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Original Article

Intravenous Albumin in Patients With Cirrhosis: Evaluation of Practice Patterns and Secular Trends of Usage in Ontario 2000 to 2017

David Mario Rodrigues, MD MSc[1], Maya Djerboua, MSc[2], Jennifer A. Flemming, MD MAS[1,2,3]

[1]Department of Medicine, Queen's University, Kingston, Ontario, Canada; [2]ICES, Queen's University, Kingston, Ontario, Canada; [3]Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada.

Correspondence: Jennifer Anne Flemming, MD, FRCPC, MAS, Departments of Medicine and Public Health Sciences, Division of Gastroenterology, Kingston Health Sciences Centre – HDH Site, 166 Brock Street, Kingston, Ontario K7L 5G2, Canada, e-mail: Jennifer.Flemming2@Kingstonhsc.ca

Abstract

Background: Intravenous (IV) albumin has evidence-based indications in cirrhosis that are limited in most guidelines to spontaneous bacterial peritonitis (SBP), type 1 hepatorenal syndrome (HRS) and large volume paracentesis (LVP).
This study aimed to describe the trends of IV albumin usage in patients with cirrhosis at the population level and evaluate indications for IV albumin in the hospital setting.
Methods: A retrospective study identified albumin infusions in health care data from Ontario, Canada between 2000 and 2017 in those with and without cirrhosis. Annual rates of IV albumin by cirrhosis status were calculated per 10,000 person-years (PY) and described using Poisson regression and rate ratios. Secondly, patients with cirrhosis receiving IV albumin while hospitalized at Kingston Health Sciences Centre (KHSC) in 2017 were identified and underwent detailed chart abstraction to determine the reason for IV albumin administration.
Results: The overall rate of provincial IV albumin usage doubled over the study period (2000: 8.4/10,000 PY versus 2017: 16.3/10,000 PY; rate ratio 1.94, 95% confidence interval 1.90 to 1.99, P <0.001). The majority of albumin was used during hospitalization (88%) and 22% was used in patients with cirrhosis. At KHSC, there were134 admissions where a patient with cirrhosis received IV albumin. Of these, 49% of prescriptions were for evidence-based indications (LVP 30%, type 1 HRS 10%, SBP 10%), whereas other indications included non-HRS renal failure, hypovolemia and sepsis.
Conclusion: IV albumin use has doubled over two decades and is frequently used in hospitalized patients with cirrhosis with only 50% being prescribed for evidence-based indications. These results highlight the impact of cirrhosis on albumin use and highlight potential quality improvement opportunities.

Keywords: *Albumin; Cirrhosis; Guidelines*

INTRODUCTION

The prevalence of cirrhosis is increasing throughout North America (1,2) with the greatest health care utilization and hospital admission rates occurring in those with decompensated disease and ascites (3).

Intravenous (IV) albumin is a colloidal resuscitation fluid derived from human blood that is used to increase intravascular volume and maintain plasma oncotic pressure to avoid third spacing especially in the setting of hypoalbuminemia (4). Due to circulatory dysfunction in decompensated cirrhosis, IV

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albumin has been used extensively in this population with evidence-based indications of benefit for large volume paracentesis (LVP), spontaneous bacterial peritonitis (SBP) and type 1 hepatorenal syndrome (HRS) (5). Further, data are emerging, suggesting that IV albumin may also be beneficial outside of traditional indications (6,7).

An important caveat is that IV albumin costs over 50-fold greater than IV crystalloid and is associated with risks similar to blood transfusion including allergic reactions, volume overload and theoretical risks of infection (8). Therefore, the decision to utilize IV albumin outside of evidence-based guidelines is discouraged by Choosing Wisely recommendations (9). Despite this, recent survey data of clinicians managing patients with cirrhosis suggest that IV albumin is routinely administered in clinical practice outside of recommended indications, including non-SBP sepsis and small-volume paracentesis (10).

Despite the growing burden of cirrhosis, there has been no data on how this has impacted the usage of IV albumin at the population level. Furthermore, there is little understanding of actual hospital-based clinical practice patterns with regards to IV albumin administration in patients with cirrhosis. This knowledge could help inform quality improvement initiatives into resource utilization. Therefore, the aims of this study were to describe secular trends in the use of IV albumin in those with and without cirrhosis in Ontario over the past two decades and to describe practice patterns for the use of IV albumin in a contemporary cohort of patients with cirrhosis hospitalized at a tertiary care teaching centre.

