



# Managing Acute Severe Ulcerative Colitis in the Older Patient: A Growing Concern

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## Abstract

Since the prevalence of older patients with ulcerative colitis is increasing, hospitalizations for severe disease in this age group are expected to rise. Older patients are more likely to present with comorbidities and, consequently, frailty, the latter being one of the major drivers of worse outcomes. The conventional sequencing of therapies in acute severe ulcerative colitis—i.e., intravenous steroids followed, in case of refractoriness, by antitumor necrosis factor (TNF) agents, ciclosporin A, or Janus kinase inhibitors such as tofacitinib or upadacitinib—may frequently be contraindicated in older patients or may carry an increased risk of severe adverse events beyond infections. In the absence of specific guidelines, the implementation of and strict adherence to a structured, time-bound decision tree is essential in order to avoid unnecessarily prolonged treatment with systemic steroids in frail patients, which may lead to deleterious outcomes, particularly in those requiring surgery. Recent reports on adjunctive measures, such as hyperbaric oxygen therapy or total enteral nutrition, may also be considered given their encouraging safety profile.

## Key Points

The management of severe ulcerative colitis in older patients is poorly defined.

Almost all specific first- or second-line therapies will lead to an increased risk of infections or postoperative complications with a high risk of mortality, especially in frail patients.

In order to avoid protracted and at times ineffective and potentially harmful therapies, a strict time-bound protocol is necessary.

Adjunctive measures, unexplored in older subjects but apparently safe, should be considered.

## 1 Introduction

The management of acute severe ulcerative colitis (ASUC) in older patients is poorly defined and generally not considered in current clinical guidelines [1, 2], largely owing to the lack of dedicated studies in this age group. Older patients are defined as being over 60 years of age according to the former literature [3] and the definition of the World Health Organization [4]. The purpose of the present paper was to evidence the knowledge gaps and to indicate where future research should be oriented in the hope to reduce the risks of adverse events, the risk of infections, and, finally, mortality.

## 2 ASUC in Older Adults

Recent literature shows that hospital admissions for ulcerative colitis (UC) in older adults account for approximately 30% of all UC-related hospitalizations, and mortality is three times higher than in younger patients [5]. Although it is often argued that UC follows a milder course in patients with late-onset disease—an assumption based on the less frequent use of advanced therapies and on comparisons with paediatric populations—studies indicate that disease behaviour is largely comparable to that of adult-onset UC. Approximately 40% of patients present with a more aggressive course and

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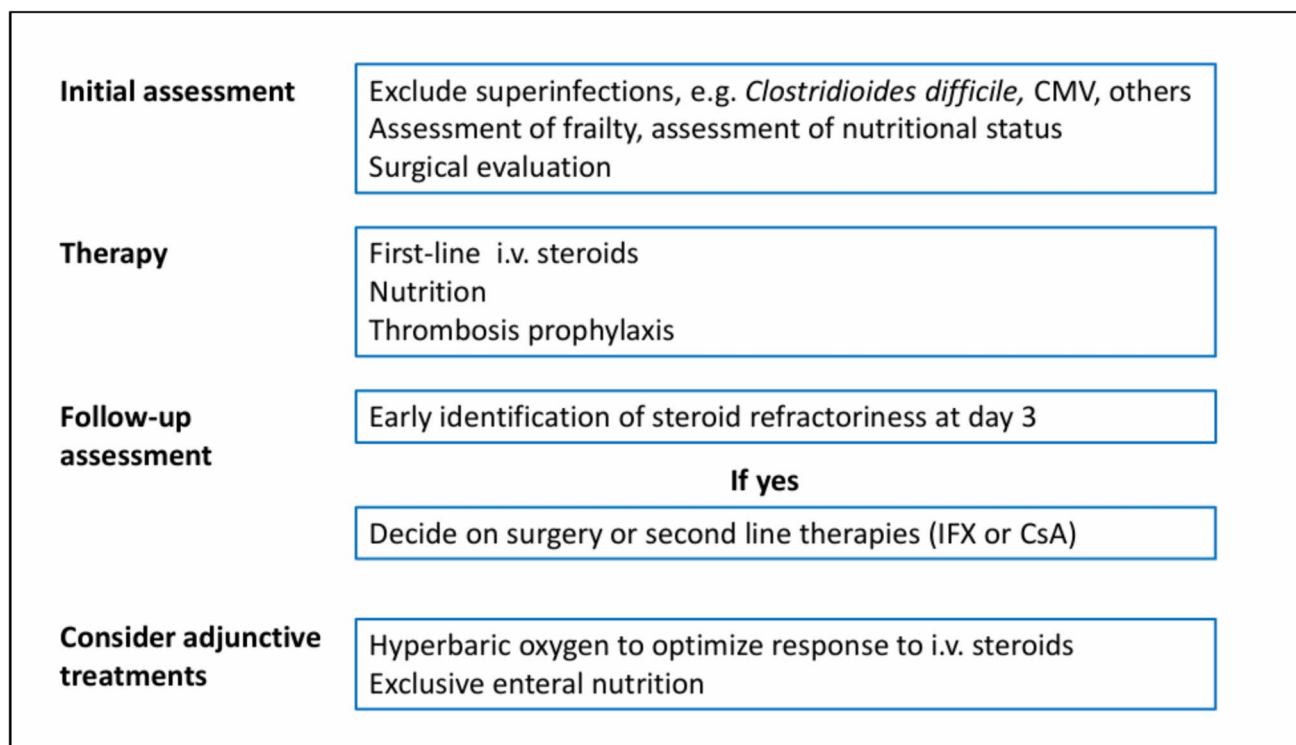
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rates of steroid use and surgery are similar [6, 7]. Far less information is available on the disease course of patients diagnosed with UC earlier in life who reach geriatric age.

