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Severe ulcerative colitis

Ciężki rzut wrzodziejącego zapalenia jelita grubego

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Słowa kluczowe
wrzodziejące zapalenie jelita grubego, ciężki rzut wrzodziejącego zapalenia jelita grubego, nieswoiste choroby zapalne jelit

Summary

Ulcerative colitis is a chronic, intermittent inflammatory bowel disease usually involving the rectum and, in majority of patients, proximal bowel segments. Left-sided and extensive colitis may present as severe colitis, with numerous bloody stools, systemic inflammation symptoms including tachycardia and pyrexia, anemia and laboratory markers of inflammation. Severe colitis is a life-threatening condition and indication for hospital treatment. Multidisciplinary care by gastroenterologist, surgeon and radiologist, begun at the admission, is necessary to achieve uncomplicated recovery. Following exclusion of exacerbating factors, and infections in particular, systemic corticosteroids are given as the first line therapy. Fluids and electrolytes supplementation and antithrombotic therapy are the other essential measures. Lack of response to steroids is an indication to second line of immunosuppressive drugs (infliximab or cyclosporine) or surgical treatment. Possible contraindications to these drugs should be revised immediately at the admission. In addition to lack of response to first or second line of pharmacologic treatment, indications to proctocolectomy include uncontrolled bleeding and toxic megacolon.

Streszczenie

Wrzodziejące zapalenie jelita grubego jest przewlekłą nieswoistą chorobą zapalną jelit, która zwykle zajmuje odbytnicę, a u większości pacjentów także proksymalne odcinki jelita grubego. Lewostronne i rozległe wrzodziejące zapalenie jelita grubego może przebiegać w postaci ciężkiego rzutu z licznymi krwistymi wypróżnieniami, objawami układowymi, takimi jak tachykardia i gorączka, oraz laboratoryjnymi wykładnikami stanu zapalnego. Ciężki rzut wrzodziejącego zapalenia jelita grubego jest stanem zagrożenia życia i wskazaniem do hospitalizacji. Multidyscyplinarna opieka nad pacjentem z udziałem gastroenterologa, chirurga i radiologa, od chwili przyjęcia do szpitala, jest niezbędna do prawidłowego postępowania w tym stanie. Po wykluczeniu czynników zaostrzających zapalenie jelita, przede wszystkim infekcyjnych, w leczeniu pierwszego rzutu podaje się kortykosteroidy. Inne niezbędne elementy postępowania to suplementacja płynów i elektrolitów oraz leczenie przeciwzakrzepowe. Brak odpowiedzi na kortykosteroidy jest wskazaniem do leczenia immunosupresyjnego drugiego wyboru (infliksymabem lub cyklosporyną) lub leczenia operacyjnego. Przeciwwskazania do leczenia immunosupresyjnego należy rozważyć już w chwili przyjęcia pacjenta do szpitala. Oprócz braku odpowiedzi na leczenie farmakologiczne, wskazaniem do proktokolektomii jest nieopanowane krwawienie z jelita grubego oraz toksyczne rozszerzenie okrężnicy.

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease affecting large bowel's mucosa. It usually affects the rectum and in continuity, differing in length, proximal parts of large bowel.

The extent of disease is usually described using Montreal classification, presented in table 1 (1). This classification takes into account a maximum extent of inflammatory altered mucosa, as seen in colonoscopy.

Disease activity, or otherwise exacerbation severity, is defined by Truelove and Witts scale (tab. 2) (2), based on several clinical and laboratory parameters, however it is advisable to endoscopically confirm the presence of active inflammation in large bowel.

Table 1. Montreal classification for UC distribution.

Term	Distribution	Description
E1	Proctitis	Involvement limited to the rectum
E2	Left-sided	Involvement limited to the colon distal to the splenic flexure
E3	Extensive	Involvement extends proximal to the splenic flexure, including pancolitis

Table 2. Truelove and Witts' criteria of UC exacerbation severity with ECCO modification.

