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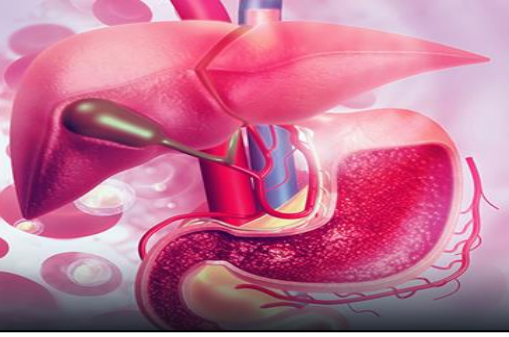

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Dear Doctor,

Greetings from Micro Labs limited. We are happy to bring you "ENTERON" which contains latest and interesting news in the field of Gastroenterology.

Inside This Issue:

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Looking forward to your valuable feedback

Best Regards,

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STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD

Background:

Knowledge of clinically relevant targets of individual treatments is important for improving management of patients with inflammatory bowel diseases (IBD). The Selecting Therapeutic Targets in IBD (STRIDE) program was initiated by the International Organization for the Study of IBD (IOIBD) in 2013 using an evidence based expert consensus process. It subsequently led to apposition statement determining therapeutic targets for IBD to be used for a "treat-to-target" clinical management strategy. Since then, the rapid advent of novel biologics and small molecules has increased our ability and aspirations in reaching beyond the conventional treatment goals of STRIDE-I. In parallel, advanced diagnostic tools are becoming widely available, such as bedside bowel ultrasound and home-based measurement of fecal inflammatory biomarkers, introducing new opportunities to improve disease outcomes. Nonetheless, these have also introduced further complexity into management algorithms, such as which drugs should be used in which particular sequence, when to start, when to dose-modify, when to stop, and when to consider surgery. This complexity is inevitably associated with discussions on new treatment goals and targets, such as histological healing, transmural healing, and molecular-based measures. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) has proposed treatment targets in 2015 for adult patients with inflammatory bowel disease (IBD).

Aim: To update the original STRIDE statements for incorporating treatment targets in both adult and pediatric IBD.

Methods:

Based on a systematic review of the literature and iterative surveys of 89 IOIBD members, recommendations were drafted and modified in 2 surveys and 2 voting rounds. Consensus was reached if >75% of participants scored the recommendation as 7 to 10 on a 10-point rating scale.

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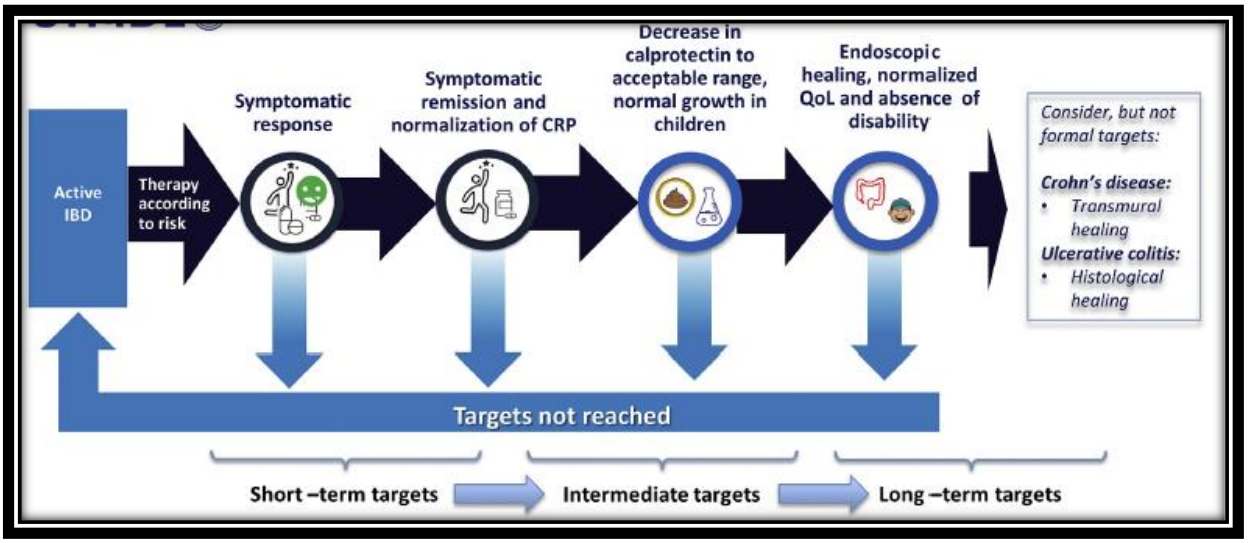
Results:

