Bacterial infections in patients with acute variceal bleeding in the era of antibiotic prophylaxis

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Table S1. Missing data of each variable

Variable	**All patients (n=1656)** **Missing data (N; %)**
Age, years	None
Gender, male	None
Etiology of cirrhosis, alcohol	None
Active alcoholism	30 (1.8)
Previous antibiotics	None
Diabetes	None
Severity of cirrhosis	
Child-Pugh at admission	None
Hepatic encephalopathy	None
Bilirubin, mg/dL	None
Albumin, g/dL	None
INR	None
Index bleed: severity	
Hematemesis	None
Active bleeding at endoscopy	2 (0.1)
Shock	65 (3.9)
Haemoglobin, g/dL	None
Number of packed red blood cells	24 (1.4)
Index bleed: management	
Use of antibiotic prophylaxis	None

Nasogastric tube	48 (2.9)
Sedation for endoscopy	70 (4.2)
Orotracheal intubation for endoscopy	31 (1.9)
Time to endoscopy	82 (5.0)
Initial hemostatic treatment	None
Endoscopic treatment	118 (7.1)
Balloon tamponade	None
Pre-emptive TIPS	None
Infection outcome	
Infection during admission	None
Type of infection during admission	None
Time from admission to infection	8 (0.5)
Bacterial isolations	277 (75.9)
Hospitalization and mortality	
Length, days	19 (1.1)
In-hospital mortality	None
Mortality at 6-weeks	None

Table S2. Other patient characteristics

Variable	All patients n=1656	Without bacterial infection n=1336	With bacterial infection n=320	p value
Previous decompensation	855 (51.6)	696 (52.1)	159 (49.7)	0.94
Portal hypertensive bleeding	532 (32.1)	442 (33.1)	90 (28.1)	0.09
Spontaneous bacterial peritonitis/bacteremia	53 (3.2)	42 (3.1)	11 (3.4)	0.08
Hepatorenal syndrome	16 (1.0)	14 (1.0)	2 (0.6)	0.87
Previous active therapies				
Beta-blockers	560 (33.8)	491 (36.8)	69 (21.6)	0.09
Anticoagulants	73 (4.4)	55 (4.1)	18 (5.6)	0.21
Simvastatin	80 (4.8)	69 (5.2)	11 (3.4)	0.32
Diuretics	713 (43.1)	588 (44.0)	125 (39.1)	0.29
Previous antibiotics	202 (12.2)	164 (12.3)	38 (11.9)	0.27
Norfloxacin	104 (6.3)	80 (6.0)	24 (7.5)	0.54
Rifaximin	74 (4.5)	63 (4.7)	11 (3.4)	0.75
Others	24 (1.5)	21 (1.6)	3 (0.9)	0.34
Hepatocellular carcinoma	207 (12.5)	171 (12.8)	36 (11.3)	0.51
Portal vein thrombosis	205 (12.4)	172 (12.9)	33 (10.3)	0.34

Categorical variables are expressed as N(%)

Table S3. Characteristics of patients and outcomes of the retrospective (2011-2013) and prospective (2013-2015) cohorts

Variable	All patients n=1656	Retrospective cohort n=733	Prospective cohort n=923	p value
Age, years	59.1 (12.4)	58.3 (11.2)	59.1 (11.9)	0.08
Gender, male	1225 (74.0)	543 (74.1)	682 (73.9)	0.09
Etiology of cirrhosis, alcohol	895 (54.1)	404 (55.1)	491 (53.2)	0.20
Active alcohol use	584 (35.3)	271 (37.0)	313 (33.9)	0.29
Previous antibiotics	203 (12.3)	88 (12.0)	115 (12.5)	0.50
Diabetes	510 (30.8)	225 (30.7)	285 (30.9)	0.46
Severity of cirrhosis				
Child-Pugh at admission				
A	230 (13.9)	102 (13.9)	128 (13.9)	0.66
B	984 (59.4)	454 (61.9)	530 (57.4)	
C	442 (26.7)	177 (24.2)	265 (28.7)	
Hepatic encephalopathy				
No	1177 (71.1)	528 (72.0)	649 (70.3)	0.87
Grade I-II	307 (18.5)	132 (18.0)	175 (19.0)	
Grade III-IV	172 (10.4)	73 (10.0)	99 (10.7)	
Bilirubin, mg/dL	2.8 (3.8)	2.5 (2.1)	2.3 (2.9)	0.72
Albumin, g/dL	2.8 (0.6)	2.8 (0.6)	2.8 (0.7)	0.73
INR	1.6 (0.5)	1.3 (0.8)	1.4 (0.9)	0.15
Index bleed: severity				

