Prevalence and Impact of Ceftriaxone-Resistant Pathogens on Mortality in Spontaneous Bacterial Peritonitis (SBP)

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REVISED ABSTRACT

Objective: To (1) assess the prevalence of ceftriaxone (CRO)-resistant pathogens, (2) identify risk factors for CRO-resistant pathogens, and (3) evaluate the impact of inappropriate empiric therapy on all-cause 30-day mortality in cirrhotic patients with SBP.

Methods: This case-case-control study at a large tertiary center in the US included adults with liver cirrhosis admitted from 2011-2016. Case group 1 comprised patients with SBP with a CRO-resistant (CRO-R) pathogen. Case group 2 comprised patients with SBP with a CRO-susceptible (CRO-S) pathogen. Control group were patients without SBP.

Results: There were 22 patients in case group 1, 26 in case group 2, and 96 in control group. Of the 51 isolates identified in 48 case patients, 45% (23/51) were CRO-R. Risk factors for CRO-R pathogens included longer duration of previous β-lactam therapy, recent invasive GI procedure, and high MELD-Na (p<0.05). Patients with CRO-R pathogens were more likely to receive inappropriate empiric therapy (OR, 5.53; 95% CI, 1.28-23.88). Inappropriate empiric therapy was independently associated with mortality (OR, 10.42; 95% CI, 1.76-61.54).

Conclusions: CRO-R pathogens commonly caused SBP. Risk factors for CRO-R pathogens included recent invasive GI procedure, high MELD-Na, and longer duration of previous β-lactam therapy. CRO-R pathogens were more likely to be treated with inappropriate empiric therapy. Inappropriate empiric therapy was associated with increased mortality.

BACKGROUND

- SBP is diagnosed in 1 of 4 cirrhotic patients hospitalized with bacterial infections, and all-cause 30-day mortality is 26-49%.
- Ceftriaxone (CRO) is often used empirically for SBP, but recent studies outside of the US have showed increased rates of SBP due to CRO-resistant (CRO-R) pathogens (16-67%).
- Little is known about the current epidemiology of SBP in the US.

OBJECTIVES

- Assess the prevalence of CRO-R pathogens
- Identify risk factors for CRO-R pathogens
- Evaluate the impact of inappropriate empiric therapy on all-cause 30-day mortality

METHODS

Study design, population, setting

- 1:1:4 retrospective case-case-control study
- Adults with liver cirrhosis admitted to a large tertiary center in Houston, TX, from 11/2011 to 03/2016
- Case group 1 = Cirrhotic, SBP, CRO-resistant (CRO-R) pathogen
- Case group 2 = Cirrhotic, SBP, CRO-susceptible (CRO-S) pathogen
- Control group = Cirrhotic, no SBP (randomly selected)
- Exclusion criteria = patients with ascitic fluid culture positive for skin contaminants or patients with secondary peritonitis

Definitions

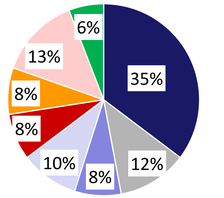
- SBP = ascitic fluid PMN count ≥250 cells/mm^3
- CRO-R pathogen = intrinsically resistant to CRO or classified as intermediate or resistant to CRO based on CLSI breakpoints

Statistical analysis (SPSS version 23.0 for Windows)

- Univariate analysis: Fisher's exact test or chi-square test for categorical data & Mann-Whitney U for continuous data
- Multivariate analysis: multiple logistic regression models

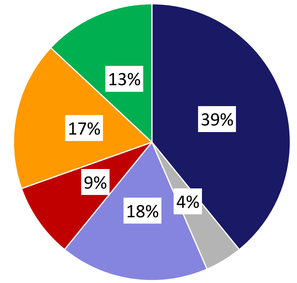
RESULTS

Etiologic Agents of SBP (n=51)



- *E. coli*
- *K. pneumoniae*
- *P. aeruginosa*
- Other Enterobacteriaceae
- *S. aureus*
- *Enterococcus spp.*
- *Streptococcus spp.*
- *Candida spp.*

CRO-R Pathogens (n=23)



- *ESBL E. coli*
- *ESBL K. pneumoniae*
- *P. aeruginosa*
- MRSA
- *Enterococcus spp.*
- *Candida spp.*

RESULTS CONTINUED

Table 1. Risk factors for CRO-R and CRO-S pathogens (univariate)

