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Clinical profile and short-term outcomes of acute severe ulcerative colitis in Vietnam: insights from a resource-limited setting

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Abstract. – OBJECTIVE: Acute severe ulcerative colitis (ASUC) is a significant complication of ulcerative colitis, affecting roughly 25% of patients and increasing the risk of colectomy and hospital mortality. While intravenous steroids are a primary treatment, only 67% of patients respond, necessitating rescue therapy for non-responders. Data on ASUC in the Vietnamese population are scarce. This study aims to provide insights into the clinical characteristics and short-term outcomes of Vietnamese patients with ASUC.

PATIENTS AND METHODS: We conducted a prospective case series on ASUC patients admitted to the University Medical Center in Ho Chi Minh City from January 2021 to June 2023. Steroid response was assessed using the Travis Oxford criteria. We evaluated clinical features, in-hospital steroid response rates, endoscopic remission, and colectomy rates 12 months post-hospitalization.

RESULTS: Seventeen patients with a median age of 42 years (70.6% male) were included. The median time from symptom onset to diagnosis was six weeks, and 47.1% had a history of ulcerative colitis. Median CRP value was 75.8 mg/L, and 76.5% had fecal calprotectin concentrations above 800 µg/g. All patients had a Mayo endoscopic subscore of ≥2, with 12.5% showing deep ulcers. Eleven patients (64.7%) responded to in-hospital steroid treatment, while 6 (35.3%) required rescue therapy with infliximab or tofacitinib. After one year, 10 of 11 (90.1%) achieved mucosal healing, and no patients underwent colectomy.

CONCLUSIONS: Corticosteroids remain the cornerstone for initial ASUC therapy, though many patients do not respond. Anti-TNF agents and tofacitinib show potential benefits for those unresponsive to steroids. This study highlights the effectiveness of corticosteroids and biologics in managing ASUC in Vietnam.

Key Words:
Acute severe ulcerative colitis, Steroid, Infliximab, Tofacitinib, Vietnam.

Abbreviations

ASA: Aminosalicylic acid; ASUC: Acute severe ulcerative colitis; CMV: Cytomegalovirus; CRP: C-reactive protein; CT: Computed tomography; ESR: Erythrocyte sedimentation rate; IBD: Inflammatory Bowel Disease: IQR: Interquartile range; IV: Intravenous; MES: Mayo Endoscopic Subscore; OCTAVE: Oral Clinical Trials of Tofacitinib in Ulcerative Colitis; TNF-α: Tumor necrosis factor-alpha; UC: Ulcerative colitis; USA: United States of America; WBC: White blood cell; IFX: Infliximab; AZA: Azathioprine; CsA: Cyclosporin A; VDZ: Vedolizumab; HBV: Hepatitis B virus.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by continuous mucosal inflammation extending from the rectum to the colon[1]. Traditionally, UC has been more prevalent in Western countries; however, in recent decades, the incidence of UC has increased in regions such as Asia, including Vietnam, likely as a result of Westernized lifestyle changes[2]. Acute severe ulcerative colitis (ASUC) is a serious complication of UC, affecting approximately 25% of patients at some point during their disease course[3]. ASUC is associated with a significant risk of morbidity and mortality, with the need for colectomy remaining high despite advances in medical management. Although the introduction of biological therapies has improved outcomes in ASUC, colectomy rates during hospitalization

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remain as high as 21%, and at 12 months post-diagnosis, approximately 30%-35% of patients still require colectomy[4,5]. Intravenous corticosteroids remain the first-line therapy for ASUC[6,7]. However, approximately one-third of patients fail to respond adequately to steroids and require salvage therapy with agents such as infliximab or ciclosporin[7,8]. Tofacitinib, a Janus kinase inhibitor, has also emerged as a potential therapy for patients with steroid-refractory ASUC[9].

While substantial data exist regarding the clinical course and management of ASUC in Western populations, there is limited research on its presentation and outcomes in Southeast Asia, particularly in Vietnam. It is likely that genetic predispositions, environmental exposures, and disparities in healthcare access contribute to the variability in disease presentation and therapeutic outcomes observed in these regions. Moreover, managing ASUC in resource-constrained settings like Vietnam poses unique challenges due to the high costs and limited availability of biologic agents, such as infliximab and tofacitinib, which are often inaccessible to the broader patient population. Additionally, diagnostic and therapeutic protocols are not yet standardized, and the availability of advanced treatments is limited. Therefore, understanding these local factors is critical to developing optimal management strategies for ASUC in such settings. This study aims to elucidate the clinical characteristics, therapeutic approaches, and short-term outcomes of Vietnamese patients with ASUC. Through this investigation, we seek to inform future strategies for improving ASUC management in resource-limited healthcare environments.

Materials and Methods

Study Design

A prospective case series was conducted at the IBD unit of the University Medical Center of Ho Chi Minh City, a tertiary referral hospital in Vietnam, from January 2021 to June 2023. This design was chosen to provide detailed clinical insights and short-term outcomes in a specific patient population, especially in a resource-limited setting where large-scale studies are still impractical.

