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High Prevalence of Antibiotic-Resistant Bacterial Infections Among Patients With Cirrhosis at a US Liver Center

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Abstract

BACKGROUND & AIMS—There are limited data on the prevalence or predictors of antibiotic-resistant bacterial infections (AR-BI) in hospitalized patients with cirrhosis in North America. Exposure to systemic antibiotics is a risk factor for AR-BI; however, little is known about the effects of the increasingly used oral nonabsorbed antibiotics.

METHODS—We analyzed data from patients with cirrhosis and bacterial infections hospitalized in a liver unit at a US hospital between July 2009 and November 2010. Multivariate logistic regression was used to determine predictors of AR-BI. Data were analyzed on the first bacterial infection of each patient (n = 115), and a sensitivity analysis was performed on all infectious episodes per patient (n = 169).

RESULTS—Thirty percent of infections were nosocomial. Urinary tract infections (32%) and spontaneous bacterial peritonitis (24%) were most common. Of the 70 culture-positive infections, 33 (47%) were found to be antibiotic resistant (12 were vancomycin-resistant *Enterococci*, 9 were extended-spectrum *β*-lactamase–producing *Enterobacteriaceae*, 7 were quinolone-resistant gram-negative rods, and 5 were methicillin-resistant *Staphylococcus aureus*). Exposure to systemic antibiotics within 30 days before infection was associated independently with AR-BI, with an odds ratio (OR) of 13.5 (95% confidence interval [CI], 2.6–71.6). Exposure to only nonabsorbed antibiotics (rifaximin) was not associated with AR-BI (OR, 0.4; 95% CI, 0.04–2.8). In a sensitivity analysis, exposure to systemic antibiotics within 30 days before infection and nosocomial infection was associated with AR-BI (OR, 5.2; 95% CI, 1.5–17.7; and OR, 4.2; 95% CI, 1.4–12.5, respectively).

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Conflicts of interest
The authors disclose no conflicts.

Supplementary Material
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CONCLUSIONS—The prevalence of AR-BI is high in a US tertiary care transplant center. Exposure to systemic antibiotics within 30 days before infection (including those used for prophylaxis of spontaneous bacterial peritonitis), but not oral nonabsorbed antibiotics, is associated with development of an AR-BI.

Keywords

Multidrug Resistance; SBP; Epidemiology; Bacteriology

Bacterial infections are a major cause of morbidity and mortality in cirrhosis.[1] Over the past decade, the treatment of these infections has become more challenging as a result of the development of antibiotic-resistant bacteria.

Studies performed mostly in Europe[2–6] have shown increasing rates of infections caused by antibiotic-resistant organisms in patients with cirrhosis, particularly in those acquired while hospitalized. In studies performed in a liver unit in Spain, the development of antibiotic-resistant infections was correlated to an increased mortality rate.[2,3] Because Spain has disproportionately high rates of antibiotic resistance,[7–11] this may not be representative of the situation in the United States. Although even within the United States the resistance patterns may vary from center to center based on infection control and antibiotic use practices, the prospective collection of data from patients with cirrhosis admitted to a North American hospital is a starting point to identify the rate of antibiotic-resistant organisms and the factors that predict their presence. Both exposure to systemic antibiotics and selective intestinal decontamination using oral norfloxacin have been identified as predictors of the development of antibiotic-resistant bacterial infections (AR-BI) in patients with cirrhosis.[2,12] The impact of the increasingly used oral nonabsorbed antibiotics such as rifaximin in the development of AR-BI, although theoretically low,[13] has not been established. Our aims were to investigate the prevalence of AR-BI in patients with cirrhosis hospitalized in a liver unit in a US hospital and to determine the predictors of the presence of these infections, including prior exposure to antibiotics, categorized by type (systemic or oral nonabsorbed).

Methods

Patients

In the period between July 1, 2009, and November 20, 2010, the names, date of admission, and type of infection of all patients with cirrhosis admitted to the Liver Unit at the Yale New Haven Hospital who either had a bacterial infection at admission or developed an infection during their admission were collected prospectively. Charts were reviewed retrospectively for the remaining data. Post–liver transplantation patients were excluded. The primary analysis was performed using only the first bacterial infection per patient, but for the purposes of further analysis, data on repeat infections occurring during the course of an admission or in the same patient on separate admissions also were collected.

Data Collection

Data collected at the time of bacterial infection included patient demographics, etiology and severity of liver disease, reason for the septic work-up, laboratory values, co-existing medical diagnoses (diabetes mellitus, human immunodeficiency virus), medication use, and antibiotic use within 30 days of diagnosis of the bacterial infection. In the case of culture-positive infections, all microorganisms and their antibiotic susceptibility patterns were recorded.

