Intensive intravenous regime for acute severe colitis

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ABSTRACT

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Acute severe exacerbation of ulcerative colitis is a potentially life threatening medical emergency. The management of acute severe ulcerative colitis depends on early recognition and prompt initiation of intensive intravenous treatment along with continuous objective monitoring for possible medical failure. The intensive regime is the accepted standard of care. This includes primarily a) intravenous corticosteroids, b) intravenous supportive management, and d) intravenous antibiotics in instances. This review discusses the timing, duration and dosage of the intensive intravenous treatment including the evidence based protocol for effective monitoring to enable timely escalation to second line therapy & colectomy.

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Introduction

Ulcerative colitis (UC) is a complex disorder with diffuse colonic mucosal inflammation causing recurrent symptoms and morbidity. Acute severe exacerbation of ulcerative colitis (ASC) is a potentially life-threatening medical emergency, and requires prompt and effective management. The lifetime risk of a severe exacerbation is estimated to be around 15% and is significantly higher in pediatric-onset disease (50-80% vs. 8-20%).^{1,2,3} The management of ASC depends on early recognition and prompt initiation of intensive intravenous treatment along with continuous objective monitoring for possible medical failure.

Prior to the corticosteroid era, a severe attack of UC was associated with high mortality. First year mortality from ASC was found to 75% and 22% in studies from Birmingham (1933) and Oxford (1950), respectively.⁴ The landmark work of Truelove in 1955 showed a reduction in mortality from 24% in the placebo group to 7% in the steroid-treated group.⁵ A similar efficacy was reported by Lennard-Jones et al.⁶ The mortality rates subsequently came down to <1% with timely second-line medical rescue therapy or colectomy.⁷

Today; an intensive regime including intravenous corticosteroids has become the standard of care. However, despite the undisputed improved outcome with such intensive intravenous regime, the dose and duration of treatment are yet to be optimized. This review discusses the intensive intravenous treatment for ulcerative colitis including the evidence-based protocol for effective monitoring of disease progress and treatment escalation when needed.

The time to initiate intensive intravenous treatment

Acute severe ulcerative colitis, (ASC) is usually defined as per the original classification proposed by Truelove and Witts.⁵ They suggested that six or more bowel motions per day associated with one or more of the following: temperature >37.8°C, large amounts of rectal bleeding, heart rate >90 beats per minute, hemoglobin <10.5 g/dL or an erythrocyte sedimentation rate (ESR) >30 mm/h indicate severe colitis. These criteria have subsequently been validated and allow

simple, rapid stratification of ulcerative colitis outpatients.⁸ Unprepared sigmoidoscopy with minimal inflation also provides additional information on disease severity. Endoscopic scoring systems particularly the Baron score have been helpful.^{9,10} It is generally accepted that all patients fulfilling criteria of ASC must be admitted to the hospital and instituted on intensive intravenous treatment.

The intensive intravenous regime

The intensive intravenous regime for acute severe ulcerative colitis comprises of a) intravenous corticosteroids, b) intravenous supportive and preventive management, c) intravenous nutrition, and d) intravenous antibiotics.

Intravenous corticosteroids

Intravenous corticosteroids remain the first line of therapy for ASC ever since Truelove and Jewell¹¹ published their first trial 1974. Forty-nine patients were treated with intensive intravenous corticosteroids and 36 of 49 (73%) achieved complete remission by day 5. The role of IV corticosteroids has been validated and confirmed since then. A systematic review of 32 trials consisting of over 2000 patients treated with corticosteroids for acute severe UC between 1974 and 2006 showed an overall 67% response rate to steroids.¹²

A number of parenteral corticosteroids, including hydrocortisone, prednisolone, methylprednisolone, bethamethasone, and adrenocorticotrophic hormone, have been tried for the treatment of severe UC. No significant difference in response has been observed between the various formulations used.¹² However, there have been very few trials comparing different treatment regimens. A small study by Meyers et al compared adrenocorticotrophic hormone with hydrocortisone. Of the 31 patients who had not received any prior oral corticosteroids, ACTH induced remission in 63% vs. 27% with hydrocortisone. However in 35 patients who had received prior corticosteroids, 53% responded to hydrocortisone vs. 25% on ACTH.¹³