Study Participants

We included all patients aged 18 years or older who were admitted with a first episode of acute severe ulcerative colitis (ASUC). Qualified gastroenterologists confirmed the diagnosis of ulcerative colitis (UC) based on a combination of clinical evaluation, endoscopic findings, histological results, and radiological or biochemical evidence[1]. Patients with recurrent ASUC admissions were excluded to focus on the initial presentation and the effectiveness of first-line therapy. Recurrent cases were omitted due to the potential confounding effects of prior therapies and disease progression on treatment responses.

Data Collection

Clinical and demographic data were prospectively recorded at the time of admission. Collected data included patient age, sex, time from symptom onset to diagnosis, and the extent of UC, categorized according to the Montreal classification. Symptom burden at admission was assessed by stool frequency, presence of bloody stools, abdominal pain, fever, and weight loss. Vital signs, including heart rate, blood pressure, and temperature were also recorded.

Laboratory data at admission included white blood cell (WBC) count, neutrophil count, C-reactive protein (CRP) levels, hemoglobin, serum albumin, and fecal calprotectin. All patients underwent endoscopic evaluation to assess disease severity, which was quantified using the Mayo Endoscopic Subscore (MES). Treatment regimens –including the use of mesalamine, corticosteroids, immunomodulators, infliximab, and tofacitinib – were documented, alongside treatment responses, adverse events, and any surgical interventions. Twelve-month follow-up data were collected to assess endoscopic healing, serious infections, and the need for colectomy.

Definition

The diagnosis of ASUC was established by the presence of six or more bowel movements per day accompanied by at least one of the following abnormalities: heart rate > 90 bpm, temperature > 37.8°C, hemoglobin < 10.5 g/dL, CRP > 30 mg/dL, or ESR > 30 mm/hr[10]. UC disease extension was defined according to the Montreal classification [i.e., proctitis (E1), left-sided colitis (E2), and extensive colitis (E3)].

In-hospital IV steroid response based on at least one criterion: fewer than 3 bowel movements per day on day 3 (complete response) or 3 to 8 bowel movements per day with CRP < 45 mg/L on day 3 (partial response)[11]. For patients

who achieved partial response, IV steroids were continued until day 7. Patients who had fewer than 3 bowel movements per day on day 7 were considered to have a steroid response. Steroid resistance was diagnosed when patients did not meet the criteria for a steroid response and required rescue therapies (i.e., ciclosporin, infliximab, and tofacitinib).

Endoscopic healing was defined based on an MES of 0 points. Similarly, bowel surgeries are related to IBD. Severe infection was defined as a diagnosis of an infection requiring hospitalization and administering intravenous antibiotics.

Treatment Protocol

All patients received intravenous corticosteroids, typically methylprednisolone (40-60 mg/day) or hydrocortisone (400 mg/day). Blood transfusions were administered when necessary to maintain hemoglobin levels above 9 g/dL. Oxford criteria were used to predict steroid response, and patients who did not respond to steroids by day 3 or 7 were considered for rescue therapy, provided there were no immediate indications for colectomy, such as toxic megacolon, perforation, uncontrolled severe hematochezia, or multi-organ dysfunction. The specific treatment protocol followed at our institution is outlined in Figure 1.

Outcome Measures

The primary outcome was the in-hospital response to corticosteroid therapy. Secondary outcomes included time to clinical response, the need for rescue therapy, treatment-related complications, colectomy during hospitalization, endoscopic remission at 12 months, and the maintenance therapies prescribed.