Definitions

Cirrhosis was identified by laboratory features of hepatic dysfunction or clinical features of portal hypertension in the presence of compatible radiologic and/or histologic findings. Nosocomial infections were defined as those developing more than 48 hours after admission to the hospital. We considered the following to be antibiotic-resistant organisms: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), quinolone-resistant gram-negative rods (QRGNR) (isolated resistance to a quinolone), extended-spectrum β-lactamase–producing *Enterobacteriaceae* (ESBL) (resistance to ceftazidime or ceftriaxone), *Enterobacter* infection with an AmpC β-lactamase mutation and bacterial isolates resistant to 3 or more classes of antibiotics.[14] Because it is often a contaminant, coagulase-negative *Staphylococcus epidermidis* was not classified as an antibiotic-resistant organism. Cases of spontaneous bacterial peritonitis (SBP) caused by this organism were counted as culture-negative SBP and cases of line infection or endocarditis, for which this organism is known to be a pathogen, were counted as culture-positive infections. SBP and spontaneous bacterial empyema (SBE) were defined by a fluid polymorphonuclear cell count of 250/mm^3 or higher irrespective of culture results. Spontaneous bacteremia was defined by a positive blood culture in the absence of a secondary source of infection. Notably, our definition of a urinary tract infection (UTI) was adapted from the recent Centers for Disease Control guidelines[15] and required a positive urine culture in addition to either symptoms of a UTI, hepatic encephalopathy, or associated bacteremia. This is a more stringent definition than previously used definitions of either leukocytosis or positive urine culture.[2] Pneumonia was diagnosed in the setting of compatible clinical signs, symptoms, and radiologic findings (2 or more serial chest radiographs with a persistent infiltrate or consolidation). Cellulitis was defined by physical examination findings of swelling, erythema, heat, and tenderness irrespective of culture results. Other infections were defined per standard guidelines.[15]

Systemic antibiotics are those administered intravenously or those administered orally that are partially (eg, norfloxacin) or completely absorbed (eg, ciprofloxacin). Nonabsorbed antibiotics are those administered orally that are not absorbed (eg, rifaximin, neomycin). A patient on both a systemic and a non-absorbed antibiotic was considered to have systemic antibiotic exposure.

Statistical Analysis

Statistical analysis was performed using SPSS version 17.0 (SPSS, Inc, Chicago, IL). Categoric values were described using percentages and compared using either the χ^2 or the Fisher exact test. Continuous values were described using the mean and standard deviation and were compared using the Student *t* test. Univariate and multivariate logistic regression modeling were used to determine predictors of antibiotic resistance. All variables with a *P* value of less than .05 on univariate analysis were entered into the multivariate model. Unless otherwise specified, on both univariate and multivariate logistic regression, antibiotic use was categorized into 3 groups: (1) no antibiotics, (2) oral non-absorbed antibiotics only, and (3) systemic antibiotics (± oral nonabsorbed antibiotics). The primary analysis was performed for the first infectious episode per patient. Further sensitivity analysis was performed using multiple infectious episodes per patient.

Results

Primary Analysis: Data for First Bacterial Infection Only (n = 115)

Baseline characteristics—Of an estimated 746 patients with cirrhosis admitted to the Liver Unit at the Yale New Haven Hospital during the 17-month study period, 115 unique patients with bacterial infection were identified. Table 1 shows baseline characteristics of

the patients. Sixty-eight percent (78 of 115) of the patients were men and had a mean age of 55.6 ± 10.3 years. Alcohol-related liver disease (31 cases), hepatitis C virus infection (40 cases), or a combination of the two (22 cases) accounted for 81% of the causes of cirrhosis. At the time of diagnosis of infection, the mean Child–Pugh score was 9.3 ± 1.6 and the mean Model for End-stage Liver Disease (MELD) score was 21.6 ± 10.0. The main reasons for pursuing a septic work-up were infectious symptoms in 47%, hepatic encephalopathy with or without infectious symptoms in 32%, acute kidney injury in 16%, and gastrointestinal bleeding in the remaining 5%.

Bacterial infections—Of the 115 bacterial infections, 40 (35%) were spontaneous infections (28 SBP, 2 SBE, and 10 spontaneous bacteremias), 37 (32%) were UTIs, 22 (19%) were pneumonias, and 12 (10%) were cases of cellulitis. Of the remaining cases, 2 were septic arthritis, there was 1 liver abscess, and 1 cerebritis/mastoiditis. Thirty percent (34 of 115) of the infections were nosocomial.

