ORIGINAL ARTICLE

Retrospective Study

Influence of antibiotic-regimens on intensive-care unit-mortality and liver-cirrhosis as risk factor

Mireen Friedrich-Rust, Beate Wanger, Florian Heupel, Natalie Filmann, Reinhard Brodt, Volkhard AJ Kempf, Johanna Kessel, Thomas A Wichelhaus, Eva Herrmann, Stefan Zeuzem, Joerg Bojunga

Mireen Friedrich-Rust, Beate Wanger, Florian Heupel, Stefan Zeuzem, Joerg Bojunga, Department of Internal Medicine I (Gastroenterology, Pulmonology, Endocrinology), J.W. Goethe-University Hospital, 60590 Frankfurt, Germany

Natalie Filmann, Eva Herrmann, Institute of Biostatistics and Mathematical Modeling, Faculty of Medicine, J.W. Goethe-University, 60590 Frankfurt, Germany

Reinhard Brodt, Johanna Kessel, Department of Internal Medicine II (Infectious Disease, Oncology, Hematology), J.W. Goethe-University Hospital, 60590 Frankfurt, Germany

Volkhard AJ Kempf, Thomas A Wichelhaus, Institute of Medical Microbiology and Infection Control, J.W. Goethe-University Hospital, 60590 Frankfurt, Germany

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Correspondence to: Dr. Mireen Friedrich-Rust, Professor, Department of Internal Medicine I (Gastroenterology, Pulmonology, Endocrinology), J.W. Goethe-University Hospital, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany. mireen.friedrich-rust@kgu.de
Telephone: +49-69-63015297
Fax: +49-69-63016247

Abstract

AIM: To assess the rate of infection, appropriateness of antimicrobial-therapy and mortality on intensive care unit (ICU). Special focus was drawn on patients with liver cirrhosis.

METHODS: The study was approved by the local ethical committee. All patients admitted to the Internal Medicine-ICU between April 1, 2007 and December 31, 2009 were included. Data were extracted retrospectively from all patients using patient charts and electronic documentations on infection, microbiological laboratory reports, diagnosis and therapy. Due to the large hepatology department and liver transplantation center, special interest was on the subgroup of patients with liver cirrhosis. The primary statistical-endpoint was the evaluation of the influence of appropriate versus

inappropriate antimicrobial-therapy on in-hospital-mortality.

RESULTS: Charts of 1979 patients were available. The overall infection-rate was 53%. Multiresistant-bacteria were present in 23% of patients with infection and were associated with increased mortality ($P <$ 0.000001). Patients with infection had significantly increased in-hospital-mortality (34% *vs* 17%, $P <$ 0.000001). Only 9% of patients with infection received inappropriate initial antimicrobial-therapy, no influence on mortality was observed. Independent risk-factors for in-hospital-mortality were the presence of septic-shock, prior chemotherapy for malignoma and infection with *Pseudomonas* spp. Infection and mortality-rate among 175 patients with liver-cirrhosis was significantly higher than in patients without liver-cirrhosis. Infection increased mortality 2.24-fold in patients with cirrhosis. Patients with liver cirrhosis were at an increased risk to receive inappropriate initial antimicrobial therapy.

CONCLUSION: The results of the present study report the successful implementation of early-goal-directed therapy. Liver cirrhosis patients are at increased risk of infection, mortality and to receive inappropriate therapy. Increasing burden are multiresistant-bacteria.

Key words: Intensive care unit; Sepsis-bundle; Early goal-directed therapy; Liver cirrhosis; Mortality

Core tip: This is a retrospective study evaluating the association of appropriate and inappropriate antimicrobial therapy on intensive care unit-mortality with special focus on patients with liver cirrhosis. Charts of 1979 patients were available for analysis. Patients with infection had significantly increased in-hospital mortality. Only 9% of patients with infection received inappropriate initial antimicrobial therapy. Multiresistant bacteria were detected in 23% of patients with infection and were associated with increased mortality. Infection increased mortality 2.24-fold in patients with cirrhosis. Patients with liver cirrhosis were at an increased risk to receive inappropriate initial antimicrobial therapy.

INTRODUCTION

Infections are a worldwide problem concerning patients admitted to intensive care units (ICU), since they are associated with an increased mortality, morbidity and financial burden[1-4]. A 51%-prevalence of infection has been reported for ICU-patients and previously 20% of patients admitted with septic-shock to an ICU received inappropriate antimicrobial-therapy[5]. This knowledge led to increased efforts to implement early-goal-directed therapy with timely initiation of appropriate antimicrobial-therapy in clinical practice[4].

The aim of the present study was to assess the rate of infection, as well as appropriate- and inappropriate antimicrobial-therapy after implementation of early-goal-directed therapy of infection and sepsis on an Internal-Medicine-ICU and to assess the association of appropriate-and inappropriate antimicrobial-therapy on mortality. In addition, special focus was drawn on the subgroup of patients with liver cirrhosis. This special interest was derived due to the hepatologic focus of our unit with a large hepatology outpatient and inn-patient clinic including transplantation unit. A previous meta-analysis reported a 4-fold increase in mortality in patients with liver-cirrhosis that acquire an infection[6].

MATERIALS AND METHODS

All patients admitted to the Internal-Medicine-ICU of the Goethe-University-Hospital-Frankfurt between April 1, 2007 and December 31, 2009 were included in the study. Data were extracted retrospectively from all patients using patient-charts and electronic-documentations on infection, microbial-isolates, diagnosis and therapy. The study was approved by the local ethical-committee. The study protocol included the special focus on liver cirrhosis patients and was approve prior to the study recruitment.

Demographic, physiological, antimicrobial and therapeutic-data were collected from all patients. Only the first seven days after ICU-admission were evaluated concerning microbial-isolates and antibiotic-regimen. Patient characteristics are shown in Tables 1 and 2.

Infection was defined according to the definitions of the International Sepsis-Forum[7] and adjudicated by the senior-physicians. Data concerning infection were extracted from the ICU-doctor´s final-report, from imaging (Computed-Tomogaphy, Magnetic-Resonance-Imaging, X-ray, ultrasound, endoscopy) and from the microbiological laboratory-reports.

