ORIGINAL ARTICLE

Hospitalization Type and Subsequent Severe Sepsis

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Abstract

Rationale: Hospitalization is associated with microbiome perturbation (dysbiosis), and this perturbation is more severe in patients treated with antimicrobials.

Objectives: To evaluate whether hospitalizations known to be associated with periods of microbiome perturbation are associated with increased risk of severe sepsis after hospital discharge.

Methods: We studied participants in the U.S. Health and Retirement Study with linked Medicare claims (1998–2010). We measured whether three hospitalization types associated with increasing severity of probable dysbiosis (non–infection-related hospitalization, infection-related hospitalization, and hospitalization with *Clostridium difficile* infection [CDI]) were associated with increasing risk for severe sepsis in the 90 days after hospital discharge. We used two study designs: the first was a longitudinal design with between-person comparisons and the second was a self-controlled case series design using within-person comparison.

Measurements and Main Results: We identified 43,095 hospitalizations among 10,996 Health and Retirement Study–Medicare participants. In the 90 days following non–infection-related hospitalization, infection-related hospitalization, and hospitalization with CDI, adjusted probabilities of subsequent admission for severe sepsis were 4.1% (95% confidence interval [CI], 3.8–4.4%), 7.1% (95% CI, 6.6–7.6%), and 10.7% (95% CI, 7.7–13.8%), respectively. The incidence rate ratio (IRR) of severe sepsis was 3.3-fold greater during the 90 days after hospitalizations than during other observation periods. The IRR was 30% greater after an infection-related hospitalization versus a non–infection-related hospitalization. The IRR was 70% greater after a hospitalization with CDI than an infection-related hospitalization without CDI.

Conclusions: There is a strong dose–response relationship between events known to result in dysbiosis and subsequent severe sepsis hospitalization that is not present for rehospitalization for nonsepsis diagnoses.

Keywords: microbiota; humans; dysbiosis; patient readmission; self-controlled case series

The role of the microbiome in human health is increasingly recognized (1, 2). Disruption to the microbiome (dysbiosis) is associated with increased host inflammation and has been implicated in the pathogenesis of many chronic diseases, including asthma (3), rheumatoid arthritis (4), inflammatory bowel disease (5), obesity (6), and cancer (7).

Animal studies have shown that gut microbiota may play an important role in the resistance to sepsis (8). However, there are few human studies in this regard. In a recent human case report, antibiotics were unable to resolve septic shock in a 29-year-old woman but fecal microbiota transplant cured her acute illness (9). Furthermore, small studies suggest that

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At a Glance Summary

Scientific Knowledge on the Subject: Hospitalization is associated with microbiome perturbation, especially in the setting of antibiotic therapy. Microbiome perturbation is, in turn, implicated in the pathogenesis of many diseases, including the inability to resist sepsis in animal models.

What This Study Adds to the Field: This study finds that the rate of sepsis is increased in the 90 days after hospital discharge and that the degree of increased sepsis risk correlates with type of prior hospitalization. Hospitalizations with higher probable microbiome perturbation are associated with greater risk of subsequent severe sepsis. This study raises the intriguing possibility that hospitalization-associated microbiome perturbation may be a mediator and actionable target for the pathogenesis of subsequent sepsis.

distortion of the microbiome is associated with the development of sepsis in preterm infants (10, 11). With this evidence in mind, we hypothesized that periods of dysbiosis may impair a patient's ability to resist pathogenic assault. The disrupted microbial homeostasis and elevated inflammatory response inherent to dysbiosis create an environment conducive to the overgrowth of a single pathogen coupled with an overwhelming host inflammatory response (12, 13): the condition of severe sepsis. Determining whether dysbiosis is a risk factor for severe sepsis is critical because the human microbiome can be adjusted through therapeutic manipulation (14–16).

Rather than measure microbiome composition directly, we studied three major events that result in increasing degrees of probable dysbiosis: (1) hospitalization without infection, (2) hospitalization with infection, and (3) hospitalization with *Clostridium difficile* infection (CDI) (17–19). We hypothesized that all hospitalized patients experience diet, sleep, and lifestyle disruptions that perturb microbiome homeostasis (20), as confirmed through direct measurement of fecal diversity in hospitalized patients (17, 18).

Patients hospitalized with infection experience further microbiome disruption, both from the infection and antimicrobial therapy (17, 19). Finally, *C. difficile* exploits a disordered microbiome, and thus serves as the gold-standard marker for dysbiosis (15, 21).

