Risk of bacteremia in hospitalised patients with inflammatory bowel disease: a 9-year cohort study

United European Gastroenterology Journal
2020, Vol. 8(2) 195–203
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DOI: 10.1177/2050640619874524
journals.sagepub.com/home/ueg

Idan Goren¹ , Adi Brom², Henit Yanai¹, Amir Dagan³, Gad Segal² and Ariel Israel⁴

Abstract

Background: Patients with inflammatory bowel disease might be at increased risk of invasive bacterial infections. **Objectives:** The objective of this study was to identify the rate of bacteremia in hospitalised patients with inflammatory bowel disease and risk factors.

Methods: An observational cohort of hospitalised patients with inflammatory bowel disease, aged 16–80 years, from 2008 to 2017 in a large tertiary hospital. Patients with Charlson comorbidity index of 2 or greater were excluded. Patients with one or more positive blood culture were reviewed. Logistic regression was used to evaluate risk factors for bacteremia.

Results: Of 5522 admitted patients, only 1.3% had bacteremia (73/5522) (39, Crohn's disease; 25, ulcerative colitis; nine, unclassified inflammatory bowel disease). The most common pathogen was *Escherichia coli* (19/73 patients). The mortality rate at 30 days of patients with bacteremia was 13.7% (10/73). Longer hospitalisations (mean length of stay 21.6 ± 31.0 vs. 6.4 ± 16.0 days; $P < 0.0001$) and older age (mean age 47.5 ± 18.0 vs. 40.2 ± 15.4 years, $P < 0.0001$) were associated with an increased risk of bacteremia. In multivariate analysis, treatment with either anti-tumour necrosis factor α , purine analogues, steroids or amino salicylates was not associated with an increased risk of bacteremia. Risk was greatest among patients aged 65 years or older (relative risk 2.84, 95% confidence interval 1.6–4.8; $P = 0.0001$) relative to those under 65 years.

Conclusion: Age over 65 years, but not inflammatory bowel disease-related medications, is associated with an increased risk of bacteremia in hospitalised patients with inflammatory bowel disease.

Keywords

Inflammatory bowel disease, ulcerative colitis, Crohn's disease, bacteremia, risk factors, hospitalization, anti-TNF

Received: 21 June 2019; accepted: 8 August 2019

Key summary

1. Summarise the established knowledge on this subject:

- The hospitalisation of patients with inflammatory bowel disease is not uncommon, despite advances in patient care.
- The mere presence of disease as well as immunomodulatory and biological therapy are risk factors for invasive bacterial infections in patients with inflammatory bowel disease.

The final two authors contributed equally.

*Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

#Affiliated to the Faculty of Medicine, Ben-Gurion University, Beer Sheva, Israel.

Corresponding author:

Idan Goren, Division of Gastroenterology, Rabin Medical Center, Petah-Tikva, Israel.
Email: idango1@clalit.org.il

¹Division of Gastroenterology, Rabin Medical Center*, Petah Tikva, Israel

²Internal Medicine T, Chaim Sheba Medical Center*, Tel-Hashomer, Ramat-Gan, Israel

³Rheumatology Unit, Assuta Medical Center, Ashdod, Israel[#]

⁴Clalit Jerusalem Research Center, Clalit Health Services, Jerusalem, Israel

- Scarce data are known on risk factors for bacteremia in the general population of hospitalised patients with inflammatory bowel disease.
- 2. What are the significant and/or new findings of this study?
- In a large cohort of hospitalised patients with inflammatory bowel disease, bacteremia was a rare event, occurring in only 1.3% of the cases, but carries a high mortality rate of 13.7% at 30 days.
- *Escherichia coli* was the most commonly isolated pathogen, and the overall rate of multidrug resistant bacteria was 13.7%.
- Inflammatory bowel disease-related medications were not associated with an increased risk of bacteremia.
- Clinicians should consider the increased risk of bacteremia among patients with advanced age (>65 years) and multiple comorbidities.

