Recent Anti-Microbial Exposure Is Associated with More Complications after Elective Surgery

Christopher A. Guidry,¹ Puja M. Shah,² Zachary C. Dietch,² Nathan R. Elwood,²
Elizabeth D. Krebs,² J. Hunter Mehaffey,² and Robert G. Sawyer³

Abstract

Background: Recent anti-microbial exposure has been associated with poor outcomes after infection in a mixed population. We hypothesized that recent anti-microbial exposure would be associated with poor outcomes of elective surgery.

Methods: From August 2015 to August 2016, all elective surgical patients were questioned prospectively about anti-microbial exposure during the prior three months. Multivariable models were used to calculate risk-adjusted odds ratios for anti-microbial exposure controlling for surgeon influence. Primary outcomes were any serious complication, any complication, any infection, and surgical site infection. Secondary outcomes were length of stay, *C. difficile* infection, and death. A separate analysis of patients excluding those having colorectal surgery who had undergone an oral antibiotic bowel preparation also was performed.

Results: Ninety-four percent of eligible patients (n = 1,538) answered the exposure question, with a three-month anti-microbial exposure rate of 34.1%. Colorectal surgery patients had the highest exposure rate, whereas hernia patients had the lowest. Exposed patients had higher rates of any complication, any infection, and surgical site infection, as well as a median two-day longer hospital stay. There were no differences in *C. difficile* infection or death between the groups. After risk adjustment, anti-microbial exposure was independently associated with any serious complication for all patients as well as with complications and infection in patients having an operation other than colorectal surgery.

Conclusion: Recent anti-microbial exposure is associated with more complications of elective surgery. Anti-microbial drug-induced alterations in microbiome-related inflammatory responses may play a role, highlighting an opportunity for pre-surgical intervention in this at-risk population.

Keywords: antimicrobials; exposure; outcome; surgery

ANTIMICROBIAL PRESCRIBING PRACTICES differ widely, with generally poor adherence to published guidelines and high rates of inappropriate usage [1–6]. The majority of these prescriptions are provided in the out-patient setting [7]. Each year, an estimated 30.1% of out-patients are prescribed at least one anti-microbial drug, with the annual prevalence of use being as high as 79% in long-term care facilities [8, 9]. The National Center for Health Statistics estimates that in 2010, there were more than 9.6 million inpatient and 28.6 million ambulatory surgical visits in the United States [10, 11]. The potential cross-section of surgical patients who have been exposed recently to anti-microbial drugs is enormous.

Recent data suggest that anti-microbial drug exposure in the previous 90 days is associated with poor outcomes after a second significant stressor [12,13]. Additionally, sepsis survivors have inferior long-term outcomes than non-septic comparators [14–16]. Anti-microbial drug exposure is known to alter the microbiome, which may in turn affect one's ability to regulate inflammatory stress brought about by surgical intervention [17,18]. These data suggest that anti-microbial drugs may be a common exposure with a potentially negative impact on surgical outcomes [8].

There are no studies evaluating the effects of prior anti-microbial drug exposure on post-operative outcomes. We hypothesized that recent anti-microbial exposure would be

¹Division of Trauma and Surgical Critical Care, Department of Surgery, Vanderbilt University Medical Center, Nashville, Tennessee.

²Department of Surgery, The University of Virginia Health System, Charlottesville, Virginia.

³Department of Surgery, Western Michigan University Homer Stryker MD School of Medicine, Kalamazoo, Michigan.

Presented at the 37th Annual Meeting of the Surgical Infection Society, St. Louis, Missouri, May 2–5, 2017.

associated with poor outcomes in a group of patients having elective surgery.