In the systematic review, 11,278 manuscripts were screened, of which 435 were included. The first IOIBD survey identified the following targets as most important: clinical response and remission, endoscopic healing, and normalization of C-reactive protein/erythrocyte sedimentation rate and calprotectin. Fifteen recommendations were identified, of which 13 were endorsed.

Treatment targets in Chron's disease and Ulcerative colitis



STRIDE-II confirmed STRIDE-I long-term targets of clinical remission and endoscopic healing and added absence of disability, restoration of quality of life, and normal growth in children. Symptomatic relief and normalization of serum and fecal markers have been determined as short-term targets. Transmural healing in Crohn's disease and histological healing in ulcerative colitis are not formal targets but should be assessed as measures of the remission depth.

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New in STRIDE II

- The STRIDE group, under the auspices of the IOIBD, has updated the 2015 first reported STRIDE recommendations and has developed 13 updated and new recommendations for treating to target in CD and UC (STRIDE-II recommendations).
- Time to expected response, remission, and endoscopic healing with the different treatments have been introduced for incorporating the treatment targets.
- STRIDE-II added clinical response and remission as well as normalization of CRP as immediate and short-term targets.
- Reduction of FC to an acceptable range has been added as a formal intermediate treatment target.
- Pediatric targets, reflected by different measuring scales and the addition of restoration of normal growth as a formal treatment target have been added.
- Restoration of QoL and absence of disability have been added to EH as long-term targets.
- Transmural healing in CD and histological healing in UC have been newly recognized as important adjunctive measures but were not endorsed as formal new treatment targets.

Conclusions:

STRIDE-II confirms that the most important long-term achievable treatment targets for patients with IBD are clinical remission, EH, restoration of QoL, and absence of disability. Symptomatic relief has been determined as an immediate goal, acknowledging that this is rated highest by patients in studies. With the accumulating clinical evidence, serum and fecal biomarkers are endorsed as intermediate medium-term feasible treatment goals, meaning that at times treatment could be revisited solely based on these tests, to facilitate care in the clinic setting.

Source: Turner D et al; International Organization for the Study of IBD. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021 Apr;160(5):1570-1583.

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AGA Clinical Practice Update on the Management of Refractory Helicobacter pylori Infection: Expert Review

Introduction:

Helicobacter pylori infection is one of the most common chronic bacterial infections worldwide. It affects approximately half of the global population. H pylori is a World Health Organization-designated carcinogen and the strongest known risk factor for non-cardia gastric adenocarcinoma and causally linked to peptic ulcer disease. Even though only 1% to 3% of infected individuals will develop malignant complications, H pylori accounts for 15% of the total cancer burden globally, with up to 89% of all gastric cancer attributable to H pylori infection. Accordingly, all major gastroenterological societies recommend that H pylori be eradicated in individuals who test positive. Downstream consequences of failed treatment include clinical complications related to persistent H pylori infection and repeated exposure to antibiotics and high-dose acid suppression, generation of antibiotic resistance in H pylori and other organisms, as well as the associated direct and indirect costs to the health care system. Because the likelihood of successful eradication decreases with each subsequent therapeutic attempt, every effort should be made to address factors that might contribute to eradication failure. Several guidelines exist to help providers choose regimens to eradicate H pylori on the first attempt and also include advice on management after initial treatments fail.

BEST PRACTICE ADVICE STATEMENTS

- The usual cause of refractory Helicobacter pylori infection (persistent infection after attempting eradication therapy) is antibiotic resistance. Providers should attempt to identify other contributing etiologies, including inadequate adherence to therapy and insufficient gastric acid suppression.

