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MAJOR ARTICLE

# Association Between Infectious Diseases Consultation and Mortality in Hospitalized Patients With Gram-negative Bloodstream Infection: A Retrospective Population-wide Cohort Study

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***Objectives.*** Data supporting routine infectious diseases (ID) consultation in gram-negative bloodstream infection (GN-BSI) are limited. We evaluated the association between ID consultation and mortality in patients with GN-BSI in a retrospective population-wide cohort study in Ontario using linked health administrative databases.

***Methods.*** Hospitalized adult patients with GN-BSI between April 2017 and December 2021 were included. The primary outcome was time to all-cause mortality censored at 30 days, analyzed using a mixed effects Cox proportional hazards model with hospital as a random effect. ID consultation 1–10 days after the first positive blood culture was treated as a time-varying exposure.

***Results.*** Of 30 159 patients with GN-BSI across 53 hospitals, 11 013 (36.5%) received ID consultation. Median prevalence of ID consultation for patients with GN-BSI across hospitals was 35.0% with wide variability (range 2.7%–76.1%, interquartile range 19.6%–41.1%). In total, 1041 (9.5%) patients who received ID consultation died within 30 days, compared to 1797 (9.4%) patients without ID consultation. In the fully adjusted multivariable model, ID consultation was associated with mortality benefit (adjusted hazard ratio [HR] 0.82, 95% confidence interval [CI] .77–.88, $P < .0001$; translating to absolute risk reduction of −3.8% or number needed to treat [NNT] of 27). Exploratory subgroup analyses of the primary outcome showed that ID consultation could have greater benefit in patients with high-risk features (nosocomial infection, polymicrobial or non-Enterobacterales infection, antimicrobial resistance, or non-urinary tract source).

***Conclusions.*** Early ID consultation was associated with reduced mortality in patients with GN-BSI. If resources permit, routine ID consultation for this patient population should be considered to improve patient outcomes.

**Keywords.** bloodstream infections; gram-negative bacteria; health services research; infectious diseases; health administrative data.

## BACKGROUND

Gram-negative bloodstream infections (GN-BSI) are common and are associated with high mortality, with estimates ranging from 12% to 25% at 30 days [1–3]. An international surveillance program showed that the proportion of BSIs caused by gram-negative bacilli (GNB), in particular multi-drug resistant (MDR) GNB, has increased over the 20-year period from 1997 to 2016 [4]. The burden of GN-BSI will likely continue to increase over time with increasing antimicrobial resistance, coupled with an increasingly susceptible aging population [5, 6]. It is thus essential that we find ways to optimize management and improve clinical outcomes.

The "bundle-of-care" approach, comprising a checklist of interventions to improve quality-of-care, has been used extensively in the management of *Staphylococcus aureus* and *Candida* BSI, and has been associated with improved clinical outcomes including mortality [7–10]. A component common to these care bundles is routine infectious diseases (ID) consultation, which has also been independently associated with

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reduced mortality in these 2 infections in large cohort and quasi-experimental pre-post studies [11–14].

In contrast, the data supporting routine ID consultation in GN-BSI are less robust. A prior systematic review examined this question and identified six studies, however five of these focused only on *Pseudomonas* or MDR-GNB infections rather than GN-BSI in general [15]. Two cohort studies found a significant mortality benefit associated with ID consultation in GN-BSI with hazard ratios (HR) of 0.60 and 0.33 [16, 17]; however, these studies did not account for immortal time bias and may have thus resulted in over-inflated effect estimates [18].

To re-examine this question, we conducted a retrospective population-wide cohort study of patients with GN-BSI in Ontario, Canada. Our primary objective was to determine if ID consultation was associated with a reduction in 30-day all-cause mortality in adult patients hospitalized with GN-BSI.

## METHODS

### Study Setting and Data Sources

The study cohort has been previously described in a separate paper that evaluated the impact of follow-up blood culture collection on mortality in patients with GN-BSI [19]. This population-wide cohort comprised all hospitalized adult patients >18 years old with GN-BSI between April 2017 and December 2021 in Ontario, Canada. Data were obtained from multiple linked health administrative databases at ICES, Ontario. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement. Blood culture data were obtained from the Ontario Laboratories Information System (OLIS), which combines microbiology laboratory data from >100 laboratories across Ontario in a single repository [2, 20]. The full list of data sources is reported in Supplementary Methods.

### Site and Patient Selection

To minimize confounding by hospital, we only included hospitals with ID services available, defined as having at least 5 ID consultations during the 5-year study period. We also excluded patients from hospitals with fewer than 25 patients with GN-BSI in total as these were likely facilities that do not typically manage acute medical problems. Patients who died within 48 hours of the index blood culture collection were excluded. Other patient-level exclusion criteria are reported in Supplementary Methods.

### Primary Exposure: ID Consultation

The primary exposure was ID consultation, defined as any ID physician review between 1 and 10 days following the index date. This was identified using a list of unique fee codes for ID consultations in the Ontario Health Insurance Plan, which can only be charged by accredited ID specialists. To mitigate immortal time bias, we treated ID consultation as a time-dependent exposure, such that patients were considered in the non-exposed group (and contributed unexposed person-time in the Cox model) until the day of ID consultation (as determined by the date of billing code), after which they were switched over to the exposed group [21].