Patients and Methods

The University of Virginia Institutional Review Board for Health Sciences Research approved this study with a waiver of consent. Between August 4, 2015, and August 3, 2016, all patients having elective surgery at the University of Virginia Health System were queried prospectively about recent anti-microbial exposure. Specifically, each patient was asked “Have you taken any antibiotics in the last three months?” while in the pre-operative holding area. Our pre-operative nursing staff collected responses and recorded them in our electronic medical record system as either “Yes,” “No,” or “Unsure.” The three-month prevalence window was chosen by literature review [12,13,19–21]. We thought that patients would be able to recall such an exposure with a high degree of accuracy. However, we believed that patients would be unlikely to recall more detailed information regarding drug class, duration, or indication with the same accuracy. Therefore, our survey was limited to the single question. Only patients who provided a response to this question were included in the final analysis. For the purposes of this study, “Unsure” responses were considered to reflect an exposure.

Anti-microbial exposure responses were matched to our local American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) sample from the same time period. Eligible cases were sampled for inclusion in ACS NSQIP according to an eight-day cycle. Demographic and comorbidity variables were recorded according to the definitions from the ACS NSQIP Risk Calculator [22]. Incision classification also was recorded. Current Procedural Terminology (CPT) codes were classified by procedure type. Primary outcomes were ACS NSQIP-defined serious complication and any complication, as well as any infection and any surgical site infection (SSI). Secondary outcomes recorded were *Clostridium difficile* infection, length of stay, and 30-day mortality rate. Only elective general surgery and gynecology cases were included in the final test sample. Urgent or emergency cases, as well as those with pre-operative evidence of systemic inflammatory response syndrome (SIRS), sepsis, or septic shock, were excluded.

The ACS NSQIP Participant Use File (PUF) for the year 2014 was used to create risk models for our four primary outcome measures. The 2014 file year was chosen specifically for its temporal proximity to the test data yet without including any of the study participants. The file was narrowed to include only elective cases and CPT codes identified in our test sample. Risk models were created for each primary outcome using multivariable logistic regression including all recorded demographics, co-morbidities, and procedure data a priori. Use of the large PUF file allowed us to create models with more robust estimates of regression coefficients than we would have been able to create using our local sample. These models were then applied to our local test sample to create risk-adjusted odds ratios (ORs) for anti-microbial exposure while further controlling for individual surgeon influence using mixed effects modeling.

Standard univariable techniques were used. The Wilcoxon rank sum test was used for continuous variables, and the χ^2 and Fisher exact test were used for categorical variables where appropriate. Regression analyses were performed as

described above. A post-hoc analysis of all outcomes with and without patients undergoing colorectal surgery, who routinely received anti-microbial drugs pre-operatively, also was conducted. The threshold for statistical significance was set at $p < 0.05$. All statistical analysis was conducted using SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

There were 2,397 cases in our ACS NSQIP sample during the study period of which 1,645 (68.9%) met our inclusion criteria. Of these, 1,538 (93.5%) provided a response to our anti-microbial use survey with an overall three-month exposure prevalence of 34.1%. Five hundred patients (32.5%) responded “Yes” whereas only 24 patients (1.6%) responded “Unsure.”

Demographics and co-morbidities are listed in Table 1. Exposed patients tended to be slightly older, had higher rates of steroid use and disseminated cancer, and had higher American Society of Anesthesiologists (ASA) scores. Exposed patients were more likely to have a clean-contaminated, contaminated, or dirty/infected incision classification and were more likely to have a normal body mass index (BMI). Procedure groups are listed in Table 2. Patients having colorectal surgery had the highest prevalence of exposure, whereas hernia patients had the lowest. The prevalence of recent anti-microbial exposure in the colorectal surgery population was 71.7%, 25.6 percentage points higher than the next highest exposure group. This finding prompted a post-hoc analysis with and without these patients, as pre-operative bowel preparation, including oral anti-microbial drugs (erythromycin and neomycin), is standard practice at our institution and may have introduced bias in this subgroup, resulting in the elevated response rate [23].

Exposed patients had higher rates of complications, overall infection, and SSI (Table 3). When evaluated by SSI type, exposed patients had higher rates of organ space infection. Exposure was associated with a median one-day longer hospitalization. There was a higher rate of return to the operating room and deep venous thrombosis in the full cohort, whereas the non-colorectal surgery cohort had a slightly higher rate of pneumonia. There were no differences in the *Clostridium difficile* infection or 30-day mortality rates.

