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Editorial Board Member of *World Journal of Clinical Cases*, Alessandro Leite Cavalcanti, DDS, MSc, PhD, Associate Professor, Department of Dentistry, State University of Paraiba, Campina Grande 58429500, Paraiba, Brazil. alessandrouepb@gmail.com

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REVIEW

Role of hospitalization for inflammatory bowel disease in the post-biologic era

Celine R Soriano, Charleston R Powell, Michael V Chiorean, Vlad V Simianu

ORCID number: Celine R Soriano 0000-0003-0440-9439; Charleston R Powell 0000-0002-1955-3540; Michael V Chiorean 0000-0002-4238-9988; Vlad V Simianu 0000-0003-1255-0221.

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Celine R Soriano, Vlad V Simianu, Department of Surgery, Virginia Mason Franciscan Health, Seattle, WA 98101, United States

Charleston R Powell, Department of Internal Medicine, Madigan Army Medical Center, Tacoma, WA 98431, United States

Michael V Chiorean, Department of Gastroenterology, Swedish Medical Center, Seattle, WA 98109, United States

Corresponding author: Vlad V Simianu, MD, Surgeon, Department of Surgery, Virginia Mason Franciscan Health, 1100 9th Ave, C6-GS, Seattle, WA 98101, United States.
val.simianu@virginiamason.org

Abstract

Treatment for inflammatory bowel disease (IBD) often requires specialized care. While much of IBD care has shifted to the outpatient setting, hospitalizations remain a major site of healthcare utilization and a sizable proportion of patients with inflammatory bowel disease require hospitalization or surgery during their lifetime. In this review, we approach IBD care from the population-level with a specific focus on hospitalization for IBD, including the shifts from inpatient to outpatient care, the balance of emergency and elective hospitalizations, regionalization of specialty IBD care, and contribution of surgery and endoscopy to hospitalized care.

Key Words: Inflammatory bowel disease; Hospitalization; Elective; Emergent surgery; Endoscopy

Core Tip: Inflammatory bowel disease (IBD)-related hospitalizations are costly and have increased despite the introduction of advanced therapeutic agents. Over the past few decades, utilization of endoscopy and emergency surgery during hospital admissions have decreased, with a concomitant rise in elective bowel resections. With increased complexity of inpatient and outpatient management of IBD, improved care delivery and outcomes may consist of multidisciplinary teams led by IBD specialists,

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), collectively termed inflammatory bowel disease (IBD), are chronic, relapsing and remitting conditions that contribute significantly to the public health and economic burden worldwide. The incidence of IBD ranges from 5.0-24.3 per 100000 people globally, and the prevalence is expected to continue to rise given more patients being diagnosed at a young age and the low mortality associated with the disease[1,2].

One of the most important advances in the treatment of IBD over the past several decades is the introduction of biologics. The first clinical trial studied anti-TNF-α therapy for patients with CD where short term efficacy of biologics were established with increased clinical response and remission rates compared to placebo[3]. Further randomized control studies were promising showing increased remission rates at over one year[4]. Subsequent trials were conducted evaluating the efficacy of infliximab in UC, also showing improved clinical response and remission compared to placebo[5]. Given the success and mainstream acceptance of biologics for both induction and maintenance for IBD, a reasonable hypothesis would be that superior disease control would result in a decreased need for hospitalizations and surgery.

Despite the fact that the medical treatment has improved significantly after the introduction of biological drugs, recent studies have shown variable trends in rates of hospital admissions[6-8]. While the IBD patient population is heterogenous and may have an expected course of disease, the need for inpatient medical or surgical care may act as a surrogate for disease severity and failure of outpatient medical treatment or complications thereof. As such, the healthcare burden, population level impact, and drivers of IBD hospitalizations in the current, so-termed "post-biologic era" are important to understand. In this paper, the determinants of cost, utilization, and outcomes of hospital care in patients with inflammatory bowel disease are reviewed.

IMPACT OF HOSPITALIZATION ON HEALTHCARE BURDEN

IBD patients have high healthcare utilization as evident by increased readmission rates, longer length of stay, and increased costs[9,10]. Total and incremental lifetime healthcare costs incurred by patients with CD and UC are much higher than patients with other chronic diseases, and the estimated lifetime cost burden for patients with CD and UC are expected to be $498 billion and $377 billion, respectively.[11] Hospitalizations are an important contributor of total lifetime costs, with $1 in $4 spent on inpatient services for both CD and UC[11,12]. Furthermore, approximately one-fourth of patients with IBD are admitted to the hospital within the first two years of diagnosis [13].