MATERIALS AND METHODS

Secular Trends in IV Albumin Administration

Study Design and Databases

We performed a retrospective population-based cohort study using routinely collected administrative health care data from the province of Ontario, Canada housed at ICES-Queen's. Ontario provides universal health care coverage for its population of approximately 14 million through the Ontario Health Insurance Program (OHIP). The population of Ontario is ethnically diverse with 25% belonging to a visible minority and 2% being of indigenous descent (11,12). The primary databases used in this analysis were the Registered Persons Database (RPDB), which includes demographic and vital status information for individuals covered under OHIP, the Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD), which captures diagnostic and procedural information from inpatient hospital admissions, the National Ambulatory Care Reporting System (NACRS), which captures diagnostic and procedural information from ambulatory care and emergency room (ER) visits, and the OHIP Physician Claims Database which includes all claims made by physicians for universally insured services. These databases were linked using unique encoded identifiers at the individual level and analyzed at ICES. This study was approved by the Health Sciences Research Ethics Board at Queen's University (DMED 2176-18).

Study Population and Identification of IV Albumin Administration

All individuals insured under OHIP from 2000 to 2017 served as the study base. Those ≥18 years of age with a diagnosis of cirrhosis were identified using a validated case definition in ICES data that requires one inpatient or outpatient OHIP or International Classification of Diseases (ICD) code for cirrhosis or non-bleeding esophageal varices (13). Those with cirrhosis and refractory ascites were further identified if an individual with cirrhosis required three or more therapeutic paracenteses during a 3-month period with at least one paracentesis occurring ≥1 month after the first. Therapeutic paracenteses were identified using OHIP billing code Z591. The use of IV albumin was identified using a mandatory inpatient and outpatient reporting variable which is recorded in both CIHI DAD and NACRS datasets and has been extensively validated for accuracy for this purpose (14,15). This variable indicates that IV albumin was administered; however, it does not provide details on the type or dosage infused. The location of IV albumin administration was considered to be inpatient if recorded in the CIHI DAD and outpatient/ER if recorded in NACRS. We also identified whether patients had comorbid congestive heart failure (CHF) and diabetes based on validated case definitions (16–18).

Statistical Analysis

The overall number of encounters with an IV albumin infusion per year was described for the overall Ontario population and stratified by both cirrhosis status and location (inpatient versus outpatient/ER). The rate of IV albumin infusion per 10,000 person-years (PY) was calculated overall and stratified by cirrhosis status as a denominator. As a result, changes in the rate are expressed both at the general population level and the cirrhosis population level to account for increases in the burden of cirrhosis over the study period. The annual rate of IV albumin administration was compared between those with and without cirrhosis using Poisson regression and described using rate ratios (RRs). All statistical analyses were performed using SAS version 9.4.

Practice Patterns of IV Albumin Administration in Hospitalized Patients With Cirrhosis

Study Design and Database

We performed a single-centre retrospective cohort study of patients with cirrhosis admitted to Kingston Health Sciences Centre (KHSC) from January 1, 2017 to December 31, 2017. Patients ≥18 years were identified initially from the hospital database using ICD codes for cirrhosis and its complications

(K746, K7469, K703, K7031, I859, I982, I9821, K766, R18, K767, I850, I983, l9820, K72990, K7291). Next, a detailed primary chart review was performed by a senior gastroenterology resident (D.M.R.) and patients were included if: (i) a diagnosis of cirrhosis was confirmed, based on either (a) diagnosis of cirrhosis by a hepatologist or gastroenterologist, (b) liver biopsy showing F4 fibrosis or (c) a combination of clinical features, imaging and biochemical parameters suggestive of cirrhosis (elevated bilirubin, elevated international normalizing ratio, platelet count less than 150 or radiographic findings suggestive of portal hypertension); and (ii) at least one dose of IV albumin was infused during the hospital stay based on review of pharmacy records and the nursing chart. Data abstracted from the electronic medical record included patient demographics, etiology of cirrhosis, Model for End-stage Liver Disease (MELD-Na) score, indication for admission, admitting service, gastroenterology consultation, length of stay and inpatient mortality. The indication for IV albumin administration was assigned for each patient as either guideline-based or non-guideline based. Guideline-based indications included (i) SBP, with an ascitic neutrophil count ≥250 cells/μL or a microorganism cultured from the patients' ascitic fluid (5); (ii) LVP of ≥5 L; or (iii) HRS type 1 (19) as per the ascites club definition from 2015. All other indications were considered non-guideline based and the indication in these cases was attempted to be determined by reviewing the documentation by the treating physician. The type of albumin infused (5% versus 25%) and total dosage administered during the hospital stay was abstracted from pharmacy records.