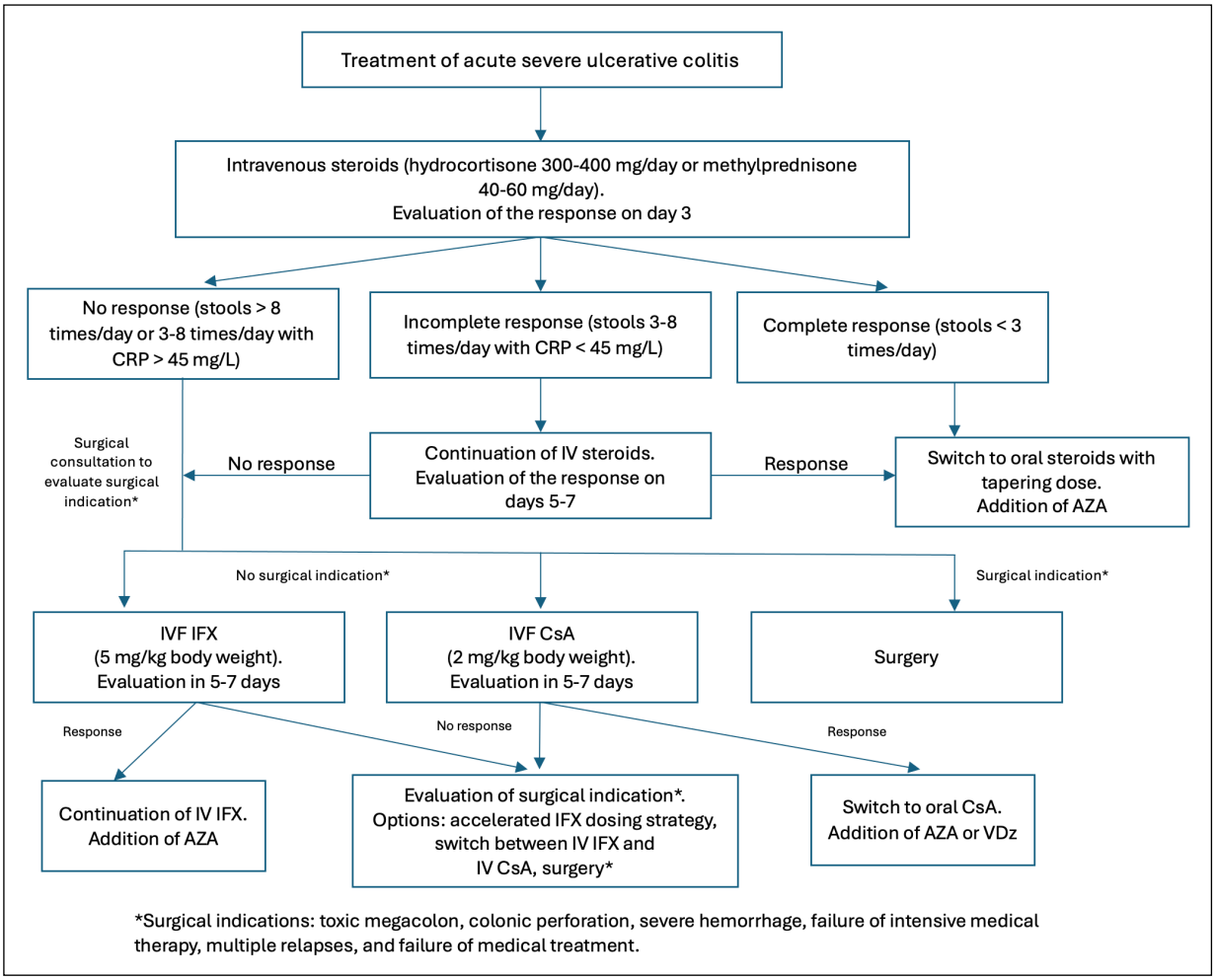

Figure 1. Protocol for the treatment of ASUC in our facility. IV: intravenous, IFX: infliximab, AZA: azathioprine, CsA: cyclosporin A, VDZ: vedolizumab.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics, treatments, and clinical outcomes. Continuous variables with a non-normal distribution were reported as medians and interquartile ranges (IQR), while categorical variables were expressed as frequencies and percentages. All statistical analyses were conducted using SPSS software (version 24.0; IBM Corp., Armonk, NY, USA).

Results

Between January 2021 and June 2023, 17 patients met the inclusion criteria and participated in this case series. The male-to-female ratio was 2.4:1, and the median age was 42 years (IQR: 30-48). All patients presented with hematochezia, with a median time from symptom onset to diagnosis of 6 weeks (IQR, 2-36). A previous diagnosis of ulcerative colitis had been confirmed in 47.1% of patients prior to admission. Endoscopic findings from prior colonoscopies indicated ulcerative colitis in 38.5% of cases and nonspecific colitis in 61.5%. According to the Montreal classification, 87.5% of patients had extensive colitis (E3), and 12.5% had left-sided colitis (E2) (shown in Table I).

Clinical Presentation and Laboratory Findings

At the time of hospital admission, all patients reported diarrhea (100%) and bloody stools (100%), with 53% experiencing more than 10 bowel movements per day. Abdominal pain was present in 76.5% of patients, and 35.3% exhibited fever, while 23.5% reported weight loss. The median pulse rate was 103 beats per minute (IQR, 81-123), median systolic blood pressure was 110 mmHg (IQR, 100-120), and median diastolic blood pressure was 70 mmHg (IQR, 60-80) (Table I).

Laboratory findings revealed leukocytosis, with a median white blood cell count of 12,500/mm³ (IQR, 10,400-14,300) and a median neutrophil count of 8,800/mm³ (IQR, 7,100-12,100). Most patients had elevated C-reactive protein (CRP) levels with a median of 63 mg/L (IQR: 19.2-72.5). The median hemoglobin level was 111 g/L, and the median albumin level was 27 g/L (IQR: 22.8-29.3). All patients had elevated fecal calprotectin levels, with 76.5% having levels greater than 800 µg/g. Stool examination revealed positivity for *Entamoeba histolytica* in 17.6% of the patients. All patients tested negative for *Clostridium difficile* toxin. Endoscopic evaluation was performed in 94.1% (1 patient did not perform due to colonic

Table I. Baseline clinical and laboratory characteristics of ASUC patients.