Culture-positive antibiotic-resistant infections—Sixty-one percent (70 of 115) of all infections were culture-positive. This included all of the UTIs and spontaneous bacteremias (by definition), 43% (13 of 30) of the SBP/spontaneous bacterial empyemas, 27% (6 of 22) of the pneumonias, and 8% (1 of 12) of the cellulitis cases. Fifty-four percent (38 of 70) of the culture-positive infections were caused by gram-negative organisms, 44% (31 of 70) were owing to gram-positive organisms, and 1 UTI case was caused by mixed gram-positive and gram-negative organisms (Table 2).

In 70 culture-positive infections, 33 antibiotic-resistant bacteria were identified: 12 VRE (36%), 9 ESBL (27%), 7 QRGNR (21%), and 5 MRSA (15%) (Table 2). Of the culture-positive infections, these AR-BIs occurred in 20 of 37 (54%) of the UTIs, 7 of 13 (54%) of the SBP/SBEs, 2 of 10 (20%) of the spontaneous bacteremia cases, 2 of 6 (33%) of the pneumonias, 1 of 2 (50%) of the septic arthritis cases, and in the only liver abscess case.

Antibiotic exposure—Although the impact of antibiotic exposure on antibiotic resistance could be evaluated only in culture-positive cases, we nevertheless examined the exposure to antibiotic therapy within the 30 days before admission in all episodes of infection so that an assessment could be made on the burden of antibiotic exposure. Of the 115 episodes of bacterial infection, exposure to systemic antibiotics in the previous 30 days occurred in 41 (36%) patients. These systemic antibiotics were mostly quinolones, piperacillin-tazobactam, and/or a third-generation cephalosporin. Forty-seven (41%) patients had not been exposed to antibiotics in the month before admission, and 27 (24%) patients had exposure only to oral nonabsorbed antibiotics.

Of the 70 patients with a culture-positive infection, 31 (44%) had been exposed to one or several systemic antibiotics in the 30 days before infection (Table 3), 23 (33%) had not been exposed to antibiotics, and 16 (23%) had been taking only oral nonabsorbed antibiotics alone (rifaximin in all).

Predictors of antibiotic-resistant infections—As shown in Table 4, on univariate analysis, exposure to antibiotics (systemic and nonabsorbed grouped together) was a significant predictor of AR-BI, with an odds ratio (OR) of 7.7 (95% confidence interval [CI], 2.2–26.1). When separated into 3 categories: (1) no antibiotic exposure, (2) oral nonabsorbed antibiotics, or (3) systemic antibiotics, the risk of AR-BI was only significant for systemic antibiotics but not for oral nonabsorbed antibiotics. All 4 variables significant on univariate analysis ($P < .05$) were entered into the multivariate analysis (MELD score, nosocomial infection, albumin level, exposure to systemic antibiotics within the past 30 d). We chose to enter the MELD score into the multivariate model instead of the Child–Pugh

score because the retrospective collection of laboratory values was less subjective than the grading of ascites and encephalopathy. In the final multivariate model, exposure to systemic antibiotics within the preceding 30 days was the only significant independent predictor for AR-BI with an OR of 13.5 (95% CI, 2.6–71.6).

Predictors of resistance to recommended first-line antibiotic therapy for the culture-positive spontaneous infections and urinary tract infections—As per current guidelines, third-generation cephalosporins have been recommended as first-line therapy for the spontaneous bacterial infections (spontaneous bacteremia, SBP, SBE), and ciprofloxacin for UTIs.[16] For these specific infections, we identified independent predictors of resistance to recommended first-line antibiotic therapy.

Of a total of 37 culture-positive UTIs, 17 (46%) were resistant to both ciprofloxacin and third-generation cephalosporins, 6 (16%) were resistant to ciprofloxacin alone, and 1 (3%) was resistant to third-generation cephalosporins alone. Of the 13 culture-positive SBP/SBE infections, 6 (46%) were resistant to both ciprofloxacin and third-generation cephalosporins and 2 (15%) were resistant to ciprofloxacin alone. Of 10 spontaneous bacteremias, 3 (30%) were resistant to both ciprofloxacin and third-generation cephalosporins and 4 (40%) were resistant to ciprofloxacin alone.

In this set of 60 culture-positive UTIs or spontaneous infections (SBP, SBE, spontaneous bacteremia), a univariate analysis was performed to identify predictors of resistance to a recommended first-line antibiotic therapy (ciprofloxacin for UTI and third-generation cephalosporin antibiotics for spontaneous infections). Exposure to systemic antibiotics within the preceding 30 days (OR, 32 [6.3–162.5]), nosocomial infection (OR, 13.2 [3.6–48.2]), and the MELD score (OR, 1.07 [1.01–1.13]) were significant on univariate analysis and therefore were entered into the multivariate model. On multivariate analysis, both exposure to systemic antibiotics (OR, 14.5 [2.4–86.8]) and nosocomial infection (OR, 9.4 [1.1–78.5]) were independent predictors of resistance to first-line antibiotic therapy.