Hematemesis	1260 (76.1)	568 (77.5)	692 (75.0)	0.15
Active bleeding at endoscopy	528 (31.9)	213 (29.1)	315 (34.1)	0.23
Shock	454 (27.4)	191 (26.1)	263 (28.5)	0.69
Haemoglobin, g/dL	9.1 (2.2)	9.1 (2.1)	9.2 (2.0)	0.74
Number of packed red blood cells	2.1 (2.0)	2.2 (2.0)	1.2 (1.1)	**0.02**
Index bleed: management				
Antibiotic prophylaxis Third generation cephalosporines Quinolones Amoxicillin/clavulanic Others	 1262 (76.2) 314 (19.0) 48 (2.9) 32 (1.9)	 545 (74.4) 146 (19.9) 26 (3.5) 13 (1.8)	 717 (77.7) 168 (18.2) 22 (2.4) 19 (2.1)	0.33
Nasogastric tube	532 (32.1)	278 (37.9)	254 (27.5)	**0.01**
Sedation for endoscopy	1143 (69.0)	505 (68.9)	638 (69.1)	0.34
Orotracheal intubation for endoscopy	323 (19.5)	163 (22.2)	160 (17.3)	**0.01**
Time to endoscopy <12h 12-24 >24h	 1386 (83.7) 129 (7.8) 59 (3.6)	 587 (80.0) 57 (7.8) 31 (4.2)	 799 (86.6) 72 (7.8) 28 (3.0)	0.21
Initial hemostatic treatment Drugs plus endoscopy Drugs alone	 1422 (85.9) 166 (10.0)	 601 (82.0) 74 (10.1)	 821 (88.9) 92 (10.0)	0.17 1

Endoscopy alone	54 (3.3)	25 (3.4)	29 (3.1)	0.26
Balloon tamponade	50 (3.0)	22 (3.0)	28 (3.0)	0.79
Esophageal stent	2 (0.1)	1 (0.1)	1 (0.1)	0.81
Endoscopic treatment				
Ligation	1225 (74.0)	541 (73.8)	684 (74.1)	0.77
Sclerotherapy	159 (9.6)	68 (9.3)	91 (9.9)	0.48
Tissue glue injection	111 (6.7)	51 (7.0)	60 (6.5)	0.73
Others	43 (2.6)	23 (3.1)	20 (2.2)	0.77
Pre-emptive TIPS	53 (3.2)	19 (2.6)	34 (3.7)	0.17
Infections outcomes				
Infection during admission	320 (19.3)	156 (21.3)	164 (17.8)	**0.01**
Respiratory infection	159 (9.6)	79 (10.8)	80 (8.7)	0.08
Hospitalization and mortality				
Length, days	10.1 (7.7)	12.1 (8.4)	11.8 (6.3)	0.57
In-hospital mortality	164 (9.9)	79 (10.8)	85 (9.2)	0.15
Mortality at 6-weeks	220 (13.3)	110 (15.0)	110 (11.9)	0.37

Continuous variables are expressed as mean (standard deviation) or as median (interquartile range). Categorical variables are expressed as N (%)