Introduction

During hospitalisation, patients with inflammatory bowel disease (IBD), both Crohn's disease (CD) and ulcerative colitis (UC), may be at increased risk of infections both inside and outside the gastrointestinal tract.^{1,2} Of particular importance are invasive bacterial infections that might become life-threatening.³

Several factors put patients with IBD at increased risk of invasive bacterial infections. These include alteration of barrier function in the inflamed intestine leading to increased permeability,^{4,5} malnutrition-associated immune dysfunction,⁶ as well as IBD-associated surgical complications.⁷ Similar to the general population, aging and comorbidities are additional risk factors for immune dysregulation and invasive bacterial infections.⁸ Importantly, IBD-related medications such as steroids, immunomodulatory and biological therapies have previously been found to be independently associated with infectious complications.^{9–11} Previous studies have linked IBD therapies, particularly steroids, with serious infections,^{12,13} and anti-tumour necrosis factor (TNF) α with an increased risk of specific invasive bacterial infections (e.g. *Mycobacterium tuberculosis*^{14,15} and *Staphylococcus aureus*).¹⁶ However, specific data on risk factors for bacteremia in the general population of hospitalised patients with IBD are scarce.^{16–19}

The aim of this study was to identify bacteremia rates among hospitalised patients with IBD, risk factors associated with bacteremia and the associated mortality rates.

Methods

Study design and patient selection

In this study we analysed a cohort of consecutive adult IBD inpatients from Chaim Sheba Medical Center, the largest tertiary medical centre in Israel. The study was approved by the institutional ethical review board (# 3284-16-SMC, July 2016, study protocol extended on July 2017) based on the ethical guidelines of the Declaration of Helsinki. Due to the retrospective nature of the study protocol, the review board waived

the requirement to obtain any informed consent from study participants. Access to the Israeli national population registry was approved by the committee for research review of the Ministry of Health (# 20162054).

Data were retrieved from the electronic medical records (EMRs) of all hospitalised patients with IBD between January 2008 and December 2016. Patient records were maintained using the Chameleon information system (Elad Healthcare Solutions). Data collection was performed using structured query language and custom Python scripts. Identification of patients with IBD was based on International Classification of Disease (ICD)-9CM diagnosis code of 555.x (Crohn's disease, CD) or 556.x (ulcerative colitis, UC) recorded at the time of hospital admission. Medication use prior to admission was retrieved from the EMR.

Patients were uniquely identified by their national ID number. Blood cultures were retrieved from the computerised registry of blood cultures taken at the hospital. Mortality events were queried from the Israeli national population registry for these patients. Hospitalisation charts of all hospitalised patients with IBD having one or more blood culture were retrieved and hospitalisation data were searched. We included for analysis all admissions of patients with an IBD diagnosis during the study period, to either medical or surgical departments, aged 16–80 years at the date of admission. Patients with significant comorbidities, defined as Charlson comorbidity index (CCI)²⁰ of 2 or greater (excluding age component) were excluded, as these patients may have a high a priori risk of invasive infections.

Study definitions

For validation purposes, hospitalisation records of patients with positive blood cultures were reviewed by an internal medicine specialist to assess whether bacteremia occurred. In summary, organisms that are commonly identified as contaminants (such as coagulase-negative staphylococci) were excluded, unless clinically correlated with invasive bacterial infection, resulting in two or more separate cultures and/or cultures from different venipunctures. Otherwise, only organisms known to cause true bacteremia were considered.

These bacteria include, for instance, *S. aureus*, *E. coli* and other Enterobacteriaceae and *P. aeruginosa*.²¹

Antimicrobial-resistant bacteria (ARB) were documented based on the following classification: methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant Enterococcus species (VRE), extended-spectrum β -lactamase (ESBL)-producing *E. coli* and Klebsiella species, penicillin-resistant *Streptococcus pneumoniae* and carbapenem-resistant Enterobacteriaceae and *P. aeruginosa*.

Confirmed bacteremia not related to an infection at another site that developed in patients with a central line, was defined as central line-associated bloodstream infections.