Secondary Analysis of All Bacterial Infections in the Study Period (n = 169)

To add strength to the primary analysis, further sensitivity analysis was performed including all infections occurring in the study period. A total of 169 bacterial infections occurred in the 115 patients. Seventy percent (80 of 115) of patients had only 1 bacterial infection during the study period, 21% (24 of 115) had 2 infections, 7% (8 of 115) had 3 infections, and 1 patient each had 4, 6, and 7 infections.

Of these 169 infections, 111 (66%) were culture-positive, of which 49 (44%) were caused by AR bacteria: 16 VRE (33%), 14 QRGNR (29%), 9 ESBL (18%), 8 MRSA (16%), and 2 *Enterobacter* infections with an AmpC β-lactamase mutation (4%) (Table 5). Univariate analysis of predictors of AR-BI showed that exposure to systemic antibiotics (OR, 8.8 [95% CI, 3.1–24.7]), MELD score (OR, 1.05 [95% CI, 1.009–1.10]), albumin level (OR, 2.2 [95% CI, 1.2–3.9]), nosocomial acquisition of infection (OR, 6.5 [95% CI, 2.8–14.9]), and Child–Pugh score (OR, 1.5 [95% CI, 1.1–1.9]) had *P* values of less than .05. When the first 4 factors were entered into a multivariate model, exposure to systemic antibiotics within the preceding 30 days (OR, 5.2 [95% CI, 1.5–17.7]) and nosocomial acquisition of infection (OR, 4.2 [95% CI, 1.4–12.5]) were independently predictive of AR-BI.

By using the larger set of all infections in the study period, we assessed the impact of exposure to antibiotics used for SBP prophylaxis (trimethoprim-sulfamethoxazole, fluoroquinolones) vs alternate systemic antibiotics, by categorizing antibiotic use within the past 30 days into 3 groups: (1) no antibiotic exposure or the use of oral nonabsorbed antibiotics (40 of 42 cases on oral nonabsorbed antibiotics were taking rifaximin and 2 of 42

were taking neomycin), (2) SBP prophylaxis antibiotics, and (3) other systemic antibiotic exposure. This categoric variable was significant on univariate analysis for the prediction of AR-BI and therefore was entered into the multivariate model with the MELD score, albumin level, and nosocomial acquisition of infection. Nosocomial acquisition of infection again independently was predictive of AR-BI with an OR of 5.1 (95% CI, 1.6–15.9). With the use of oral nonabsorbed antibiotics or no antibiotic exposure as the reference category, exposure to antibiotics used for SBP prophylaxis was predictive of AR-BI with an OR of 15.5 (95% CI, 3.3–72.8). Exposure to other systemic antibiotics also independently was predictive with an OR of 4.7 (95% CI, 1.5–14.2).

By using this larger set of bacterial infections, we also evaluated predictors of resistance to first-line antibiotic therapy in those patients with culture-positive UTIs and spontaneous bacterial infections (SBP, SBE, spontaneous bacteremia). Of a total of 52 culture-positive UTIs, 19 (37%) were resistant to both ciprofloxacin and third-generation cephalosporins, 11 (21%) were resistant to ciprofloxacin alone, and 2 (4%) were resistant to third-generation cephalosporins alone. Of the 18 culture-positive SBP/SBE infections, 7 (39%) were resistant to both ciprofloxacin and third-generation cephalosporins and 4 (22%) were resistant to ciprofloxacin alone. Of the 23 spontaneous bacteremias, 6 (26%) were resistant to both ciprofloxacin and third-generation cephalosporins and 11 (48%) were resistant to ciprofloxacin alone. We repeated the analysis for predictors of resistance to first-line antibiotic therapy for this group of 93 infections. Again, the MELD score (OR, 1.05 [95% CI, 1.002–1.10]), nosocomial infection (OR, 5.9 [95% CI, 2.4–14.5]), and exposure to systemic antibiotics (OR, 11.4 [95% CI, 3.5–37]) were significant predictors on univariate analysis. In multivariate analysis, exposure to systemic antibiotic therapy in the past 30 days (OR, 7.0 [95% CI, 1.9–26.1]) and nosocomial infection (OR, 4.3 [95% CI, 1.3–14.0]) were identified as the only independent predictive factors of resistance to first-line antibiotic therapy.