Appropriate/inappropriate antimicrobial-therapy was determined for all patients with infection. Appropriate initial antimicrobial-therapy was defined as: (1) Initiation of appropriate empirical antimicrobial-therapy at symptom begin (recurrence or persistent hypotension) with *in vitro* activity appropriate to isolated pathogenic organisms according to the Sanford Guide on Antimicrobial Therapy 2010 (40th edition)[8] and the national guidelines 2010 of the Paul-Ehrlich-society for chemotherapy[9] or according to the antibiotic susceptibility-testing; and (2) Appropriate empiric therapy for culture negative infections accor-

Table 1 Characteristics of patients *n* (%)

Characteristic	All patients (*n* = 1979)	Patients without infection (*n* = 937)	Patients with infection (*n* = 1042)	OR (95%CI)	*P* value
Age (yr), mean ± SD (range)	61 ± 16 (16-96)	61 ± 16 (16-96)	61 ± 16 (16-95)	1.003 (0.997-1.008)	> 0.20
Male sex	1236 (62.5)	614 (65.5)	622 (60)	0.779 (0.649-0.935)	0.0074
Days on ICU, mean ± SD (range)	5.53 ± 9.88 (1-217)	2.89 ± 5.97 (1-76)	8.12 ± 12 (1-217)	0.877 (0.858-0.897)	< 0.000001
Hospital-mortality	489 (24.7)	140 (14.9)	349 (33.5)	2.883 (2.312-3.595)	< 0.000001
Severity score on admission day					
SAPS II, mean ± SD (range)	35 ± 16 (5-93)	30 ± 14 (5-80)	39 ± 16 (5-93)	0.958 (0.950-0.965)	< 0.000001
TISS, mean ± SD (range)	9.5 ± 8.8 (0-55)	6.3 ± 7.4 (0-35)	11.6 ± 9.1 (0-55)	0.925 (0.912-0.938)	< 0.000001
Highest severity score within 7 d after admission					
SAPS II, mean ± SD (range)	39 ± 17 (6-93)	32 ± 15 (6-91)	44 ± 17 (6-93)	0.954 (0.947-0.961)	< 0.000001
TISS, mean ± SD (range)	12.0 ± 9.4 (0-55)	7.5 ± 8.0 (0-35)	14.6 ± 9.1 (0-55)	0.909 (0.897-0.921)	< 0.000001
Type of admission					< 0.000001
Internal medicine ICU	825 (41.7)	275 (29.3)	550 (52.8)		
Cardiology ICU	1154 (58.3)	663 (70.8)	491 (47.1)		
Source of admission					< 0.000001
Emergency department	923 (46.6)	468 (49.9)	455 (43.7)	Reference	
Other hospital	274 (13.8)	87 (9.3)	187 (17.9)	2.211 (1.662-2.941)	< 0.000001
Hospital ward	613 (31.0)	276 (29.5)	337 (32.2)	1.256 (1.023-1.541)	0.029
Operating room	132 (67.0)	98 (10.5)	34 (3.3)	0.357 (0.237-0.538)	0.000001
Surgical IMC/ICU	38 (1.9)	9 (0.96)	29 (2.8)	3.314 (1.552-7.079)	0.0020
Comorbid conditions	1410 (71.2)	607 (64.8)	803 (77.1)	1.840 (1.511-2.241)	< 0.000001
COPD	233 (11.8)	84 (9.0)	149 (14.3)	1.696 (1.278-2.252)	0.00026
Heart failure (EF < 30%)	114 (5.8)	59 (6.3)	55 (5.3)	0.830 (0.569-1.212)	> 0.20
Coronary artery disease	455 (23.0)	244 (26.0)	211 (20.2)	0.722 (0.585-0.891)	0.0024
Chronic renal failure	342 (34.2)	140 (14.9)	202 (19.4)	1.371 (1.082-1.736)	0.0089
Diabetes mellitus	474 (24.0)	227 (24.2)	247 (23.7)	0.973 (0.791-1.197)	> 0.20
Liver-cirrhosis	175 (8.8)	57 (6.1)	118 (11.3)	1.974 (1.420-2.744)	0.000052
Cancer	229 (11.6)	89 (9.5)	140 (13.4)	1.481 (1.117-1.962)	0.0063
Hematologic neoplasia	111 (5.6)	39 (4.2)	72 (6.9)	1.711 (1.147-2.553)	0.0085
HIV	76 (3.8)	15 (1.6)	61 (5.9)	3.826 (2.160-6.779)	0.0000043
Immunosuppressive Tx	106 (5.4)	29 (3.1)	77 (7.4)	2.501 (1.616-3.870)	0.000039
Chemotherapy	108 (5.5)	32 (3.4)	76 (7.3)	2.230 (1.461-3.403)	0.00020
Number of cormobid conditions					0.000023
0	566 (28.6)	330 (35.2)	236 (22.6)		
1	593 (30.0)	257 (27.4)	336 (32.2)		
2	415 (21.0)	174 (18.6)	241 (23.1)		
3	260 (13.1)	109 (11.6)	151 (14.5)		
> 3	146 (7.4)	68 (7.3)	78 (7.5)		
Mechanical ventilation	942 (47.6)	265 (28.3)	677 (65.0)	4.710 (3.892-5.701)	<0.000001
Hemodialysis	274 (13.8)	61 (6.5)	213 (20.4)	3.694 (2.736-4.987)	<0.000001

SAPS II: Simplified Acute Physiology Score II; TISS: Therapeutic Intervention Scoring System; ICU: Intensive care unit; IMC: Intermediate care unit, Internal Medicine ICU includes patients from Gastroenterology, Hepatology, Pulmonology, Endocrinology, Oncology, Hematology, Infectiology, Rheumatology departments, while Cardiology-ICU include patients from Cardiology, Angiology, Nephrology department; EF: Ejection fraction.

ding to the underlying clinical syndrome, risk-factors (hospital-stay, previous antibiotics, immunosuppressive patient) in accordance to the Sanford Guide on Antimicrobial Therapy 2010 (40th edition)[8] and national guidelines 2010 of the Paul-Ehrlich-society for chemotherapy and the local hospital resistance-statistics[9] and initiation of appropriate antimicrobial-therapy at symptom begin.

In addition appropriate adjustment of antimicrobial-therapy within the first 7 d of ICU-stay was recorded.

Statistical analysis

The primary statistical-endpoint was the evaluation of the influence of appropriate versus inappropriate antimicrobial-therapy on in-hospital-mortality. Multi-variate-logistic regression-analysis was performed. The statistical analysis was performed using SPSS-version-20 (SPSS-Inc, Chicago, IL, United States).

Data were expressed as mean ± SD for normally distributed variables and median and range for others. All statistical tests were 2-sided and *P* < 0.05 was considered statistically significant. No correction for multiple-testing was done. Wilcoxon-Mann-Whitney-test was used to compare numeric variables between the main-groups of patients. Ordinal-variables were analyzed using Chi-square-test and *via* binary-logistic regression-analysis. A multivariate-logistic regression-analysis was performed by forward binary-logistic-regression including all relevant nominal-variables, in which the significant variables were selected.