Data analysis

We used the *t*-test to determine the statistical significance of differences in ordinal features and the Fisher's exact test for categorical features. We used logistic regression models to evaluate associations between demographics, clinical parameters and medications used before admission and the occurrence of bacteremia. For each medication, we calculated the odds ratios (ORs) for bacteremia using univariable models, and adjusted ORs in multivariable models, adjusted for age, gender, comorbidity differences (using CCI and Norton scale),²² estimated glomerular filtration rate and fasting glucose; 95% confidence intervals (CIs) were computed using the Wald test. All statistical analyses were performed using R statistical language (R 3.5.1).

Results

Study population

During the study period, 8733 hospitalised IBD cases were identified, of which 3155 were excluded: 2632 cases due to CCI 2 and greater and 523 due to age criteria (<16 and >80 years). Of the remaining 5578 cases, 129 had positive blood cultures and underwent screening. Overall, we eliminated 56 cases from the final analysis: in 37 cases, we identified contamination, and in 19 patients there was inconclusive clinical evidence to define bacteremia (Figure 1). Finally, only 1.3% (73/5522) of the entire cohort of hospitalised patients with IBD had a diagnosis of bacteremia, of which 53.4%, 34.2% and 12.4% had CD, UC and IBD unclassified, respectively. Table 1 summarises the baseline characteristics of these groups.

Background diagnoses in patients with and without bacteremia were comparable (see Supplementary Table 1). Comparison of clinical indices and main laboratory analyses obtained at the first emergency department

Figure 1. Flowchart of study population.

Table 1. Demographic data.

	No bacteremia (n = 5449)	Bacteremia (n = 73)	P value
Sex, male (%)	2315 (42.5)	43 (58.9)	0.007
Age, mean (SD)	40.2 (15.4)	47.5 (18.0)	<0.0001
LOS in days, mean (SD)	6.4 (16.0)	21.6 (31.1)	<0.0001
CD (%)	3,364 (61.7)	39 (53.4)	0.18
UC (%)	1,685 (30.9)	25 (34.2)	0.63
Charlson comorbidity score, ^a mean (SD)	0.11 (0.31)	0.21 (0.41)	0.007
Norton score, mean (SD)	19.9 (0.4)	19.9 (0.4)	0.83

SD: standard deviation; LOS: length of hospital stay; CD: Crohn's disease; UC: ulcerative colitis.

^aMean Charlson scores excluding age component.

measurement on hospital admission is presented in Supplementary Table 2.

Cause of admission in patients with bacteremia

Table 2 lists the admission diagnosis for patients who have been subsequently diagnosed with bacteremia. The most common cause of hospital admission was IBD exacerbation (20/73, 27.4%). Seven patients

were hospitalised due to surgical complications of IBD: abdominal or perianal abscesses (5/73, 6.8%), bowel perforation (1/73, 1.3%) and gastrointestinal bleeding (1/73, 1.3%). Supplementary Table 3 compares the characteristics of the subgroup of patients

who were admitted to the hospital due to (suspected) infection, namely urinary tract infection, cholangitis, cellulitis, line sepsis, fever or neutropenic fever, with patients who developed bacteremia, but were not admitted with a working diagnosis of infection.

Table 2. Cause of admission in patients who were diagnosed with bacteremia during hospitalisation.

Initial diagnosis at admission, N (%)	73 (100)
Inflammatory IBD exacerbation	20 (27.4)
Sepsis and/or septic shock	13 (17.8)
Fever and/or neutropenic fever	8 (10.9)
Abdominal or perianal abscesses	5 (6.8)
Cholangitis	5 (6.8)
Pneumonia	4 (5.4)
Bowel obstruction	3 (4.1)
Postpartum infection	3 (4.1)
Bone marrow suppression	2 (2.7)
Central line sepsis	2 (2.7)
Gastrointestinal bleeding	2 (2.7)
Urinary tract infection	1 (1.4)
Bowel perforation	1 (1.4)
Elective surgery	1 (1.4)
Gastrointestinal bleeding	1 (1.4)
Cellulitis	1 (1.4)
Meningitis	1 (1.4)

IBD: inflammatory bowel disease.