A daily dose equivalent to 400 mg hydrocortisone (100 mg four times daily) or 60 mg methylprednisolone is generally given. No studies examining the dose range of the various intravenous corticosteroids has been carried out for ASC. Limited data available does not suggest that higher doses are more effective; higher doses tend to expose the patient to greater

side effects. Suboptimal doses are less effective.¹⁴ A recent meta-analysis of response to corticosteroid treatment controlled for baseline disease severity showed no correlation between corticosteroid dose and colectomy rate, further confirming no significant advantage of increasing the dose beyond 60 mg methylprednisolone per day or equivalent.¹² Prednisolone or methylprednisolone are preferred at some centers because of less sodium-retention and potassium-wasting.

Bolus administration of corticosteroids as single or daily divided doses is standard practice. No other dosing regimens have been shown to be superior or safer to bolus dosing. Bossa et al randomized 66 patients to receive up to 60 mg methylprednisolone per day by either twice a day bolus or continuous infusion. There were no differences in treatment response or adverse effects between the two groups. About 50% patients in each group achieved clinical remission by day 7, and 35% of the continuous infusion group had undergone elective colectomy by one year compared to 28% in the bolus group.¹⁵ Two prospective studies have shown that pulsed therapy can be effective for treatment of UC.^{16,17} However, both these studies used unusually high corticosteroid doses and did not have a control arm. With no obvious difference in terms of efficacy or safety, the selection of a parenteral steroid and its dosing regimen is often based on the physician and center's experience.

Intravenous supportive and preventive therapy

Intravenous corticosteroids remain the cornerstone of ASC treatment. However supportive management is equally essential. This includes intravenous fluids and electrolytes, blood transfusions and thromboembolism prophylaxis. Majority of hospitalized patients with ASC need intravenous fluids and correction of electrolyte imbalance. Serum potassium is particularly important since hypokalemia predisposes to colonic dilatation. Serum potassium >4 mmol/L is considered adequate and most patients need routine potassium replacement at 60 mmol/L over 24 h.¹⁸ Patients with hemoglobin <10 g/dL should be advised a blood transfusion. This is important because oral iron therapy can aggravate mucosal inflammation induced by oxygen free radicals ('Fenton' reaction) and is best avoided.^{18,19} Antidiarrhoeal agents, anticholinergics and opiates are to be avoided as they can decrease colonic motility thereby increasing the risk of colonic dilatation and toxic megacolon.^{8,20}

Intravenous heparin and low molecular heparin therapy have been advocated for acute severe colitis to prevent the development of venous thromboembolism.^{8,21} However the risk is age dependant and is much higher in older patients. In a recent analysis, 27 cases of deep vein thrombosis per 10,000 person-years were noted in the 0–20 year age group (95% CI: 3.4–29.3) vs. 207 per 10,000 in the >60 year age group.²² Hence routine heparin prophylaxis is perhaps not justified in children. It is important to clarify that numerous meta-analyses have shown that heparin has no role in inducing remission and is not a therapeutic adjunct.^{23,24}

Intravenous nutrition

Three prospective RCTs have compared TPN and bowel rest with either a standard oral diet or enteral nutrition as adjunct therapy with intravenous corticosteroids. There was no difference in the need for colectomy between the groups.^{25–27} There is no evidence that keeping patients on complete bowel rest with total parenteral nutrition or elimination diets improves the course of TPN is associated with complications such as pneumothorax, electrolyte imbalance and sepsis. However, continuous nutritional assessment, including measuring daily weight and calorie counts, is essential for optimization of nutritional status. Short-term parenteral nutrition should be advised if severe nausea and vomiting are present, or in the presence of severe abdominal pain when the patient is unable to tolerate oral diet. Total enteric nutrition with polymeric formula has been found to be safe and well-tolerated in a small prospective cohort of severe UC.²⁸ However, the results of enteral administration of formulated foods which is known to work in paediatric Crohn's disease could not be replicated in ASC. Milk and milk products (lactose) restriction is not recommended routinely and is beneficial only in individuals with lactose intolerance.²⁹