### Outcomes

The collection date of the first positive blood culture that diagnosed the GN-BSI was considered the index date and start of the follow-up period. The primary outcome was time to all-cause mortality censored at 30 days, counted from the index date. Secondary outcomes were 90-day all-cause mortality, and—for the sub-group of patients ≥65 years old—the duration of oral antibiotics prescribed on discharge from index hospitalization. We could only explore antibiotic prescriptions on discharge in this sub-group as population-level data are not available in Ontario for inpatient medications or outpatient medications in those <65 years old.

### Statistical Analyses

To describe variation in ID consultation practices across hospitals, we calculated the proportion of patients receiving ID consultation; we tested if this was associated with size of hospital (measured by total number of patients with GN-BSI) using Pearson's correlation test. To account for clustering by site, the primary outcome was analyzed using a frailty model, an extension of the Cox proportional hazards model with hospital as a random effect (ie, each hospital could have a varying baseline hazard, also known as a frailty term) [22]. We identified a priori confounders based on clinical reasoning for inclusion in the model. These variables were included as time-fixed covariates: patient age, sex, material resources index, Deyo-Charlson comorbidity index [23], immunosuppression, nosocomial infection, infection source, pathogen sub-group, and antimicrobial resistance. Disease severity, as measured by intensive care unit (ICU) admission, was treated as a time-varying covariate. Detailed covariate definitions are specified in the Supplementary Methods. To quantify potential residual confounding, we calculated E-values to determine the minimum strength of association for an unmeasured confounder to significantly change our conclusions [24]. To identify subgroups in whom ID consultation may have a greater benefit, we also conducted a range of subgroup analyses using the primary model. Subgroup analyses were not corrected for multiple testing and findings should be considered exploratory. The secondary outcome of duration of oral antibiotics prescribed on discharged was analyzed using a negative binomial mixed model adjusting for the same confounders as the primary model.

We conducted 3 secondary analyses to (a) evaluate ID consultation as both a fixed and random effect, (b) evaluate the impact of day of ID consultation among the subset of patients who received ID consultation, and (c) estimate from the primary model the absolute risk reduction in 30-day mortality if the entire cohort were to receive ID consultation on day 2 of illness. We also conducted multiple sensitivity analyses, which (a) varied hospital inclusion criteria, (b) varied definition of time window for ID consultation, and (c) excluded outlier sites identified in the secondary random effect model. Methodologic details of these additional analyses are provided in Supplementary Methods.

*P* values < .05 were considered statistically significant, and all hypothesis tests were 2-sided. All analyses were conducted in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) using the coxme, lme4, survival, and forester packages.

## RESULTS

Among 58 335 patients with GN-BSI during the study period, 30 159 patients from 53 hospitals were eligible for inclusion (study flowchart in Figure 1). The mean age was 71.0 years, and 15 882 (52.7%) were male. 11 013 (36.5%) patients received an ID consultation between 1 and 10 days after the index blood culture. Patients with an ID consultation were younger but had a greater comorbidity burden, with a higher proportion of patients with Deyo-Charlson score ≥2 and who were immunosuppressed (Table 1). Patients with an ID consultation also had more high-risk features, such as infection by non-Enterobacterales species, infection by MDR organisms, nosocomial infection, and polymicrobial infection.

The proportion of patients receiving ID consultation varied widely by hospital (median 35.0%, range 2.7%–76.1%, interquartile range [IQR] 19.6%–41.1%, Figure 2*A*). The size of the hospital, as indicated by the total number of patients with GN-BSI, and the proportion of patients with ID consultations were weakly correlated (Pearson's correlation coefficient 0.277, $P = .044$). Most patients received ID consultation early in the course of illness, with the number of ID consultations falling with increasing time from index blood culture (Figure 2*B*).

1041 (9.5%) of patients who received ID consultation died within 30 days, compared to 1797 (9.4%) of patients without ID consultation. In the fully adjusted multivariable model including potential confounders and with ID consultation as a time-varying exposure, ID consultation was associated with a mortality benefit (adjusted hazard ratio [aHR] 0.82, 95% confidence interval [CI] .77–.88, $P < .0001$; Table 2). Obtaining predictions using this adjusted model on the entire study cohort resulted in a predicted 30-day mortality of 10.5% if no patient received ID consultation versus 6.7% if all patients received ID consultation on day 2 of illness, translating to an estimated absolute risk reduction of 3.8% or number needed to treat of 27.

The mortality benefit with ID consultation was still observed when the follow-up period was prolonged from 30 days to 90 days (aHR 0.87, 95% CI .83–.91). It was also robust to changing the definition of ID consultation to 1–5 days instead of 1–10 days (aHR 0.80, 95% CI .75–.86), or including patients already on active ID follow-up from before the GN-BSI episode (aHR 0.82, 95% CI .76–.86). The effect estimate was consistent across multiple sensitivity analyses where we modified hospital exclusion criteria by changing the minimum number of total patients or total consults required for inclusion in the analysis (Supplementary Table 1).