Discussion

Bacterial infections are an important cause of morbidity and mortality in patients with cirrhosis.[1,17] Over time, the efficacy of antibiotics has been threatened by the emergence of antibiotic resistance.[18] Although several published studies from Europe and Asia have reported high rates of antibiotic-resistant organisms in patients with cirrhosis admitted with bacterial infections,[2,3,6,19–21] there are limited published US data.

Our study showed a high rate of antibiotic resistance in our culture-positive infections, with 47% (33 of 70) of the infections meeting our definition of antibiotic resistance and 39% (9 of 23) of the spontaneous infections (SBP/SBE, spontaneous bacteremias) being resistant to third-generation cephalosporins, the recommended empiric antibiotic for these infections.[16] Our rate of cephalosporin resistance in patients with SBP (45% or 5 of 11) is at the high end of the range of 22% to 41% reported in the literature.[4,6,19,20]

The administration of ineffective antibiotic therapy to a patient with AR-BI is associated with increased rates of septic shock and death.[3,6,21–24] To allow for the early identification of these high-risk patients, we investigated factors that would predict the presence of AR-BI. In the select group of patients with the most common infections (spontaneous bacterial infections and UTIs), we also investigated factors that would predict resistance to accepted first-line antibiotic therapy. Previously described risk factors for the development of AR-BI have included antibiotic exposure,[3,4,21,25] nosocomial acquisition of infection,[3,4,21,26] recent hospitalization,[25,27,28] and a past history of colonization with resistant organisms.[3,25,27]

In our series, we were able to evaluate and confirm the contribution of recent antibiotic exposure (within the past 30 d) and nosocomial acquisition of infection in a group of North American cirrhotic patients. Seventy-six percent (22 of 28) of patients with culture-positive nosocomial infections were exposed to systemic antibiotics in the 30 days preceding bacterial infection. By using data on the first infection, although both factors were significant on univariate analysis, only the recent use of systemic antibiotics was an independent predictor of the presence of AR-BI. When the analysis was broadened to include repeat infections in the prediction of AR-BI, both nosocomial acquisition of infection and exposure to systemic antibiotics in the 30 days preceding bacterial infection were significant predictors. In the prediction of resistance to first-line antibiotic therapy for the spontaneous infections and for UTIs, again the use of systemic antibiotics within the past 30 days and nosocomial acquisition of infection emerged as independent predictors. The contribution of antibiotic use to the development of bacterial resistance is well described.[18,29] Antibiotic exposure induces antibiotic selection pressure and resistance to the antibiotic in question or cross-resistance to other antibiotics by multiple complex mechanisms, including bypassing of antibiotic targets, the active efflux of antibiotics from the cell, and enzyme-catalyzed antibiotic modifications.[29–36] Nosocomial acquisition of infection also has been recognized as a risk factor for the failure of empiric antibiotic therapy.[2,3] The development of antibiotic resistance in nosocomial infections in large part is owing to the recent use of antibiotics, but resistance rates also can increase owing to person-to-person transmission of resistant organisms or by the use of indwelling medical devices (urinary catheters, intravascular catheters, endotracheal tubes).[2,18] Because of the retrospective nature of this study, we could not accurately evaluate the impact of indwelling medical devices, recent hospitalizations, or a past history of colonization with resistant organisms, the latter 2 factors in which antibiotic use also conceivably plays a major role.

The relative impact of antibiotics given for SBP prophylaxis (fluoroquinolones or trimethoprim-sulfamethoxazole) vs other systemic antibiotics on the development of AR-BI was evaluated in the larger group of patients with repeat infections. Both classes of systemic antibiotics had a significant impact on the development of AR-BI when all culture-positive infections were considered. This is similar to the findings from the recent Spanish series that grouped multiple types of bacterial infections in the analysis and found the use of β-lactam antibiotics and the use of norfloxacin prophylaxis predictive of AR-BI.[3] The impact of fluoroquinolones on the development of AR-BI or third-generation cephalosporin resistance in patients with SBP remains unclear. Because of the small numbers in our series, we could not evaluate this group separately. Older studies support the theory that SBP prophylaxis, most commonly with fluoroquinolone agents, results in a higher rate of fluoroquinolone-resistant gram-negative organisms, as we also found, and in infection with gram-positive organisms, but has no impact on the rate of third-generation cephalosporin resistance.[2,37] More recent studies of SBP have recognized cephalosporin use as an independent predictor of AR-BI, but the use of fluoroquinolones has not reached statistical significance.[4,21] It is possible that some predictive factors are dependent on the specific type of infection and this will require further study in larger series.