RESULTS

Characteristics of infection

Between April 1, 2007 and December 31, 2009, 2148 patients were admitted to the Internal-Medicine-ICU

Table 2 Site of infection and types of microorganisms in culture-positive infected patients *n* (%)

	All patients with infection (*n* = 1042)	Appropriate therapy (*n* = 948)	Inappropriate therapy (*n* = 94)	*P* value
Site of primary infection				
Respiratory tract	716 (68.7)	658 (69.4)	58 (61.7)	0.12
Abdomen/GIT	49 (4.7)	46 (4.9)	3 (3.2)	> 0.20
Renal/urinary tract	33 (3.2)	32 (3.4)	1 (1.1)	> 0.20
Skin	13 (1.2)	13 (1.4)	0	> 0.20
CNS	12 (1.2)	10 (1.1)	2 (2.1)	> 0.20
Endocarditis	26 (2.5)	24 (2.5)	2 (2.3)	> 0.20
Bloodstream	5 (0.5)	5 (0.5)	0	> 0.20
Others	35 (3.4)	33 (3.5)	2 (2.1)	> 0.20
Sepsis	207 (19.8)	179 (18.9)	28 (29.8)	0.011
Sites with detection of microorganism				
Respiratory tract	400 (38.4)	345 (36.4)	55 (58.5)	0.000026
Gastrointestinal	215 (20.6)	184 (19.4)	31 (33.0)	0.0019
Bloodstream	156 (15.0)	130 (13.7)	26 (27.7)	0.00030
Renal/urinary tract	185 (17.8)	155 (16.4)	30 (31.9)	0.000165
Skin	174 (16.7)	145 (15.3)	29 (30.9)	0.00012
Catheter-related	51 (4.9)	39 (4.1)	12 (12.8)	0.00021
CNS	10 (1.0)	10 (1.1)	0	> 0.20
Others	87 (8.4)	70 (7.4)	17 (18.1)	0.00055
Culture-positive	697 (66.9)	606 (63.9)	91 (69.8)	< 0.000001
Gram-positive isolates	473 (45.4)	400 (42.2)	73 (77.7)	< 0.000001
S. aureus	187 (17.9)	171 (18.0)	16 (17.0)	> 0.20
MRSA	45 (4.3)	31 (3.3)	14 (14.9)	< 0.000001
S. epidermidis	17 (1.6)	15 (1.6)	2 (2.1)	> 0.20
S. pneumoniae	16 (1.5)	12 (1.3)	4 (4.3)	0.025
VSE	93 (8.9)	67 (7.1)	26 (27.7)	< 0.000001
VRE	91 (8.7)	68 (7.2)	23 (24.5)	< 0.000001
Others	172 (16.5)	138 (14.5)	34 (36.2)	< 0.000001
Gram-negative isolates	368 (35.3)	320 (33.8)	48 (51.1)	0.00081
E. coli	99 (9.5)	89 (9.4)	10 (10.6)	> 0.20
Enterobacter spp.	45 (4.3)	39 (4.1)	6 (6.4)	> 0.20
Klebsiella spp.	56 (5.4)	49 (5.2)	7 (7.4)	> 0.20
Pseudomonas spp.	93 (8.9)	79 (8.3)	14 (14.9)	0.033
Acinetobacter spp.	10 (1.0)	5 (0.5)	5 (5.3)	0.0000055
ESBL-producing Enterobacteriaceae	42 (4.0)	37 (3.9)	5 (5.3)	> 0.20
Others	148 (14.2)	122 (12.8)	26 (27.7)	0.00099
Other bacteria	17 (1.6)	11 (1.2)	6 (6.4)	0.00014
Fungi	484 (46,5)	421 (40,4)	63 (6,1)	0.00028
Candia albicans	406 (39.0)	359 (37.9)	47 (50)	0.021
Other *Candida* spp.	197 (18.9)	165 (17.4)	32 (3.4)	0.010
C. glabrata	128 (12.3)	108 (11.4)	20 (21.3)	
C. tropicalis	39 (3.7)	33 (3.5)	6 (6.4)	
C. krusei	17 (1.6)	13 (1.4)	4 (4.3)	
Others	13 (1.3)	11 (1.2)	2 (2.1)	
Aspergillus spp.	27 (2.6)	8 (0.8)	19 (20.2)	< 0.000001
Pneumocystis jiroveci	14 (1.3)	4 (0.4)	10 (10.6)	< 0.000001
Other fungi	10 (1.0)	10 (1.1)	0	> 0.20
Parasites	1 (0.1)	1 (0.1)	0	0.00072
Multiresistant-bacteria	235 (22.6)	180 (19.0)	55 (58.5)	< 0.000001
MRSA	45 (4.3)	31 (3.3)	14 (14.9)	
VRE	91 (8.7)	68 (7.2)	23 (24.5)	
ESBL-producing Enterobacteriaceae	42 (4.0)	37 (3.9)	5 (5.3)	
Pseudomonas spp.	16 (1.5)	14 (1.5)	2 (2.2)	
Stenotrophomonas spp.	19 (1.8)	12 (1.3)	7 (7.4)	
Acinetobacter spp.	3 (0.29)	1 (0.1)	2 (2.2)	
Others	21 (2.01)	19 (2.0)	2 (2.2)	