Using 279,469 elective cases identified from the 2014 PUF file, we created risk-adjustment models for our primary outcomes: Any serious complication, any complication, any infection, and any SSI. These models had c-statistics of 0.72, 0.75, 0.75, and 0.75, respectively. The Brier scores were 0.052, 0.054, 0.047, and 0.033, respectively [22]. The Hosmer-Lemeshow test had a p value < 0.0001 for all models. See the Supplemental Table (supplementary material is available online at www.liebertpub.com/sur) for full model details. After applying these models to our local ACS NSQIP data and further controlling for surgeon influence, the adjusted odds ratios for anti-microbial exposure were calculated and are listed in Table 4 (c-statistics 0.57–0.70). Anti-microbial drug exposure within the previous three months was independently associated with more complications. When patients having colorectal surgery were excluded, anti-microbial exposure was independently associated with both higher complication and infection rates.

Discussion

We have demonstrated a high prevalence of anti-microbial exposure within the previous three months in the elective

TABLE 1. DEMOGRAPHICS AND CO-MORBIDITIES

Variable	Exposure no. (%)		p
	Unexposed (n=1,104)	Exposed (n=524)	
Age (years)			
<65	731 (72.1)	356 (67.9)	0.09
65–74	200 (19.7)	111 (21.2)	0.50
74–85	55 (5.4)	46 (8.8)	0.01
>85	11 (1.1)	6 (1.1)	0.91
Body mass index			
Underweight (<18.5)	14 (1.4)	14 (2.7)	0.07
Normal weight (18.5–24.9)	197 (19.4)	127 (24.2)	0.03
Overweight (25.0–29.9)	240 (23.7)	131 (25)	0.56
Class 1 obesity (30.0–34.9)	208 (20.5)	101 (19.3)	0.57
Class 2 obesity (35.0–39.9)	125 (12.3)	55 (10.5)	0.29
Class 3 obesity (≥40.0)	230 (22.7)	96 (18.3)	0.05
Sex: Female	794 (78.3)	396 (75.6)	0.23
Hypertension	493 (48.6)	277 (52.9)	0.11
Congestive heart failure ^a	0 (0)	1 (0.2)	0.34
Ventilator dependent ^b	0 (0)	0 (0)	–
Current smoker within 1 year	159 (15.7)	85 (16.2)	0.78
Chronic obstructive pulmonary disease	46 (4.5)	22 (4.2)	0.76
Dyspnea			
On exertion	68 (6.7)	45 (8.6)	0.18
At rest	6 (0.6)	1 (0.2)	0.43
Diabetes			
Type 1	70 (6.9)	36 (6.9)	0.98
Type 2	111 (10.9)	62 (11.8)	0.60
Chronic corticosteroid use	40 (3.9)	45 (8.6)	0.0002
Acute renal dysfunction	0 (0)	0 (0)	–
Hemodialysis	8 (0.8)	6 (1.1)	0.49
Ascites ^a	8 (0.8)	4 (0.8)	1.0
Disseminated cancer	37 (3.6)	35 (6.7)	0.008
Functional status			
Independent	1006 (99.2)	515 (98.3)	0.1
Partially dependent	7 (0.7)	9 (1.7)	0.06
Totally dependent	1 (0.1)	0 (0)	1.0
ASA Class			
1	41 (4)	9 (1.7)	0.01
2	585 (57.7)	274 (52.3)	0.04
3	381 (37.6)	235 (44.8)	0.006
4	7 (0.7)	6 (1.1)	0.36
Incision class			
Clean	359 (35.4)	108 (20.6)	<0.0001
Clean-contaminated	648 (63.9)	396 (75.6)	<0.0001
Contaminated	4 (0.4)	7 (1.3)	0.05
Dirty/infected	3 (0.3)	13 (2.5)	<0.0001

^aWithin 30 d prior to surgery.^bWithin 48 h prior to surgery.