Rate of antimicrobial-resistant bacteria

Table 3 summarises the ten most common bacterial pathogens isolated from blood cultures. The most common pathogen isolated was *E. coli*, accounting for 19 (26%) of bacteremia cases, followed by *P. aeruginosa* (14%), methicillin-sensitive *S. aureus* (MSSA) (11%), MRSA (3%), *Klebsiella pneumoniae* (10%) and coagulase-negative Staphylococcus (CONS) (10%).

As patients with IBD are frequently being exposed to repeated antibiotic therapies, we also analysed the prevalence of ARB within the group. The overall rate of ARB was 13.7% (10/73): five patients with ESBL-producing *E. coli*, two patients with ESBL-producing *K. pneumoniae*, two with MRSA and one patient with VRE.

Mortality rates in patients with IBD and bacteremia

Mortality rates at 7 days varied according to the pathogen, and ranged from 29% in patients with CONS to 13% and 10% in patients with MSSA and *E. coli* bacteremia, respectively. Overall, among patients with bacteremia the 30-day mortality rate

Table 3. Ten most common pathogens identified among hospitalised patients with IBD and bacteremia and associated mortality rates.

	n (% within bacterial group)		
	Mortality at 7 days	Mortality at 30 days	Mortality at 1 year
<i>Escherichia coli</i> ^a (n = 19)	2 (11)	2 (11)	3 (16)
<i>Pseudomonas aeruginosa</i> (n = 10)	0 (0)	2 (20)	2 (20)
<i>Staphylococcus aureus</i> ; MSSA (n = 8)	1 (13)	1 (13)	1 (13)
<i>Staphylococcus aureus</i> ; MRSA (n = 2)	0 (0)	0 (0)	0 (0)
<i>Klebsiella pneumoniae</i> ^b (n = 7)	0 (0)	0 (0)	0 (0)
Coagulase-negative staphylococcus (n = 7)	2 (29)	2 (29)	4 (57)
<i>Enterococcus faecalis</i> ^c (n = 3)	1 (33)	2 (67)	3 (100)
<i>Campylobacter jejuni</i> (n = 2)	0 (0)	0 (0)	1 (50)
<i>Listeria monocytogenes</i> (n = 1)	1 (100)	1 (100)	1 (100)
Enterobacter species (n = 1)	0 (0)	0 (0)	0 (0)

IBD: inflammatory bowel disease.

^aFive cases of *E. coli* extended-spectrum beta-lactamase (ESBL).

^bTwo cases of *Klebsiella pneumoniae* ESBL.

^cOne case of vancomycin-resistant enterococci (VRE).

was 13.7% (10/73) and the one-year mortality rate was 20.5% (15/73) (Table 3).

Advanced age is a risk factor for bacteremia

In general, patients who developed bacteremia were relatively older when compared to patients without bacteremia (47.5 ± 18.0 vs. 40.2 ± 15.4 years; $P < 0.0001$), and the relative risk of bacteremia was greatest in patients older than 65 years (RR 2.84, 95% CI 1.6–4.8; $P = 0.0001$), compared with those 65 years or younger. Patients with bacteremia had relatively higher overall morbidity, as determined by the CCI score (0.21 ± 0.41 vs. 0.11 ± 0.31 ; $P = 0.007$). The mean length of stay (LOS) was significantly longer for patients with bacteremia compared to those with no bacteremia (21.6 ± 31.1 vs. 6.4 ± 16.0 ; $P < 0.001$, $P < 0.001$).

Patients with community-acquired bacteremia had shorter hospitalisations compared with nosocomial bacteremia

The average number of hospitalisation days before the first positive blood culture was 5.5 ± 9.8 , whereas the remaining hospital days after the first culture was 17.43 ± 26.5 days on average among the bacteremia group. To assess differences between community-acquired bacteremia (CAB) and nosocomial bacteremia (NB), we then evaluated the characteristics of patients whose blood cultures were obtained within 48 hours ($n = 49$) compared to those obtained more than 48 hours from admission ($n = 24$) (Table 4). The age of patients with CAB was comparable to that of patients with NB (45.2 ± 17.8 vs. 52.4 ± 17.8 ; $P = 0.11$), but patients with CAB had significantly shorter LOS compared to those with NB (10.6 ± 14.6 vs. 43.8 ± 42.3 days; $P < 0.0001$). The one-week mortality rate since the diagnosis of bacteremia was comparable between

NB and CAB groups (8.3% vs. 6.1%; $p = 0.99$). Although the one-month and one-year mortality rate among patients with NB was higher, these differences did not reach statistical difference (16.7% vs. 8.2%; $P = 0.48$ and 29.2% vs. 16.3%; $P = 0.33$, respectively).