Intravenous antibiotics

Several trials have shown that empiric use of intravenous antibiotics along with corticosteroids does not offer any additional benefit over corticosteroid treatment alone. Chapman et al randomized hospitalized patients with ASC to receive intravenous metronidazole 500 mg every 8 hours (n=19) or placebo (n=20) in addition to corticosteroids. The authors found no difference in outcome.³⁰ A second study randomized 39

patients to receive metronidazole 500 mg three times a day and tobramycin 4 mg/kg in divided doses every 8 hours (n=19) or placebo (n=20) in addition to corticosteroids and found no difference in response.³¹ Another study investigated patients randomized to receive either intravenous ciprofloxacin 400 mg twice daily or placebo for 10 days in addition to corticosteroids.³² Like other studies no difference in treatment response was found. However, these studies were underpowered to detect an effect. Antibiotics are indicated in patients who develop signs of sepsis or have a high likelihood of infection due to an impending perforation or toxic megacolon. Metronidazole or vancomycin is also indicated in patients with concurrent *C. difficile* infection. Empiric antibiotic treatment should also be strongly considered if the patient presents with ASC and stool *C. difficile* cultures are pending.^{8,33}

Duration of intensive intravenous treatment and predicting need for salvage therapy

Around 30% of ASC patients will not respond to corticosteroids, and this figure has stayed remarkably constant over the years.^{7,11,34} Also, approximately 80% of patients who fail corticosteroids require a colectomy within next 10 years regardless of treatment.¹⁰ All clinical guidelines recommend a second-line salvage therapy in patients with no response to corticosteroids. A timely decision can significantly improve outcome.^{35,36} However the length of time that should be allowed for patients to respond to intravenous therapy is contentious. In 1974, Truelove and Jewell recommended colectomy if there was no response to intravenous corticosteroids after five days. This 5-day rule has been widely adopted. Others however have reported that steroids can be given safely up to 10 days thereby allowing patients more time to respond.³⁷ There appears to be no proven benefit of extending IV corticosteroids beyond 10 days.³⁸ The decision between colectomy or salvage therapy should be made within the first 3–5 days for a favorable outcome.

Simple clinical and laboratory variables are often used to predict response to corticosteroid therapy.^{12,39} The Travis criterion at day 3 of corticosteroid therapy is often used. Accordingly patients with a stool frequency of more than eight per day or a stool frequency of three per day plus a CRP >45 mg/dL have a 85% likelihood of requiring colectomy.³⁴ A time-bound approach for predicting steroid responsiveness has also been demonstrated in other studies. Lindgren et al prospectively studied admissions with ASC and suggested a mathematical

model to predict colectomy. A value of (number of stools in 24 hours + 0.143 CRP (mg/dL)) >8 in the model predicted a 72% colectomy rate.⁴⁰ Ho and colleagues did a retrospective analysis of ASC and identified certain criteria to score for predicting colectomy or need for rescue therapy. The number of stools (score 1-4), hypoalbuminaemia <30 g/L (score 1) and colonic dilatation >5.5 cm (score 4) were noted as predictors, with 85% of patients with a score of 4 or more requiring colectomy or second-line therapy.⁴¹

For children, the PUCAI (Pediatric UC Activity Index) is the only validated index of UC severity. In a prospective study of 128 hospitalized pediatric patients, the PUCAI scores at days 3 and 5 could predict response to steroids. Patient with PUCAI score >45 on day 3 were likely to fail steroids (negative predictive value >94%). A score >70 on day 5 reliably guided implementation of salvage therapy with a positive predictive value of 100% and high specificity.⁴² In addition, two studies have shown endoscopic severity to be a predictor of steroid failure and the need for colectomy,^{1,43} but a full length colonoscopy can increase the risk of perforation and is not recommended.

Conclusion

Approximately 15% of patients with UC experience an acute severe attack which requires hospital admission. The intensive intravenous regime is the standard of care for ASC patients. This includes intravenous corticosteroids together with fluid and electrolyte support. Intravenous antibiotics are not recommended unless there is obvious sepsis, impending perforation or toxic megacolon. Intravenous heparin is recommended in adults to prevent thromboembolic complications. A time-bound approach with assessment of response predictors is needed to ensure timely switch to second-line therapy with infliximab, cyclosporine or colectomy. Overall an intensive treatment with early, objective decision, made by an experienced multidisciplinary team for salvage therapy, is the key to successful management of acute severe colitis.

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