The effect of ID consultation was similar in a mixed model where ID consultation was included as both a fixed and random effect (fixed effect aHR 0.85, 95% CI .78–.93). Supplementary Figure 1 shows the distribution of site-specific HR. There were 2 outliers identified in this model, where >75% of patients with GN-BSI received ID consultation and the observed effect was much larger (HR < 0.6). The mortality benefit of ID consultation was consistent in a sensitivity analysis which excluded these 2 potential influential hospitals (aHR 0.86, 95% CI .80–.92).

Subgroup analyses of the primary outcome showed that ID consultation had a greater benefit in patients with several high-risk features (nosocomial infection, non-Enterobacterales organisms, antimicrobial resistance, non-urinary tract source, or polymicrobial infection; Figure 3). The direction of effect estimate was consistent in the direction of benefit across all subgroup analyses.

Unadjusted 30-day mortality appeared to be lower for patients who received ID consultation earlier in the course of illness compared to those who received ID consultation later (Supplementary Figure 2). After adjustment for the same covariates in the primary model, those who received earlier consultation had lower odds of mortality (adjusted odds ratio [aOR] 0.93, 95% CI .89–.96 per each earlier day of consultation).

To quantify the potential bias introduced through residual confounding, we calculated E-values required to shift the point estimate and upper bound of the confidence interval to an HR of 1.0 (ie, null effect) [24]. To shift the point estimate or upper CI to 1.0, the E-values were 1.74 or 1.56, respectively. This can be interpreted as the minimum strength of association that a confounder (or set of confounders) must have on the same HR scale, to "explain away" the exposure-outcome association observed. Put another way, patients in the no ID consultation group must be significantly different from the ID consultation group by a set of confounders that increases the hazard for mortality in the unexposed group by 1.74- or 1.56-fold for our findings to be invalid.

We had access to outpatient antibiotic prescription data in the subset of patients ≥65 years old (21 277 patients or 70.5% of the cohort). Also, 699 patients who were on long-term antibiotics (defined as having received antibiotics >28 days) were