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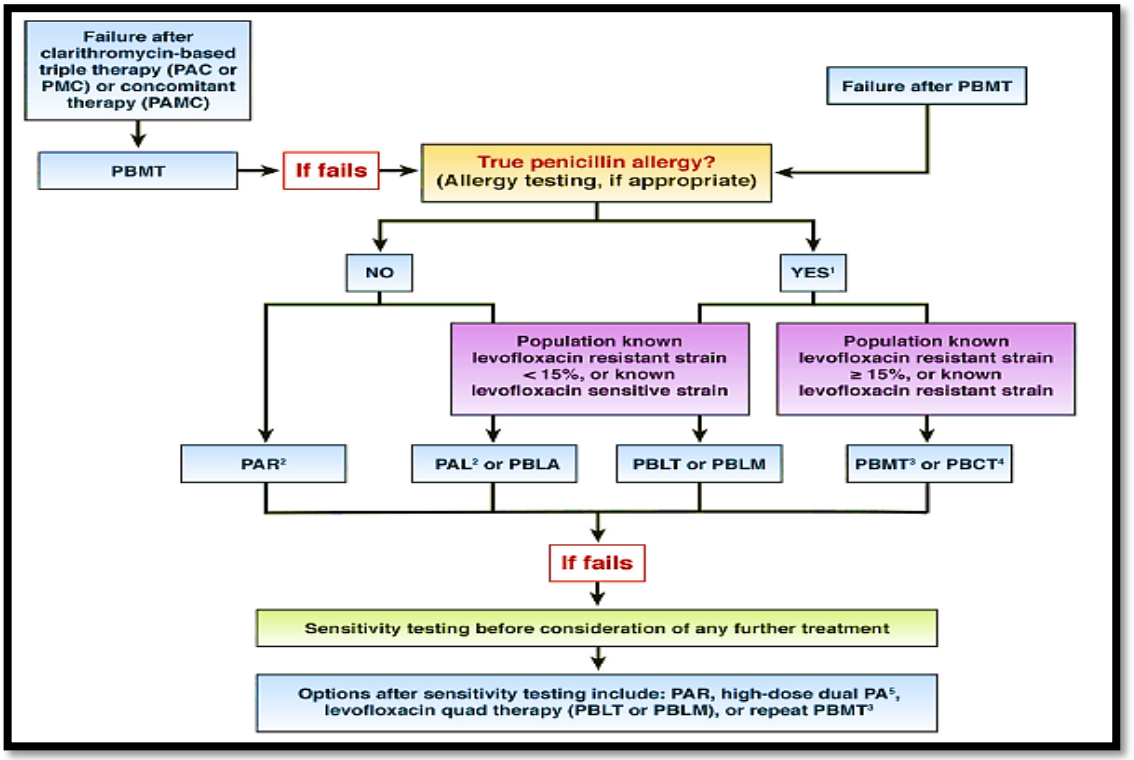

- Providers should conduct a thorough review of prior antibiotic exposures. If there is a history of any treatment with macrolides or fluoroquinolones, then clarithromycin- or levofloxacin-based regimens, respectively, should be avoided given the high likelihood of resistance. By contrast, resistance to amoxicillin, tetracycline, and rifabutin is rare, and these can be considered for subsequent therapies in refractory H pylori infection.
- Eradication regimens for H pylori are complex and might not be fully comprehended by patients. Barriers to adherence should be explored and addressed prior to prescribing therapy. Providers should explain the rationale for therapy, dosing instructions, expected adverse events, and the importance of completing the full therapeutic course.
- If bismuth quadruple therapy failed as a first-line treatment, shared decision making between providers and patients should guide selection between (a) levofloxacin- or rifabutin-based triple-therapy regimens

with high-dose dual proton pump inhibitor (PPI) and amoxicillin, and (b) an alternative bismuth-containing quadruple therapy, as second-line options.