We tested whether (1) hospitalizations with probable dysbiosis are associated with increased risk of subsequent severe sepsis, (2) there is a correlation between the probable severity of dysbiosis during hospitalization and the magnitude of severe sepsis risk, and (3) there is specificity in the dose–response effect of hospitalization type on severe sepsis risk. Although this study cannot serve as definitive proof that dysbiosis is the mediator of the associations we test, we suggest that this work may be hypothesis-generating and brings a novel population-based perspective to the potential clinical importance of these associations. We have previously reported some of these results in an abstract (22).

Methods

Data Source

The Health and Retirement Study (HRS) is an ongoing, nationally representative, cohort study of older Americans. Started in 1992, the HRS has enrolled more than 37,000 participants, of whom 19,722 have agreed to link their data with Medicare (23). The cohort is reinterviewed every 2 years, with a follow-up rate consistently over 90% (23). Patients provided informed consent on enrollment in the HRS and again for linkage to Medicare. This work was approved by the University of Michigan Institutional Review Board.

Subjects

We included all fee-for-service Medicare beneficiaries with a baseline HRS survey in 1998–2008 for whom there were claims-based data on at least one hospitalization without inpatient mortality during 1998–2010.

Primary Outcome: Severe Sepsis Hospitalization

We identified severe sepsis hospitalizations with a commonly used, claims-based definition of severe sepsis that requires International Classification of Diseases (ICD)-9-CM codes for infection and acute organ dysfunction within the same

hospitalization (24). This operationalization of severe sepsis has been validated against physician chart-review and found to have higher sensitivity and similar specificity to other claims-based definitions (25).

Exposures: Hospitalization, Hospitalization with Infection, and Hospitalization with CDI

Our exposures of interest were three types of hospitalizations: (1) non–infection-related hospitalizations, (2) infection-related hospitalizations (without CDI), and (3) hospitalizations with CDI (17, 18). We selected these exposures because we hypothesized that they would be associated with increasing magnitude of dysbiosis. We identified hospitalizations with infection as those with an ICD-9-CM code for infection (the same diagnostic codes included in the severe sepsis definition [24]) in any diagnosis field of the hospital claim. We identified hospitalization with CDI as those with ICD-9-CM code 008.45 ("intestinal infection due to *Clostridium difficile*") in any diagnosis field. This identification method has been validated against a gold standard definition of positive toxin assay and/or visualization of pseudomembranes on colonoscopy, and been found to have high sensitivity and excellent specificity (26).

We considered the duration of the resulting microbiome perturbation to be the 90 days after hospitalization, because several studies suggest that the human microbiome closely resembles its predisturbance state within a few weeks to months after antibiotic exposure (27, 28). Any misspecification of the duration of the exposure biases our results toward the null hypothesis by imprecisely delineating higher and lower risk periods.

Covariates

We calculated Elixhauser comorbidities (n = 31) from inpatient and outpatient claims data for the year before each hospitalization (29). We identified functional limitations in six activities of daily living and five instrumental activities of daily living from the HRS survey immediately before each hospitalization (30). We also determined self-reported race, ethnicity, education, and wealth (sum of all assets and debts standardized to 2013 U.S. dollars) from survey data (23). Wealth, activities of daily living limitations, and instrumental activities of daily living

limitations were missing in 0.1%, 4.1%, and 0.2%, respectively, and these values were imputed. The remaining covariates were present for 100% of the study population.

Statistical Analyses

We present categorical data as numbers (percentages) and continuous data as means (SDs) or medians (interquartile ranges) depending on the distribution. All analyses were conducted with Stata software version 13 (StataCorp, College Station, TX). We used two-sided hypothesis testing and set statistical significance at *P* less than 0.05.

Retrospective Longitudinal Design

We used multiple logistic regression models to evaluate the independent association between the three hospitalization types and probability of readmission for severe sepsis in the 90 days following live hospital discharge. In the regression model, we included all covariates (listed previously). We used hospitalization as the unit of analysis, adjusting for the nonindependence of observations within patients with Stata's vce(cluster) command (31). We estimated missing covariate values (functional limitations, wealth) with multiple imputation by chained equations and five imputations (32).

To confirm that the observed differences in probability of severe sepsis following the three exposures represent differences in severe sepsis risk (not merely differences in propensity for hospital readmission), we also measured the associations with 90-day readmission for diagnoses other than severe sepsis. In the online supplement, we present supplemental analyses that account for patients' competing risk of death before hospital readmission.