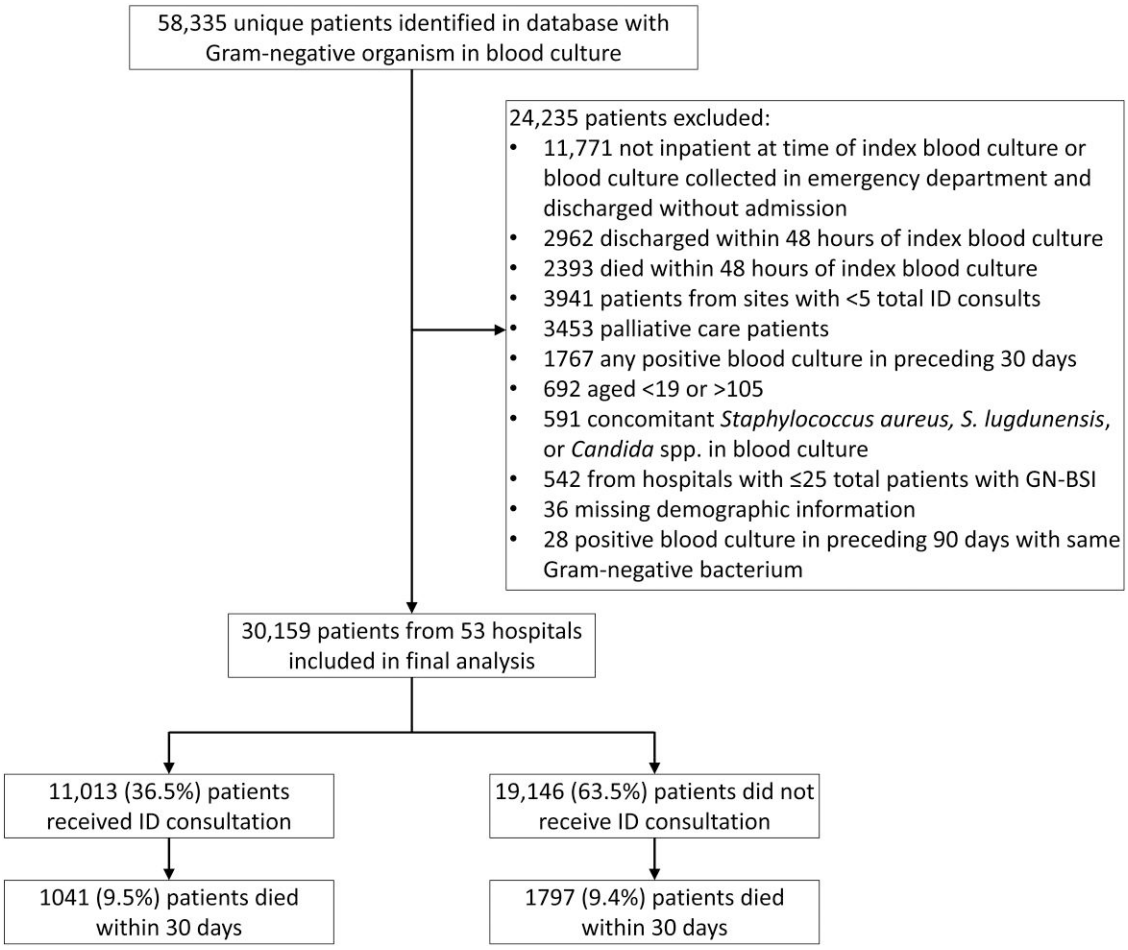


**Figure 1.** Study flowchart. Abbreviations: GN-BSI, gram-negative bloodstream infection; ID, infectious diseases.

additionally excluded, leaving 20 578 or 68.2% of the cohort in this analysis). Patients with ID consultation were less likely to be prescribed antibiotics on discharge (2050 [30.0%] vs 5882 [42.8%]) and had significantly shorter antibiotic durations on discharge (adjusted RR 0.82, 95% CI .76–.87, $P < .0001$).

## DISCUSSION

In a large population-wide cohort of patients with GN-BSI, we found that ID consultation was associated with significantly lower all-cause mortality at 30 and 90 days. We believe that this finding is genuine for several reasons. First, the mortality benefit was consistent across multiple sensitivity analyses where we varied hospital exclusion criteria, changed the consultation definition time window, and excluded potential outlier sites. Second, there was suggestion that earlier consultation could be associated with greater benefit compared to later consultation, consistent with a gradient effect. Third, in subgroup analyses, the observed benefit appeared to be greater in patients with specific high-risk features, which is biologically plausible. It is likely that these patients are the patients for whom ID consultation would make the greatest impact.

Although we could not determine the mechanism of ID consultation that led to this downstream reduction in mortality in our cohort, we hypothesize that ID consultation could lead to more appropriate selection of antibiotics, identification of patients with complicated disease, improved diagnostic workup identifying infectious foci or complications, and early and aggressive source control interventions. These associations have been demonstrated in other BSIs caused by *S. aureus*, *Candida*, *P. aeruginosa*, and *Enterococcus*, where patients receiving ID consultation were more likely to have appropriate antimicrobial selection and adequate source control [11, 13, 26, 27]. Inadequate antibiotic therapy, or a longer time to appropriate antibiotic selection, has been associated with increased mortality in GN-BSI in multiple studies [28–30]. A shorter time to optimal management could explain why greater benefit was seen among patients with earlier consultation.

Separate from this impact on mortality, we also show that ID consultation has additional benefits in reducing oral

**Table 1. Baseline Characteristics of Patients With Gram Negative Bloodstream Infection (GN-BSI) Overall and According to Receipt of Infectious Diseases (ID) Consultation**