Most patients are initiated on medical management for IBD, tailored to disease activity, location, behavior, extraintestinal manifestations and will often require lifelong therapy. Especially with acute presentations or hospitalization for IBD, systemic corticosteroids are one of the oldest remedies still used today[14-17]. However, steroids have been associated with significant risks including serious and opportunistic infections as well as mortality in patients with IBD and therefore their long-term use has been discouraged in recent guidelines[18,19]. There has been a concomitant shift towards early use of biologics and other therapeutic agents for both CD and UC. Additionally, there has been a movement of healthcare costs from hospitalization and surgery towards anti-TNF therapy, with a Dutch study suggesting anti-TNF-α medications account for 64% and 31% of total costs for CD and UC respectively [20].

Length of stay is also an important measurement of costs and healthcare burden. Extended length of stay is associated with higher hospitalization costs, and hospitalizations related to disease severity are longer in duration than non-IBD causes[12,21,22]. Furthermore, IBD patients requiring critical needs have longer intensive care unit stays than non-IBD patients[23,24]. Factors predisposing IBD patients to increased hospitalization days include immunosuppression, malnutrition, increased risk of Clostridium difficile, and need for interventions, such as gastrointestinal endoscopy or abdominal surgery[24-26].

DRIVERS OF HOSPITALIZATION IN THE CONTEMPORARY ERA

Despite the introduction of advanced therapeutics, hospitalizations remain high, and variable among countries. For instance, a meta-analyses found significant variability in hospitalization rates in 9 European countries, but stable, age-adjusted rates, with a large peak in younger CD patients followed by a smaller peak in elderly patients, and a small peak in younger UC patients followed by a larger peak in elderly patients[27]. It is at odds, therefore, that with what is believed to be increasingly more effective medical therapy, hospitalization rates are stable or increasing[28-30]. Biologics and immunosuppressants are expected to reduce flares, and consequently, hospitalizations for management of acute symptoms are expected to decrease[31-33].

On the other hand, the increased hospitalizations can be explained by more patients being diagnosed, given that the incidence of IBD rising[1,34,35]. A global, population-based study using the Organization for Economic Co-operation and Development database found high IBD hospitalization rates in Western countries that were stabilizing or decreasing over a 25 year period, and conversely, low IBD hospitalization rates in newly industrialized countries that were increasing over time[36]. Counts of hospitalizations could also be affected by patients requiring readmission. Early and late readmissions are common in this patient population. Fifty percent of 30-d readmissions for IBD are due to acute flares, and unplanned admissions rates are up to 39% at 1 year from initial hospitalization[37,38]. These readmissions come from the full spectrum of IBD-related morbidity including bowel obstruction, pain control, complications from surgery, and presence of comorbid conditions[39,40]. While IBD therapeutic agents are safe, there is also data suggesting increased hospitalizations may be due to side effects and complications related to the medication, which then may be categorized as IBD-related admissions. For example, it is well established that patients on these medications are at increased risk for serious or opportunistic infections, an annual incidence ranging from 1.1%-2.2%, especially within the first 90 d of initiating treatment[41,42].

As a result, classification of hospitalizations into elective *vs* emergent may provide insight on disease control. A United Kingdom study calculating age- and sex- adjusted rates of IBD-related hospitalizations found a significant increase in hospitalizations over time with a broad shift from emergency care to shorter elective hospital stays in the setting of increased cytokine infusion rates[43]. Alternatively, an analysis of Washington State IBD-related hospitalizations revealed fewer than one in four hospitalizations for IBD were elective, and the vast majority were related to surgery, whereas emergent admissions were primarily for medical management.[44] These different practice patterns may suggest that perhaps variation can be explained by regional differences, but also point to a gap in clinical data to match the population.

IMPACT OF ENDOSCOPY ON HOSPITALIZATION

The contribution of endoscopy to hospitalization for IBD has been evolving. Endoscopy plays an important role in all facets of IBD care including initial diagnosis, assessing response to therapy, neoplasia and post-surgical surveillance and therapeutic interventions. Despite this, the proportion of lower endoscopies performed during inpatient admissions for CD has decreased significantly over the past several decades, while this has been stable in patients with UC (6.3% to 3.7% for CD and 18.4% to 17.6% for UC)[44]. One reason for this change could be improved disease control in outpatient setting, including the introduction of biologics. The role of diagnostic endoscopy in IBD will likely remain essential over time with studies showing improved outcomes when medical treatment is targeted for endoscopic remission[45]. Most endoscopic procedures are done in the outpatient setting and have the potential to prevent hospitalizations through early detection of disease progression or neoplasia

in the setting of IBD. Population-level data demonstrating this impact, to date, is lacking.