Statistical Approach

Descriptive statistics for all patients were performed using means and standard deviations and medians and interquartile ranges (IQRs) for normal and non-normally distributed continuous data respectively. Categorical variables were described as proportions. Analyses were performed using STATA/SE v. 12.1.

RESULTS

Secular Trends in IV Albumin Administration

Over the study period, a total of 301,882 encounters with IV albumin infusion were identified. In total, over 230,000 encounters with IV albumin involved patients that did not have cirrhosis. These individuals had comorbid illnesses including diabetes (38%) and CHF (34%). Therefore, 22% (n = 65,833) of total provincial albumin was infused in patients with cirrhosis, and in those with cirrhosis, 35% (n = 22,778) were in the subpopulation with refractory ascites (Figure 1). The majority (88%) of IV albumin was given during a hospital admission. The overall annual rate of IV albumin usage nearly doubled in Ontario comparing the year 2000 to 2017 (8.4 per 10,000 PY versus 16.3 per 10,000 PY; RR 1.94, 95% CI 1.90 to 1.99, P < 0.001; Figure 2). Compared to patients without cirrhosis, the rate of IV albumin administration was 46-fold higher in those with cirrhosis (9.9/10,000 PY versus 457/10,000 PY; RR 46.0, 95% CI 45.6 to 46.4; P < 0.001). When comparing annual RRs, there was an average increase of 3% per year in patients with cirrhosis, and 4% per year in those without cirrhosis, giving an average annual increase of 5% per year (P < 0.01) (Supplementary Table 1).

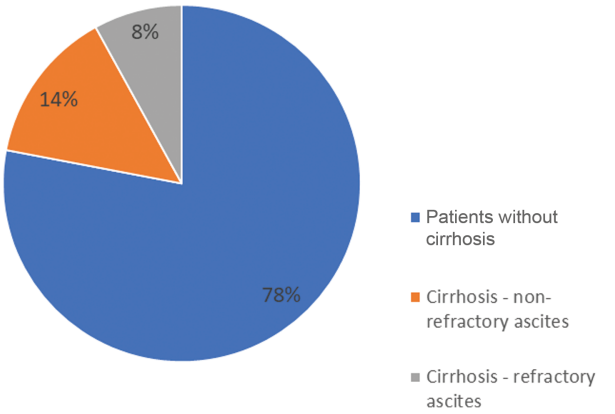

Figure 1. Pie chart demonstrating the allocation of IV albumin prescriptions based on cirrhosis status and whether a patient with cirrhosis belonged to the refractory ascites cohort.

Practice Patterns of IV Albumin Administration in Hospitalized Patients With Cirrhosis

Patient Demographics

A total of 134 admissions of patients with cirrhosis, representing a total of 100 unique patients, and who received IV albumin at KHSC in 2017 were identified and included in the cohort (Table 1). Most patients were male sex (71%) with a median age at admission of 62 years. The most common causes of cirrhosis were alcohol-related (43%) followed by non-alcoholic fatty liver disease (20%) and hepatitis C (16%). The most common indications for admission were hepatic encephalopathy (20%), ascites management (21%), non-variceal gastrointestinal bleeding (10%) and infection/sepsis (7%). The median MELD-Na at admission was 22 (IQR 17 to 27), the majority were admitted to an Internal Medicine service (59%), 24% were admitted to the intensive care unit and 22% of patients died during their hospitalization.