ASA = American Society of Anesthesiologists, body mass index calculated as weight in kilograms divided by height in meters squared, NA = not applicable.

surgical population, reflecting our previously reported data [24]. This high prevalence may reflect an overuse of anti-microbial drugs by the general population, and some data suggest that as many as 30% of such use may be inappropriate [6]. We observed that this exposure was independently associated with complications after elective surgery. Unadjusted data additionally suggest higher overall infection and SSI rates and increased length of stay.

Our findings are most similar to those of Dr. Kollef's group, who identified increased length of stay (median five

days) as well as a higher mortality rate in gram-negative sepsis after anti-microbial drug exposure in the prior three months [12,13]. Their cohort consisted mostly of intensive care medical patients, resulting in a much higher observed mortality rate than in our study. Both studies demonstrate an increase in the length of stay associated with exposure, although our observed difference is less pronounced, likely attributable to a healthier cohort in general. Their studies identified prior anti-microbial exposure to be associated with a higher rate of inappropriate initial empiric therapy,

TABLE 2. MUTUALLY EXCLUSIVE PROCEDURE GROUPS

Procedure class	Prevalence (%)	Exposure no. (%)		p
		Unexposed (n = 1,014)	Exposed (n = 524)	
Bariatric	25.4	103 (10.2)	35 (6.7)	0.02
Breast	24.3	28 (2.8)	9 (1.7)	0.21
Colorectal	71.7	64 (6.3)	162 (30.9)	<0.0001
Endocrine	35.1	24 (2.4)	13 (2.5)	0.89
Gynecologic	26.4	382 (37.7)	137 (26.1)	<0.0001
General	45.2	34 (3.4)	28 (5.3)	0.06
Hepatobiliary	37.5	120 (11.8)	72 (13.7)	0.28
Hernia	20.8	259 (25.5)	68 (13)	<0.0001

suggesting that broader or combination empiric coverage may improve outcomes [12,25]. However, the patients in our study were not septic on the day of surgery and were deemed healthy enough to undergo elective surgery. Adherence to surgical prophylaxis choice based on Surgical Care Improvement Project (SCIP) guidelines is in excess of 90% nationally [26,27]. Although organ space SSI rates were higher in the exposed cohort, exposure was not associated independently with SSI in our multivariable models. It is

unlikely that additional or alternative anti-microbial drugs at the time of surgery would address the differences in outcomes we observed.

The patients in our exposure cohort experienced a prior presumed infection for which they were prescribed anti-microbial drugs. Similar to our patients, patients who survive sepsis have poor long-term outcomes, including a higher mortality rate [14–16]. Sepsis survivors also may be at higher risk of subsequent infection, similar to the increased infection