Importantly, we did not find a significant risk of AR-BI with the use of nonabsorbed antibiotics, with rifaximin being the most commonly used.[38–40] To our knowledge, this finding has not been described in a series of cirrhotic patients. It is important because the use of rifaximin for hepatic encephalopathy has been increasing, particularly in hospitalized patients. Although not yet published in a group of cirrhotic patients, the lack of a relationship between rifaximin use and AR-BI can be rationalized given the characteristics of rifaximin[13]: (1) it reaches very high fecal concentrations and is poorly absorbed, with an estimated bioavailability in the blood after oral administration of less than 0.4%[13,41]; (2) an anaerobic environment, similar to that found in the colon, reduces the selection of rifaximin-

resistant mutants[13]; and (3) it reduces the expression of bacterial virulence factors and compromises plasmid transfer, a key pathway for the transfer of bacterial resistance.[42,43] Moreover, small studies of stool antibiotic resistance testing after rifaximin exposure have shown a low level of resistance to rifaximin and no increase in resistance development to tested antibiotics.[44,45] Because antibiotic resistance can develop in a time-dependent manner, however, it will be important to reassess the impact of long-term rifaximin exposure in future studies.

In conclusion, this study showed a high rate of antibiotic-resistant bacterial infections in patients with cirrhosis hospitalized in a tertiary transplant center in the United States, not unlike data reported in Spain. In our series, we found that prior exposure to systemic antibiotics is the most important predictor of the development of these infections, and in the most commonly seen infections, both recent antibiotic exposure and nosocomial acquisition of infection are predictors of resistance to empiric antibiotic therapy.

As suggested by published European data,[3,46] our findings support the recommendation for broad-spectrum antibiotic coverage (eg, the carbapenem class of antibiotics) in patients with nosocomial infections. Whether the patient has been exposed to systemic antibiotics within the past 30 days also should be considered when determining the empiric antibiotic choice. As is standard infectious disease practice, patients should not receive empiric therapy with an antibiotic class they recently have been exposed to; for example, third-generation cephalosporins should not be used as empiric therapy to treat patients recently exposed to cephalosporins. In addition, although it is clear that patients on fluoroquinolone prophylaxis should not receive empiric therapy with fluoroquinolone, there are no strong data to support that patients on fluoroquinolone prophylaxis require empiric broad-spectrum antibiotic coverage.[2,37] In all culture-positive patients, once antibiotic susceptibilities are available, antibiotic coverage should be narrowed. Lastly, although these recommendations are evidence-based and form a good starting point, because there can be significant variation in resistance patterns from center to center, in the ideal situation, individual centers would collaborate with experts in microbiology and infections to confirm the generaliz-ability of these recommendations to their own patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations used in this paper

AR-BI	antibiotic-resistant bacterial infections
CI	confidence interval
ESBL	extended-spectrum *β*-lactamase–producing *Enterobacteriaceae*
MELD	Model for End-Stage Liver Disease
MRSA	methicillin-resistant *Staphylococcus aureus*
OR	odds ratio
QRGNR	quinolone-resistant gram-negative rods
SBE	spontaneous bacterial empyema
SBP	spontaneous bacterial peritonitis
UTI	urinary tract infection

VRE vancomycin-resistant *Enterococcus*

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Table 1

Baseline Characteristics per Patient (n = 115)

Characteristic	Non-AR-BI/culture negative	AR-BI	*P* value
N	82	33	—
Male sex	57 (69.5%)	21 (63.6%)	.66
HCV infection or HCV + ETOH liver disease	69 (84.1%)	24 (72.7%)	.19
Age, *y*	54.4 ± 10.2	58.6 ± 10.3	.07
Diabetes	26 (31.7%)	13 (39.4%)	.52
HIV infection	3 (3.7%)	0 (0%)	.56
Nosocomial infection	12 (14.6%)	22 (66.7%)	.001
On β-blockers	37 (45.1%)	17 (51.5%)	.54
On proton pump inhibitors	43 (52.4%)	24 (72.7%)	.06
On lactulose	45 (54.9%)	21 (63.6%)	.41
Antibiotics within 30 d of bacterial infection (oral nonabsorbed or systemic)	39 (47.6%)	29 (87.9%)	.001
Antibiotics within 30 d of bacterial infection			.001
No antibiotic	43 (52.4%)	4 (12.1%)	
Oral nonabsorbed antibiotic	25 (30.5%)	2 (6.1%)	
Systemic antibiotic	14 (17.1%)	27 (81.8%)	
Type of bacterial infection			.001
Spontaneous infections (SBP, SBE, bacteremia)	31 (37.8%)	9 (27.3%)	
UTI	17 (20.7%)	20 (60.6%)	
Pneumonia	20 (24.4%)	2 (6.1%)	
Other	14 (17.1%)	2 (6.1%)	
White blood cell count	7.8 ± 5.1	9.1 ± 8.9	.83
Platelet count	107.4 ± 79.2	88.5 ± 52.9	.32
Albumin level, *g/dL*	2.8 ± 0.7	3.2 ± 0.8	.01
Bilirubin level, *mg/dL*	6.5 ± 8.5	13.2 ± 14.9	.02
INR	1.6 ± 0.5	1.8 ± 0.6	.06
Creatinine level, *mg/dL*	1.4 ± 1.0	2.4 ± 1.4	.001
Sodium level, *mEq/L*	131.2 ± 15.3	135.4 ± 7.1	.06
Child–Pugh score	9.0 ± 1.5	10.1 ± 1.4	.001
MELD score	19.5 ± 9.4	26.5 ± 9.8	.001