Albumin Use in Inpatients With Cirrhosis

In the 134 admissions, IV albumin was prescribed 173 separate times (Table 2). The median total dose of IV albumin administered per patient during their admission was 125 g (IQR 50 g to 300 g; Table 2). Overall, IV albumin was prescribed for guideline-based indications in 50% (LVP [30%], SBP [10%] and HRS type 1 [10%]) while the other

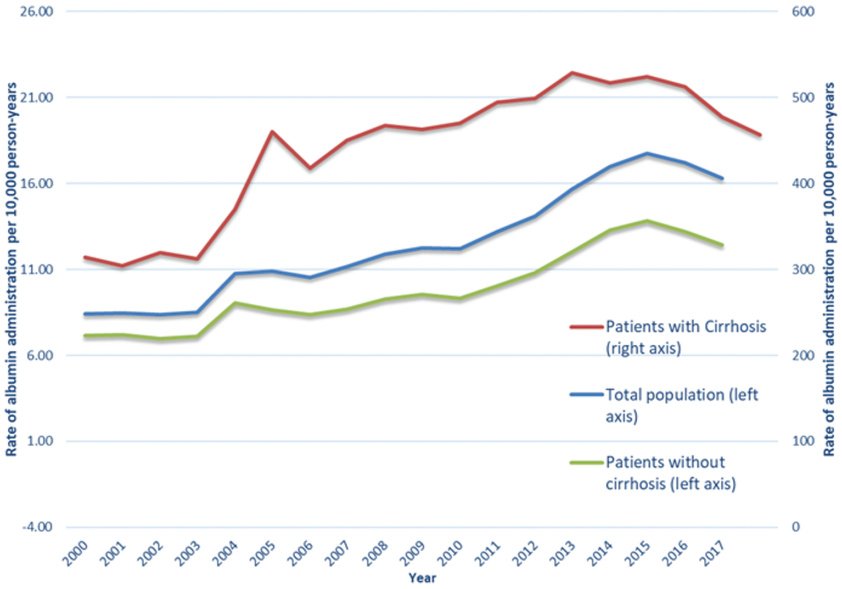

Figure 2. Rate of albumin administration per 10,000 person-years in the Ontario population between the years 2000 and 2017. The light grey line indicates the rate of albumin administration in patients with cirrhosis (right axis). The dark grey and black lines indicate the rate of albumin administration per 10,000 person-years in the total population and those without cirrhosis respectively (left axis).

50% had IV albumin prescribed for indications outside of guidelines. Non-guideline indications for IV albumin administration included hypovolemia (10%), acute kidney injury not meeting HRS criteria (10%), sepsis (8%), paracentesis of less than 5 L (1%), volume overload (1%) and hyponatremia (1%). In the remaining 20%, no clear indication was identified after detailed chart review.

A total of 4750 g albumin was infused for LVP, 3782.5 g was infused in patients with SBP and 6037.5 g was infused for HRS. When albumin was used for LVP, a median of 7.6 g/L of ascites removed was administered (IQR 4.3 g/L to 9.6 g/L).

For SBP, the median dose infused was 200 g (IQR 100 g to 200 g, range 50 g to 800 g), suggesting a wide variance in practice. In total, 53% of patients received a weight-based dose of 2.5 g/kg in total ±25g of IV albumin as per the index trial showing a mortality benefit of IV albumin in the treatment of SBP (20).

The majority of albumin, a total of 16,235g, was prescribed without a guideline-based indication, representing 53% of all albumin used. This would correspond to cost of nearly $34,000 Canadian dollars (CAD) using our institutional purchase price of $2.06 CAD/g of albumin.

Discussion

In this large population-based study, we demonstrate that the provincial rates of IV albumin administration have almost doubled in Ontario over a 17-year period, the majority of which is being prescribed in hospital, with the rate of IV albumin usage being over 40 times higher in those with cirrhosis compared to those without. Further, in a tertiary care teaching hospital, the indications for albumin administration in patients with cirrhosis were for guideline-based indications in 50%, with the other half being prescribed outside of guideline recommended indications.