Of the 30 patients admitted with a working diagnosis of an infection (Supplementary Table 3), 87% had a positive culture within 48 hours of admission, compared to 53% of IBD patients who developed bacteremia but were not admitted due to infection ($P < 0.01$). Regarding differences in the rate of ARB, with the exception of two patients with community-acquired MRSA and one patient with community-acquired ESBL-producing *E. coli*, the remaining seven patients with ARB were part of the NB group.

IBD-related medications and the risk of bacteremia

Finally, we assessed for IBD and non-IBD-related medications predisposing hospitalised patients with IBD to develop bacteremia using logistic regression models (Table 5). Some agents were associated with an increased relative risk of bacteremia (e.g. bile acid analogues and iron), whereas statins were associated with a significantly reduced risk. The effects of IBD medications were assessed for five pharmaceutical categories (5-aminosalicylic acid, systemic steroids, topical steroids, immunomodulatory agents and anti-TNF α as single agent or in combination). Among IBD-related medications, none was associated with an increased risk of bacteremia. However, mycophenolate mofetil (MMF) was associated with a significantly increased risk of bacteremia.

Discussion

The hospitalisation of patients with IBD is not uncommon, despite advances in patient care.²³ In this large

Table 4. Patient characteristics according to the timing of bacteremia.

IBD patient with bacteremia characteristics	Community acquired bacteremia ^a ($n = 49$)	Nosocomial bacteremia ^b ($n = 24$)	<i>P</i> value
Sex, male, n (%)	30 (61.2)	13 (54.2)	0.75
Age, mean (SD)	45.2 (17.8)	52.4 (17.8)	0.11
LOS (mean (SD))	10.7 (14.7)	43.9 (42.4)	<0.001
CD (%)	29 (59.2)	10 (41.7)	0.25
UC (%)	17 (34.7)	8 (33.3)	1.00
Charlson comorbidity score, mean (SD)	0.11 (0.31)	0.21 (0.41)	0.97
Norton score, mean (SD)	19.9 (0.45)	19.8 (0.45)	0.83

IBD: inflammatory bowel disease; LOS: length of (hospital) stay; CD: Crohn's disease; UC: ulcerative colitis.

^aDefined as bacteremia identified <48 hours of admission.

^bDefined as bacteremia identified ≥ 48 hours of admission.

Table 5. Univariate and multivariate analysis of pre-admission medication and risk of bacteremia.

Medication	Univariate analysis			Multivariate analysis		
	RR	95% CI	P value	RR	95% CI	P value
Glucocorticoids	1.5	0.8–2.6	0.190	1.5	0.8–2.7	0.16
Calcineurin inhibitors	3.4	0.5–25.8	0.232	2.0	0.3–15.5	0.50
Anti-TNF	0.7	0.3–11.6	0.429	0.9	0.4–2.0	0.78
MTX	1.8	0.4–7.4	0.428	1.5	0.4–6.6	0.55
Azathioprine	0.9	0.4–2.0	0.759	1.1	0.5–2.6	0.83
Anti-TNF and immunomodulatory	1.2	0.5–2.3	0.65	1.4	0.6–2.8	0.37
MMF	21.9	4.5–107.3	<0.001	11.1	2.2–57.2	<0.01
Bile acid analogues	6.6	2.8–15.7	<0.001	4.3	1.7–10.7	<0.01
Calcium and vitamin D	3.4	1.7–6.8	<0.001	2.9	1.4–5.9	<0.01
VKA	5.2	2.0–12.3	<0.001	3.9	1.5–9.9	<0.01
Statins	0.3	0.1–1.4	0.13	0.1	0.0–0.5	<0.01
Parenteral iron	3.8	0.9–16.5	0.06	7.1	1.6–31.1	<0.01
Oral iron	3.8	1.2–12.6	<0.05	3.7	1.1–12.2	0.03
Beta-blockers	7.3	2.2–24.2	0.001	4.3	1.2–15.4	0.02
Aldosterone antagonists	8.7	3.0–25.2	<0.001	3.6	1.1–11.1	0.04
Anti-propulsive agents	4.5	1.4–14.9	0.01	3.7	1.1–12.6	0.03