Self-controlled Case Series

Because of the possibility for residual confounding with regression models, we also performed a self-controlled case series analysis (33). In the self-controlled case series method, each person serves as his or her own control, so that risk of severe sepsis in the 90 days after a hospitalization is compared with the patient's own baseline risk of severe sepsis, before and after this 90-day period. As a result, temporally invariant covariates are controlled for implicitly. This method uses conditional fixed-effect Poisson regression to measure within-person differences in the rate of an outcome following different exposures (33). We modeled the marginal risk of severe sepsis (outcome) during four different time periods for each subject: (*1*) the 90-day window after hospitalization with CDI; (*2*) the 90-day window after infection-related hospitalization (non-CDI); (*3*) the 90-day window after non–infection-related hospitalization; and (*4*) all other times in the patient's observation period, both before and after the 90-day windows. Figure 1 provides a conceptual diagram of the self-controlled case series analysis, linking the clinical history, microbiome health, and risk periods for a single hypothetical patient. Incidence rate ratios and 95% confidence intervals (CI) were generated to compare severe sepsis rates across different time periods.

For each patient, we considered the start of his or her observation period to be the later of either the first date for which we had linked Medicare claims or the date when the patient was 65 years and 4 months old. We assumed that all Part A fee-for-service beneficiaries were enrolled by age 65 year and 4 months because this signifies the end of the standard enrollment, after which patients incur penalties for late enrollment (34). We considered the end of each patient's observation to be the earlier of either the date of the patient's death, determined from the National Death Index and confirmed by HRS interviewers and the Medicare Denominator File, or the date of the administrative censoring of the entire cohort at the end of the HRS–Medicare linkage on December 31, 2010. Because the incidence of severe sepsis rises precipitously with age (24), we controlled for age using a categorical age variable: 65–74, 75–79, 80–84, and greater than or equal to 85 years.

Results

We identified 43,095 exposure hospitalizations (28,465 hospitalizations without infection, 14,243 hospitalizations with non-CDI infection, and 387 hospitalizations with CDI) among 10,996 patients for inclusion in the longitudinal study (Table 1). Patients were predominantly female (58%), white persons (81%), with good baseline functional status, and mean age of 77 years.
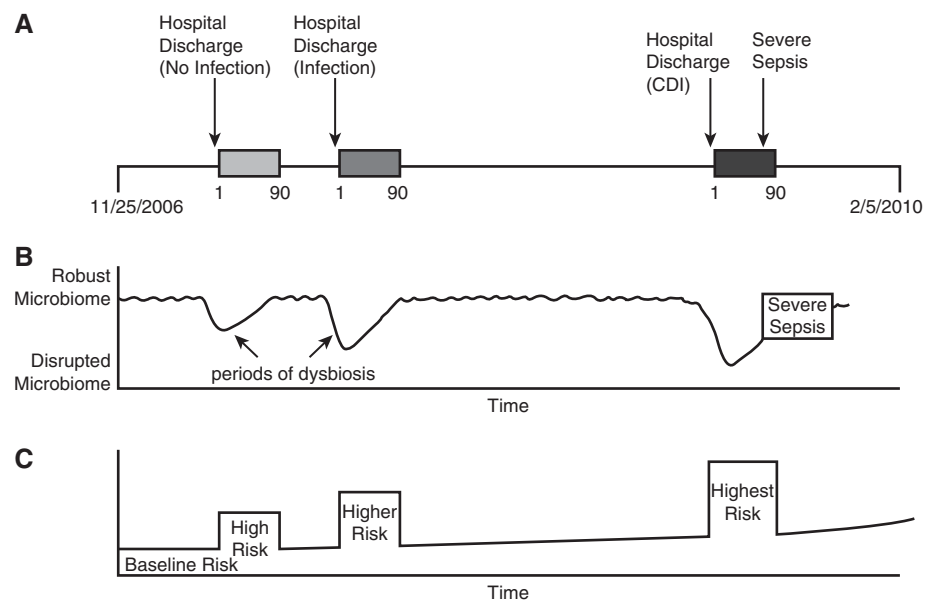
Figure 1. Conceptual diagram of the self-controlled case series analysis. (*A*) Hypothetical timeline for a patient with three exposures and one severe sepsis hospitalization. (*B*) Hypothetical shifts in microbiome health associated with the patient's clinical history. Microbial diversity is in constant flux, with periods of disruption (dysbiosis) corresponding with hospitalization. (*C*) Classification of baseline and higher risk periods used to calculate the incidence risk ratios for severe sepsis following each of the three exposures. The baseline risk of sepsis increases over time as patients age, which is accounted for in the model. CDI = *Clostridium difficile* infection.