Diagnostic endoscopy is also used during hospital admissions for several reasons. In addition to its diagnostic role in differentiating CD from ulcerative colitis, endoscopy is recommended in the inpatient setting to assess initial disease severity and response to therapy or co-infection in patients with acute severe UC or to manage complications in patients with stricturing CD[46]. Additionally, a study analyzing UC-related hospitalizations in the Nationwide Inpatient Sample database found that early sigmoidoscopy or colonoscopy, defined as within 2 days of admission, was associated with lower in-hospital mortality, costs, and length of stay compared to delayed endoscopy[47].

In addition to diagnosis, therapeutic endoscopy is playing an increasingly important role in IBD and IBD-related complications. Examples of this include stricture and fistula evaluation and treatment. Short, straight-angled strictures (commonly ileocolonic or ileal pouch anastomotic strictures) have been shown to be amenable to endoscopic balloon dilation and can improve symptoms and replace or delay surgery. Needle-knife stricturotomy (NKSt) and self-expanding metal stent placement are under investigation[48]. Endoscopic ultrasound has been shown to be as effective in evaluating peri-anal fistulae as exam under anesthesia or magnetic resonance imaging. Endoscopy with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is an accepted treatment modality for patients with focal IBD-related neoplasia[49,50]. It is important to note that the majority of these procedures are done on an outpatient basis, but may have an important effect on hospitalizations. A study evaluating efficacy and safety of NKSt showed that only 15.3% of patients needed stricture-related surgery after almost one year[51]. More data will need to be collected to assess the impacts of interventional IBD treatments and hospitalization rates.

IMPACT OF SURGERY ON HOSPITALIZATIONS

Historically, it has been reported that 30% of patients with UC and 70% of patients with CD will ultimately require surgical intervention within 10 years of diagnosis[52,53]. Over the past few decades, the risk of needing surgery has decreased, with 10-year estimated risk among patients with UC being 10%-16% and 45%-50% for CD[54-56]. However, surgery still accounts for at least 40% of overall hospitalizations[12]. More recently, the overall rate of IBD patients requiring surgery has remained relatively stable with a shift towards more elective, rather than urgent or emergent, operations [57-59]. Thus, we may not see that expected reduction in hospitalizations that we were anticipating with the advent of advanced therapeutics.

Indications for emergent surgery for UC include perforation, life-threatening hemorrhage, toxic megacolon, and fulminant colitis whereas surgical management in the emergency setting for CD is observed for the fistulizing and stricturing phenotypes causing intestinal obstruction, bleeding, or abscess[60]. In both patient populations, emergency intestinal resections carry higher morbidity and mortality compared to elective cases[61]. Fortunately, the rates of emergency surgery for both UC and CD have been declining[58,59,62-64]. With this shift towards elective surgeries, operative strategies have also been affected. For instance, in UC, options include staged restorative surgery. Recent studies have reported a shift towards total abdominal colectomy rather than total proctocolectomy as the most commonly performed index operation and more ileoanal pouches constructed at a subsequent operation[65,66]. In patients with CD, there have been fewer emergency stomas created[67].

Elective IBD surgery is often performed for medically refractory disease, complications, and in UC specifically, for curative intent. The rates of elective procedures have been increasing[59], as has optimization of elective surgery with shifts towards minimally invasive surgery and enhanced recovery after surgery[68-70]. The use of laparoscopic and robotic-assisted colon resections and enhanced recovery pathways decrease hospital length of stay and are cost-effective at the population level[71-73]. Furthermore, utilization of newer techniques such as Kono-S anastomosis and mesentery exclusion for ileocolic CD have shown favorable results of decreased rates of disease recurrence[74-77], and may result ultimately in fewer operations over a patient's lifetime. Future studies are needed to assess long-term outcomes and the need for subsequent operations that may ultimately lead to standardization of these techniques in the elective setting.

While emergent and elective surgeries have had distinct trends over the past two decades, the drivers leading to overall variable surgery rates remain poorly

understood. Rates of colectomy have varied based on geographic region, time period, and extent of disease. With the increasing use of biologic agents and immunomodulators, several time-trend population-based studies have attempted to determine if there is a correlation between these drugs and need for surgery. Early studies have found relatively stable surgery rates in patients with CD with the introduction of infliximab[78]. More recently, some researchers demonstrated a decrease in surgeries for medically refractory CD during a time period before and after the induction of infliximab and adalimumab, suggesting that declining trends also involve other factors. Conversely, studies investigating trends of colectomy in patients with ulcerative colitis have found decreasing rates in patients undergoing treatment with infliximab or other biologics[79-81], but may have higher postoperative morbidity and mortality[66,82,83]. Additionally, these therapeutic agents may instead have a role in delaying surgery, rather than reducing the overall number of procedures, which is also supported by the shift from emergent to elective operations[64,84]. The changes in prevalence of modifiable risk factors affecting IBD, such as smoking and obesity, may also be contributing to surgical rates[85,86].