Characteristic	Result
Demographics	
Male/female	12/5 (2.4:1)
Median age (years)[b]	42 (30-48)
Medical history	
Hematochezia[a]	17/17 (100)
Time from onset to diagnosis with UC (weeks)[b]	6 (2-36)
Previous colonoscopy[a]	13/17 (76.4)
Diagnosis with UC[a]	8/17 (47.1)
Montreal classification	
E1[a]	0/8 (0)
E2 (Left-sided colitis)[a]	1/8 (12.5)
E3 (Extensive colitis)[a]	7/8 (87.5)
Symptoms on admission	
Diarrhea[a]	17/17 (100)
Bloody stool[a]	17/17 (100)
Abdominal pain[a]	13/17 (76.5)
Fever[a]	6/17 (35.3)
Weight loss[a]	4/17 (23.5)
Median pulse (pulse/min)[b]	103 (81-123)
Median systolic blood pressure (mmHg)[b]	110 (100-120)
Median diastolic blood pressure (mmHg)[b]	70 (60-80)
Laboratory findings	
WBC (/mm³)[b]	12.4 (10.4-14.3)
Neutrophil (/mm³)[b]	8.8 (7.1-12.1)
CRP (mg/L)[b]	75.8 (22.1-105.4)
Hemoglobin (g/L)[b]	111 (78-127.5)
Albumin (g/L)	27 (22.8-29.3)
- Not performed[a]	27 (22.8-29.3)
- Not applicable[a]	4/17 (23.5)
- Median (g/L)[b]	13/17 (76.5)
Fecal calprotectin levels	
>800 µg/g[a]	13/17 (76.5)
>150 µg/g[a]	17/17 (100)
Stool microscopy with positive for *E. histolytica*[a]	3/17 (17.6)
CMV screening test[a]	17/17 (100)
Tuberculosis screening[a]	17/17 (100)
HBV screening[a]	17/17 (100)
Clostridium difficile (*C. difficile*) toxin[a]	0/17 (0)
Endoscopic findings at admission	
Mayo subscore 2[a]	2/16 (12.5)
Mayo subscore 3[a]	14/16 (87.5)
Deep ulcers[a]	2/16 (12.5)
Histological diagnosis	
Ulcerative colitis[a]	13/15 (86.6)
Chronic inflammation[a]	2/15 (13.3)

[a]Number (%); [b]Median (IQR). NR-not reported. UC-ulcerative colitis.

dilation, as we were concerned about the risk of perforation), revealing that 100% had a Mayo endoscopic score of 2 or 3, with over 85% having a score of 3 and 12.5% having deep ulcers (Figure 2). The histopathological results were consistent with a diagnosis of ulcerative colitis in 82.2% of the patients (Table I).

Treatment and In-Hospital Outcomes

All patients received intravenous corticosteroids as initial treatment, with 41.2% receiving 40 mg and 58.8% receiving 60 mg doses. By day 3, 82.4% of patients had responded to steroids (half with complete response and half with partial response), whereas 17.6% had no response. The median time from initial treatment to response was 3 days (IQR: 2-6), and the median duration of steroid use was 8 days (IQR: 5-9.5). By day 7, one-third of patients (33.3%) had not responded to initial treatment and required rescue therapy, primarily infliximab (83.3%) and tofacitinib (16.7%). The median time from admission to rescue therapy was 6.5 days (IQR: 4.8-11.5), and rescue therapy led to a response in 83.3% of patients. No patients underwent colectomy during admission, but one patient developed colonic dilatation (7.1%) (Figure 3). The median length of hospital stay was 13 days (IQR: 9.3-14), and no adverse event was reported (Table II).

12-Month Follow-Up Outcomes

At the 12-month follow-up, 11 out of 17 patients continued follow-up. Four steroid-responsive patients were on 5-ASA and azathioprine, one on