Variable	CRO-R n = 22	CRO-S n = 26	Control n = 96	p (CRO-R vs control)	p (CRO-S vs control)
Age, years	56 (53-68)	59 (56-65)	59 (54-65)	0.534	0.824
Male	13 (59)	20 (77)	55 (57)	0.878	0.068
Caucasian	11 (50)	19 (73)	53 (56)	0.658	0.100
Cirrhosis etiology: HCV or alcohol	9 (41)	17 (65)	67 (70)	0.011	0.667
MELD-Na score	31 (25-33)	25 (22-30)	22 (17-29)	0.001	0.161
Child-Pugh score	12 (11-13)	11 (10-12)	10 (8-12)	0.003	0.336
Previous SBP episode	8 (36)	8 (31)	9 (9)	0.003	0.010
ICU admission	10 (46)	4 (15)	21 (22)	0.023	0.467
Hospitalization in past 90 days	7 (32)	10 (39)	35 (37)	0.682	0.851
Nursing home or long term care	2 (9)	2 (8)	5 (5)	0.613	0.640
Invasive GI procedure in past 2 weeks	8 (36)	2 (8)	6 (6)	0.001	0.678
CRO-R pathogen on previous cultures	8 (36)	2 (8)	12 (13)	0.012	0.732
Prior hospital length of stay, days	1.5 (0-7)	0.5 (0-1)	1 (1-4)	0.838	0.006
Antibiotic therapy duration in past 90 days					
• Third-generation cephalosporin, days	0.5 (0-7)	0 (0-4)	0 (0-4)	0.255	0.758
• β-lactam, days	11 (0-27)	0 (0-10)	2 (0-6)	0.007	0.747

Values expressed as median (25-75th percentiles) or n (%).

Table 2. Risk factors for CRO-R and CRO-S pathogens (multivariate)

Variable	CRO-R vs control OR	95% CI	p	CRO-S vs control OR	95% CI	p
Duration of β-lactam therapy in past 90 days, days	1.07	1.02-1.13	0.011	-	-	-
MELD-Na score	1.08	1.00-1.16	0.043	-	-	-
Invasive GI procedure in past 2 weeks	10.41	2.52-42.93	0.001	-	-	-
Previous SBP episode	-	-	-	4.30	1.46-12.64	0.008

Hosmer-Lemeshow goodness-of-fit test for CRO-R vs control logistic regression model p = 0.797

Table 3. Risk factors for 30-day mortality (univariate)

Variable	Dead n = 9	Alive n = 39	p
Age, years	57 (50-65)	59 (54-67)	0.466
Male	6 (67)	27 (69)	>0.99
Caucasian	6 (67)	24 (62)	>0.99
Cirrhosis etiology: HCV or alcohol	6 (67)	20 (51)	0.478
MELD-Na score	25 (23-37)	28 (23-32)	0.567
Child-Pugh score	12 (9-13)	11 (10-13)	0.876
Hepatocellular carcinoma	1 (11)	5 (13)	>0.99
Diabetes mellitus	5 (56)	16 (41)	0.477
Cardiovascular disease	0 (0)	9 (23)	0.176
CKD or ESRD	2 (22)	12 (31)	>0.99
Acute kidney injury	3 (33)	19 (49)	0.478
ICU admission	4 (44)	10 (26)	0.416
Septic shock	1 (11)	3 (8)	>0.99
Nosocomial infection	4 (44)	8 (21)	0.199
Prior hospital length of stay, days	2 (0-9)	1 (0-3)	0.375
Invasive GI procedure in past 2 weeks	4 (44)	8 (21)	0.075
CRO-R pathogen*	8 (89)	14 (36)	0.007
Inappropriate empiric therapy	7 (78)	10 (26)	0.006

Values expressed as median (25-75th percentiles) or n (%).
*In multivariate analysis, 2 variables were independently associated with inappropriate empiric therapy: CRO-R pathogen (p=0.022) and recent invasive GI procedure (p=0.023)

Table 4. Risk factors for 30-day mortality (multivariate)

Variable	OR	95% CI	p
Inappropriate empiric therapy	10.42	1.76-61.54	0.010
Nosocomial infection	3.27	0.57-18.65	0.182

Hosmer-Lemeshow goodness-of-fit test p = 0.991

CONCLUSIONS

↑ Recent β-lactam use
↑ MELD-Na score
Recent invasive GI procedure

→ CRO-resistant pathogens in almost half of SBP cases

→ Inappropriate empiric therapy

→ ↑ All-cause 30-day mortality

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