Table 1. Baseline Characteristics of Subjects in the Longitudinal Study

	Noninfection (n = 28,465)	Infection (n = 14,243)	CDI (n = 387)
Age, yr, mean (SD)	76.8 (9.0)	78.3 (9.5)	79.6 (8.4)
Male, n (%)	12,244 (43.7%)	5,695 (40.0%)	159 (41.1%)
Self-reported race, n (%)			
White	23,307 (81.9%)	11,470 (80.5%)	312 (80.6%)
Black/African American	4,562 (16.0%)	2,447 (17.2%)	69 (17.8%)
Self-reported Hispanic ethnicity, n (%)	2,008 (7.1%)	1,185 (8.3%)	30 (7.8%)
Self-reported education, n (%)			
No degree	10,042 (35.3%)	5,792 (40.7%)	150 (38.8%)
General Education Development	1,251 (4.4%)	668 (4.7%)	13 (3.4%)
High school diploma	12,470 (43.8%)	5,930 (41.6%)	174 (45.0%)
College degree (2- or 4-yr)	3,135 (11.0%)	1,266 (8.9%)	39 (10.1%)
Master or professional degree	1,567 (5.5%)	587 (4.1%)	11 (2.8%)
Self-reported wealth, n (%)			
Net negative or zero assets	1,412 (5.0%)	1,101 (7.7%)	38 (9.8%)
Quartile 1	4,860 (17.1%)	3,036 (21.3%)	61 (15.8%)
Quartile 2	5,142 (18.1%)	2,819 (19.8%)	92 (23.8%)
Quartile 3	5,521 (19.4%)	2,454 (17.2%)	64 (16.5%)
Quartile 4	5,674 (19.9%)	2,129 (15.0%)	60 (15.5%)
Comorbidities, n (%)			
Congestive heart failure	9,889 (34.7%)	6,338 (44.5%)	193 (50.1%)
Kidney disease	4,563 (16.0%)	3,039 (21.3%)	111 (28.7%)
Liver disease	1,133 (4.0%)	676 (4.8%)	26 (6.7%)
Metastatic cancer	1,352 (4.8%)	742 (5.2%)	20 (5.2%)
Diabetes with complication	3,987 (14.0%)	2,651 (18.6%)	86 (22.2%)
Functional disability			
Limitations of ADLs, median (IQR)	0 (0–1)	0 (0–2)	0 (0–2)
Limitations of IADLs, median (IQR)	0 (0–1)	0 (0–2)	0 (0–2)

Definition of abbreviations: ADL = activities of daily living; CDI = *Clostridium difficile* infection; IADL = instrumental activities of daily living; IQR = interquartile range.

In unadjusted analyses, the probability of a 90-day readmission for severe sepsis was 3.7% (95% CI, 3.6–3.9%) following non–infection-related hospitalization; 8.4% (95% CI, 7.7–9.1%) following infection-related hospitalization, and 16.8% (95% CI, 12.2–21.4%) following hospitalization with CDI infection. After accounting for potential confounders, adjusted probabilities of 90-day readmission for severe sepsis were 4.1% (95% CI, 3.8–4.4%), 7.1% (95% CI, 6.6–7.6%), and 10.7% (95% CI, 7.7–13.8%), respectively, *P* less than 0.007 for each pairwise comparison (Figure 2, Table 2). Thus, risk of severe sepsis hospitalization was greater following infection-related hospitalization and still greater after a hospitalization with CDI, even after accounting for potential confounders.

However, in contrast to severe sepsis, the probability of readmission for nonsepsis diagnoses did not differ following the three types of hospitalizations in adjusted analyses. The probability of a 90-day readmission for nonsepsis diagnoses was 33.1% (95% CI, 32.4–33.7%) after non–infection-related hospitalization,

32.7% (95% CI, 31.9–33.6%) after infection-related hospitalization, and 32.4% (95% CI, 27.8–37.0%) after hospitalization with CDI, *P* greater than 0.5 for each pairwise comparison (Figure 2, Table 2). Supplemental analyses accounting for the competing risk of death demonstrated a similar stepwise increase in the risk for severe sepsis rehospitalization across hospitalization types and no difference in risk for other readmissions (*see* Table E1 in the online supplement).