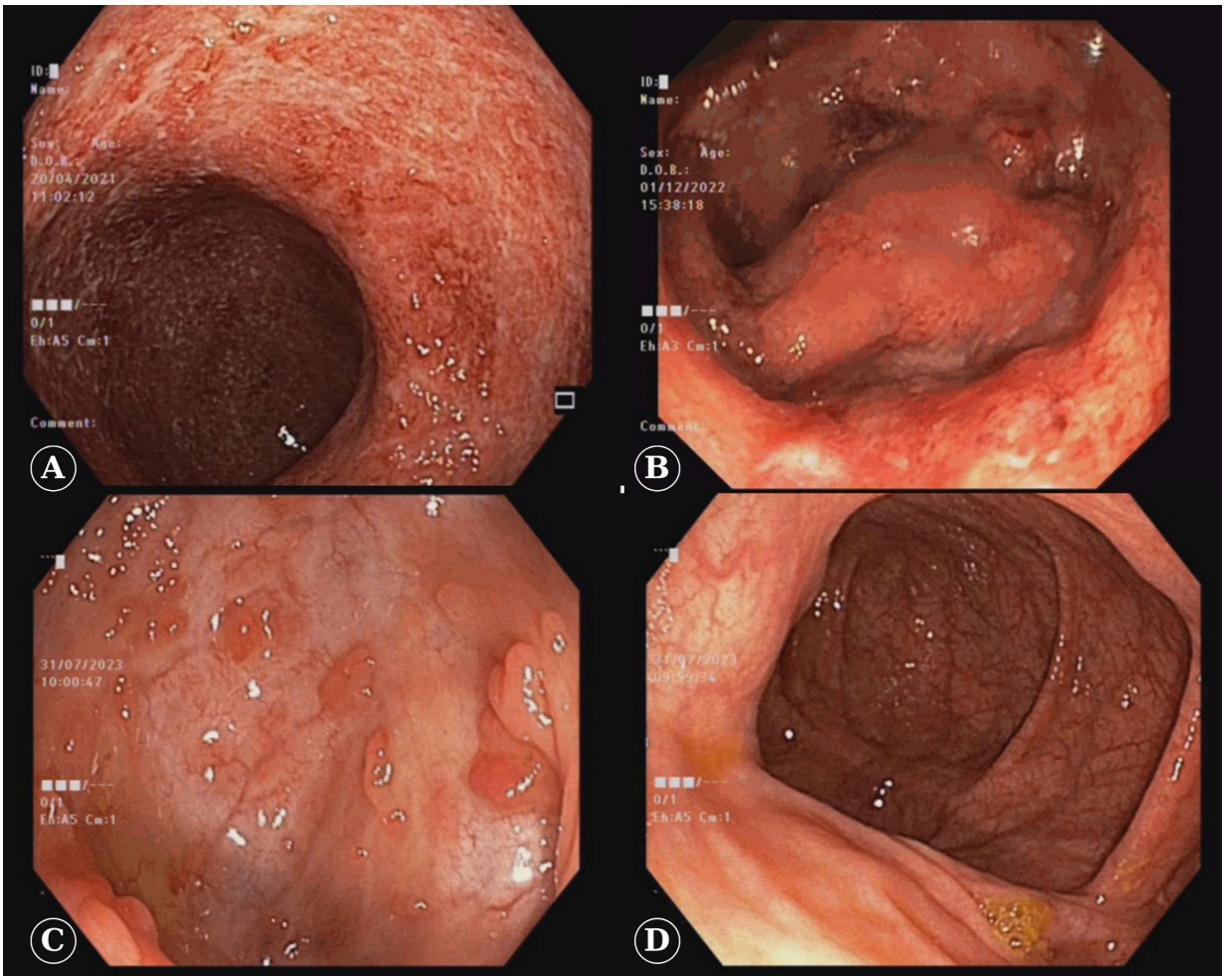

Figure 2. Endoscopic features at admission and after one year of treatment. **A,** Upon admission, endoscopy revealed a decreased vascular pattern, friability, erosions, spontaneous bleeding, and ulceration in the rectum and sigmoid colon (Mayo Endoscopic Subscore – MES: 3) **B,** Upon admission, endoscopy revealed deep ulcerations. **C,** Endoscopy after one year of treatment showed mucosal bridging and significant healing. **D,** Endoscopy after one year of treatment with infliximab showed a normal vascular pattern and mucosal healing in the rectum and sigmoid colon (MES: 0).