Appropriate therapy: Patients who received appropriate antimicrobial-therapy; Inappropriate therapy: Patients who received inappropriate antimicrobial-therapy; GIT: Gastrointestinal tract; CNS: Central nervous system; VSE: Vancomycin-sensitive *Enterococcus*; VRE: Vancomycin-resistant *Enterococcus*; ESBL: Extended-spectrum β-lactamase producing bacteria; MRSA: Methicilline-resistant *Staphylococcus aureus*.
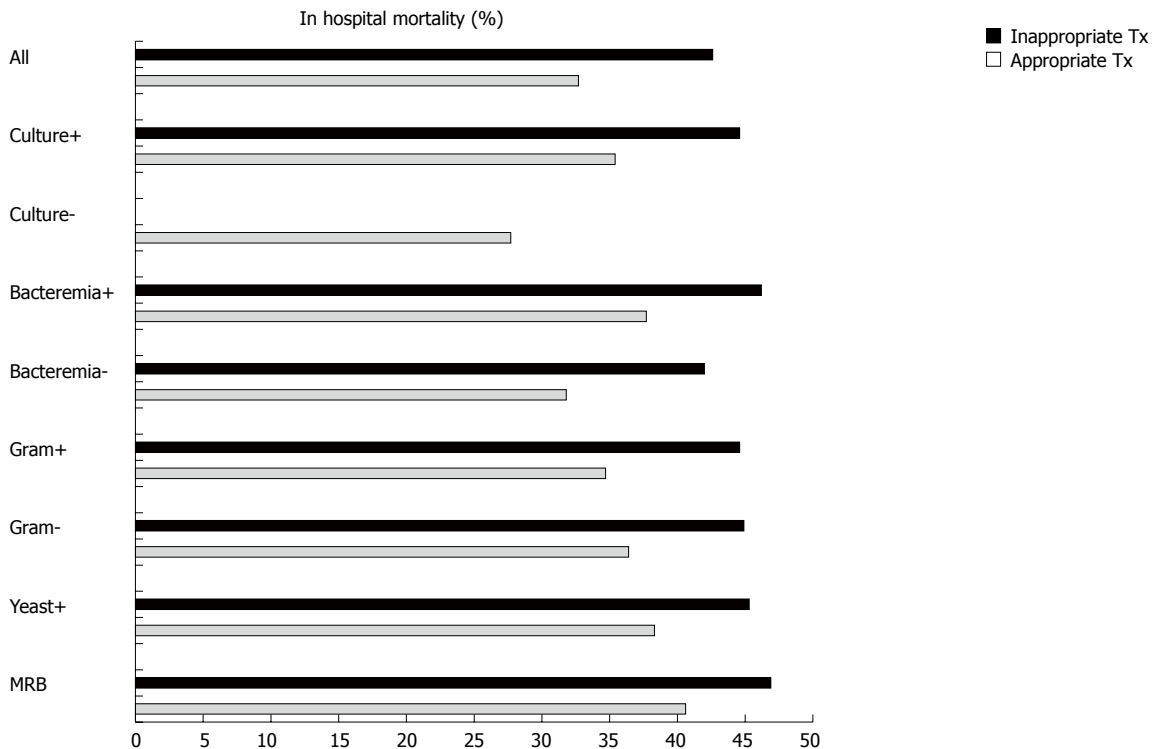
In hospital mortality (%)

Figure 1 Impact of appropriate and inappropriate antimicrobial-therapy on in hospital-mortality. Culture+: Culture-positive infection; Culture-: Culture-negative infection; Bacteremia+: Patients with positive blood cultures; Bacteremia-: Patients with negative blood cultures; Gram+: Culture-positive for gram-positive bacteria; Gram-: Culture-positive for gram-negative bacteria; Yeast+: Culture-positive for yeast; MRB: Multiresistant-bacteria.

of the Goethe-University-Hospital-Frankfurt. From 1979 patients enough data were available to include them into the analysis. Of the 1979 patients, 1042 (53%) were classified as having an infection. Infected patients had more comorbid conditions, higher SAPS-II and TISS-scores, received more often mechanical-ventilation and hemodialysis, and had a higher in-hospital-mortality-rate than patients without infection. Details are shown in Table 1.

The most frequent site of infection was the respiratory-tract, followed by gastrointestinal-infections, genitourinary-infections, endocarditis and skin-infections (Table 2).

In 697 patients (67%) from overall 1042 patients with infection underlying microorganisms were identified. Gram-positive isolates (*S. aureos*, *S. epidermidis*, *S. pneumoniae*, VSE, VRE, and others) were found in 45% (473/1042) of patients with infections and gram-negative isolates (*E. coli*, *Enterobacter* spp., *Klebsiella* spp., Pseudomonas spp., Acinetobacter spp., ESBL-producing Enterobacteriaceae, and others) in 35% (368/1042). Details are shown in Table 2. Multiresistant-bacteria were present in 23% of patients with infection; these were most frequently vancomycin-resistant *Enterococcus faecium* (VRE) (8.7%), followed by methicilline-resistant *Staphylococcus aureus* (MRSA) (4.3%) and extended-spectrum-betalactamase (ESBL)-producing enterobacteriaceae (4.0%).

Overall, the rate of survival to hospital-discharge was 66% in patients with infection as compared to

83% of patients without infection ($P < 0.000001$).

Appropriateness of initial antimicrobial-therapy

From all patients with infection, 91% of patients received appropriate and 9% inappropriate initial antimicrobial-therapy. From the 697 patients with infection and positive blood-culture, 87% received appropriate initial antimicrobial-therapy. The survival-rate to hospital discharge was higher in the group of patients receiving appropriate antimicrobial-therapy (67% *vs* 57%). However, this difference was not statistically significant ($P = 0.054$). The rate of inappropriate antimicrobial-therapy in septic-shock was 13.5%. In the group of patients with septic-shock (20% of patients with infection) no significant difference in survival-rate to hospital discharge was found between patients receiving appropriate ($n = 179$) versus inappropriate ($n = 28$) initial antimicrobial-therapy (44% *vs* 36%, $P > 0.20$). Details are shown in Figure 1 and Table 3.

Patients who received inappropriate initial antimicrobial-therapy had a longer ICU stay and suffered from higher rates of liver-cirrhosis, HIV, and prior chemotherapy. In addition, patients with multiresistant-bacterial infection received significantly more often inappropriate initial antimicrobial-therapy as compared to patients with other bacterial-infection [58% *vs* 19%, $P < 0.000001$; OR = 6.25 (2.59-15.15), $P = 0.000046$]. Details are shown in Table 3.

Escalation of antimicrobial-therapy was documented

Table 3 Characteristics of patients with infection according to appropriate or inappropriate antimicrobial-therapy *n* (%)