HIV, human immunodeficiency virus; INR, international normalized ratio.

Table 2

Organisms Isolated in Culture-Positive Infections: First Infection per Patient (n = 70)

	UTI (n = 37)	SBP/SBE (n = 13)	Spontaneous bacteremia (n = 10)	Pneumonia (n = 6)	Other (n = 4)
Gram-negative bacilli					
β-lactam–susceptible *Escherichia coli*	10[a] (4 QR, 0 CR)	2 (1 QR, 0 CR)			
ESBL-producing *Escherichia coli*	2 (2 QR, 2 CR)	1 (1 QR, 1 CR)			
β-lactam–susceptible *Klebsiella pneumoniae*	6 (2 QR, 0 CR)	2 (0 QR, 0 CR)	1 (0 QR, 0 CR)	2	
ESBL-producing *Klebsiella pneumoniae*	2[a] (1 QR, 2 CR)	1 (1 QR, 1 CR)		1	1
β-lactam–susceptible *Pseudomonas aeruginosa*	1 (0 QR, 0 CR)				
ESBL-producing *Pseudomonas aeruginosa*	1 (1 QR, 1 CR)				
β-lactam–susceptible *Citrobacter freundii*	1 (0 QR, 0 CR)	1 (0 QR, 0 CR)			
β-lactam–susceptible *Enterobacter aerogenes*		1 (0 QR, 0 CR)			
Proteus mirabilis	1 (0 QR, 0 CR)		1 (0 QR, 0 CR)		
Haemophilus influenzae				1	
Gram-positive cocci					
Vancomycin-susceptible *Enterococcus*	4 (4 QR, 4 CR)		1 (1 QR, 1 CR)		
VRE	8 (8 QR, 8 CR)	2 (2 QR, 2 CR)	2 (2 QR, 2 CR)		
Streptococcus (S viridans [1], *S mitis* [1], *β-hemolytic Strep* [1], *group B Strep* [1])			3 (3 QR, 0 CR)		1
Methicillin-sensitive *S aureus*		1 (1 QR, 0 CR)	2 (1 QR, 0 CR)	1	1
Methicillin-resistant *S aureus*	1 (1 QR, 1 CR)	2 (2 QR, 2 CR)		1	1

CR, third-generation cephalosporin resistant; QR, quinolone resistance.

NOTE. Infections in the “Other” category consisted of 2 septic arthritis, 1 cellulitis, and 1 liver abscess.

[a]Infection with 2 organisms (occurred with 2 UTIs [1 was mixed gram-negative and gram-positive]; only 1 organism counted for the purpose of this Table).

Table 3

Specific Antibiotic to Which Patients With Culture-Positive Infections Were Exposed to in the 30 Days Before the Development of Infection: Culture-Positive Episodes in First Infection Only (n = 70)

Antibiotic	Patients, n
No antibiotic	23
Oral nonabsorbed antibiotics	16 (all on rifaximin)
Systemic antibiotics	31
Oral, fully or partially absorbed antibiotics used for SBP prophylaxis (ciprofloxacin, norfloxacin, or trimethoprim/sulfamethoxazole)	9
Other systemic antibiotics	22
Piperacillin-tazobactam	8
Third-generation cephalosporin	7
Ampicillin/amoxicillin based	2
Linezolid or ticarcillin	2
Levofloxacin	1
Doxycycline	1
Vancomycin	1

Table 4

Predictors of AR-BI in 70 Culture-Positive Infections: 115 First Infection Only Patients

