis. Consider early colonoscopy in immunosuppressed patients to exclude CMV colitis and perform colonoscopy in patient with positive fecal CMV by PCR.
[7] Screening tests include HIV antibody; T-spot tuberculosis; hepatitis A, B and C panel; and urine *Histoplasma* antigen

CMV = cytomegalovirus
ANA = antinuclear antibodies

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GENERAL EVALUATION - continued

PRESENTATION

Other causes(s) for colitis excluded

ASSESSMENT

Is the CT abdomen positive for colitis/ enteritis or are there positive inflammatory markers[1]?

Yes

A

- Consult GI
- Full colonoscopy[2] and biopsy[3]
- Consider EGD[2,4] and biopsy[3]

No

Refer to assessment and treatment of diarrhea on Page 4

ENDOSCOPY FINDINGS

Low-risk features:
- Normal colon appearance and normal histology

Moderate-risk features:
- Normal colon appearance with pathology showing inflammation
- Focal erythema, friability, or loss of vascularity
- Small ulcer < 1 cm, shallow ulcer < 2 mm, and/or number of ulcers < 3
- No infection identified on biopsy

High-risk features:
- Large ulcer ≥ 1 cm, deep ulcer ≥ 2 mm, and/or number of ulcers ≥ 3
- Extensive inflammation beyond left colon
- No infection identified on biopsy

EGD results with confirmed inflammation to stomach and duodenum

For upper GI management, see Page 6

For management of lower GI toxicity/colitis, see Page 3

EGD = esophagogastroduodenoscopy

[1] Stool: lactoferrin and calprotectin; blood: ESR and CRP
[2] Perform colonoscopy and EGD only if ANC greater than 0.5 K/microliter
[3] Examine biopsies for the presence of CMV and other opportunistic infections in immunosuppressed patients
[4] Order EGD if there are signs and symptoms of concurrent nausea/vomiting and/or epigastric pain

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LOWER GI/COLITIS MANAGEMENT

ENDOSCOPY FINDINGS

Low-risk features

- Corticosteroid[1] with taper for total treatment duration less than 30 days
- If refractory to corticosteroids after 3 days, consider one dose of infliximab or vedolizumab

→ Clinical follow-up for recurrent clinical symptoms

→ Clinical remission achieved?

- Yes → Resume immunotherapy (PD-1 or PD-L1) after completion of corticosteroids
- No →
  - Consider longer duration of infliximab or vedolizumab
  - Consider fecal microbiota transplant (FMT)
  - Consider repeat colonoscopy if colitis symptoms develop

(for endoscopy findings and subsequent management, see Page 2)

Moderate or high-risk features

- Corticosteroids[2] **and**
- Start infliximab **or** vedolizumab within one week of corticosteroid initiation

→ Repeat colonoscopy[3] after 3 doses of infliximab or vedolizumab (8-10 weeks after initiation)

→ Response seen on colonoscopy?

- Yes → Residual inflammation seen on colonoscopy?
  - Yes → Symptom improvement?
    - Yes →
      - Continue infliximab or vedolizumab until resolution of inflammation on repeat endoscopy
      - Resume immunotherapy[4] (PD-1 or PD -L1) after improvement of mucosal inflammation confirmed by repeat endoscopy
    - No → Consider repeat GI Multiplex PCR panel if more than 1 week after first test
      - Consider FMT **or**
      - Consult surgery
  - No → Discontinue infliximab or vedolizumab if imunotherapy is not resumed[4]
- No → Consider repeat GI Multiplex PCR panel if more than 1 week after first test
  - Consider FMT **or**
  - Consult surgery

[1] May consider budesonide as an additional option
[2] Start steroid taper over 2 weeks after starting infliximab or vedolizumab (total corticosteroid treatment duration should be less than 30 days)
[3] Consider early repeat colonoscopy after 2 doses of infliximab or vedolizumab if symptoms persist
[4] If resuming immunotherapy, continue long-term vedolizumab concurrently