| | All Patients (N = 30 159) | ID Consult (n = 11 013) | No ID Consult (n = 19 146) | SMD[a] |
|---|---|---|---|---|
| Male sex | 15882 (52.7) | 6152 (55.9) | 9730 (50.8) | 0.101 |
| Age, years | 71.0 (15.9) | 68.5 (16.4) | 72.4 (15.4) | 0.245 |
| Material resources indicator quintile[b] | | | | |
| 1st | 5276 (17.7) | 1881 (17.2) | 3395 (18.0) | 0.020 |
| 2nd | 5600 (18.8) | 1972 (18.1) | 3628 (19.2) | 0.030 |
| 3rd | 5728 (19.2) | 2164 (19.8) | 3564 (18.9) | 0.024 |
| 4th | 5979 (20.1) | 2182 (20.0) | 3797 (20.1) | 0.003 |
| 5th | 7216 (24.2) | 2717 (24.9) | 4499 (23.8) | 0.025 |
| Rural residence | | | | |
| Yes | 1426 (4.7) | 417 (3.8) | 1009 (5.3) | 0.071 |
| No | 28585 (94.8) | 10547 (95.8) | 18038 (94.2) | 0.071 |
| Missing | 148 (0.5) | 49 (0.4) | 99 (0.5) | 0.010 |
| Deyo-Charlson comorbidity index | | | | |
| No previous hospitalization[c] | 9836 (32.6) | 3070 (27.9) | 6766 (35.3) | 0.161 |
| 0 | 5636 (18.7) | 2039 (18.5) | 3597 (18.8) | 0.007 |
| 1 | 3121 (10.3) | 1071 (9.7) | 2050 (10.7) | 0.032 |
| 2+ | 11566 (38.4) | 4833 (43.9) | 6733 (35.2) | 0.179 |
| Immunosuppressed[d] | 2541 (8.4) | 1303 (11.8) | 1238 (6.5) | 0.187 |
| Gram-negative organism in index blood culture[e] | | | | |
| *E. coli* | 16150 (53.5) | 4931 (44.8) | 11219 (58.6) | 0.279 |
| *Klebsiella* spp. | 5530 (18.3) | 2065 (18.8) | 3465 (18.1) | 0.017 |
| *Pseudomonas* spp. | 1988 (6.6) | 1007 (9.1) | 981 (5.1) | 0.157 |
| *Enterobacter* spp. | 1684 (5.6) | 800 (7.3) | 884 (4.6) | 0.112 |
| *Proteus* spp. | 1456 (4.8) | 479 (4.3) | 977 (5.1) | 0.036 |
| *Bacteroides* spp. | 1091 (3.6) | 526 (4.8) | 565 (3.0) | 0.095 |
| *Serratia* spp. | 590 (2.0) | 326 (3.0) | 264 (1.4) | 0.109 |
| *Citrobacter* spp. | 464 (1.5) | 221 (2.0) | 243 (1.3) | 0.058 |
| *Acinetobacter* spp. | 393 (1.3) | 213 (1.9) | 180 (0.9) | 0.084 |
| *Haemophilus* spp. | 342 (1.1) | 143 (1.3) | 199 (1.0) | 0.024 |
| Other gram-negatives[f] | 1882 (6.2) | 955 (8.7) | 927 (4.8) | 0.153 |
| Organism subgroup | | | | |
| Enterobacterales | 23819 (79.0) | 7825 (71.1) | 15994 (83.5) | 0.301 |
| Anaerobes | 1268 (4.2) | 613 (5.6) | 655 (3.4) | 0.104 |
| Non-fermenters | 2021 (6.7) | 1021 (9.3) | 1000 (5.2) | 0.157 |
| Others | 724 (2.4) | 379 (3.4) | 345 (1.8) | 0.103 |
| Multiple | 2327 (7.7) | 1175 (10.7) | 1152 (6.0) | 0.169 |
| Polymicrobial index blood culture | 3168 (10.5) | 1515 (13.8) | 1653 (8.6) | 0.163 |
| Multi-drug resistant organism[g] | 2800 (9.3) | 1399 (12.7) | 1401 (7.3) | 0.180 |
| Nosocomial infection[h] | 5565 (18.5) | 2461 (22.3) | 3104 (16.2) | 0.156 |
| Infection source | | | | |
| Urinary tract | 15594 (51.7) | 4724 (42.9) | 10870 (56.8) | 0.280 |
| Respiratory | 2109 (7.0) | 945 (8.6) | 1164 (6.1) | 0.096 |
| Intra-abdominal | 4655 (15.4) | 1747 (15.9) | 2908 (15.2) | 0.019 |
| Skin and soft tissue | 1395 (4.6) | 770 (7.0) | 625 (3.3) | 0.170 |
| Other/multiple | 6406 (21.2) | 2827 (25.7) | 3579 (18.7) | 0.169 |
| ICU admission | 3418 (11.3) | 1459 (13.2) | 1959 (10.2) | 0.094 |

Numbers indicate mean (standard deviation) for continuous variables and number (percentage) for categorical/binary variables.

Abbreviations: ICU, intensive care unit; SMD, standardized mean difference.

[a]Standardized mean difference >0.1 suggests a significant difference between the two groups.

[b]The material resources index is a component of the Ontario marginalization index that combines multiple socioeconomic indicators and determinants of health at the neighborhood level. Individuals in the 1st quintile experience the least socioeconomic marginalization, while those in the 5th quintile experience the most socioeconomic marginalization.

[c]Therefore unable to calculate Deyo-Charlson comorbidity index.

[d]Defined as active hematologic malignancy in the preceding 12 m, hematopoetic stem cell transplant in the preceding 12 m, or any previous solid organ transplant.

[e]Total proportions do not add up to 100% as some index blood cultures had >1 organism.

[f]In order of decreasing frequency: *Morganella* spp., *Fusobacterium* spp., *Salmonella* spp., *Providencia* spp., *Stenotrophomonas* spp., *Neisseria* spp., *Moraxella* spp., *Prevotella* spp., *Veillonella* spp., *Pantoea* spp., *Campylobacter* spp., *Raoultella* spp., *Aeromonas* spp., *Pasteurella* spp., *Achromobacter* spp., *Sphingomonas* spp., *Yersinia* spp., *Shigella* spp.

[g]Definition adapted from Dutch antimicrobial resistance surveillance guidelines; refer to Supplementary Methods for full definition.

[h]Defined as index blood culture positive >48 h from admission.