TABLE 3. UNADJUSTED OUTCOMES

	All patients no. (%)			Excluding colorectal surgery no. (%)		
	Unexposed (n = 1,014)	Exposed (n = 524)	p	Unexposed (n = 950)	Exposed (n = 362)	p
<i>Primary outcomes</i>						
Any serious complication	59 (5.8)	59 (11.3)	0.0001	50 (5.3)	39 (10.8)	0.0004
Any complication	65 (6.4)	60 (11.5)	0.0006	54 (5.7)	40 (11)	0.0008
Any infection	54 (5.3)	49 (9.4)	0.003	46 (4.8)	34 (9.4)	0.002
Any surgical site infection	34 (3.4)	32 (6.1)	0.01	27 (2.8)	21 (5.8)	0.01
Surgical site infection						
Superficial incisional ^a	18 (1.8)	14 (2.7)	0.24	15 (1.6)	10 (2.8)	0.16
Deep incisional	2 (0.2)	4 (0.8)	0.19	1 (0.1)	2 (0.6)	0.19
Organ space	16 (1.6)	18 (3.4)	0.02	12 (1.3)	12 (3.3)	0.01
<i>Secondary outcomes</i>						
Length of stay	1 (1–3)	3 (1–4)	<0.0001	1 (1–2)	2 (1–3)	<0.0001
<i>Clostridium difficile</i>	7 (0.7)	4 (0.76)	1.0	5 (0.5)	2 (0.6)	1.0
30-day death ^b	4 (0.4)	1 (0.19)	0.67	4 (0.4)	0 (0)	0.58
<i>Individual components of composite outcomes</i>						
Stroke ^a	0 (0)	0 (0)	NA	0 (0)	0 (0)	NA
Myocardial infarction	1 (0.1)	1 (0.2)	1.0	1 (0.1)	0 (0)	1.0
Cardiac arrest ^b	3 (0.3)	2 (0.4)	1.0	2 (0.2)	1 (0.3)	1.0
Ventilator requirement >48 h ^a	5 (0.5)	2 (0.4)	1.0	5 (0.5)	1 (0.3)	1.0
Unplanned intubation	6 (0.6)	4 (0.8)	0.74	5 (0.5)	2 (0.6)	1.0
Pneumonia	3 (0.3)	6 (1.1)	0.07	3 (0.3)	5 (1.4)	0.04
Urinary tract infection	16 (1.6)	9 (1.7)	0.83	15 (1.6)	8 (2.2)	0.44
Return to operating room ^a	17 (1.7)	21 (4)	0.005	16 (1.7)	11 (3)	0.12
Acute renal dysfunction	1 (0.1)	0 (0)	1.0	1 (0.1)	0 (0)	1.0
Progressive renal insufficiency	3 (0.3)	4 (0.8)	0.24	2 (0.2)	1 (0.3)	1.0
Incision disruption	1 (0.1)	3 (0.6)	0.12	1 (0.1)	1 (0.3)	0.48
Deep venous thrombosis	2 (0.2)	6 (1.1)	0.02	1 (0.1)	3 (0.8)	0.07
Pulmonary embolism	3 (0.3)	1 (0.2)	1.0	1 (0.1)	1 (0.3)	0.48
Systemic sepsis	13 (1.3)	11 (2.1)	0.22	11 (1.2)	3 (0.8)	0.77

^aComponent of Any Complication only based on ACS NSQIP definition.

^bComponent of any serious complication based only on ACS NSQIP definition.

Components of composite outcomes add up to more than 100% of composite outcome as some patients had multiple complications.

TABLE 4. RISK-ADJUSTED OUTCOMES

	<i>Antimicrobial exposure odds ratios (95% CI)</i>		
	<i>Unadjusted</i>	<i>Risk-adjusted: all patients</i>	<i>Risk-adjusted: excluding colorectal surgery</i>
Any serious complication	2.05 (1.41–3.00)	1.53 (1.03–2.28)	1.83 (1.17–2.87)
Any complication	1.88 (1.31–2.73)	1.33 (0.90–1.99)	1.72 (1.10–2.68)
Any infection	1.83 (1.23–2.74)	1.33 (0.87–2.04)	1.75 (1.09–2.81)
Any surgical site infection	1.88 (1.14–3.08)	1.24 (0.73–2.10)	1.75 (0.96–3.20)

CI = confidence interval.

rate we observed in our univariable data [16,28]. Although the etiology of these associations is unknown, pro-inflammatory profiles at hospital discharge are associated with subsequent poor post-acute outcomes in septic patients [29]. Interestingly, similar pro-inflammatory patterns may be seen in patients with low gut microbiome diversity and may be a key driver of these findings [30]. In the healthy state, a robust and diverse commensal population serves an immune-modulatory role, suppressing inflammation overall [18,31,32]. Anti-microbial drug exposure decreases microbiome diversity with further decreases in diversity immediately after severe stressors [17,32,33]. Excessive anti-microbial duration or aggressive initiation also has been associated with both a decreased mortality rate and a higher subsequent infection rate, further suggesting that these exposures may not be completely benign [34–36]. We are unable to evaluate the reason each patient received anti-microbial drugs or the extent of time the anti-microbial drugs were prescribed, as most of the drugs were provided in the out-patient setting [7,37].