Parameter	Mild	Moderate	Severe
Bloody stools per day	< 4	≥ 4	≥ 6
Pulse	< 90/min	≤ 90/min	> 90/min
Temperature	< 37.5°C	< 37.8°C	< 37.8°C
Hemoglobin	< 11.5 g%	≥ 10.5 g%	< 10.5 g%
ESR	< 20 mm/h	≤ 30 mm/h	> 30 mm/h
CRP	normal	≤ 30 mg/l	> 30 mg/l

A severe exacerbation is defined as 6 or more bloody stools per 24 hours and at least one systemic symptom (tachycardia, fever, anemia, high level of CRP or increased ESR). Severe colitis is a life-threatening condition and an indication for urgent hospitalization in order to perform necessary diagnostic procedures and to initiate intensive treatment.

PATIENT ASSESSMENT AT HOSPITAL ADMISSION

It is crucial to take a medical history of present exacerbation symptoms, including extraintestinal manifestations, probable causative factors, current medical treatment (including medications for other conditions) and the course of previous exacerbations. During physical evaluation it is necessary to assess vital signs, hydration, bloating, peristalsis, pain and presence of peritoneal signs. Conditions other than inflammatory bowel disease are necessary to be considered in differential diagnosis of any abdominal symptoms.

Laboratory work-up, which is includes: blood count, basic biochemical tests, albumin ratio, CRP level and ESR. Moreover it is crucial to assess microbiological status, as infections may be a cause of UC exacerbation or may occur simultaneously. This includes *Clostridium difficile* toxin in stool sample, basic stool culture and cytomegalovirus (CMV) status (either IgG and IgM antibodies, or blood sample PCR for CMV DNA).

Abdominal x-ray should be performed immediately after admission in order to exclude large bowel perforation or toxic megacolon. It is advised to perform an abdominal computed tomography or magnetic resonance, preferably with oral contrast intake (enterography) in patients without prior diagnosis of inflammatory bowel disease to look for Crohn's disease as a possible cause.

Sigmoidoscopy without prior preparation should be performed shortly after admission in order to assess the endoscopic activity and extent of disease and to perform a forceps biopsy for CMV infection evaluation. Findings typical for pseudomembranous colitis are an indication to start *C. difficile* infection treatment, however lack of typical findings does not exclude this infection. When deep ulcerations are present, a full colonoscopy should be avoided due to increased risk of perforation and toxic megacolon. Suspicion of the latter, based on radiological findings, is a contraindication to endoscopy.

Approximately 30% of the patients with severe exacerbation of UC do not respond to conventional treatment (intravenous corticosteroids), therefore preparation for second line treatment should start at the admission, so that when first choice treatment fails, the second choice treatment could be started immediately (3, 4). Contraindications to any considered drugs should be excluded. Hypomagnesaemia and hypocholesterolemia are contraindications to cyclosporine treatment, because of increased convulsions risk. Exclusion of tuberculosis (either overt or latent) by chest x-ray and IGRA (interferon-gamma reactivity assay) is necessary prior to infliximab treatment. It is crucial to assess cardiologic status.

Gastrointestinal surgeon's consultation should be obtained on admission and immediately after performing all examinations necessary to assess the exacerbation severity, as surgeon should be aware of the patient and take part in therapeutical decisions in case of deterioration.

FIRST CHOICE PHARMACOLOGICAL THERAPY

UC prognosis significantly improved in 1950's, when corticosteroids were introduced to pharmacotherapy (2). Mortality due to severe exacerbation was reduced from 75% in 1933 to 7% in 1950's, whereas nowadays it has been reduced to 2.9%, or even less than 1% in referral centers. Colectomy risk during hospitalization due to severe exacerbation is 9%, however the total colectomy risk reaches 27% (3-6).

The patient admitted to the hospital due to severe exacerbation should receive intravenous methylprednisolone (40 to 60 mg daily, however no more than 1 mg per 1 kg of body mass), even if oral corticosteroids were administered prior to admission. A response to such treatment occurs in approximately 60% of patients and clinical improvement is very fast – usually remission occurs in 5 to 7 days (7). Intravenous corticotherapy usually lasts 7 to 10 days and the following treatment is based on oral corticosteroid intake, either 40 mg of prednisolone or 32 mg of methylprednisolone daily. After next 10 to 14 days the daily dose is reduced by 5 mg or 4 mg respectively per week, and gradually discontinued.