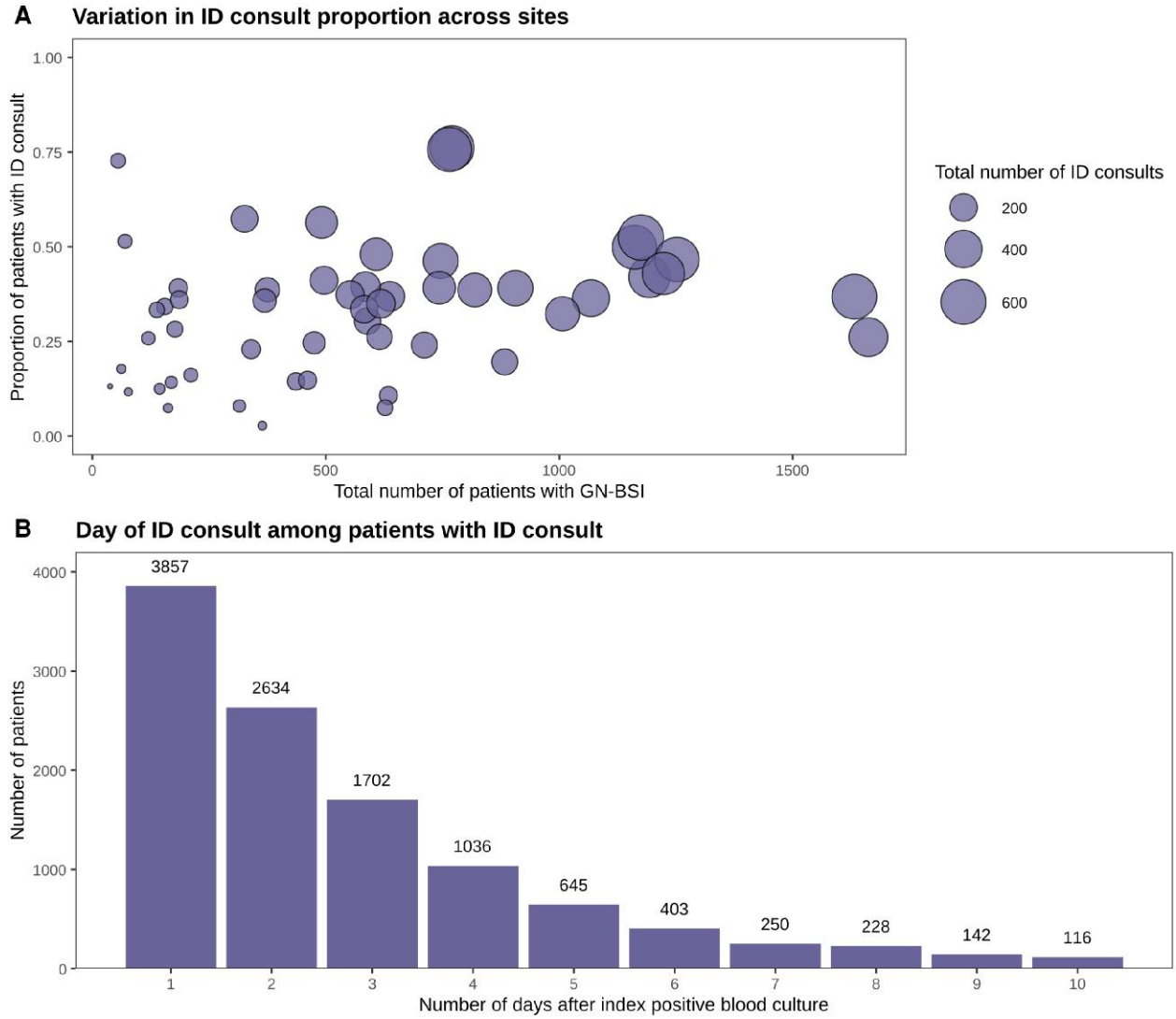


**Figure 2.** Variation in ID consult proportion across sites and breakdown of day of ID consult among patients with ID consult. Panel (*A*) depicts the variation in proportion of GN-BSI patients receiving ID consultation across all hospitals included. Each point represents one hospital, with the size of the point proportional to the number of ID consults at that hospital. The *x*-axis shows the total number of patients with GN-BSI, whereas the *y*-axis shows the proportion of GN-BSI patients who received an ID consultation. Panel (*B*) depicts the breakdown of timing of ID consultation among all patients who received ID consultation in the entire study cohort. Abbreviations: GN-BSI, gram-negative bloodstream infection; ID, infectious diseases.

antibiotic use on discharge. Although we could not explore inpatient antibiotic durations in our cohort, it is possible that this effect applied to inpatient intravenous antibiotic durations as well. Multiple previous studies have demonstrated that ID consultation is associated with more appropriate antibiotic prescribing [31–34]. ID consultation can work synergistically with antimicrobial stewardship programs to increase real-world implementation of shorter treatment durations.

Our findings are consistent with those of previous studies evaluating the impact of ID consultation on outcomes in patients with GN-BSI [16, 17]. However, our study has several advantages over previous work. We used appropriate methodology to address immortal time bias by treating the exposure of interest (ID consultation) as a time-varying exposure. This increases confidence in our conclusions and may also explain why our estimate of benefit may be lower in magnitude than prior studies. Our population-wide cohort allowed us to evaluate the heterogeneity in uptake and effect of ID consultation across different hospitals.