RR: relative risk; CI: confidence interval; anti-TNF: anti-tumour necrosis factor; MMF: mycophenolate mofetil; VKA: vitamin K antagonists.

cohort of hospitalised patients without significant comorbidities other than IBD, we identified bacteremia as a rare event, occurring in only 1.3% of the cases. Among patients with IBD with bacteremia during hospitalisation, the mortality rate was 13.7% at 30 days. *E. coli* was the most commonly isolated pathogen causing bacteremia. Advanced age was a risk factor for bacteremia and poor clinical outcomes. In particular, patients aged 65 years and more were at increased risk of bacteremia with a RR of 2.84. None of the IBD-related medications was associated with an increased risk of bacteremia.

The prevalence of bacteremia was low in our cohort. Consistent with our finding, a 10-year Danish multi-centre all-cause hospitalisation cohort study of more than 276,000 adult patients has identified the incidence of bacteremia to be as low as 14.2 per 1000 admissions.²⁴ Particularly in patients with IBD, in a recent large-scale study in a nationwide French cohort of more than 190,000 hospital discharge records of adult patients with IBD, only 611 cases classified as sepsis, systemic inflammatory response syndrome (SIRS) of infectious origin and septic shock were reported over a 5-year period.²⁵ As in our analysis, age older than 65 years has been found to be a risk factor. Similarly, among patients with CD followed prospectively as part of the TREAT registry,²⁶ fewer than 1.5% of serious infections necessitating hospitalisation were due to sepsis or bacteremia.

We found no significant baseline differences between patients with community and nosocomial acquired bacteremia, besides that the latter had a longer LOS. Prolonged LOS has previously been shown both to contribute to the risk of bacteremia as well as to result from prolonged hospital stay.^{27,28} Indeed, our data show that most bacteremia cases were identified 5.5 days from hospital admission, which may imply that this infectious complication may potentially have contributed to the longer LOS within this group of patients compared to patients with no bacteremia (21.6 vs. 6.4 days). However, delay in the identification of invasive bacterial infection as well as complicated medical conditions necessitating a longer hospital stay may contribute as well and cannot be excluded.

In our cohort, the 30-day mortality rate among patients with bacteremia was 13.7%. Data regarding mortality due to invasive bacteremia vary significantly between studies and may be highly dependent on differences in both patient characteristics (i.e. age groups and comorbidities), healthcare settings (i.e. outpatient, intensive care) and the use of different methodologies and definitions. For instance, data from the American Nationwide Inpatient Sample, collecting longitudinal hospital care data from multiple centres, showed a high in-hospital mortality rate of 26.5% in patients with IBD hospitalised with severe sepsis.²⁹ Conversely, in our cohort, less than one fifth of patients presented with sepsis or severe sepsis. Among the

French cohort mentioned previously,²⁵ the mortality rate at 3 months among patients with serious infection was only 3.9%. However, these results are based solely on administrative data that were identified on hospital discharge. In a recent Japanese study on patients with IBD developing central line-associated bloodstream infection while on supportive intravenous therapy in an ambulatory setting, none of the 83 cases resulted in death.³⁰

In line with previous cohorts,²⁵ the source of most cases of bacteremia were not related directly to IBD complications, despite the fact that IBD exacerbation was the most common indication of hospitalisation accounting for 27% of admissions. As patients with IBD are exposed repeatedly to antibiotic therapies,³¹ the prevalence of ARB within this group in our cohort was 13.7%. Half of the ARBs in our cohort were related to ESBL-producing *E. coli* and 70% were acquired during NB. Similarly, a Canadian case-control study on the prevalence of ARB in hospitalised patients with IBD has identified ESBL-producing Enterobacteriaceae colonisation to be relatively common in this group.¹⁹