IMPACT OF HIGH VOLUME IBD-CARE ON HOSPITALIZATIONS

With the increasing number of patients afflicted by this disease coupled with the increased complexity for inpatient and outpatient treatment, there is mounting data demonstrating improved outcomes for patients when care is specialized (Table 1). Multidisciplinary teams (MDTs) exist in the United States and abroad and the makeup of teams varies from institution to institution. Committees of expert opinion have met and made reasonable recommendations for what should comprise an IBD MDT[87]. Colectomies performed by high-volume IBD colorectal surgeons show better outcomes, even when adjusted for volume of cases at their institutions[88,89]. In one study, IBD-specialized gastroenterologists have shown tighter adherence to guidelines, in general[90]. Inpatient IBD care models have found that a personalized, therapeutic approach led by an inpatient IBD gastroenterologist may lead to greater rates of remission and earlier surgical referral and intervention[91]. Increased emphasis has been placed on limiting narcotic use, antibiotic stewardship, enteral nutrition, and venous thromboembolism (VTE) prophylaxis[92-94]. The effects of VTE prophylaxis for IBD patients on hospitalization cannot be overstated as this population has an estimated 2-3 fold increase in incidence of VTE compared to normal population [95,96] as well as higher mortality with VTE[1]. Gastroenterologists with significant IBD experience (greater than 50% of patient volume with IBD) are more likely to provide anticoagulation for hospitalized patients[97], something that is recommended by multiple gastroenterology societies[98,99].

Fragmentation of care, however, appears to be an important risk factor for worse outcomes[100,101]. This may be the case because different institutions may not share documentation, have the same resources or expertise with IBD or directly communicate with a patient's primary gastroenterologist during an admission. Considering these possibilities, it should not be a surprise that fragmented care is associated with worse outcomes. To overcome this obstacle, developing more specialized IBD centers as well as improving communication between providers who care for IBD should be considered.

Regionalization may also impact hospitalization and IBD outcomes. Hospitals with high volume IBD cases, defined as greater than 150 annual IBD-related hospitalizations, have lower in-hospital mortality among patients requiring surgery and shorter post-operative stays[102]. While the care complexities related to IBD may make it a suitable target for regionalization, barriers to implementation include fragmentation, increased travel distance, and patient socioeconomic status. For example, a single-site study showed direct correlation between distance patients live from specialty center and outcomes including need for surgery, biologics and immunomodulators after follow-up period[103]. Additionally, rural IBD patients have greater rates of emergency department visits and hospitalizations compared to urban IBD patients [104]. These are important factors to consider and may aid in the shared decision-making between patients and providers.

Table 1 Components of high-value inflammatory bowel disease care

Component of IBD care	Outcome	Ref.
Availability of subspecialty surgeon	In-hospital mortality for patients undergoing colectomy is lower (2.4%) when performed by subspecialized surgeons when compared to those without subspecialty training (4.8%) after adjusting for hospital and surgeon volume as well as patient characteristics	Callahan *et al* [88]
Patient proximity to specialized IBD center	Need for surgery, immunomodulators and biologic therapy all significantly increased in patients who live furthest from a specialty IBD center	Borren *et al*[103]
Establishment of a specialized IBD unit	Patients treated in IBD specialty units found to have greater remission rates at 90 days, equal surgery rates (yet higher non-resection surgery rates at 30 d) and earlier initiation of high-dose biologic therapy when compared to non-specialized group	Law *et al*[91]
Fragmentation of care	Patients receiving fragmented care (*i.e.*, readmission to non-index hospital) found to have larger in-hospital mortality	Cohen-Mekelburg *et al* [100]

IBD: Inflammatory bowel disease.

CONCLUSION

An understanding of the burden of IBD hospitalizations is important for cost containment and disease management. Population-based studies provide the best reflection of real-world strategies and have shown that there has been an overall increase in IBD hospitalization rates and decrease in endoscopy and emergency surgery. IBD hospitalization is impacted by disease epidemiology as well as medical, endoscopic, and surgical treatment. Improved inpatient care for IBD patients over time may comprise of the increased utilization of disease modifying agents in the outpatient setting, assessment of short and long-term outcomes of elective surgeries, and early access to high-volume IBD care.

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