Our study has several limitations. First, given its retrospective observational design, we cannot exclude the possibility of residual confounding. We did not have access to inpatient parameters to calculate quantitative severity indexes such as SOFA scores and hence could only adjust for ICU admission as a surrogate indicator for disease severity. However, it is likely

**Table 2. Results of Primary Analysis for Primary Outcome of Time to All-cause Mortality Censored at 30 Days**

| Variable | Adjusted HR | 95% CI | *P* Value |
|---|---|---|---|
| ID consultation | 0.82 | .77–.88 | <.0001 |
| Male sex | 1.03 | .97–1.09 | .32 |
| Age (per year increase in age) | 1.02 | 1.02–1.03 | <.0001 |
| Organism subgroup | | | |
| Enterobacterales | Ref | Ref | Ref |
| Anaerobes | 1.62 | 1.44–1.81 | <.0001 |
| Non-fermenters | 1.33 | 1.21–1.46 | <.0001 |
| Others | 1.00 | .83–1.21 | .99 |
| Multiple | 1.09 | .92–1.29 | .32 |
| Material resources index[a] | | | |
| 1st quintile | Ref | Ref | Ref |
| 2nd quintile | 1.03 | .93–1.13 | .56 |
| 3rd quintile | 1.05 | .95–1.15 | .34 |
| 4th quintile | 1.06 | .97–1.17 | .2 |
| 5th quintile | 1.12 | 1.02–1.22 | .02 |
| Deyo-Charlson comorbidity index | | | |
| No previous hospitalization[b] | Ref | Ref | Ref |
| 0 | 0.78 | .7–.86 | <.0001 |
| 1 | 1.06 | .96–1.19 | .25 |
| 2+ | 1.48 | 1.37–1.6 | <.0001 |
| Immunosuppressed[c] | 1.35 | 1.24–1.48 | <.0001 |
| ICU admission | 6.33 | 5.93–6.76 | <.0001 |
| Infection source | | | |
| Urinary tract | Ref | Ref | Ref |
| Respiratory | 1.86 | 1.70–2.04 | <.0001 |
| Intra-abdominal | 1.18 | 1.07–1.29 | .0006 |
| Skin and soft tissue | 1.80 | 1.60–2.02 | <.0001 |
| Other/multiple | 1.89 | 1.76–2.03 | <.0001 |
| Multi-drug resistant organism[d] | 1.34 | 1.22–1.46 | <.0001 |
| Nosocomial infection[e] | 1.11 | 1.04–1.19 | .0032 |
| Polymicrobial infection | 1.24 | 1.07–1.44 | .0048 |

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; ID, infectious diseases; Ref, reference group.

[a]The material resources index is a component of the Ontario marginalization index that combines multiple socioeconomic indicators and determinants of health at the neighborhood level. Individuals in the 1st quintile experience the least socioeconomic marginalization, whereas those in the 5th quintile experience the most socioeconomic marginalization.

[b]Therefore unable to calculate Deyo-Charlson comorbidity index.

[c]Defined as active hematologic malignancy in the preceding 12 m, hematopoietic stem cell transplant in the preceding 12 m, or any previous solid organ transplant.

[d]Definition adapted from Dutch antimicrobial resistance surveillance guidelines [25]; refer to eMethods for full definition.

[e]Defined as index blood culture positive >48 h from admission.

that residual confounding should shift the effect estimate in the opposite direction—patients who receive ID consultation are more likely to be those with more severe disease or with a greater comorbidity burden. Nonetheless, we quantified that any potential unmeasured confounding must be in the opposite direction by a relatively large margin (1.74-fold) to explain away the observed association. Residual confounding may also affect the finding that earlier consultation is superior to later consultation—for example, patients may be referred later in the illness course if they develop complications or have persistent bacteremia, which may independently be associated with increased mortality. Second, we could not directly identify the mechanism through which ID consultation impacted mortality, as we had no data available on inpatient antibiotic therapy or source control interventions. Third, the billing code we used to define ID consultation only captures consultations by a registered ID specialist. Other interventions that may review microbiologic data or appropriateness of antibiotic therapy would not be captured (eg, antimicrobial stewardship or pharmacy review), and our findings cannot be extrapolated to those interventions. Fourth, although we had data available for all patients with GN-BSI in the province, we excluded a large number who were admitted to hospitals where no ID consultation service was routinely available. This may compromise the applicability of our findings to similarly less well resourced, community, or rural settings without ID coverage. A previous survey of the distribution of ID specialists in the United States showed that 80% of counties are not served by even a single ID physician [35]. We did not explore access to concomitant services such as surgery or interventional radiology for source control. It is plausible that ID consultation may be more common in centres where these services are more easily available, resulting in potential confounding. Nonetheless, the mortality benefit observed was consistent in our sensitivity analyses restricted to only hospitals with high volume of GN-BSI patients and a high number of ID consultations. These are likely to be academic or tertiary centres with all these services available.

Implementation of routine ID consultation for all patients with GN-BSI may be difficult given resource limitations, even in high-resource settings. ID physicians are in short supply and training positions for ID physicians are regularly undersubscribed [35–37]. One major reason is the lack of competitive remuneration for ID physician services [38]. Similar studies like ours demonstrating the value of ID consultation can support advocacy for improved remuneration and increased capacity for ID physician services in all healthcare settings. Even if routine ID consultation is not logistically feasible for all patients with GN-BSI, we should minimally be prioritizing routine ID consultation for the highest risk patients where it is likely to make the greatest impact. We identified several high-risk features (eg, antimicrobial resistance, non-Enterobacterales infection, non-UTI source) in our subgroup analyses that were associated with greater benefit. Further research should confirm our findings in a prospective quasi-experimental pre-post implementation study or cluster-randomized trial. These should also identify the specific "value-add" components of ID consultation such as the impact on antibiotic choice, added investigations, or source control interventions. Given limited resource availabilities, it will also be important to examine the cost-effectiveness of different implementation policies for routine ID consultation in GN-BSI patient populations.