Characteristic	All patients with infection (*n* = 1042)	Appropriate therapy (*n* = 948)	Inappropriate therapy (*n* = 94)	OR (95%CI)	*P* value
Age (yr), mean ± SD (range)	61 ± 16 (16-95)	61 ± 16 (16-95)	61 ± 14 (21-88)	1.003 (0.99-1.017)	> 0.20
Male sex	622 (60.0)	376 (39.7)		0.747 (0.488-1.143)	0.18
Days on ICU, mean ± SD (range)	8.12 ± 12 (1-217)	7.68 ± 11.958 (1-217)	10.02 ± 11.134 (1-59)	1.011 (0.998-0.024)	0.092
ICU-mortality	324 (31.3)	287 (30.3)	37 (39.4)	0.669 (0.432-1.035)	0.071
Hospital-mortality	350 (33.6)	310 (32.7)	40 (42.6)	0.656 (0.426-1.009)	0.055
Severity score on admission day					
SAPS II, mean ± SD (range)	38.67 ± 15.64 (5-93)	38.54 ± 15.82 (5-93)	39.95 ± 13.78 (8-68)	1.006 (0.992-1.020)	> 0.20
TISS, mean ± SD (range)	11.57 ± 9.11 (0-55)	11.74 ± 9.25 (0-55)	9.86 ± 7.42 (0-28)	0.976 (0.951-1.002)	0.071
Highest severity score within 7 d after admission					
SAPS II, mean ± SD (range)	43.88 ± 16.57 (6-93)	43.68 ± 16.71 (6-93)	45.87 ± 15.09 (8-81)	1.008 (0.994-1.022)	> 0.20
TISS. mean ± SD (range)	14.65 ± 9.14 (0-55)	14.68 ± 9.27 (0-55)	14.32 ± 7.73 (0-38)	0.996 (0.971-1.021)	> 0.20
Type of Admission					0.0022
Internal Medicine ICU	550 (52.8)	486 (51.3)	64 (68.1)		
Cardiology ICU	491 (47.1)	461 (48.7)	30 (31.9)		
Source of admission					> 0.20
Emergency department	455 (43.7)	418 (44.1)	37 (39.4)	Reference	
Other hospital	187 (17.9)	170 (17.9)	17 (18.1)	0.425 (0.153-1.179)	0.10
Hospital ward	337 (32.3)	305 (32.2)	32 (34.0)	0.48 (0.162-1.429)	0.19
Operating room	34 (3.3)	31 (3.3)	3 (3.2)	0.504 (0.18-1.411)	0.19
Surgical IMC/ICU	29 (2.7)	24 (2.6)	5 (5.3)	0.465 (0.101-2.14)	> 0.20
Comorbid conditions	806 (77.4)	729 (76.9)	77 (81.9)	0.842 (0.498-1.424)	> 0.20
COPD	149 (14.3)	137 (14.5)	12 (12.8)	1.154 (0.613-2.172)	> 0.20
Heart failure (EF < 30%)	55 (5.3)	50 (5.3)	5 (5.3)	0.991 (0.385-2.549)	> 0.20
Coronary artery disease	211 (20.2)	195 (20.6)	16 (17.0)	1.262 (0.721-2.211)	> 0.20
Chronic renal failure	202 (19.4)	182 (19.2)	20 (21.3)	0.879 (0.523-1.478)	> 0.20
Diabetes mellitus	247 (23.7)	220 (23.2)	27 (28.7)	0.750 (0.468-1.202)	> 0.20
Liver-cirrhosis	118 (11.3)	100 (10.5)	18 (19.1)	0.498 (0.286-0.866)	0.014
Cancer	140 (13.4)	122 (12.9)	18 (19.1)	0.624 (0.361-1.079)	0.091
Hematologic neoplasia	72 (6.9)	68 (7.2)	4 (4.3)	1.739 (0.620-4.877)	> 0.20
HIV	61 (5.9)	51 (5.4)	10 (10.6)	0.478 (0.234-0.975)	0.042
Immunosuppressive Tx.	77 (7.4)	69 (7.3)	8 (8.5)	0.844 (0.393-1.813)	> 0.20
Chemotherapy	53 (5.1)	47 (5.0)	6 (6.4)	2.634 (1.691-4.102)	0.000018
Number of cormobid conditions					> 0.20
0	236	219 (23.1)	17 (18.1)		
1	336	304 (32.1)	32 (34.0)		
2	241	219 (23.1)	22 (23.4)		
3	151	138 (14.6)	13 (13.8)		
> 3	78	68 (7.2)	10 (10.6)		
Mechanical ventilation	677 (65.0)	621 (65.5)	56 (59.6)	1.289 (0.836-1.987)	> 0.20
Hemodialysis	213 (20.4)	194 (20.5)	19 (20.2)	1.016 (0.599-1.721)	> 0.20

Appropriate therapy: Patients who received appropriate antimicrobial-therapy; Inappropriate therapy: Patients who received inappropriate antimicrobial-therapy; SAPS II: Simplified Acute Physiology Score II; TISS: Therapeutic Intervention Scoring System; ICU: Intensive care unit; IMC: Internal Medicine ICU includes patients from Gastroenterology, Hepatology, Pulmonology, Endocrinology, Oncology, Hematology, Infectiology, Rheumatology departments, while Cardiology-ICU include patients from Cardiology, Angiology, Nephrology department; EF: Ejection fraction.

within the first 7 d of ICU stay in 20% of patients with infection, and de-escalation in 31%, respectively. From the 94 patients with infection who received inappropriate initial antimicrobial-therapy, antimicrobial-therapy was adjusted appropriately within the first seven days in 38 (40%) of patients according to the AST.

Mortality
In hospital-mortality-rate was 25% in the overall ICU population and 34% in patients with infection. Details are shown in Table 4.

Multivariate-logistic regression-analysis including all significant variables revealed as independent risk-factors for in hospital-mortality the presence of septic-shock at admission [OR = 2.928 (1.246-6.787), *P* =

0.0057], chemotherapy for malignoma received within 3 mo prior to ICU admission [OR = 4.274 (1.37-13.33), *P* = 0.012] and infection with *Pseudomonas* spp.[OR = 4.187 (1.665-12.579), *P* = 0.0030].

Risk factors for in-hospital mortality in patients with infection are shown in Table 5.

Multivariate-logistic regression-analysis for patients with infection only revealed as independent risk-factors for in hospital-mortality the presence of septic-shock at admission [OR = 3.576 (2.347-5.448), *P* < 0.000001], SAPS-II-score at admission [OR = 1.014 (1.002-1.027), *P* = 0.017], presence of comorbid-disease [OR = 2.228 (1.443-3.627), *P* = 0.00043], mechanical-ventilation [OR = 1.712 (0.993-2.959), *P* = 0.034], pulmonary focus of infection [OR = 1.885 (1.200-2.963), *P* = 0.0061], liver-cirrhosis [OR =

Table 4 Risk factors for in hospital mortality *n* (%)

Characteristic	Patients who died in hospital	Patients surviving	Odds ratio	*P* value
Age (yr)	63	60		0.0011
SAPS II score (mean)	47	37		< 0.000001
TISS score (mean)	12.8	8.5		< 0.000001
Number of comorbid conditions			1.851 [1.446-2.369]	< 0.000001
Chemotherapy for malignoma within 3 mo prior to admission			2.385 [1.605-3.543]	0.000017
Clinical infection on admission			2.883 [2.312-3.595]	< 0.000001
Septic-shock on admission			4.993 [3.707-6.727]	< 0.000001
Bacteriemia			2.119 [1.515-2.962]	< 0.000001
Multiresistant-bacterial infections			2.189 [1.664-2.879]	< 0.000001
mechanical ventilation during ICU stay			5.018 [3.981-6.324]	< 0.000001
C-reactive-protein at admission (mg/dL)	8.76	6.23		< 0.000001
Creatinine-values at admission (mg/dL)	1.93	1.644		< 0.000001
Bilirubin-values at admission (mg/dL)	3.175	1.818		0.0014
INR	1.81	1.46		< 0.000001

SAPS II: Simplified Acute Physiology Score II; TISS: Therapeutic Intervention Scoring System; ICU: Intensive care unit.