Our study is the first to describe an increase in the rate of IV albumin administration at the population level, in both patients with and without cirrhosis. This increase is independent of the growing cohort of cirrhosis patients in Ontario given that the total annual cirrhosis population served as the denominator in rate calculations. Our observation is supported by a recent audit by the Ontario Regional Blood Coordinating Network demonstrating an increase in albumin shipments to Ontario hospitals from approximately 156,000 units in 2012 to 189,000 units in 2018 (21). Similar trends of increasing albumin use have been described at the hospital level, including an Italian study where the use of albumin and hospital expense for albumin vials more than doubled between 1998 and 2002 (22). Unfortunately, our data are unable to determine what factors are driving the increased utilization of IV albumin. It is plausible that these trends may also be explained by an increase in the use of evidence-based medicine and publication of clinical practice guidelines for this population. Over the past two decades, the indications for benefit from IV albumin in patients with cirrhosis have largely remained unchanged with randomized control trial data for the use in SBP, HRS and LVP all being published before the year 2000. Interestingly, the annual RRs remained stable between 2000 and 2004 at which point there was an annual increase in IV albumin utilization in both patients with and without cirrhosis. This corresponds to the year the landmark SAFE trial was published in the *New England Journal of Medicine* which contraindicated an earlier Cochrane

Table 1. Demographics of patients admitted to KHSC in 2017

Sample size	134 admissions (100 unique patients)
Age, median years	62 (IQR 56–69)
Male sex, n (%)	95 (70.9)
Length of stay, median days	10 (IQR 7–19)
Cause of cirrhosis, n (%)	
EtOH-related	57 (42.5)
NAFLD	27 (20.2)
Hepatitis C	21 (15.7)
Hepatitis C + EtOH	18 (13.4)
AIH, PBC, PSC	1 (0.8)
Other	8 (7.5)
Reason for admission, n (%)	
Hepatic encephalopathy	41 (20)
Ascites	23 (11.2)
Non-variceal GI bleeding	20 (9.8)
Sepsis	15 (7.3)
HRS type 1	11 (5.4)
EtOH hepatitis	9 (4.4)
Spontaneous bacterial peritonitis	8 (3.9)
Variceal bleed	7 (3.4)
Acute renal failure, non-HRS type 1	5 (2.4)
Other	66 (32.2)
Admitting service, n (%)	
General Internal Medicine	79 (58.9)
Surgery	17 (12.7)
Intensive Care Unit	32 (23.9)
Other	6 (4.5)
Gastroenterology consulted, n (%)	55 (41)
MELD on admission, median	22 (IQR 17–27)
MELD on discharge, median	22.5 (IQR 17–33)
In-hospital mortality, n (%)	29 (21.6)

AIH, autoimmune hepatitis; EtOH, alcohol; GI, gastrointestinal; HRS, Hepatorenal syndrome; IQR, Interquartile range; MELD, Model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

review that suggested there may be increased mortality with IV albumin administration in critically ill patients (23), showing instead there was no significant difference between 4% IV albumin and crystalloid for resuscitation in this patient population (24).

Additionally, recent data have suggested that IV albumin may be beneficial in patients with cirrhosis outside of traditional indications. These data have been largely fuelled by potential physiologic benefit of IV albumin in this patient population. Albumin is thought to reside in the intravascular space more so than crystalloid and therefore may provide sustained volume repletion in those with hypoalbuminemia (5). In addition, albumin may have anti-inflammatory properties including binding proinflammatory molecules such as reactive oxygen species (25) and pathogen-associated molecular patterns (26). This is supported by recent trials showing a decrease in numerous cytokines when albumin is administered to those with decompensated cirrhosis (7). A recent randomized trial has investigated the routine administration of albumin in outpatients with cirrhosis and uncomplicated cirrhosis and found a mortality benefit in those receiving albumin which supports the above mechanisms (6). However, the patients receiving albumin were seen far more frequently by nurses and physicians and, therefore, it is difficult to conclude that albumin was the driving factor in improving mortality. There remains a paucity of evidence for the use of albumin in settings outside of SBP, HRS and LVP. Further studies into the use of albumin in non-SBP sepsis are ongoing and will hopefully provide some guidance. However, it should be noted that the majority of albumin usage in our study was in those without cirrhosis. It is unclear what is driving the increase in these individuals as most

Table 2. Characteristics of albumin administration in patients admitted with cirrhosis