We hypothesize that each of our exposed patients presented on the day of surgery with some degree of anti-microbial-induced dysbiosis and altered ability to respond appropriately to the inflammatory stress of surgery. Although a full analysis of the host microbiome was outside the capabilities of our study, this idea provides an exciting area for future research and innovation. Intra-luminal phosphate administration, fecal microbiota transplantation, and probiotic administration have been suggested as methods of modulating the microbiome and reducing subsequent inflammation [17,38–41]. If this association proves true, one of these interventions may optimize the microbiome prior to surgical intervention. A simple delay of truly elective procedures may achieve the same goal, although the time to recolonization by commensal flora is variable [42,43]. It is possible that in the future, microbiologic optimization will be a common component of pre-surgical preparation.

We are limited in our ability to control for both the degree of prior sepsis and the duration and type of anti-microbial drug administration. Our results may indicate that recent anti-microbial exposure is a marker of increased fragility: That after a recent illness requiring antibiotics, patients may be less capable of handling surgical stress. Dysbiosis may be one explanation. However, the heterogeneity of our co-morbidity data also suggests that exposed and unexposed patients may represent slightly different populations. Because pre-illness co-morbidities may ultimately be the largest drivers of outcomes, appropriate risk adjustment is key [44]. Using the larger PUF file, we were able to create more robust risk-adjustment models to account for this heterogeneity than our

sample size would otherwise have allowed. The Brier Score is a model performance assessment score describing both discrimination and calibration, with smaller values representing higher accuracy. It is the model performance tool preferred by ACS NSQIP [22]. We used the ACS NSQIP Risk Calculator measures as the base of our risk adjustment models, adding incision classification and replacing individual CPTs with procedure groupings. Our models performed on a par with the Brier Scores reported for the morbidity and SSI portions of the universal risk calculator, suggesting that they are functioning appropriately [22].

Our study has several limitations worth discussing. First, although our anti-microbial use data were collected prospectively, we were able neither to verify these data nor to capture specific anti-microbial regimens. Most medical and surgical history reported by patients is not verified in practice, giving us no reason to suspect that these data are more or less valid than other patient-reported history items. Data on specific anti-microbial drug regimens would be helpful to include in future studies. Second, data collected retrospectively from ACS NSQIP may be subject to observation bias. However, ACS NSQIP has proved to be a reliable and well-validated tool for risk stratification that strengthens our analysis. Third, our sample size was confined to that included in the ACS NSQIP sample. A larger analysis of the entire cohort without this sampling restriction may yield different results. Additionally, we were unable to assess or control for the degree of prior illness that resulted in anti-microbial drug administration prior to surgery. Finally, although we propose that pre-operative dysbiosis associated with anti-microbial drug exposure might explain our findings, a formal microbiologic evaluation of each patient's microbiota was outside scope of this study.

Conclusion

In this study of patients undergoing elective surgery, we identified that anti-microbial drug exposure within the three months prior to surgery was independently associated with complications, particularly for patients not having colorectal surgery. We propose anti-microbial-induced dysbiosis as one possible mechanism for this finding. Further work is needed to evaluate more thoroughly the complex interactions between anti-microbial drugs, the host microbiome, and responses to surgical stress.

Author Disclosure Statement

No competing financial interests exist for any of the authors.