Among the different groups of immunosuppressants including combination therapy, only MMF was associated in our cohort with a significantly increased risk of bacteremia. Of note, MMF is not part of the mainstay therapy in patients with IBD. In our cohort only two patients from the bacteremia group and seven patients without bacteremia were treated with MMF. Of the former, one received MMF as adjuvant to steroids for controlling pemphigus vulgaris and the second as part of a combination of immunosuppressive medications to prevent the rejection of a transplanted kidney. As for the commonly used anti-inflammatory medications, our findings are consistent with data from a cohort of more than 10,000 patients with IBD, treated with immunomodulatory drugs or anti-TNF and showing a low incidence rate of bacteremia over 1.4 years of follow-up.³² A recent systematic review and meta-analysis of studies involving biological agents, mostly anti-TNF, corroborated our findings and did not show an increased risk of serious infections, necessitating hospital admission, the use of intravenous antibiotics or resulting in death.^{25,33} Notwithstanding, registries such as TREAT²⁶ did demonstrate an increased risk of serious infections among patients treated with infliximab compared to non-infliximab therapies; however, sepsis and catheter-associated bacteremia were less common in the infliximab-treated group compared to other treatments, and disease activity, rather than medical therapy, was the strongest predictor of serious infection.

Interestingly, unlike anti-inflammatory medications, iron therapy both parenteral and oral, was independently associated with an increased risk of bacteremia. Previous studies have linked iron deficiency with an increased risk of bloodstream infections in a

population-based cohort,³⁴ and iron therapy was reported to impair neutrophil function³⁵ and to serve as a growth factor for bacterial pathogens.³⁶ In addition, in our cohort, bile salt replacement therapy in patients with pancreatic insufficiency was associated with an increased risk of bacteremia. Indeed, studies on animal models suggest a role of bile salts in antibacterial protection caused in part by disruption of bacterial membranes and protein denaturation.³⁷ Moreover, lack of bile salts in a mouse model resulted in bacterial proliferation and mucosal injury in the ileum that may consequently lead to bacterial translocation across the epithelial barrier and results in systemic infection.³⁸ On the other hand, the use of statins showed a significantly lower risk for bacteremia. Such a protective effect had been shown previously in a large population-based registry from Italy suggesting that the use of statins decreased the risk of hospitalisation with bacterial infections.³⁹

Some limitations should be noted. Firstly, as this was a retrospective study, it might be subject to potential bias in the associations. To control for misclassification of bacteremia, medical records of all cases with suspected bacteremia were assessed thoroughly by an independent specialist. Secondly, because of the relatively small number of bacteremia cases, the effect of repeated or concurrent bacteremia on patient mortality was not analysed. Similarly, creating a predictive model for mortality based on limited events of bacteremia could result in overfitting, thus preventing the reliable prediction of future observations. Future larger-scale analysis, separated into training and validation groups, may be used for such a predictive model. Thirdly, the increased risk associated with MMF should be interpreted with caution because only two patients in the bacteremia group received the therapy and both in combination with additional immunosuppressants. Finally, this is a single centre cohort and therefore generalisation of these data might be limited.

In conclusion, based on a large-scale cohort, bacteremia in hospitalised patients with IBD is a rare event but carries a high mortality rate. IBD-related medications are not associated with an increased risk of bacteremia in such patients, whereas age over 65 years is a risk factor.

Declaration of conflicting interests

The authors declared no potential conflicts of interest for the research, authorship, and/or publication of this article.

Ethics approval

The study was approved by the institutional ethical review board at Sheba Medical Center (# 3284-16-SMC, July 2016, study protocol extended on July 2017) based on the ethical guidelines of the Declaration of Helsinki.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Due to the retrospective nature of the study protocol, the review board waived the requirement to obtain any informed consent from study participants.

ORCID iD

Idan Goren <https://orcid.org/0000-0002-2162-2840>

Supplemental material

Supplemental material for this article is available online.

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