INR: International normalized ratio

TIPS: Transjugular intrahepatic portosystemic shunt

Table S4. Characteristics of the patients without and with respiratory infection

Variable	All patients n=1656	Without respiratory infection n=1497	With respiratory infection n=159	P
Age, years	59.1 (12.4)	59.0 (12.1)	58.9 (12.2)	0.57
Gender, male	1225 (74.0)	1108 (74.0)	117 (73.6)	0.33
Etiology of cirrhosis, alcohol	895 (54.1)	799 (53.4)	96 (60.4)	**0.04**
Active alcohol use	584 (35.3)	508 (33.9)	76 (47.8)	**0.03**
Previous antibiotics	203 (12.3)	184 (12.3)	19 (11.9)	0.45
Diabetes	510 (30.8)	469 (31.3)	41 (25.8)	0.09
Severity of cirrhosis				
Child-Pugh				**<0.01**
A	230 (13.9)	222 (14.8)	8 (5.0)	
B	984 (59.4)	908 (60.7)	76 (47.8)	
C	442 (26.7)	367 (24.5)	75 (47.2)	
Hepatic encephalopathy				**<0.01**
No	1177 (71.1)	1087 (72.6)	90 (56.6)	
Grade I-II	307 (18.5)	285 (19.0)	22 (13.8)	
Grade III-IV	172 (10.4)	125 (8.4)	47 (29.6)	
Bilirubin, mg/dL	2.8 (3.8)	1.8 (1.9)	2.3 (1.8)	**0.04**
Albumin, g/dL	2.8 (0.6)	2.9 (0.9)	2.6 (0.7)	**0.04**
INR	1.6 (0.5)	1.4 (0.9)	1.6 (0.8)	0.43

Index bleed: severity				
Hematemesis	1260 (76.1)	1136 (75.9)	124 (78.0)	0.09
Active bleeding at endoscopy	528 (31.9)	477 (31.9)	51 (32.1)	0.34
Shock	454 (27.4)	402 (26.9)	52 (32.7)	0.13
Hemoglobin, g/dL	9.1 (2.2)	9.2 (2.1)	8.7 (2.3)	0.32
Number of packed red blood cells	2.1 (2.0)	1.7 (2.0)	2.1 (2.1)	0.09
Index bleed: management				
Antibiotic prophylaxis				
Third generation cephalosporines	1262 (76.2)	1143 (76.4)	119 (74.8)	**0.04**
Quinolones	314 (19.0)	289 (19.3)	25 (15.7)	
Amoxicillin/clavulanic	48 (2.9)	40 (2.7)	8 (5.0)	
Others	32 (1.9)	25 (1.7)	7 (4.4)	
Nasogastric tube	532 (32.1)	462 (30.9)	70 (44.0)	**<0.01**
Sedation for endoscopy	1143 (69.0)	1026 (68.5)	117 (73.6)	0.43
Orotracheal intubation for endoscopy	323 (19.5)	258 (17.2)	65 (40.9)	**<0.01**
Time to endoscopy				
<12h	1386 (83.7)	1254 (83.8)	132 (83.0)	0.61
12-24	129 (7.8)	117 (7.8)	12 (7.6)	
>24h	59 (3.6)	51 (3.4)	8 (5.0)	
Initial hemostatic treatment				
Drugs plus endoscopy	1422 (85.9)	1295 (86.5)	127 (79.9)	0.65
Drugs alone	166 (10.0)	148 (9.9)	18 (11.3)	0.57

Endoscopy alone	54 (3.3)	49 (3.3)	5 (3.1)	0.66
Balloon tamponade	50 (3.0)	37 (2.5)	13 (8.2)	**<0.01**
Esophageal stent	2 (0.1)	2 (0.1)	0 (0.0)	1
Endoscopic treatment				
Ligation	1225 (74.0)	1114 (74.4)	111 (69.8)	0.62
Sclerotherapy	159 (9.6)	146 (9.8)	13 (8.2)	0.78
Tissue glue injection	111 (6.7)	102 (6.8)	9 (5.7)	1
Others	43 (2.6)	37 (2.5)	6 (3.8)	0.44
Pre-emptive TIPS	53 (3.2)	45 (3.0)	8 (5.0)	0.08
Hospitalization and mortality				
Length, days	10.1 (7.7)	11.9 (8.9)	15.4 (7.4)	**0.01**
In-hospital mortality	164 (9.9)	123 (8.2)	41 (25.8)	**0.01**
Mortality at 6-weeks	220 (13.3)	177 (11.8)	43 (27.0)	**0.01**