Intravenous hydration and electrolyte supplementation is of crucial importance. It should be noted that hypokalemia and hypomagnesaemia rise susceptibility to toxic megacolon.

Patients malnourished and those not able to ingest orally should receive nutritional treatment, preferably enteral. Parenteral nutrition should be restricted to patients with lack of tolerance to the former approach. A nil per os diet does not improve the outcome.

There is an increased risk of venous and arterial thrombosis in patients with inflammatory bowel

disease. The risk rises when disease is active, therefore during severe exacerbation the antithrombotic prophylaxis is necessary. Subcutaneous low-molecular-weight heparin is most commonly used, despite intestinal bleeding, which is a common symptom of severe exacerbation (8).

The hemoglobin concentration should be maintained over 8-10 g/dl.

Antibiotic therapy does not improve the outcome and should be employed only on suspicion or confirmation of infective cause of exacerbation or perioperatively.

Mesalazine, sulfasalazine and other agents containing 5-aminosalicylic acid do not belong to severe UC exacerbation treatment and they can be withdrawn until clinical improvement is achieved with other agents.

MONITORING THE RESPONSE TO TREATMENT

Patients condition should be closely monitored with physical examination, vital signs (at least twice daily), blood count, serum electrolytes, CRP and albumin levels, and, in selected cases, the colon diameter in radiological examination.

A prospective study from Oxford in a group of 51 succeeding patients with severe UC exacerbation that received intravenous corticosteroids has shown that if after three days of treatment the stool frequency exceeds 8 per 24 hours, or is between 3 and 8 per 24 hours and C-reacitve peptide level exceeds 45 mg/dl, the probability of colectomy during current hospitalization is 85% (9).

Other negative prognostic factors include hypoalbuminemia, ulcerations in the mucosa of large bowel (found during endoscopy), colon diameter of more than 5.5 cm and mucosal islands found in abdominal x-ray examination.

SECOND-LINE PHARMACOLOGICAL TREATMENT

Basing on the ECCO guidelines, response to corticotherapy should be evaluated around 3rd day of treatment (11). Lack of response is an indication to colectomy or to the second-line treatment (otherwise called rescue therapy) with either cyclosporine, infliximab or tacrolimus. No response to rescue therapy is an indication to colectomy (11).

A third-line pharmacotherapy (e.g. infliximab treatment for patient that did not respond to cyclosporine) may be taken into consideration in referral centers, **however it is generally not recommended, because the risk of severe infections rises up to 20%** (12, 13).

Two randomized studies showed, that cyclosporine is more effective than placebo in steroid-refractory patients. The drug is efficient starting from dosage of 2 mg per kg per day (4 mg dosage is equally effective, however more toxic). **Approximately 80% of patients show clinical response to cyclosporine treatment after approximately 4 days** (14-16). It is crucial to monitor blood levels of the drug during treatment, due to narrow therapeutic window of 250 to 350 nanograms per ml. Cyclosporine is contraindicated in active infection, renal failure, untreated arterial hypertension and when hypomagnesaemia or hypocholesterolemia are present. Magnesium and creatinine levels should be also monitored. When clinical response is achieved, the dosage route should be changed from intravenous to oral. Moreover, thiopurine analogue treatment should be started, in order to stop cyclosporine treatment after 3 months – due to cyclosporine toxicity, it should not be used in chronic treatment. In case of patients who were previously treated with thiopurine analogues, cyclosporine probably would only postpone the colectomy, rather than avert, therefore cyclosporine usage in such clinical setting is arguable. After achieving initial response to cyclosporine, probability of averting the colectomy during the following 2-3 years is 40 to 50% (17).

A randomized study showed that tacrolimus is more effective than placebo in 27 patients with severe UC exacerbation (18). Other studies showed that both clinical response and percentage of patients with preserved bowel in long-term observation are similar to those treated with cyclosporine. Tacrolimus therapy also requires monitoring drug levels. It is worth mentioning, that this drug is not registered to use in UC patients in EU.