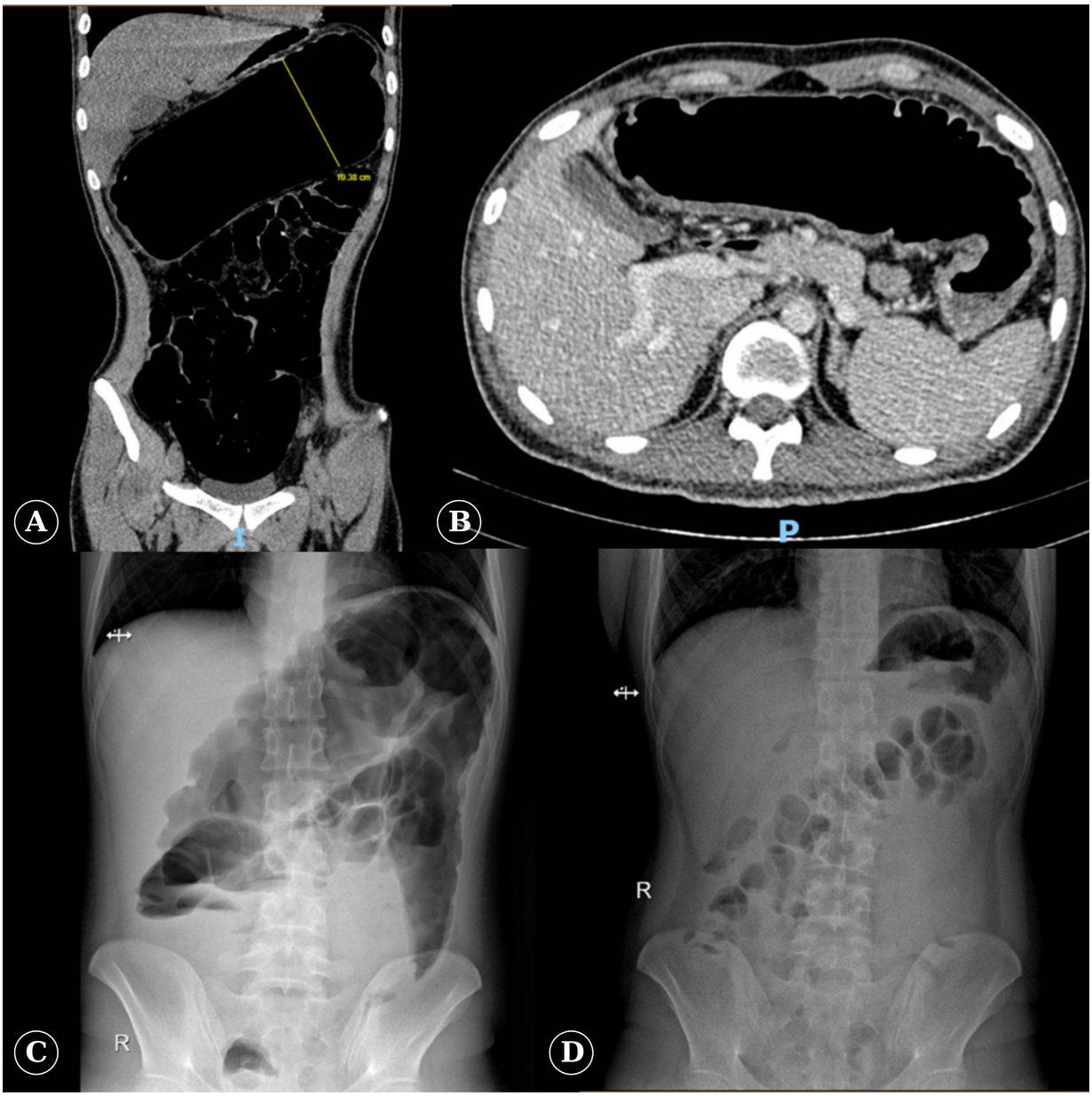

Figure 3. Imaging features of colonic dilatation are complex and indicate a response to treatment. A 22-year-old male patient developed colonic dilation without systemic toxicity. **A-C,** Abdominal X-ray and CT scans showing a significantly dilated colon with marked thickening of the wall in a patient with toxic megacolon. **D,** After accelerated infliximab treatment, an abdominal X-ray revealed a normal colon, with resolved dilation and wall thickening.

adalimumab, and three on infliximab (1 stopped due to tuberculosis). Among the steroid non-responders, five received infliximab, 1 switched to adalimumab, and one was on tofacitinib. No patients required colectomy, and 90.1% achieved mucosal healing (Table II). Figure 4 illustrates the 12-month treatment outcomes, highlighting the high rate of mucosal healing and no colectomy.

Discussion

This first case series of Vietnamese treatment-naive ASUC patients offers valuable insights into managing ASUC in a resource-limited setting. Our study population had a higher male-to-female ratio (2.4:1) than cohorts from India, Korea, and multicenter studies in Europe and the USA[3,6,8,12-14]. The median patient age was 42

Table II. Treatment and outcomes of ASUC patients.

Characteristic	Result
Treatment	
IV corticosteroids[a]	17/17 (100)
Steroid dose (40 mg/60 mg)[a]	7/17 (41.2)/10/17 (58.8)
Combination with 5-ASA[a]	17/17 (100)
Blood transfusion[a]	5/17 (29.4)
Steroid response by day 3	
No response[a]	3/17 (17.6)
Partial response[a]	7/17 (41.2)
Complete response[a]	7/17 (41.2)
Steroid response by day 7	
Response[a]	6/9 (66.7)
No response[a]	3/9 (33.3)
In-hospital steroid response	
Responders[a]	11/17 (64.7)
Non-responders[a]	6/17 (35.3)
Median time from initial treatment to response (days)[b]	3 (2-6)
Rescue therapy	
Cilosporin[a]	0/6 (0)
Infliximab[a]	5/6 (83.3)
Tofacitinib[a]	1/6 (16.7)
Rescue therapy response[a]	5/6 (83.3)
Time from admission to rescue therapy (days)[b]	6.5 (4.8-11.5)
Time from corticosteroid-used to rescue therapy (days)[b]	7(4.8-9.3)
In-hospital outcomes	
Median duration of hospitalization (day)[b]	11.5 (9.3-14)
Colectomy during admission[a]	0/17 (0)
Toxic megacolon[a]	1/17 (7.1)
Adverse events after treatment[a]	0/17 (0)

[a]Number (%); [b]Median (IQR). Steroid response by day 3 and day 7 are evaluated using the Travis Oxford Criteria. Rescue therapy includes infliximab and tofacitinib, with the response assessed based on clinical improvement and endoscopic findings.

years, with males comprising 70.6% of the group, similar to other Asian studies[12,15]. The study revealed that the clinical presentation of ASUC in Vietnamese patients is consistent with global patterns, with common symptoms including bloody stools, diarrhea, and abdominal pain. The median time from symptom onset to hospital admission was nearly four weeks, significantly longer than the 14 days reported in a Korean study[15]. This delay likely results from the recent recognition of ulcerative colitis in the region and a lack of established diagnostic guidelines. In our study, all patients had a history of bloody stools. A total of 76.4% had previous colonoscopies, but only 50% received a confirmed diagnosis of ulcerative colitis. Clinicians may not be familiar with this condition.

ASUC patients in our study presented elevated inflammatory biomarkers, such as white blood cells, CRP, and fecal calprotectin. Notably, the mean CRP value was higher than that in the Korean cohort (75.8 *vs*. 43 mg/L), potentially due to later hospital admissions and more severe inflammation. Endoscopic findings were consistent, with 100% of patients having a MES of 2 or 3, highlighting severe mucosal inflammation typical of ASUC. This result is consistent with the findings of a Korean study[15], where 99.2% had a MES of 2 or 3, and 80.5% had a score of 3.