Table 5 Risk factors for in hospital mortality of patients with infection

Characteristic	Patients who died in hospital	Patients surviving	Odds ratio	*P* value
SAPS II score (mean)	42	37		0.00021
TISS score (mean)	12.7	11.03		0.0084
Number of comorbid conditions			1.824 [1.311-2.539]	0.00036
mechanical ventilation during ICU stay			2.363 [1.765-3.164]	< 0.000001
pulmonary-infections			1.741 [1.301-2.33]	0.00020
catheter-related infection			2.578 [1.51-4.399]	0.00052
bilirubin-values at admission (mg/dL)	3.39	2.458		0.0300
INR	1.83	1.55		0.0000082

ICU: Intensive care unit.

1.816 (1.061-3.106), *P* = 0.029] and INR [OR = 1.248 (1.031-1.508), *P* = 0.022].

Liver disease

Chronic liver-disease was known in 272 patients (14%) with liver-cirrhosis present in 175 of these patients (64%). From these 272 patients with chronic liver disease, chronic viral hepatitis infection was present in 150 patients (55%), of whom 101 were infected with chronic hepatitis C and 49 with chronic hepatitis B. Only one patient had chronic alcoholic and one patient autoimmune liver disease. Patients with spontaneous bacterial infection as primary infection site were not included in the analysis.

Patients with chronic liver-disease had a higher infection-rate (69% *vs* 50%, *P* < 0.000001) and presented more often with septic-shock (15% *vs* 10%, *P* = 0.014) as compared to patients without chronic liver-disease. From all patients with chronic liver-disease, only patients infected with chronic hepatitis C had significantly higher risk of in hospital-mortality [OR = 1.660 (1.087-2.534), *P* = 0.019].

The presence of liver-cirrhosis significantly increased the risk of infection (OR = 1.974 (1.420-2.744), *P* = 0.000052], the risk of receiving inappropriate initial antimicrobial-therapy [OR = 2.008 (1.155-3.497), *P*

= 0.014] and in hospital-mortality-rate [OR = 2.320 (1.684-3.195), *P* < 0.000001]. Infection-rate and sepsis-rate was significantly higher in patients with liver-cirrhosis as compared to patients without liver-cirrhosis (67% *vs* 51%, *P* = 0.000040 and 15% *vs* 10%, *P* = 0.046). In patients with liver-cirrhosis the presence of infection significantly increased in hospital-mortality (49% *vs* 25%, *P* = 0.0019). Liver-cirrhosis was an independent risk-factor for in hospital-mortality in patients with infection [OR = 1.816 (1.061-3.106), *P* = 0.029] (Figure 2).

MELD-score was significantly higher in patients with liver-cirrhosis who died in hospital as compared to survivors (MELD-score 28 *vs* 23, *P* = 0.012) and significantly more patients with liver-cirrhosis received hemodialysis (15% *vs* 8%, *P* = 0.043). In patients with liver-cirrhosis infections with multiresistant-bacteria were found in 32% (38/118) of patients. From these 38 patients, 18% were infected with ESBL-producing bacteria enterobacteriaceae, 18% with MRSA and 55% with VRE.

No significant difference was found for diagnostic-accuracy of MELD-score (AUROC 73%, 95%CI: 65%-82%) and SAPS-II-score (AUROC 72%, 95%CI: 63%-81%) at admission in identifying risk of in-hospital-mortality (*P* > 0.20).
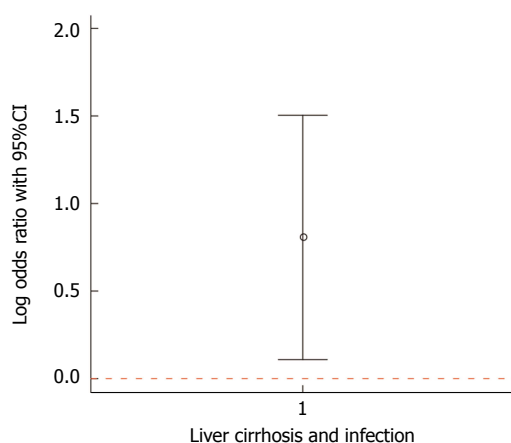
Figure 2 49% of patients with liver-cirrhosis and infection died in hospital, compared to 25% with liver-cirrhosis and without infection. The plot shows the log odds ratio (0.8063, marked by the dot) and its 95%CI [(0.1086-1.5039), marked by the whiskers], *i.e.* patients with liver-cirrhosis and infection had a 2.24 greater in-hospital-mortality than patients with liver-cirrhosis without infection.

DISCUSSION

In the present study the infection-rate of patients on the Internal Intensive Care Unit was 53%. Patients with infection had more often comorbid conditions and higher SAPS II scores on admission and during the first seven days of ICU treatment. The results of the present study are in accordance with a 1-d point international multicenter prevalence study by Vincent *et al*[5] reporting infections in 51% of ICU patients and similar associations. While the present study included Internal Medicine ICU only, the study by Vincent et al. included also surgery and trauma patients. The most common infection focus in the present study was the lung, followed by abdomen, and genitourinary tract infection. This again is in accordance with epidemiological studies concerning infections on ICU[10-12]. Positive microbiological cultures were obtained in 65% of infected patients with more gram-positive than gram-negative microorganisms. This is in accordance with previous studies that reported an increasing incidence of gram-positive microorganisms on ICUs[2]. In hospital-mortality was significantly higher in patients with infections and patients with sepsis as compared to patients without. This again supports results of previous studies[2,5].