References

- Huijts SM, van Werkhoven CH, Boersma WG, et al. Guideline adherence for empirical treatment of pneumonia and patient outcome. Treating pneumonia in the Netherlands. *Neth J Med* 2013;71:502–507.
- Pence LM, Mock CM, Kays MB, et al. Correlation of adherence to the 2012 Infectious Diseases Society of America Practice Guidelines with patient outcomes in the treatment of diabetic foot infections in an outpatient parenteral antimicrobial programme. *Diabet Med* 2014;31:1114–1120.
- Taur Y, Smith MA. Adherence to the Infectious Diseases Society of America Guidelines in the treatment of uncomplicated urinary tract infection. *Clin Infect Dis* 2007;44:769–774.
- Wu JH, Howard DH, McGowan JE Jr, et al. Adherence to Infectious Diseases Society of America Guidelines for empiric therapy for patients with community-acquired pneumonia in a commercially insured cohort. *Clin Ther* 2006;28:1451–1461.
- Ivanovska V, Hek K, Mantel Teeuwisse AK, et al. Antibiotic prescribing for children in primary care and adherence to treatment guidelines. *J Antimicrob Chemother* 2016;71:1707–1714.
- Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010–2011. *JAMA* 2016;315:1864–1873.
- Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: A cross-national database study. *Lancet* 2005;365:579–587.
- Shallcross L, Beckley N, Rait G, et al. Antibiotic prescribing frequency amongst patients in primary care: A cohort study using electronic health records. *J Antimicrob Chemother* 2017;72:1818–1824.
- van Buul LW, van der Steen JT, Veenhuizen RB, et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc* 2012;13:568 e561–513.
- National Center for Health Statistics. Table 96. Cost of hospital discharges with common hospital operating room procedures in nonfederal community hospitals, by age and selected principal procedure: United States, selected years 2000–2013. Accessed April 16, 2017. Available at: <https://www.cdc.gov/nchs/hus/contents2015.htm> - 096
- Hall MJ, Schwartzman A, Zhang J, et al. Ambulatory surgery data from hospitals and ambulatory surgery centers: United States, 2010. *Natl Health Stat Rep* 2017:1–15.
- Johnson MT, Reichley R, Hoppe-Bauer J, et al. Impact of previous antibiotic therapy on outcome of gram-negative severe sepsis. *Crit Care Med* 2011;39:1859–1865.
- Micek S, Johnson MT, Reichley R, et al. An institutional perspective on the impact of recent antibiotic exposure on length of stay and hospital costs for patients with gram-negative sepsis. *BMC Infect Dis* 2012;12:56.
- Linder A, Guh D, Boyd JH, et al. Long-term (10-year) mortality of younger previously healthy patients with severe sepsis/septic shock is worse than that of patients with nonseptic critical illness and of the general population. *Crit Care Med* 2014;42:2211–2218.
- Davis JS, He V, Anstey NM, et al. Long term outcomes following hospital admission for sepsis using relative survival analysis: A prospective cohort study of 1,092 patients with 5 year follow up. *PLoS One* 2014;9:e112224.
- Ou SM, Chu H, Chao PW, et al. Long-term mortality and major adverse cardiovascular events in sepsis survivors: A nationwide population-based study. *Am J Respir Crit Care Med* 2016;194:209–217.
- Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med* 2016;8:39.
- Krezalek MA, DeFazio J, Zaborina O, et al. The shift of an intestinal “microbiome” to a “pathobiome” governs the course and outcome of sepsis following surgical injury. *Shock* 2016;45:475–482.
- Chitnis AS, Holzbauer SM, Belflower RM, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. *JAMA Intern Med* 2013;173:1359–1367.
- Gomez-Zorrilla S, Camoez M, Tubau F, et al. Antibiotic pressure is a major risk factor for rectal colonization by multidrug-resistant *Pseudomonas aeruginosa* in critically ill patients. *Antimicrob Agents Chemother* 2014;58:5863–5870.
- Tartof SY, Rieg GK, Wei R, et al. A comprehensive assessment across the healthcare continuum: Risk of hospital-associated *Clostridium difficile* infection due to outpatient and inpatient antibiotic exposure. *Infect Control Hosp Epidemiol* 2015;36:1409–1416.
- Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: A decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg* 2013;217:833–842 e831–833.
- Thiele RH, Rea KM, Turrentine FE, et al. Standardization of care: Impact of an enhanced recovery protocol on length of stay, complications, and direct costs after colorectal surgery. *J Am Coll Surg* 2015;220:430–443.
- Guidry CA, Sawyer RG. Prevalence of recent antimicrobial exposure among elective surgical patients. *Surg Infect* 2017;18:799–802.
- Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: A retrospective analysis. *Antimicrob Agents Chemother* 2010;54:1742–1748.
- Bratzler DW, Houck PM, Richards C, et al. Use of antimicrobial prophylaxis for major surgery: Baseline results from the National Surgical Infection Prevention Project. *Arch Surg* 2005;140:174–182.
- Schonberger RB, Barash PG, Lagasse RS. The Surgical Care Improvement Project Antibiotic Guidelines: Should we expect more than good intentions? *Anesth Analg* 2015;121:397–403.
- Wang T, Derhovanessian A, De Cruz S, et al. Subsequent infections in survivors of sepsis: Epidemiology and outcomes. *J Intensive Care Med* 2014;29:87–95.
- Yende S, D’Angelo G, Kellum JA, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008;177:1242–1247.
- Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature* 2013;500:541–546.
- Palm NW, de Zoete MR, Flavell RA. Immune–microbiota interactions in health and disease. *Clin Immunol* 2015;159:122–127.