Continuous variables are expressed as mean (standard deviation) or as median (interquartile range). Categorical variables are expressed as N(%)

INR: International normalized ratio

TIPS: Transjugular intrahepatic portosystemic shunt

Table S5. Antibiotic resistance profile of the bacterial isolates with antibiotic susceptibility information available (78 bacterial isolates with antibiogram available from 64 infections)

	Respiratory	**Urinary tract**	**Primary bacteremia**	**SBP**	**Soft-tissue**
Infections with antibiogram available	N=23	N=17	N=18	N=5	N=1
Gram-negative organisms					
P. aeruginosa	8 (1 QR, 7 CR, 1 MR)	2 (2 CR)	2 (2 CR)		
K. pneumoniae	3 (1 ESBL)	3 (1 ESBL, 1 MR)	4 (1 QR, 1 ESBL)		
E. coli	2 (1 ESBL, 1 CR)	4 (2 QR, 1 CR, 1 ESBL)	8 (2 QR)	2 (1 QR, 1 CR)	
E. cloacae	2 (2 CR)	1 (1 QR, 1 CR)			
E. faecium		6 (6 QR, 6 CR)	5 (4 QR, 1 MR)	2 (1 QR,	

				1 ESBL)	
E. fecalis		2 (1 QR, 1 CR)	7 (7 QR, 7 CR)		
A. woffi	1 (1 QR, 1 CR)				
A. baumanii			1 (1 QR, 1 CR)		
Gram-positive organisms					
S. pneumoniae	3		2	1 (1 CR)	
S. aureus	4 (3 QR, 1 CR)		2 (1 QR, 1 CR)		
S. epidermidis					1 (1 CR)

CR, third-generation cephalosporin resistant. QR, quinolone resistant. ESBL, extended spectrum beta lactamase. MDR, multi-drug-resistant

Table S6. COX regression analysis of variables associated with the development of bacterial and respiratory infection

Bacterial infection			
Variable	**HR**	**95% CI**	**p**
Child-Pugh A	Ref		
Child-Pugh B	2.1	1.2-3.6	<0.01
Child-Pugh C	2.3	1.3-4.0	<0.01
Severe (grade III-IV) hepatic encephalopathy	1.8	1.3-2.5	<0.01
Nasogastric tube	1.6	1.2-2.0	<0.01
Orotracheal intubation for endoscopy	1.7	1.3-2.2	<0.01

Respiratory bacterial infection			
Variable	**HR**	**CI 95%**	**p**
Child-Pugh C	2.7	1.2-6.0	0.02
Severe (grade III-IV) hepatic encephalopathy	2.3	1.5-3.4	<0.01
Nasogastric tube	1.8	1.3-2.5	<0.01
Orotracheal intubation for endoscopy	2.3	1.6-3.3	<0.01
Esophageal balloon tamponade	1.8	1.1-3.4	0.04

Ref.: reference.

Table S7. Univariate and multivariate analysis of variables associated with 6-week mortality.

Variable	Univariate			Multivariate		
	HR	**CI 95%**	**P**	**HR**	**CI 95%**	**P**
Age	1.1	1.0-1.1	0.01	1.1	1.1-1.2	0.01
Child-Pugh B	2.4	1.2-4.8	0.01	2.2	1.1-4.4	0.02
Child-Pugh C	7.9	4.0-15.6	<0.01	7.6	3.8-15.1	<0.01
Hemoglobin (g/dL)	0.8	0.6-1.5	0.32			
Bacterial infection	1.7	1.3-2.3	<0.01			
Active bleeding	1.5	1.3-2.1	<0.01	1.5	1.2-2.0	0.01
Shock on admission	2.5	1.8-3.2	<0.01	2.1	1.6-2.7	<0.01
Pre-emptive TIPS	0.3	0.4-0.7	<0.01	0.3	0.2-0.5	<0.01

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