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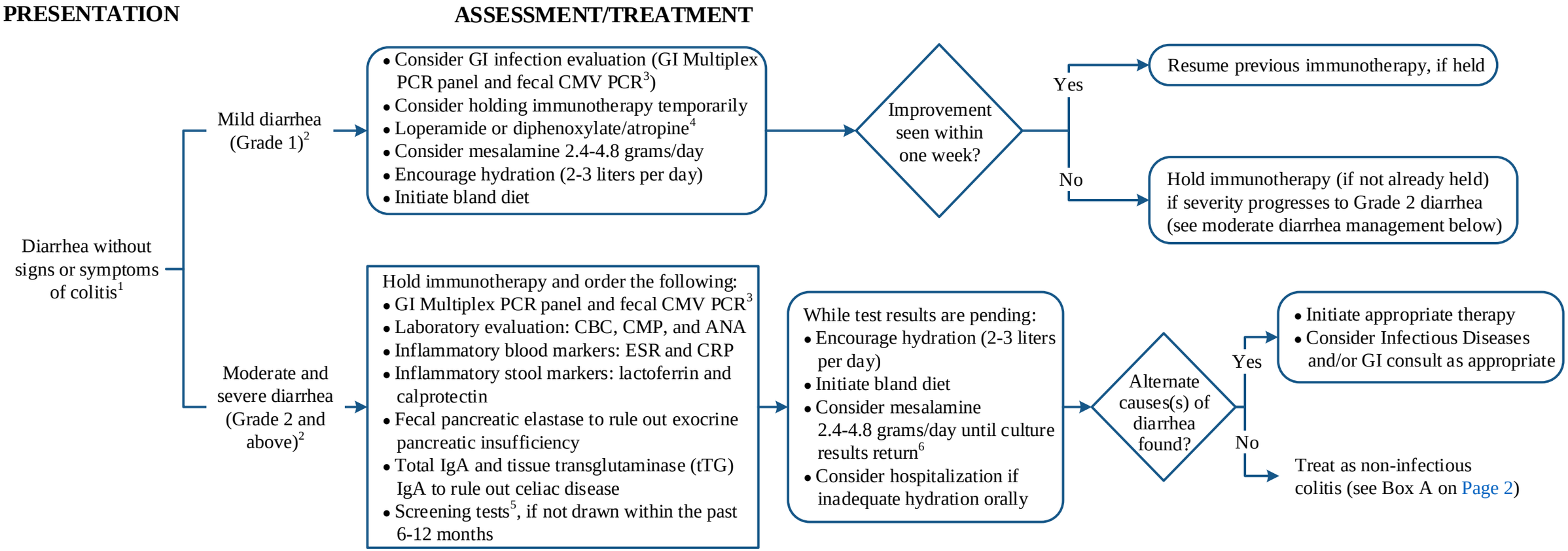
DIARRHEA MANAGEMENT



[1] Colitis symptoms include abdominal pain, rectal bleeding, and blood or mucus in stools
[2] Refer to Appendix A for Modified Common Terminology Criteria for Adverse Events (CTCAE)
[3] Fecal CMV PCR has low sensitivity and poor negative predictive value for the diagnosis of CMV colitis. Consider early colonoscopy in immunosuppressed patients to exclude CMV colitis and perform colonoscopy in patients with positive fecal CMV by PCR.
[4] Consider anti-motility agents only if non-invasive pathogens have been excluded
[5] Screening tests include HIV antibody; T-spot tuberculosis; hepatitis A, B and C panel; and urine *Histoplasma* antigen
[6] If cultures return negative and/or no improvement is seen after 2 days of treatment, discontinue mesalamine and consider starting corticosteroids. If patient has symptom improvement with mesalamine, continue treatment regardless of culture results.