32. Galley JD, Bailey MT. Impact of stressor exposure on the interplay between commensal microbiota and host inflammation. *Gut Microbes* 2014;5:390–396.
33. Hayakawa M, Asahara T, Henzan N, et al. Dramatic changes of the gut flora immediately after severe and sudden insults. *Dig Dis Sci* 2011;56:2361–2365.
34. Riccio LM, Popovsky KA, Hranjec T, et al. Association of excessive duration of antibiotic therapy for intra-abdominal infection with subsequent extra-abdominal infection and death: A study of 2,552 consecutive infections. *Surg Infect* 2014;15:417–424.
35. Hranjec T, Rosenberger LH, Swenson B, et al. Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive-care-unit-acquired infection: A quasi-experimental, before and after observational cohort study. *Lancet Infect Dis* 2012;12:774–780.
36. Guidry CA, Hranjec T, Shah PM, et al. Aggressive antimicrobial initiation for suspected intensive care unit-acquired infection is associated with decreased long-term survival after critical illness. *Surg Infect* 2017;18:664–669.
37. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801–810.
38. Zaborin A, Defazio JR, Kade M, et al. Phosphate-containing polyethylene glycol polymers prevent lethal sepsis by multidrug-resistant pathogens. *Antimicrob Agents Chemother* 2014;58:966–977.
39. Olivas AD, Shogan BD, Valuckaite V, et al. Intestinal tissues induce an SNP mutation in *Pseudomonas aeruginosa* that enhances its virulence: Possible role in anastomotic leak. *PLoS One* 2012;7:e44326.
40. Wei Y, Yang J, Wang J, et al. Successful treatment with fecal microbiota transplantation in patients with multiple organ dysfunction syndrome and diarrhea following severe sepsis. *Crit Care* 2016;20:332.
41. Klingensmith NJ, Coopersmith CM. The gut as the motor of multiple organ dysfunction in critical illness. *Crit Care Clin* 2016;32:203–212.
42. Swann JR, Tuohy KM, Lindfors P, et al. Variation in antibiotic-induced microbial recolonization impacts on the host metabolic phenotypes of rats. *J Proteome Res* 2011;10:3590–3603.
43. Zaura E, Brandt BW, Teixeira de Mattos MJ, et al. Same exposure but two radically different responses to antibiotics: Resilience of the salivary microbiome versus long-term microbial shifts in feces. *MBio* 2015;6:e01693–e01615.
44. Shankar-Hari M, Ambler M, Mahalingasivam V, et al. Evidence for a causal link between sepsis and long-term mortality: A systematic review of epidemiologic studies. *Crit Care* 2016;20:101.

Address correspondence to:
Dr. Christopher A. Guidry
1211 21st Avenue South
Nashville, TN 37212-1750

E-mail: guidryca2208@gmail.com