A randomized, placebo – controlled study showed that infliximab is efficient in treatment of severe UC exacerbation in dose of 5 mg per kg of body weight (19). Moreover, this agent has a confirmed effect in patients refractory to conventional oral treatment (20). Contraindications to infliximab therapy include active infection, NYHA grade III or IV heart failure, past or current demyelination disorders and malignancies (including lymphoproliferative). Exclusion of overt or latent tuberculosis is needed before drug administration. When response occurs to treatment, following doses are administered 2 and 6 weeks after the first dose. If the patient did not receive thiopurine analogue, such treatment should be started immediately after clinical response for sustaining remission. In case of previous thiopurine intake, a maintenance infliximab treatment should be considered.

An open-label, randomized study comparing effectiveness of cyclosporine and infliximab in the group of 115 patients, who did not receive any of these drugs nor azathioprine, was recently conducted (21). After achieving response to intravenous treatment, azathioprine was introduced on 7th day. Treatment failure was defined as no clinical response on 7th day, relapse between 7th and 98th day, an adverse effect leading treatment, colectomy or death. The effectiveness of the drugs was similar, as treatment failure was observed in 60% patients receiving cyclosporine and 54% receiving infliximab. In clinical practice the choice of drug to use is based on contraindications, physician's experience, access to laboratory monitoring cyclosporine level and treatment costs.

TOXIC MEGACOLON

Toxic widening of colon is diagnosed when, in patient with systemic symptoms of severe UC exacerbation

(also known as fulminant colitis), the colon diameter is enlarged. This may lead to large bowel's perforation.

Classical definition of fulminant colitis is based on coexistence of at least three of four symptoms: body temperature higher than 38.5 degrees Celsius, tachycardia higher than 120 beats per minute, leukocytosis higher than 10.5 thousand per cubic mm or anemia and at least one of following: dyselectrolitemia, dehydration or consciousness disturbances. **If, additionally, colon diameter is larger than 5.5 cm in abdominal radiogram, toxic megacolon is diagnosed.** Patients with *C. difficile* infection, after barium enema, or patients given narcotic, anticholinergic and antidiarrheal drugs present a higher risk of toxic megacolon development.

Daily abdominal radiographic examination is necessary to monitor the response to treatment of severe UC exacerbation. Confirmation of widening of the colon may predate large bowel perforation. In such case, it is necessary to stop administration of drugs, which may be associated with toxic megacolon development, correct the deficiencies and, due to increased risk of microperforation, administer wide-spectrum antibiotic. **However, there is a very small chance of successful pharmacological treatment, therefore urgent surgical consultation should be obtained and, if needed, an urgent colectomy performed.**

SURGICAL TREATMENT

Indications for surgical treatment in patients with severe UC exacerbation are as follows: no response to pharmacological treatment, toxic megacolon, perforation or hemorrhage persisting in spite of the treatment. Bowel perforation in UC patients can occur without widening the bowel's lumen and typical peritoneal signs. Patients in need of surgery should be quickly identified, because surgery delay has a negative impact on its outcome.

UC patients with severe disease course and resistance to pharmacological treatment or patients with dysplasia in large bowel should undergo an elective surgery performed. Two methods apply: proctocolectomy with distal ileostomy or with creation of intestinal pouch, which secures digestive tract continuity.

If the operation is urgent, as in severe exacerbation with no response to pharmacological treatment, proctocolectomy with consecutive restoration of digestive tract continuity is usually performed in three stages. The first procedure, which is meant to treat life-threatening condition, is colectomy with distal ileostomy and leaving the rectal stump. After patients' recovery and improvement of nutritional status, the second procedure is performed: the removal of rectal stump with leaving the ileostomy or with creation of the intestinal J-pouch and the loop ileostomy, which reduces the risk of pouch leakage and pelvic inflammation. The third procedure is closure of ileostomy. Older (more than 60 years) is not a contraindication for such surgery, on condition that the sphincter function is not impaired (based on preoperative functional examinations).

SUMMARY

Patient admitted to the hospital due to UC exacerbation needs a full inflammation severity assessment, exclusion of intestinal suprainfections and systemic corticotherapy. Regular assessment of response to treatment and prevention of complications (e.g. toxic megacolon or deep vein thrombosis) are important elements of treatment. Lack of response to corticosteroids is an indication to treatment with either cyclosporine or infliximab, usually in combination with azathioprine. Lack of clinical improvement after pharmacological therapy is an indication to colectomy. a detailed plan of the out-patient follow-up should be prepared on patient's discharge.

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