Albumin (g), median dose	125 (IQR 50–300)
Prescriptions for albumin use, total	173
Type of albumin used (%)	
5%	4.7%
25%	95.3%
Large volume paracentesis, n (%)	51 (29.5)
Total amount (g)	4750
Amount administered per litre, median (g/L)	7.6 (IQR 4.3–9.6)
Spontaneous bacterial peritonitis, n (%)	17 (9.8)
Total amount (g)	3782.5
Amount administered per patient, median (g)	200 (IQR 100–200)
HRS Type 1, n (%)	16 (9.2)
Total amount (g)	6037.5
Amount administered per patient, median (g)	387.5 (IQR143.75–506.25)
Other, n (%)	
Hypovolemia	18 (10.4)
Non-HRS Type 1 renal failure	18 (10.4)
Sepsis	13 (7.5)
Small-volume paracentesis	2 (1.1)
Volume overload	2 (1.1)
Hypernatremia	1 (0.5)
No indication identified	35 (20.0)

HRS, Hepatorenal syndrome; IQR, Interquartile range.

data suggest very few evidence-based indications for IV albumin outside of patients with liver disease. Further evaluation of the usage of albumin in patients without cirrhosis may help to explain our observed trends.

The finding that albumin is often prescribed outside of guidelines in patients with cirrhosis is consistent with a physician survey study from France demonstrating regular use of IV albumin outside of guideline-based indications including 70% of physicians providing IV albumin in chose receiving a <4 L paracentesis and 44% providing IV albumin for hypoalbuminemia (10). In addition, the results are in keeping with prior studies in patients without cirrhosis. In patients without cirrhosis, the only indications supported by the Canadian Blood Services for the use of albumin are either in the setting of plasmapheresis or thermal injury involving >50% of one's total body surface area that is unresponsive to crystalloid resuscitation (27). Observational studies support its use in postoperative volume resuscitation after cardiac surgery after failure of crystalloid therapy (28). In a large cohort of patients receiving IV albumin throughout a 53-hospital network in the United States, IV albumin was prescribed outside of clinical guidelines in nearly 60% of cases with the indications including shock, sepsis, intradialytic blood pressure support and hypoalbuminemia (29). A similar observational study across 22 public hospitals in Spain has showed that 24% of 242 albumin prescriptions were considered 'appropriate' by a consensus document from a multidisciplinary team, the rest of which was deemed 'inappropriate' or 'inadequately documented'. This corresponded to an excess of $140,000 USD spent to purchase albumin over a 5-month period (30). Although there is a lack of high-quality evidence-based guidelines for IV albumin administration outside of the cirrhosis population, these studies underscore a similar trend of indiscriminate utilization in the non-cirrhotic population.

This study highlights the need for institutions to consider quality initiatives to mitigate excessive albumin use. Others have shown that simple interventions can curb trends in increased utilization. For instance, the use of albumin and hospital expense for albumin vials more than doubled between 1998 and 2002 at a university-affiliated public hospital in Italy (22). When a hospital-wide clinical practice guideline was drafted in 2003 limiting the use of IV albumin, the increasing trend was attenuated, and this change persisted for at least 6 years after the intervention (22). Furthermore, studies have shown that when physicians must provide justification for administration of packed red blood cells through the use of pre-printed order sheets, the quality of transfusion orders improved (31). Similar evidence-based pre-printed order sheets for IV albumin may therefore be of benefit. If such institutional regulations are adopted in a widespread manner, this could result in substantial changes in albumin use and health care expenditure.

There are several limitations with our study. First, we used a mandatory administrative albumin reporting variable to capture albumin administration. This variable was not able to provide information on the type or volume of IV albumin infused; however, this may in fact underestimate the total amount of IV albumin. Secondly, our retrospective chart review was a cohort from a single tertiary care centre and included patients with advanced cirrhosis (median MELD 22 on admission) and therefore may not be generalizable to the general population of patients with cirrhosis admitted to hospital.

In conclusion, this is the first study to describe a large increase in the use of albumin administration at the population level in both patients with and without cirrhosis over the past two decades. After evaluating real life practice patterns of albumin administration in a tertiary care cohort of patients with cirrhosis, we found that IV albumin was prescribed outside of clinical practice guidelines in 50% of cases. These data identify patient populations where the use of quality improvement initiatives may translate into improved adherence to evidence-based medicine and substantial cost savings. Future work to determine indications for albumin use in patients without cirrhosis is warranted.

Supplementary Data

Supplementary data are available at *Journal of the Canadian Association of Gastroenterology* online.

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Conflicts of Interest: No conflicts of interest to disclose.

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