Studies have reported higher hospital-mortality in patients with blood stream infections that receive inappropriate initial antimicrobial-therapy[13-15]. In 2006 Kumar *et al*[16] reported, that effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital-discharge in patients with septic-shock. However, only 50% of septic-shock patients received effective antimicrobial-therapy within 6 h of documented hypotension[16]. In 2004, the Surviving-Sepsis-Campaign developed guidelines for the management of severe sepsis and septic-shock[17]. This included besides others, early cultures

for microbial evaluation and "early-goal-directed therapy" with initiation of antimicrobial-therapy as soon as possible[17,18]. After implementation of the "sepsis-bundle" the Surviving-Sepsis-Campaign study group published a study performed at 165 sites with 15022 subjects and reported an increase in compliance with the sepsis bundle from 11 to 31% two years after implementation and a reduction in mortality[19]. Other studies have reported a similar association[20]. The present study also started after implementation of the sepsis-bundle with early-goal-directed antimicrobial-therapy with empiric calculated therapy on the ICU-ward. Only 9% of patients with infection and 13.5% of patients with septic-shock received inappropriate antimicrobial-therapy. This was lower than reported in a study of Kumar *et al*[16] published in 2009 including 5715 patients with septic-shock with 20% of inappropriate therapy of patients with septic-shock and significant reduction of survival in those receiving inappropriate therapy (10% *vs* 52%)[16]. Although these two studies cannot be directly compared, it shows a trend towards improvement of initial antimicrobial-therapy. While in the study of Kumar[16] a significant reduction of survival (42%) was found in patients receiving inappropriate antimicrobial-therapy as compared to patients receiving appropriate antimicrobial-therapy, no significant reduction was found in the present study (10%). Antimicrobial-therapy is only one aspect of the sepsis bundle, therefore other factors might have also played a role in the present study.

Multiresistant-microorganisms are an increasing burden on ICUs worldwide[21]. Also in the present study multiresistant-bacteria were detected in 23% of patients with infection. This is higher than the overall prevalence in German hospitals[22,23]. A reason might be the high proportion of patients colonized with such bacteria which arrive from countries with high prevalence of multiresistant-bacteria to be treated at Frankfurt-University-hospital due to its close location to Frankfurt international-airport. Therefore, successful infection control measurements are strictly implemented inhibiting transmission of such pathogens from patient to patient. In addition, Frankfurt-University-Hospital is a referral-hospital and therefore many severely ill patients, who received multiple antibiotic-regimens prior to referral, receive further treatment here.

Nevertheless, inappropriate therapy was significantly associated with the presence of multiresistant-bacteria in the present study, suggesting that empirical therapy has to cover multiresistant-bacteria more regularly. Studies have shown that inappropriate antimicrobial-therapy for gram negative ESBL producers was associated with significant increase in mortality (59.5% *vs* 18.5%, *P* < 0.001)[24]. Common risk factors for infection with multiresistant-bacteria are: residence in nursery home, recent hospital stay, mechanical ventilation, age, prior antibiotic therapy and foreign

citizenship[9,25]. Also in the present study prior antimicrobial-therapy was an independent risk-factor for infection.

Since the University-Hospital is a liver transplantation center, a high number of patients with liver-disease are treated here. Chronic liver-disease was present in 14% of patients admitted to the ICU with liver-cirrhosis in 64% of these patients. Patients with liver-cirrhosis had a significantly higher infection-rate than patients without liver-cirrhosis. This is in accordance with previous studies reporting infection-rates of 32%-34% in liver-cirrhosis as compared to 5%-7% in the general hospitalized population[26,27]. A meta-analysis reported a 4-fold increase in mortality in patients with liver-cirrhosis that acquire an infection[6]. In addition, patients with sepsis and liver-cirrhosis have a significant higher mortality-rate as compared to patients with sepsis in the general hospitalized population[27], this was supported by the results of the present study. The presence of liver-cirrhosis was an independent risk factor for in hospital-mortality in patients with infection. In addition, also in patients with liver-cirrhosis infection with multiresistant-bacteria is increasing. A recent study resported an incidence of 39% multiresistant-bacteria in patients with liver-cirrhosis and nosocomial infection[28]. In the present study an infection with multiresistant-bacteria could be found in 32% of patients with liver-cirrhosis. Inappropriate antimicrobial-therapy was significantly more often in patients with liver-cirrhosis. The high rate of multiresistant-bacteria could be an explanation herefore. A recent study revealed a significantly higher rate of septic-shock and in-hospital-mortality in patients with liver-cirrhosis infected with multiresistant-bacteria (26% *vs* 10% and 25% *vs* 12%)[29].

MELD-score and SAPS-II-score at admission performed equally good concerning the prediction of in-hospital-mortality with diagnostic accuracies of 73% and 72%. A previous systematic review including 21 studies reported diagnostic accuracies of 81% for MELD-score and 83% for SOFA (sequential-organ-failure-assessment)-score[29]. Therefore both studies report comparable results for general ICU prognostic-markers and liver-specific prognostic-markers for patients with liver-cirrhosis on ICU and therefore might supplement each other.

A limitation of the present study is its monocentric retrospective study-design. Nevertheless, the distribution of infections was comparable to previous multicenter-studies[5].

The inclusion of patients with culture-negative infection might be criticized and lead to bias. However, no difference in percentage of appropriate to inappropriate antimicrobial-therapy was found in a subanalysis of patients with culture-positive infections only.

In conclusion, the results of the present study report the successful implementation of early-goal-directed therapy. Increasing burden are multiresistant-bacteria, which are associated with increased mortality.

COMMENTS

Background
Infections are a worldwide problem concerning patients admitted to intensive care units, since they are associated with an increased mortality, morbidity and financial burden. A 51%-prevalence of infection has been reported for intensive care unit (ICU)-patients and previously 20% of patients admitted with septic-shock to an ICU received inappropriate antimicrobial-therapy.

Research frontiers
Infection rate and management on ICU with special focus on liver cirrhosis patients.

Innovations and breakthroughs
In the present study the infection-rate of patients on the Internal Intensive Care Unit was 53%. Infection increased mortality 2.24-fold in patients with cirrhosis.

Applications
Retrospective analysis reporting the high prevalence of infections and the importance of early goal-directed therapy.

Peer-review
The paper presents the influence of antibiotic-regimens on ICU-mortality. It underlines the successful implementation of early-goal-directed therapy in patients treated in ICU. The topic is interesting, especially considering the rate of mortality in these patients and financial burden.