For the self-controlled case series analysis, we identified 1,983 patients with at least one severe sepsis and one exposure hospitalization. In total, the self-controlled case series analysis included 2,864 severe sepsis hospitalizations over 16,736 person-years (average 8.4-yr observation per patient).

Hospitalization, infection, and CDI were each associated with graduated increases in the rate of subsequent severe sepsis in the self-controlled case series, where each patient serves as his or her own control subject (Table 3). In the 90 days after hospitalization, the incidence rate ratio for severe sepsis was 3.3 (95% CI,

3.0–3.7; *P* < 0.001), indicating that, on average, the rate of severe sepsis was 3.3 times greater in the 90 days after hospitalization than during all times before or after this period. The rate of severe sepsis following hospitalization with non-CDI infection was 1.3 times (95% CI, 1.2–1.5; *P* < 0.001) greater than the rate following hospitalizations without infection. The rate of severe sepsis following hospitalization with CDI was 1.7 times (95% CI, 1.1–2.6; *P* = 0.015) greater than the rate following non-CDI infection.

Discussion

We have shown that the incidence of severe sepsis is elevated more than threefold in the 90 days following all-cause hospitalization among a nationally representative cohort of older adults. We have also demonstrated for the first time that the risk of severe sepsis is yet greater after hospitalizations with infection (by 30%), and greater still after hospitalizations with CDI (by 70%). Such a dose–response relationship is present for rehospitalizations with severe sepsis but not
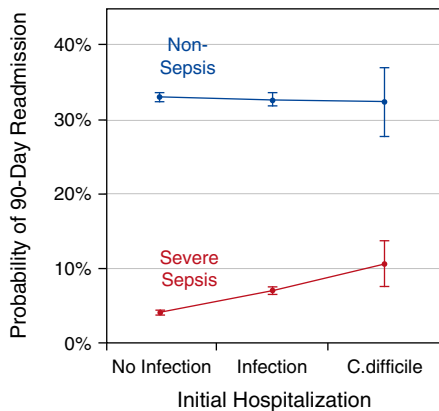
Figure 2. The probability of severe sepsis readmission correlates with probable microbiome disruption during index hospitalization. This figure depicts adjusted probabilities of 90-day hospital readmission for severe sepsis (*red*) and nonsepsis diagnoses (*blue*) following live discharge from hospitalization without infection, hospitalization with non–*Clostridium difficile* infection, and hospitalization with *C. difficile* infection. Probabilities are adjusted for age, sex, race, ethnicity, education, total wealth, limitations of activities and instrumental activities of daily living, and 31 Elixhauser comorbidities. Adjusted probabilities of rehospitalization for nonsepsis diagnoses are not different following the three exposures, whereas rehospitalization for severe sepsis is incrementally greater after exposures with increasing probable microbiome disruption.

for rehospitalizations for other diagnoses. Furthermore, we show that these progressive increases in the rates of hospitalization are present with very tight control for extraneous factors, by using patients as their own control subjects. This accounts for the temporally invariant covariates, such as sex (a known microbiota variant [35]), medical history, and genetic predispositions to sepsis. In addition, we

adjusted for age, thereby addressing the age-dependent incidence of severe sepsis.

Past studies have established that hospital readmission is frequent among Medicare beneficiaries (36), and that severe sepsis is a common reason for readmission (36, 37). Our findings advance the current understanding by demonstrating that severe sepsis readmission is not simply a reflection of patient's underlying comorbidities before hospitalization. Rather, after careful adjustment for patient's medical and sociodemographic factors, we found that the probability of severe sepsis readmission varies by hospitalization type. Hospitalizations with greater probable microbiome perturbation are associated with greater risk of subsequent severe sepsis, and this association seems to be temporally specific (to the 90 d following hospital discharge, relative to all times outside this 90-d period) and diagnosis specific (to the outcome of subsequent severe sepsis, but not hospitalizations for other diagnoses).