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RECURRENCE MANAGEMENT

ASSESSMENT

Recurrent colitis/diarrhea (Grade 2 and above)[1] after completion of immunotherapy toxicity treatment

Hold immunotherapy and order the following:
- GI Multiplex PCR panel and fecal CMV PCR[2]
- Laboratory evaluation: CBC, CMP, amylase, and lipase
- Inflammatory blood markers: ESR and CRP
- Inflammatory stool markers: lactoferrin and calprotectin
- Fecal pancreatic elastase to rule out exocrine pancreatic insufficiency

Optional workup:
- Consider infectious workup for non-GI organs if there is fever or symptoms suggesting individual organ involvement
- Screening tests[3], if not drawn within the past 6-12 months
- CT abdomen with oral and IV contrast

Alternate cause(s) of colitis/diarrhea found?

TREATMENT

Yes
- Initiate appropriate therapy
- Consider Infectious Diseases and/or GI consult as appropriate

No

Colonoscopy or flex sigmoidoscopy[4] with biopsy

For endoscopy findings and subsequent management, see Page 2

[1] Refer to Appendix A for Modified Common Terminology Criteria for Adverse Events (CTCAE)
[2] Fecal CMV PCR has low sensitivity and poor negative predictive value for the diagnosis of CMV colitis. Consider early colonoscopy in immunosuppressed patients to exclude CMV colitis and perform colonoscopy in patients with positive fecal CMV by PCR.
[3] Screening tests include HIV antibody; T-spot tuberculosi; hepatitis A, B and C panel; and urine *Histoplasma* antigen
[4] If initial colonoscopy confirmed left colon involvement, then consider flex sigmoidoscopy on follow-up

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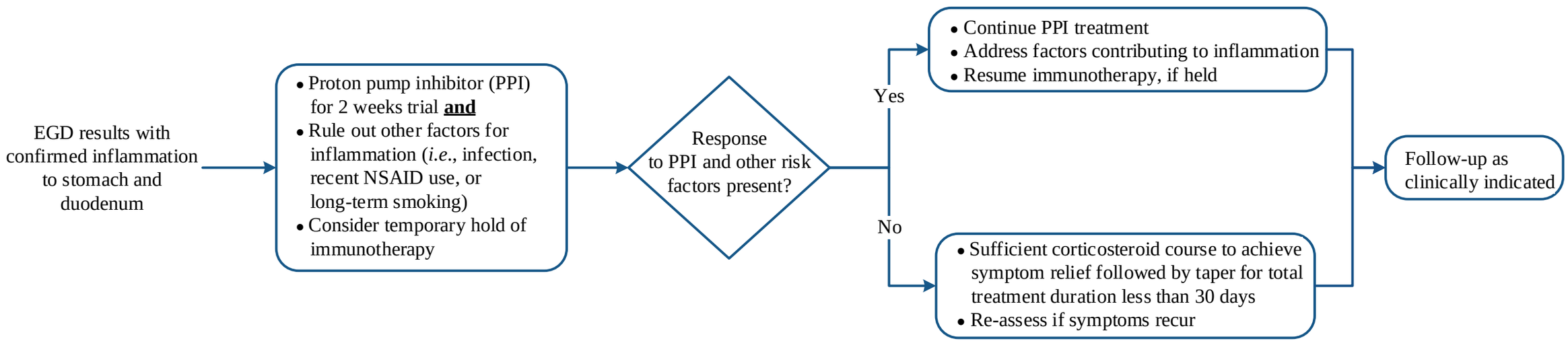
UPPER GI MANAGEMENT

ASSESSMENT/TREATMENT



NSAID = non-steroidal anti-inflammatory drugs

APPENDIX A: Modified[1] Common Terminology Criteria for Adverse Events (CTCAE)

Gastrointestinal Disorders					
Adverse Effect	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Diarrhea	Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living (ADL)	Increase of greater than 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death

[1] Modified version includes elements of version 4 and version 5

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