- When using metronidazole containing regimens, providers should consider adequate dosing of metronidazole (1.5–2 g daily in divided doses) with concomitant bismuth therapy, because this may improve eradication success rates irrespective of observed in vitro metronidazole resistance.
- In the absence of a history of anaphylaxis, penicillin allergy testing should be considered in a patient labeled as having this allergy in order to delist penicillin as an allergy and potentially enable its use. Amoxicillin should be used at a daily dose of at least 2 g divided 3 times per day or 4 times per day to avoid low through levels.
- Inadequate acid suppression is associated with H pylori eradication failure. The use of high dose and more potent PPIs, PPIs not metabolized by CYP2C19, or potassium-competitive acid blockers, if available, should be considered in cases of refractory H pylori infection.
- Longer treatment durations provide higher eradication success rates compared with shorter durations (eg, 14 days vs 7 days). Whenever appropriate longer treatment durations should be selected for treating refractory H pylori infection.
- In some cases, there should be shared decision making regarding ongoing attempts to eradicate H pylori. The potential benefits of H pylori eradication should be weighed carefully against the likelihood of adverse effects and inconvenience of repeated exposure to antibiotics and high-dose acid suppression, particularly in vulnerable populations, such as the elderly.
- After 2 failed therapies with confirmed patient adherence, H pylori susceptibility testing should be considered to guide the selection of subsequent regimens.
- Compiling local data on H pylori eradication success rates for each regimen, along with patient demographic and clinical factors (including prior non-H pylori antibiotic exposure) is important. Aggregated data should be made publicly available to guide local selection of H pylori eradication therapy.

Conclusion

H pylori management has become increasingly challenging due to declining eradication success rates coupled with increasing antibiotic resistance, resulting in more H pylori infections that are now refractory to first-line

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therapies. Accordingly, this CPU was developed to provide practitioners with practical advice on how to manage patients whose initial H pylori treatment was unsuccessful. When considering the major public health implications associated with persistent H pylori infection with respect to disease and treatment-related complications and cost, there is a clear need to prioritize systematic approaches to improve rates of successful H pylori eradication with the least number of therapeutic attempts.

Source: Shah SC, Iyer PG, Moss SF. AGA Clinical Practice Update on the Management of Refractory Helicobacter pylori Infection: Expert Review. Gastroenterology. 2021 Apr;160(5):1831-1841.

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Gastrointestinal symptoms as first remarkable signs of ANCA-associated granulomatosis with polyangiitis: a case report and reviews

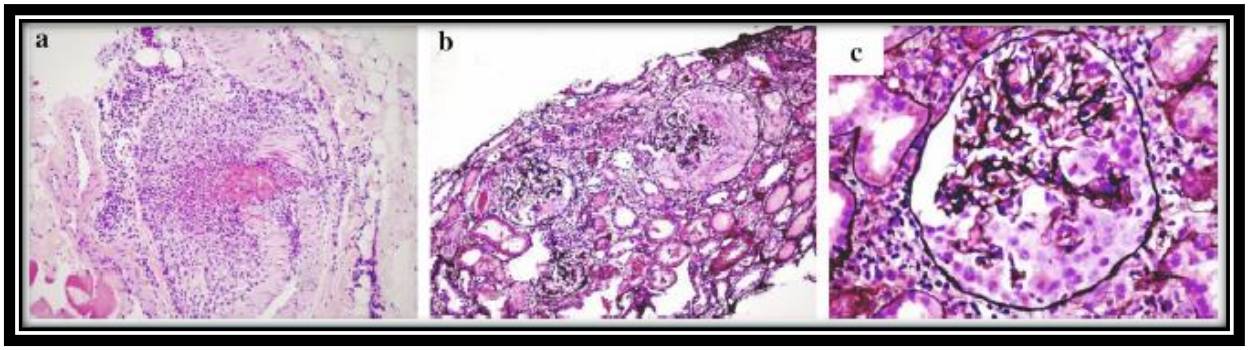
Introduction

Systemic vasculitis can produce a wide variety of clinical manifestations depending on the localization of the affected vessels, and often recognized only when severe conditions and rapid progression are present. ANCA-associated vasculitis is a necrotizing vasculitis with a few or no immune deposits in vessel walls (called pauci-immune), and usually associated with circulating antineutrophil cytoplasmic autoantibodies (ANCAs), however ANCA positivity is not mandatory. Based on the clinical and pathological findings, there are three types of ANCA-associated small-vessel vasculitis: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome). Because of the wide variety of the symptoms, ANCA associated vasculitis is challenging to be recognized even for experienced physicians. Delay of the adequate immunosuppressive therapy can accelerate the progression of the disease.