In low-resource settings, differentiating ASUC from infectious colitis is crucial. In our study, 17.6% of patients had *Entamoeba histolytica* in stool samples, and infection could not be ruled out on histopathology in 23.5% of patients, emphasizing the need to rule out amoebiasis due to clinical overlap[16].

Regarding treatment, all patients received methylprednisolone at the recommended dosage[7,8]. Approximately 57.1% of the patients received a 60 mg dose, likely due to high CRP levels and late presentations. By the third day post-steroid initiation, only 17.6% of the patients were non-responders according to the Oxford-Travis criteria and required rescue therapies. Notably, 82.4% of patients responded partially or completely to steroids, with 41.2% having a partial response and requiring extended steroid therapy. Three of these six patients (50%) responded to steroids, whereas the remaining 3 (50%) required rescue therapy. Overall, 33.3% of patients did not respond to intravenous steroids and required rescue therapy, consistent with findings from a meta-analysis of ASUC patients[17]. In clinical practice, steroids are the first choice for ASUC patients, and evaluating the response to intravenous steroids on day 3 is recommended by global and regional guidelines[6,8]. Patients with a partial response to steroids are advised to continue steroid therapy, possibly optimize the dosage, and reassess on day 7 before deciding to switch to rescue therapies. Notably, all patients with intravenous steroid resistance in our study responded to rescue therapy without the need for colectomy. The colectomy rate within 3-5 days in a Korean study of patients with ASUC was also very low (3.6%)[15]. The evidence suggests that the early colectomy rate for ulcerative colitis patients in Asia is lower than that in the West[14]. Genetic determinants influencing steroid response cannot be ruled out, as studies[17] have shown significant genetic variations between Asian and Western

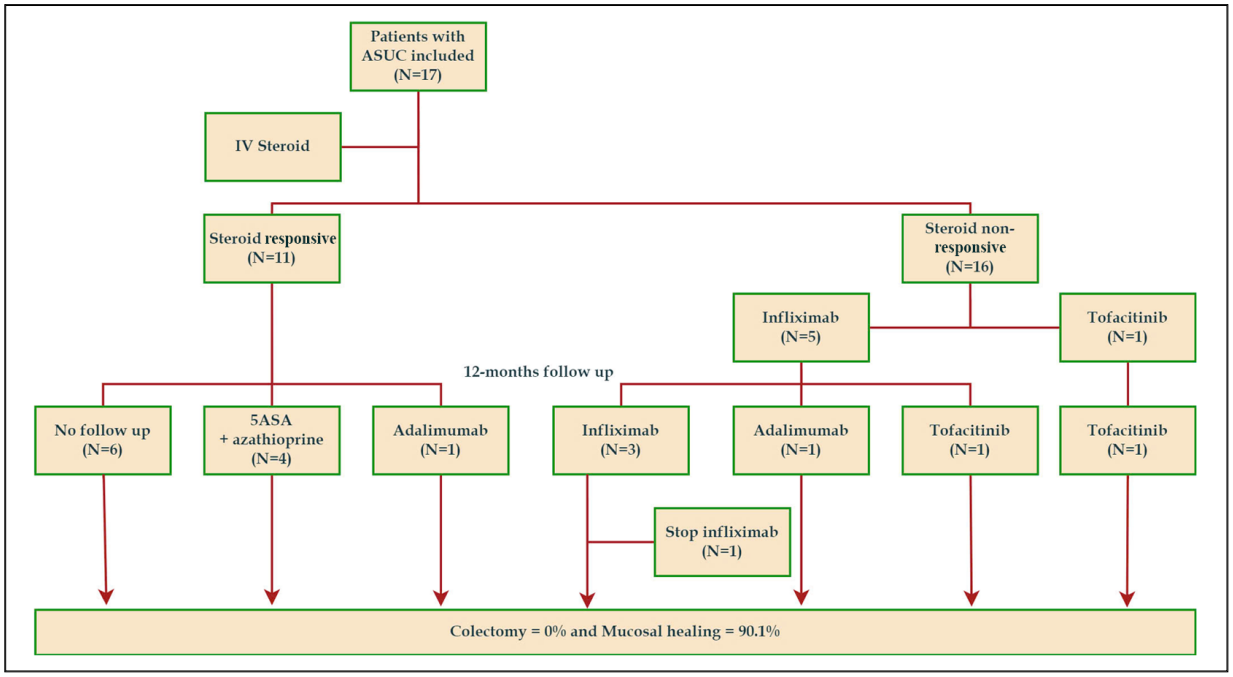

Figure 4. Flowchart showing the treatment and outcomes of patients with ASUC after 12 months of follow-up.

populations, including differences in hormone metabolism pathways, gene polymorphisms, and drug sensitivity. Environmental triggers, such as dietary patterns, gut microbial composition, or toxin exposure, may modulate steroid responsiveness but remain poorly understood[18].