We hypothesize that hospitalization-associated dysbiosis may be an important mediator underlying the dose–response relationship between hospitalization type and risk for subsequent severe sepsis. The idea has strong face validity. Humans have evolved with resident bacteria and fungi, and these organisms serve varied functions, including bidirectional interactions with the immune system, and regulation of energy balance and metabolism (1, 38). Importantly, a diverse microbial community resists pathogen overgrowth and helps modulate both innate and adaptive immune responses (21). It is possible that dysbiosis may increase the likelihood of systemic inflammatory response syndrome and subsequent organ

dysfunction by up-regulating the host inflammatory response (39, 40). Inflammasomes, which trigger the inflammatory cascade, are activated after gut microbial perturbations and are followed by a rapid sepsis-like death in the animal model (41).

Because we did not directly measure the microbiome in this study, we cannot definitively prove our hypothesis. Nevertheless, we maintain that hospitalization with *C. difficile* equates with intestinal perturbation of the microbiota. The arguments are (1) *C. difficile*, although ubiquitous in the environment, occurs almost exclusively in individuals receiving antibiotics, proton pump inhibitors, H_2 receptor antagonists, and other drugs that disrupt the bacterial composition of the gastrointestinal tract (42, 43); (2) antibiotic stewardship programs decrease the incidence of CDI through reduction in antibiotic use (44); and, most importantly, (3) restoring the normal gut microbiome in persons with CDI cures the disease (15, 45). Although CDI may not be the only instance in which dysbiosis occurs, it is certainly a hallmark indication of intestinal perturbation.

Beyond microbiome perturbation, there are alternative mechanisms that may explain our findings. Our cohorts may have differed in the activation and lingering alteration of their immune response following their initial hospitalizations. Yende and coworkers (46, 47) have shown that inflammatory and coagulation markers are commonly elevated after pneumonia or sepsis and associated with worse overall and infection-related mortality. Meanwhile, compensatory antiinflammatory response or autoimmunosuppression following severe infection may also predispose

Table 2. Probabilities of 90-Day Readmissions for Severe Sepsis and Nonsepsis Diagnoses

Index Hospitalization	Readmissions for Severe Sepsis		Readmissions for Nonsepsis Diagnoses	
	Unadjusted Probability (95% CI)	Adjusted* Probability (95% CI)[†]	Unadjusted Probability (95% CI)	Adjusted* Probability (95% CI)[‡]
Noninfection-related hospitalization	3.7% (3.6–3.9%)	4.1% (3.8–4.4%)	31.7% (31.0–32.5%)	33.1% (32.4–33.7%)
Infection-related hospitalization	8.4% (7.7–9.1%)	7.1% (6.6–7.6%)	34.7% (33.7–35.7%)	32.7% (31.9–33.6%)
Hospitalization with CDI	16.8% (12.2–21.4%)	10.7% (7.7–13.8%)	37.9% (32.7–43.3%)	32.4% (27.8–37.0%)

Definition of abbreviations: CDI = *Clostridium difficile* infection; CI = confidence interval.
*Adjusted for age, sex, race, ethnicity, education, total wealth, limitations of activities and instrumental activities of daily living, and 31 Elixhauser comorbidities.
[†]Adjusted comparisons: infection versus noninfection ($P < 0.001$); CDI versus infection ($P = 0.007$); CDI versus noninfection ($P < 0.001$).
[‡]Adjusted comparisons: infection versus noninfection ($P = 0.51$); CDI versus infection ($P = 0.88$); CDI versus noninfection ($P = 0.78$).

Table 3. Incidence Rate Ratios Comparing the Four Risk Periods*

Comparison	IRR (95% CI)	P Value
90 d after any hospitalization vs. not in the 90 d after hospitalization	3.3 (3.0–3.7)	<0.001
After infection-related hospitalization vs. after non–infection-related hospitalization	1.3 (1.2–1.5)	<0.001
After hospitalization with CDI vs. after infection-related hospitalization (non-CDI)	1.7 (1.1–2.6)	0.015

Definition of abbreviations: CDI = *Clostridium difficile* infection; CI = confidence interval; IRR = incidence rate ratio.
*The four risk periods here are illustrated in Figure 1C: baseline risk, high risk (after non–infection-related hospitalization), higher risk (after infection-related hospitalization), and highest risk (after hospitalization with CDI).

patients to a second, and more severe, infection (48). It is likely that the human microbiome and immune response both contribute to the observed relationship because they are closely entwined. A healthy microbiome is critical to the development and function of the host immune response, and conversely, inflammatory mediators influence the microbiome composition (41, 49–52). Thus, we view alteration in host immunity as a complementary, rather than competing, hypothesis to explain our findings.