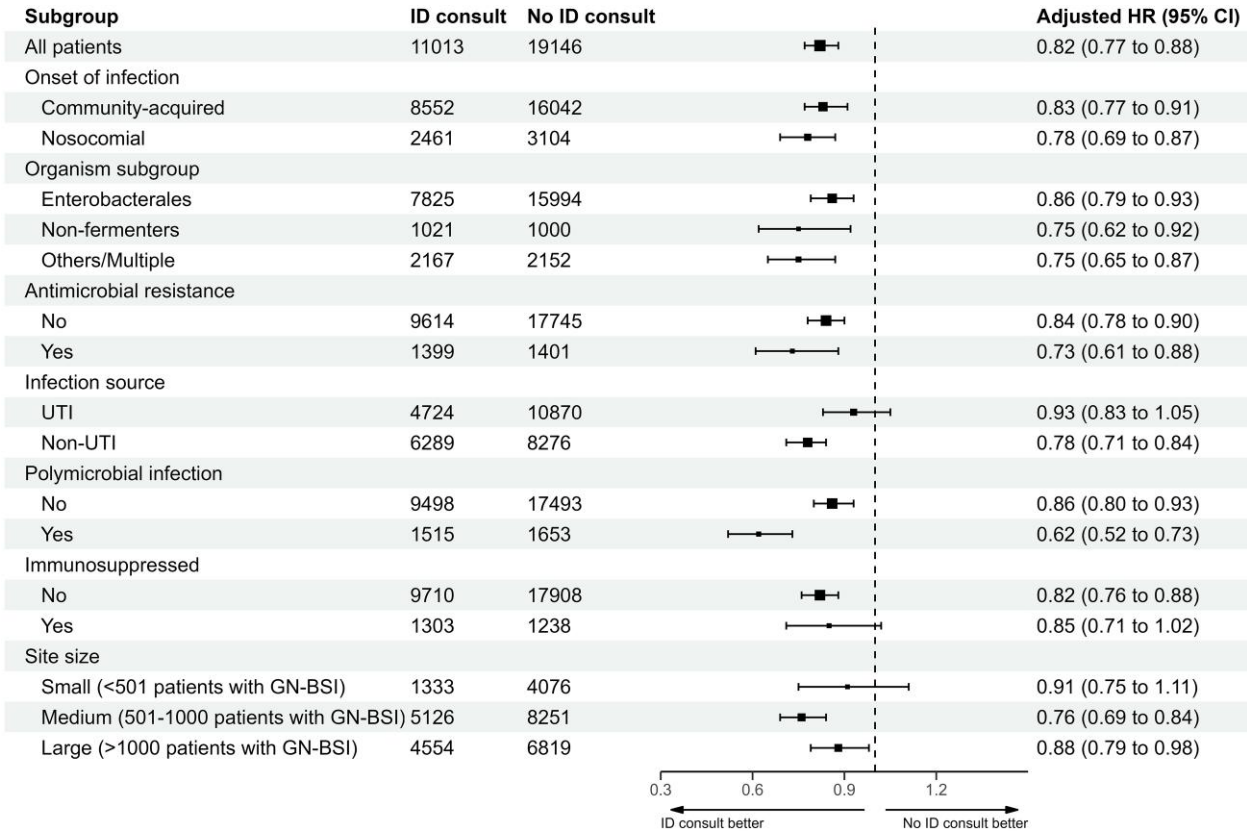


**Figure 3.** Forest plot of association of ID consult and 30-day mortality among cohort subgroups. Abbreviations: CI, confidence interval; GN-BSI, gram-negative bloodstream infection; HR, hazard ratio; ID, infectious diseases; UTI, urinary tract infection.

## CONCLUSION

ID consultation could potentially reduce mortality in patients with GN-BSI. If resources permit, routine consultation for this patient population early in the course of illness should be considered to improve patient outcomes. Future studies should examine the feasibility and cost-effectiveness of widespread implementation of ID consultation.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

***Author contributions.*** Conceptualization: S. W. X. O., N. D.; Methodology: S. W. X. O., N. D.; Formal analysis: S. W. X. O.; Resources: J. L., D. J. F., S. N. P., C. D.; Data curation: J. L., D. J. F.; Writing—original draft: S. W. X. O.; Writing—review and editing: J. J., K. L. S., D. M., B. L., S. Y. C. T., N. D.; Visualization: S. W, X. O.; Supervision: K. A. B., N. D.; Project administration: S. M. L.; Funding acquisition: K. A. B., N. D.

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***Data sharing.*** The data set from this study is held securely in coded form at ICES. Although data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available online at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from +the authors on request, with the understanding that the programs may rely on coding templates that are unique to ICES.

***Ethics approvals.*** ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation, or monitoring of the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES" Privacy and Legal Office.

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