Toxic megacolon is a serious medical condition requiring immediate attention. Failure to promptly diagnose this disorder is linked to high mortality and morbidity rates. Regarding ASUC complications, megacolon without toxicity has not been well characterized, with only three case reports[19,20]. These patients, however, had colonic dilatation less than 10 cm. In our study, one patient with colonic dilatation greater than 10 cm was included. This patient did not experience symptoms of systemic toxicity (Figure 3). Patients who did not respond to the standard dose of infliximab (5 mg/kg) opted for an accelerated infliximab dosing strategy. After one week of treatment, the patient responded well and did not need colectomy. Another study[13] revealed that 69.7% of those who did not respond to a single dose of infliximab could avoid colectomy with an accelerated rescue induction strategy without worsening postoperative outcomes. This strategy may be applied to patients with ASUC who fail to respond to the standard dose of infliximab or who develop colonic dilatation.

In our study, the use of tofacitinib as a rescue therapy in cases where steroids were ineffective was notable. Tofacitinib, an oral Janus kinase inhibitor, has shown promise in treating ASUC. Among the steroid non-responders, 16.7% were successfully treated with tofacitinib. A systematic review by Steenholdt et al[21] revealed that tofacitinib resulted in rapid clinical improvement in patients with steroid-refractory ASUC. Response rates ranged from 66% to 85% across studies. The rapid onset of action of tofacitinib, typically within three days, makes it particularly suitable for the acute setting of ASUC[22]. The OCTAVE Induction 1 and 2 trials showed that tofacitinib effectively induced remission in patients with moderate to severe ulcerative colitis, including those with more severe disease[23]. While these trials did not specifically focus on ASUC, our real-world data suggest that the benefits extend to this high-risk population. The safety profile of tofacitinib in our ASUC patients was reassuring, with no significant adverse events reported during the acute phase or follow-up period, despite concerns about increased thromboembolism risk in specific populations[24]. However, our small sample size and short follow-up period necessitate a cautious interpretation of these safety findings.

Mucosal healing is a long-term goal of UC treatment. In a meta-analysis, mucosal healing

was linked to sustained clinical remission, colectomy prevention, and clinical remission without corticosteroids[25]. Despite this suboptimal steroid response rate, we achieved favorable short-term outcomes, with 90.1% endoscopic mucosal healing at one year in those who remained in follow-up (Figure 4). This can be attributed to the timely escalation of rescue therapies such as infliximab and tofacitinib for steroid non-responders, reinforcing their efficacy in this setting. Avoiding colectomies over the 12-month period is also reassuring, although longer-term data are needed. Many patients initially responsive to corticosteroids eventually had to switch to biologics due to disease progression. The occurrence of infections, tuberculosis reactivation, and the availability of biologics also influenced patients' ability to continue or switch therapies. However, the high cost of biologic drugs like infliximab and tofacitinib, which are often not covered by insurance, poses a significant challenge in Vietnam. Consequently, a notable limitation is the dropout rate after 12 months of follow-up due to financial constraints, which limits the long-term data we could collect.

Limitations

Our study, which is based on standardized treatment protocols, objective endoscopic assessments, and one-year follow-up, provides some insights for future research in Vietnam since ASUC is, in our country, a rare and often underestimated condition. The scarcity of patients did not allow any statistical analyses. Our future research on this pathology will prioritize larger, multicenter studies with control groups and more extended follow-up periods. Investigating cost-effective diagnostic and therapeutic strategies tailored to resource-limited settings like Vietnam is essential. Additionally, exploring genetic and environmental factors influencing ASUC in Vietnamese patients could provide valuable insights for personalized management approaches.

Conclusions

In conclusion, this study highlights the effectiveness of corticosteroids and biologic therapies in managing ASUC in Vietnam. Early diagnosis and intervention are crucial to improving patient outcomes. Future research should address the study's limitations and further explore the unique factors influencing ASUC in Southeast Asia to optimize management strategies in resource-limited settings.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

Ethics Approval

This study was conducted following the Declaration of Helsinki of 1975 (as revised in 2013), and the protocol was reviewed and approved by the Institutional Review Board of the University Medical Center Ho Chi Minh City on November 25th, 2021 (approval number: 258/2021/HĐ-ĐHYD).

Informed Consent

All subjects provided written informed consent for inclusion before participating in the study.

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AI Disclosure

To improve the clarity and readability of this manuscript, we used Grammarly's AI-powered tools for grammar checks, typo corrections, and refining paragraph structure. The AI assistance was strictly limited to these tasks, ensuring that the content and scientific integrity were entirely the work of the researchers. We also confirm that no artificial intelligence or other automated technologies were used in the production of the study, including the creation of figures or illustrations.

Authors' Contributions

LMD and HHB took responsibility for the integrity of the work from its inception to the publication of the article. LMD, TMH, THD, and HHB designed the research study. LMD, CDN, and TTTT performed the research and collected the data. LMD, THD, and TMH analyzed the data. All the authors contributed to interpreting the data and critically reviewed and approved the manuscript. All the authors approved the final version of the manuscript.

Data Availability

The original clinical datasets generated from the cases are available from the corresponding author upon reasonable request.

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