REFERENCES

1   **Harrison DA**, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. *Crit Care* 2006; **10**: R42 [PMID: 16542492]

2   **Vincent JL**, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34**: 344-353 [PMID: 16424713 DOI: 10.1097/01. CCM.0000194725.48928.3A]

3   **Angus DC**, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; **29**: 1303-1310 [PMID: 11445675 DOI: 10.1097/0 0003246-200107000-00002]

4   **Kumar A**, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, Dodek P, Wood G, Kumar A, Simon D, Peters C, Ahsan M, Chateau D. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009; **136**: 1237-1248 [PMID: 19696123 DOI: 10.1378/chest.09-0087]

5   **Vincent JL**, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323-2329 [PMID: 19952319 DOI: 10.1001/jama.2009.1754]

6   **Arvaniti V**, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, Burroughs AK. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010; **139**: 1246-1256, 1256e1-e5 [PMID: 20558165 DOI: 10.1053/j.gastro.2010.06.019]

7   **Calandra T**, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med* 2005; **33**: 1538-1548 [PMID: 16003060 DOI: 10.1097/01.CCM.0000168253.91200.83]

8   **Gilbert DN**, Moellering RC, Eliopoulos GM. Clinical approach to intitial choice of antimicrobial therapy. The Sanford Guide To Antimicrobial Therapy 2010, Antimicrobial Therapy Inc., 2010. Available from: URL: http://www.sanfordguide.com/

9   **Bodmann KF**, Grabein B, Expertenkommission der Paul-Ehrlich-Gesellschaft fur Chemotherapie e.V. [Empfehlungen zur

kalkulierten parenteralen Initialtherapie bakterieller Erkrankungen bei Erwachsenen-Update 2010. Available from: URL: http://www.p-e-g.org/aktuelles/435/

10   **Martin CM**, Priestap F, Fisher H, Fowler RA, Heyland DK, Keenan SP, Longo CJ, Morrison T, Bentley D, Antman N. A prospective, observational registry of patients with severe sepsis: the Canadian Sepsis Treatment and Response Registry. *Crit Care Med* 2009; **37**: 81-88 [PMID: 19050636 DOI: 10.1097/CCM.0b013e31819285f0]

11   **Brun-Buisson C**, Meshaka P, Pinton P, Vallet B. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. *Intensive Care Med* 2004; **30**: 580-588 [PMID: 14997295 DOI: 10.1007/s00134-003-2121-4]

12   **Engel C**, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, Gruendling M, Huhle G, Jaschinski U, John S, Mayer K, Oppert M, Olthoff D, Quintel M, Ragaller M, Rossaint R, Stuber F, Weiler N, Welte T, Bogatsch H, Hartog C, Loeffler M, Reinhart K. Epidemiology of sepsis in Germany: results from a national prospective multicenter study. *Intensive Care Med* 2007; **33**: 606-618 [PMID: 17323051 DOI: 10.1007/s00134-006-0517-7]

13   **Prowle JR**, Echeverri JE, Ligabo EV, Sherry N, Taori GC, Crozier TM, Hart GK, Korman TM, Mayall BC, Johnson PD, Bellomo R. Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. *Crit Care* 2011; **15**: R100 [PMID: 21418635 DOI: 10.1186/cc10114]

14   **Kollef MH**, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; **115**: 462-474 [PMID: 10027448 DOI: 10.1378/chest.115.2.462]

15   **Ibrahim EH**, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; **118**: 146-155 [PMID: 10893372 DOI: 10.1378/chest.118.1.146]

16   **Kumar A**, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34**: 1589-1596 [PMID: 16625125 DOI: 10.1097/01.CCM.0000217961.75225.E9]

17   **Dellinger RP**, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 2004; **30**: 536-555 [PMID: 14997291 DOI: 10.1007/s00134-004-2210-z]

18   **Rivers E**, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368-1377 [PMID: 11794169 DOI: 10.1056/NEJMoa010307]

19   **Levy MM**, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, Bion J, Schorr C, Artigas A, Ramsay G, Beale R, Parker MM, Gerlach H, Reinhart K, Silva E, Harvey M, Regan S, Angus DC. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Intensive Care Med* 2010; **36**: 222-231 [PMID: 20069275 DOI: 10.1007/s00134-009-1738-3]

20   **Shiramizo SC**, Marra AR, Durão MS, Paes ÂT, Edmond MB, Pavão dos Santos OF. Decreasing mortality in severe sepsis and septic shock patients by implementing a sepsis bundle in a hospital setting. *PLoS One* 2011; **6**: e26790 [PMID: 22073193 DOI: 10.1371/journal.pone.0026790]

21   **Burgmann H**, Hiesmayr JM, Savey A, Bauer P, Metnitz B, Metnitz PG. Impact of nosocomial infections on clinical outcome and resource consumption in critically ill patients. *Intensive Care Med* 2010; **36**: 1597-1601 [PMID: 20614212 DOI: 10.1007/s00134-010-1941-2]

22   **Kresken M**, Hafner D, Schmitz FJ, Wichelhaus TA. PEG-Resistenzstudie 2004. Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. Available from: URL: http://www.p-e-g.org

23   **Geffers C**, Gastmeier P. Nosocomial infections and multidrug-resistant organisms in Germany: epidemiological data from KISS (the Hospital Infection Surveillance System). *Dtsch Arztebl Int* 2011; **108**: 87-93 [PMID: 21373275 DOI: 10.3238/arztebl.2011.0087]

24   **Tumbarello M**, Sanguinetti M, Montuori E, Trecarichi EM, Posteraro B, Fiori B, Citton R, D'Inzeo T, Fadda G, Cauda R, Spanu T. Predictors of mortality in patients with bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae: importance of inadequate initial antimicrobial treatment. *Antimicrob Agents Chemother* 2007; **51**: 1987-1994 [PMID: 17387156 DOI: 10.1128/AAC.01509-06]

25   **Kaye KS**, Fraimow HS, Abrutyn E. Pathogens resistant to antimicrobial agents. Epidemiology, molecular mechanisms, and clinical management. *Infect Dis Clin North Am* 2000; **14**: 293-319 [PMID: 10829257 DOI: 10.1016/S0891-5520(05)70249-X]

26   **Gustot T**, Durand F, Lebrec D, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology* 2009; **50**: 2022-2033 [PMID: 19885876 DOI: 10.1002/hep.23264]

27   **Tandon P**, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. *Semin Liver Dis* 2008; **28**: 26-42 [PMID: 18293275 DOI: 10.1055/s-2008-1040319]

28   **Fernández J**, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, Pavesi M, Sola E, Moreira L, Silva A, Seva-Pereira T, Corradi F, Mensa J, Ginès P, Arroyo V. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012; **55**: 1551-1561 [PMID: 22183941 DOI: 10.1002/hep.25532]

29   **Cholongitas E**, Senzolo M, Patch D, Kwong K, Nikolopoulou V, Leandro G, Shaw S, Burroughs AK. Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. *Aliment Pharmacol Ther* 2006; **23**: 883-893 [PMID: 16573791 DOI: 10.1111/j.1365-2036.2006.02842.x]