Case presentation

An 18-year-old, previously healthy white male patient was admitted to Nephrology Department with elevated serum creatinine levels. His symptoms started 2 weeks ago with severe abdominal pain, vomiting, hematemesis, and diarrhoea and was examined by two other hospitals. At the first hospital, CT (computer tomography) scan showed ileal wall thickening, based on the result of the CT scan, laboratory tests (C-reactive protein 149 mg/L) and the symptoms, inflammatory bowel disease (IBD) was diagnosed. The recommended therapy was sulfasalazine, methylprednisolone, and metronidazole. At first symptoms, kidney function was normal with a 90 μmol/L serum creatinine level and a 5.9 mmol/L BUN (blood urea nitrogen) level, although microhaematuria was detected (no sediment evaluation). Abdominal pain was worsened, so 10 days later, patient was admitted to the second hospital, where the total number of the white blood cells (21.3 × 109/ L), C-reactive protein (137 mg/L) and serum creatinine level (198 μmol/L) found elevated. Blood was not detected in the stool but calprotectin level, one of the potential indicators of IBD, was elevated (776 μg/g). The patient's renal function started to decline rapidly reaching a serum creatinine level of 429 μmol/L in 5 days. Microscopic examination of

the urinary sediment showed dysmorphic red blood cells. He developed anaemia with a haemoglobin level of 105 g/L. Abdominal ultrasound examination could not find any bowel wall thickening but found hyperechoic enlarged kidneys. The patient was transferred to Nephrology Department for further diagnostics. At the Nephrology Department, anti-proteinase 3 ANCA (PR3-ANCA) positivity (461 U) was detected, and urgent kidney biopsy showed pauci-immune, crescentic glomerulonephritis with the signs of vasculitis.



Signs of small-vessel vasculitis and crescentic glomerulonephritis in the patient's kidney biopsy sample. Inflammation of a small arteriole close to the renal capsule with fibrinoid necrosis. Magnification: × 200, haematoxylin–eosin (a). Two affected glomeruli with fibrinoid necrosis and crescent formation. Magnification: × 200, Jones' stain (b). Crescent formation in a glomerulus. Magnification: × 600, Jones' stain (c)

Based on these results, ANCA-associated vasculitis with rapidly progressive glomerulonephritis was diagnosed, and high dose intravenous (IV) methylprednisolone (500 mg/day for 3 days followed by slow dose reduction), IV cyclophosphamide (500 mg) and plasma exchange therapy were commenced with continuing the previously administered anti-hypertensive and proton-pump inhibitor therapy. Trimethoprim/sulfamethoxazole therapy was started according to the recommendation. Because of the progressive renal function decline, haemodialysis therapy was started on the fifth day of admission. The patient had a 67 g/L of haemoglobin level on the fifth day of admission; therefore, blood transfusion was performed. In search of the cause of anaemia, examinations were done to exclude extrarenal bleeding. Several stool samples were tested for blood, which were mostly negative, with one slightly positive sample (regular Weber test). An upper gastrointestinal endoscopy was performed, which showed normal oesophagus, stomach and duodenum without any sings of bleeding or inflammation. Clinically, the patient did not have bleeding from the respiratory tract. Chest X-ray and high-resolution CT scan were performed, which showed small nodules and ground glass opacity signs in a small area of the right lower lobule of the lung. Examination at the otorhinolaryngology

department found some ulcers on the nasal septum. Haemolysis was also excluded, and erythropoietin and Vitamin B12 injections were performed because of the renal disease and proven Vitamin B12 deficiency. Based on the criteria of vasculitis (clinical symptoms, nasal ulceration, necrotising glomerulonephritis, elevated PR3-ANCA levels), GPA was diagnosed. The patient was discharged on the 24th day after admission, after second administration of IV cyclophosphamide. Three days later, patient was admitted to hospital because of an early morning haematochezia with severe fatigue. Patient had epigastric abdominal pain the day before. With physical examination, the patient was pale with a new systolic murmur, with a mild epigastric and umbilical tenderness. The urgent laboratory test showed severe anaemia with a haemoglobin level of 36 g/L. With continuing haematochezia and haematemesis, the patient presented in a rapidly progressive haemorrhagic shock. Proton-pump inhibitor therapy started IV immediately. To stabilize the patient, 4500 ml crystalloid solution, several transfusions (17 units of red blood cell concentrates, 4 units of fresh frozen plasma and 24 units of platelet concentrates) were needed during the day and tranexamic acid was also administered. Gastroscopy was performed, during which "spurting" arterial bleeding of the duodenum was found. The bleeding was controlled with three clips placed on the artery. The patient stayed conscious and normotensive, the haemoglobin level could be increased to 67 g/L, and for further observation, he was transferred to the intensive care unit of our hospital. At the intensive care unit, 2 days later the bleeding restarted next to the clips, and the patient needed surgery to suture the artery. Three days after the first surgery, a reoperation was needed because of the perforation of the duodenum.