In a recent retrospective study comparing 63 older ( $\geq 65$  years) and 137 younger patients hospitalized for ASUC, older biologic-naïve patients were less likely to initiate advanced therapies (17%) compared with younger biologic-naïve patients (43%), and when they did, initiation occurred later [8]. Surgery rates were similar between the two groups, but older patients were more likely to undergo emergency surgical interventions. In-hospital mortality for ASUC was significantly higher in older patients (6.4%) than in younger ones (0.7%), confirming previous observations [5]. Even more concerning were postdischarge outcomes: 1-year mortality reached 27.8% in the older group compared with 1.6% in younger patients, with half of the deaths directly attributable to UC or UC-related complications. A previous multicentre analysis on 120 older patients reported a lower 1-year mortality rate with 15%. [9] Beyond medical and surgical factors, frailty—assessed by the Hospital Frailty Risk Score (based on ICD-9/ICD-10 codes)—strongly influenced treatment decisions. No patient identified as high-risk for frailty received advanced therapy; all were treated exclusively with intravenous corticosteroids. Similar findings of reduced

advanced therapy use in older patients were reported in two abstracts including 82 and 16 patients, respectively [10, 11].

The initial approach to older patients hospitalized for severe UC flares should not differ from that in younger adults. Superimposed infections such as *Clostridioides difficile*, cytomegalovirus, and other pathogens must be excluded and, in view of the potential use of advanced therapies, screening for latent tuberculosis infection and hepatitis C and B should be carried out at admission. Nutritional status should be closely assessed, monitored, and corrected as necessary. Several screening tools are available to assess malnutrition [12] but besides weight loss in the days before hospitalization, blood biochemistry including prealbumin, haemoglobin, serum iron, transferrin, vitamin status, and, where available, micronutrients may more accurately detect specific deficiencies. Pharmacologic prophylaxis to prevent thromboembolism with low molecular weight heparin represents standard of care. Surgical evaluation should be performed at admission and at regular intervals thereafter. In addition, careful assessment of frailty is mandatory (Fig. 1) and for this purpose the Hospital Frailty Risk Score may be used [13], a generic risk score, not validated in patients with UC.