Understanding the association between transient dysbiosis and severe sepsis risk is especially important because of the potential for therapeutic manipulation of the human microbiome to reduce the incidence of severe sepsis during periods of heightened risk. Although attempts to modulate the immune system have failed to treat or prevent infection, the microbiome provides a promising therapeutic target. The human microbiome is amenable to such interventions as basic dietary modification and probiotic supplementation (53). Moreover, there have been some preliminary successes with respect to patient outcomes. Several studies indicate that microbiome modulation may reduce ventilator-associated pneumonia (54). Furthermore, microbiome replacement for recurrent CDI has demonstrated a 94% cure rate, better than that achieved with antibiotics (15). These studies suggest that treatment of dysbiosis can indeed result in improved health outcomes.

More detailed studies using longitudinal measurements of immune markers and microbial composition and function before, during, and after hospitalization are needed to further

characterize these relationships. The microbiome composition could be assessed via 16S RNA sequencing of cheek swabs and/or stool samples, whereas microbial function could be assessed via metagenomic analysis (55). It is currently cost-prohibitive to complete serial analyses of this sort on large numbers of individuals, but may be feasible in the future as the cost of these technologies continues to decline. Functional genomics has been used to predict hospitalizations in psychiatric patients and may be feasible in select clinical populations, such as those recovering from a CDI (56). Going forward, it will also be important to understand the extent to which less severe stresses to the microbiome (e.g., minor infections not requiring hospitalization and common medications known to influence the microbiome [antibiotics, proton pump inhibitors (57), H_2 receptor antagonists (58), and antidepressants (59)]) influence patients' risk for developing severe sepsis, and whether these risks depend on the dosage and duration of medication. While we await these sorts of confirmatory studies, it may be possible to incorporate microbiome measurements into studies of selective oropharyngeal and/or gut decontamination and to monitor microbiome recovery and infections rates beyond hospital discharge.

If future studies do confirm an association between microbiome disruption and subsequent severe sepsis, then it will be important to test the extent to which preservation of the microbiome (through narrower-spectrum antibiotics, shorter treatment courses, elimination of other microbiome-altering medications, and so forth) or restoration of the microbiome (through diet, probiotic supplements, or

fecal transplant) actually reduces risk for subsequent severe sepsis.

There are several potential limitations to our study. First, we performed a within-person analysis that limits the possibility of confounding by stable patient characteristics, but cannot fully rule out time-varying factors. Second, we used hospitalizations as proxies for the severity of dysbiosis rather than measuring microbial composition directly. The duration and severity of dysbiosis following antibiotic administration may vary across patients. Likewise, because we could not measure the microbiome recovery directly, we assumed that all patients experienced 90 days of dysbiosis. Although recovery of the human microbiome following a disturbance is incompletely understood (28, 60), several studies suggest that it closely resembles its predisturbance state within a few weeks to months after antibiotic exposure (27, 28). Any misspecification of the duration of the exposure biases our results toward the null hypothesis by imprecisely delineating higher and lower risk periods. Lastly, we rely on an implicit claims-based definition for identifying severe sepsis. Although this method performs favorably relatively to other claims-based definitions, it may result in some misclassification of patients as having severe sepsis versus another diagnosis (25). However, this potential for misclassification of readmission diagnosis should not differ by initial hospitalization type.

Despite these limitations, our study has several strengths. By using data from a nationally representative cohort with linked Medicare claims, we were able to study a large population of patients to assess whether proxies for dysbiosis are associated with increased risk of severe sepsis, the most costly cause of hospitalization in the United States (54). We examined these relationships using two designs: one a between-person longitudinal comparison and the other a within-person comparison of outcomes during different risk periods. We found a dose–response by severity of dysbiosis and demonstrated specificity of the association with severe sepsis hospitalizations.

Conclusions

Using a nationally representative sample of older Americans, we have shown that severe sepsis incidence is elevated threefold in the 90 days after hospitalization. Risk of severe

sepsis is incrementally greater following hospitalizations with infection, and greater still following CDI. Although the cause of this relationship remains unproven, we hypothesize that the observed dose–response by hospitalization type may be caused by microbial perturbation.

Because there are no current means to predict or prevent subsequent sepsis, the possibility of targeted restoration of the microbiome after a period of disruption holds the potential to reduce the incidence of subsequent severe sepsis and its associated morbidity and mortality. ■

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