Characteristic	OR (95% CI)	*P* value
Univariate analysis for predictors of antibiotic-resistant infection		
Demographic variables		
Age	1.02 (0.97–1.07)	.48
Medications and comorbidities		
On β-blockers	1.4 (0.5–3.6)	.49
On proton pump inhibitors	2.3 (0.8–6.2)	.11
Diabetes mellitus	1.2 (0.5–3.2)	.71
Mode of infection acquisition and antibiotic exposure history		
Nosocomial infection	10.3 (3.3–32.1)	.001
Antibiotics within 30 d of bacterial infection (any antibiotic vs no antibiotic)	7.7 (2.2–26.1)	.001
Antibiotics within 30 d of bacterial infection		
No antibiotic	1.0	Reference category
Oral nonabsorbed antibiotics	0.7 (0.1–4.2)	.7
Systemic antibiotics[a]	32 (7–144)	.001
Laboratory test results and severity of liver disease		
Albumin level, *g/dL*	2.2 (1.0–4.6)	.04
White blood cell count	1.03 (0.96–1.11)	.44
Child–Pugh score	1.8 (1.2–2.6)	.002
MELD score	1.08 (1.03–1.14)	.004
Multivariate analysis for predictors of antibiotic-resistant infection		
Antibiotic use within 30 d of bacterial infection		
No antibiotic	1	Reference
Oral nonabsorbed antibiotic	0.4 (0.04–2.8)	.32
Systemic antibiotics[a]	13.5 (2.6–71.6)	.002
Nosocomial infection	1.6 (0.2–9.9)	.6
MELD	1.05 (0.96–1.15)	.3
Albumin level, *g/dL*	1.5 (0.6–4.1)	.4

[a]Some patients also received oral nonabsorbed antibiotics.

Table 5

Organisms Isolated in Culture-Positive Infections: Multiple Infections per Patient (n = 111)

	UTI (n = 52)	SBP/SBE (n = 18)	Spontaneous bacteremia (n = 23)	Pneumonia (n = 7)	Other (n = 11)
Gram-negative bacilli					
β-lactam–susceptible *Escherichia coli*	14 (7 QR, 0 CR)	3 (1 QR, 0 CR)	2 (2 QR, 0 CR)		
ESBL-producing *Escherichia coli*	2[a] (2 QR, 2 CR)	1 (1 QR, 1 CR)			
β-lactam–susceptible *Klebsiella pneumoniae*	9 (2 QR, 0 CR)	2 (0 QR, 0 CR)	2 (0 QR, 0 CR)	2	
ESBL-producing *Klebsiella pneumoniae*	2[a] (1 QR, 2 CR)	1 (1 QR, 1 CR)		1	1
β-lactam–susceptible *Pseudomonas* species (*P aeruginosa* [2], *P fluorescens* [1])	2 (0 QR, 0 CR)		1 (0 QR, 0 CR)		
ESBL-producing *Pseudomonas aeruginosa*	1 (1 QR, 1 CR)				
β-lactam–susceptible *Citrobacter freundii*	1 (0 QR, 0 CR)	2 (0 QR, 0 CR)			
β-lactam–susceptible *Enterobacter* (*E aerogenes* [1], *E cloacae* [2])	2 (0 QR, 0 CR)	1 (0 QR, 0 CR)			
Amp-C–producing *Enterobacter cloacae*	1 (0 QR, 1 CR)		1 (1 QR, 1 CR)		
Acinetobacter			1 (0 QR, 0 CR)		
Serratia marcescens					1
Proteus mirabilis	3 (2 QR, 0 CR)		1 (0 QR, 0 CR)		
Haemophilus influenzae				1	
Gram-positive cocci					
Vancomycin-susceptible *Enterococcus*	5[a] (5 QR, 5 CR)		1 (1 QR, 1 CR)		
VRE	9 (9 QR, 9 CR)	3 (3 QR, 3 CR)	4 (4 QR, 4 CR)		
Streptococcus (*S viridans* [6], *S mitis* [2], *S sanguis* [1], *β-hemolytic Strep* [1], *group B Strep* [1])		1 (1 QR, 0 CR)	8 (8 QR, 0 CR)		2[a]
Methicillin-sensitive *S aureus*		2 (2 QR, 0 CR)	2 (1 QR, 0 CR)	1	2
Methicillin-resistant *S aureus*	1 (1 QR, 1 CR)	2 (2 QR, 2 CR)		2	3
Coagulase-negative *Staphylococcus*					2

CR, third-generation cephalosporin resistant; QR, quinolone resistance.

NOTE. Infections in the "Other" category consisted of 3 cellulitis, 3 septic arthritis, 2 endocarditis, 2 line infections, and 1 liver abscess.

[a]Infection with 2 organisms (occurred with 3 UTIs [2 were mixed gram-negative and gram-positive] and 1 cellulitis; only 1 organism counted for the purpose of this Table).