**Fig. 1** Synopsis of essential approach and adjunctive measures in older patients with acute severe ulcerative colitis. CMV, cytomegalovirus; IFX, infliximab; CsA, Ciclosporin A; i.v. intravenous

### 3 Medical Therapy

Concerning medical therapy for ASUC, after intravenous corticosteroids, rescue options include ciclosporin A (CsA) and infliximab (IFX), the two most commonly used agents that yield comparable outcomes in adult patients with ASUC [14–16]. However, all three agents (including i.v. steroids) are associated with an increased risk of infection in older adults. Lower steroid efficacy compared with younger adults has been reported in late-onset UC [17], although this finding was not confirmed in previous prospective [18] or retrospective [19] studies. To remain focused, we will not further discuss potential differences in drug response between late-onset and long-standing UC.

Older hospitalized patients treated with high-dose intravenous steroids are at increased risk of infection; therefore, early re-evaluation is crucial to identify steroid refractoriness. In adult ASUC, the three-day Oxford criteria [20] are often used to predict steroid nonresponse and to promptly escalate to rescue therapies [21] (Fig. 1). The strict observance of this regimen is crucial in older patients since prolonging steroid therapy in case of non-response may have deleterious consequences in terms of infections and mortality.

Second-line rescue therapies, especially intensified IFX regimens, may be potentially harmful in older patients, not only with regard to infections but also in terms of cardiovascular adverse events, even in patients with no previous diagnosis of cardiac pathologies [22, 23]. A study investigating optimized IFX dosing regimens, including subjects up to 80 years of age, is currently ongoing [24]. CsA may be considered in patients with prior anti-TNF exposure or contraindications to anti-TNF agents (e.g., congestive heart failure or demyelinating disease), but requires careful monitoring of renal function, blood pressure, and serum magnesium [25, 26].

Newer therapies such as Janus kinase (JAK) inhibitors, *tofacitinib* and *upadacitinib*, appear effective in adult ASUC [27, 28], but their use should be carefully weighted in high-risk patients for thromboembolism and those at elevated risk for coronary artery disease or cerebrovascular accidents. Again, no data exist for older patients, and the use of *tofacitinib* in frail individuals, particularly at intensified doses (e.g., tofacitinib 10 mg three times daily), is difficult to advocate [29]. On the other hand, *upadacitinib*, seems to be safer to some extent in older patients [30, 31] but data on ASUC in older patients are not available.

Although safer biologics such as vedolizumab and ustekinumab are generally not recommended as second-line rescue therapies owing to their slower onset of action, they may be considered once the most critical situation

has resolved. Small studies have reported their use as after successful CsA induction in anti-TNF-experienced younger patients [32–34]. Other advanced therapies, such as interleukin (IL)-23p19 inhibitors (e.g., *mirikizumab*) or sphingosin-1-phosphate (S-1-P) receptor modulators (e.g., *ozanimod*, *etrasimod*), are currently not recommended in ASUC.

Beyond pharmacologic management, nutritional interventions should be strongly considered and applied. In the absence of contraindications, oral nutrition should be maintained with the intent to maintain barrier function, colonoocyte nutrition, and modulation of the gut microbiota. In some cases, a combination of oral and parenteral may more rapidly correct vitamin, iron, and electrolyte deficiencies. Caloric nutrition, especially protein supplements should be managed by an experienced dietician in order to avoid sarcopenia due to inflammatory activity, steroids, bed rest, and age by itself, all important factors linked to frailty and in case of surgery to worse outcomes [35, 36].

Adjunctive measures such as exclusive enteral nutrition in combination with standard of care reported an improved response to intravenous steroids and lower colectomy rates in a small cohort ( $n = 32$ ) of young adults with ASUC [37]. Additionally, the use of hyperbaric oxygen therapy during acute severe UC flares has been explored over the past decade in adult ASUC, showing potential benefits in terms of improved steroid response, lower rehospitalization rates, and reduced need for surgery [38]. Importantly, this therapy appears cost-effective and, above all, safe, making it potentially suitable for selected older patients [39] (Fig. 1), but more robust data on this topic is still required.

### 4 Conclusions

The prevalence of UC among older patients is increasing, and as the disease course remains unpredictable, the number of hospitalizations for severe flares is expected to rise. Given the lack of robust scientific evidence, the management of ASUC in older adults urgently requires dedicated studies and expert consensus to avoid prolonged, and at times ineffective, corticosteroid treatments.

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