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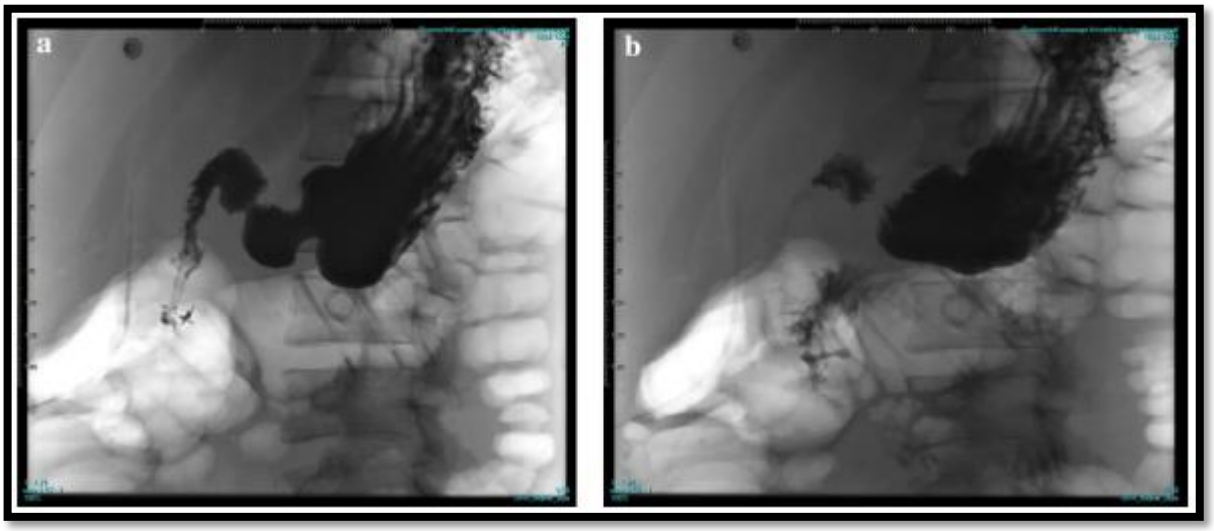

Contrast radiography of the upper gastrointestinal tract 3 days after the surgery. Early contrast radiography of the stomach (a). Late contrast radiography with contrast agent diffusion next to the clipped duodenum (b)

could be administered, and haemodialysis therapy could be terminated. After this, the cyclophosphamide therapy was continued. After 10 days of observation patient was discharged.

Conclusion:

Only a few cases where GI symptoms were the first signs of GPA. Therefore, the differential diagnostics of GI bleeding should always consider ANCA-associated vasculitis as a rare but serious condition. The proper microscopic examination of urinary sediment is a non-invasive and important tool in the diagnostics of kidney diseases, which in the case of (micro) haematuria should be performed. Additionally, gastrointestinal bleeding is a rare but potential lethal complication of vasculitis. Consequently, investigating the patients diagnosed with GPA for gastrointestinal bleeding during the treatment, especially if there were gastrointestinal symptoms among the first clinical signs of the vasculitis. This forced investigation for gastrointestinal bleeding could prevent the patients from potentially lethal complication of vasculitis.

Source: Ledó N, Pethő ÁG. Gastrointestinal symptoms as first remarkable signs of ANCA-associated granulomatosis with polyangiitis: a case report and reviews. BMC Gastroenterol. 2021 Apr 8;21(1):158.

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