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Epidemiology of hospital-acquired infections in cirrhotic patients: effect of carriage of methicillin-resistant *Staphylococcus aureus* and influence of previous antibiotic therapy and norfloxacin prophylaxis

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SUMMARY

We assessed the prevalence of carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) in anterior nares and stools, and of third-generation cephalosporin resistant enterobacteriaceae and non-fermenting Gram-negative bacilli (RE/RNF) in stools of 748 hospitalized long-stay cirrhotic patients. We also evaluated the consequences of carriage on the epidemiology of hospital-acquired spontaneous bacterial peritonitis, bacteraemia and urinary tract infection (UTI) in these patients. The prevalence of carriage of MRSA and RE/RNF was 16·7% and 14·7% respectively. Whereas RE/RNF carriage did not lead to an increased risk of infection due to RE/RNF, the overall risk of infections caused by MRSA was more than tenfold higher in MRSA carriers. MRSA and RE/RNF carriers had received prior antibiotic therapy to a greater extent than non-carriers ($P < 0{\cdot}001$) and MRSA carriers had received prior norfloxacin prophylaxis to a greater extent than the two other groups ($P < 0{\cdot}02$). The mortality rate during hospital stay was higher in MRSA and RE/RNF carriers than in non-carriers ($P < 0{\cdot}001$). Pugh score ($P < 0{\cdot}0001$), age ($P < 0{\cdot}0001$), MRSA carriage ($P = 0{\cdot}0018$) and bacteraemia ($P = 0{\cdot}0017$) were associated independently with mortality. MRSA carriage in hospitalized cirrhotic patients leads to the emergence of infections due to this strain, mainly SBP and bacteraemia. Prior antibiotic therapy and norfloxacin prophylaxis increase the risk of carriage of MRSA.

INTRODUCTION

Bacterial infections in liver cirrhosis are an important cause of morbidity and mortality. The most frequent infections are spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), pneumonia, skin infections and bacteraemia [1], with Gram-negative bacteria, mainly enterobacteriaceae, predominating. These bacteria are derived from the intestinal Gram-negative flora, and the passage of viable bacteria from the gastrointestinal tract to extra-intestinal sites seems to be an important step in the pathogenesis of SBP and other bacterial infections [2–6]. Little is known about hospital-acquired infections in cirrhosis and the risk of emergence of the resistant strains of bacteria that characterize nosocomial infections.

A high prevalence of carriage of methicillin-resistant strains of *Staphylococcus aureus* (MRSA) has been reported in hospitalized cirrhotic patients suggesting a possible increased risk of MRSA infections. Many cirrhotic patients receive antibiotics for sepsis and norfloxacin prophylaxis decreases the risk of such infections due to Gram-negative bacteria but may facilitate the emergence of resistant Gram-negative bacteria and Gram-positive pathogens [7]. Thus, evaluation of the risk of emergence of infections caused by resistant bacterial strains seems important in patients with advanced liver disease who are exposed to frequent or long-term hospitalization.

In this prospective study, we investigated the

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epidemiology of hospital-acquired infections in a large population of cirrhotic patients. We assessed carriage of the most common bacterial strains involved in nosocomial infections, namely MRSA and third-generation cephalosporin resistant enterobacteriaceae and non-fermenting Gram-negative bacilli. We evaluated the consequences of carriage on the spectrum of bacteria causing infections developing during hospitalization. Our final aim was to assess the influence of previous antibiotic therapy and norfloxacin prophylaxis on carriage of these resistant bacterial strains.

PATIENTS AND METHODS

From 1 January 1996 to 30 January 2000, patients with liver cirrhosis admitted to our unit for chronic liver diseases were included in the study. Before admission to the unit, patients had been hospitalized for at least 2 weeks in another hospital for a complication of the disease such as severe malnutrition, sepsis, gastro-intestinal bleeding, refractory ascites or hepato-renal syndrome. Our unit is specially devoted to chronic liver disease and receives patients from many hospitals in the Paris area when long hospital stay is required because of the complications and severity of the disease. The diagnosis of cirrhosis was based on liver biopsy or conventional clinical, biological and endoscopic findings. The degree of liver failure was assessed by Child–Pugh classification (class A, well-preserved liver function; class B, mild liver failure; class C, severe liver failure). Pugh scores are in the range 5–15 and increase as severity of liver failure worsens [8]. The aetiology of cirrhosis was alcoholism in 90% of cases, hepatitis C in 5% of cases (associated with alcoholism in 2% of cases), hepatitis B in 2·5% of cases and biliary or cryptogenic in the remaining cases.

The study included 748 patients who were screened within 48 h of admission for nasal carriage of *Staphylococcus aureus*, stool carriage of *Staphylococcus aureus* and Gram-negative bacilli resistant to third-generation cephalosporins including resistant enterobacteria and resistant non-fermenting bacilli (RE/RNF) and for urinary tract infection (UTI). None of the patients included in the study had a central venous catheter at the time of admission to our unit.

Nasal specimens (5 rotations in the 2 anterior nares) and stools (collected in small sterile containers) were sent to the bacteriology laboratory within 1 h of admission. Nasal swabs and stool samples were streaked onto Chapman agar to detect *Staphylococcus aureus*. Stool samples were also streaked onto two MacConkey agar plates supplemented respectively with cefotaxime (0·5 μg/ml) and ceftazidime (2 μg/ml) to detect RE/RNF. Media were incubated at 37 °C for 48 h. After morphological and microscopic examination, relevant bacteria were further identified.

Urine samples were collected as follows: the urethral meatus was washed with soap and rinsed with sterile water. The first morning urine was collected in sterile containers using a midstream clean-catch technique, and transported to the laboratory for urine analysis and culture no more than 1 h after collection. Urine samples were cultured by inoculating 0·05 ml of 1/100 diluted (in sterile water) specimen onto blood agar and MacConkey agar plates, with incubation at 37 °C overnight. Colonies were counted and the organisms were identified.

If SBP and/or bacteraemia were suspected, blood and/or ascitic fluid was collected in blood-culture bottles at the bedside, incubated at 37 °C for 7 days, and examined daily for turbidity. Bottles were subcultured after 2 and 7 days on chocolate-enriched agar plates for aerobic and anaerobic growth. Plates were incubated for 1 or 2 days at 37 °C, and organisms were identified.

All organisms were identified by their biochemical and immunological characteristics. A rapid slide-agglutination test simultaneously detecting fibrinogen activity (clumping factor), protein A and capsular polysaccharides was used to identify *Staphylococcus aureus* (Pastorex Staph Plus, Sanofi Pasteur Diagnostics, Marne la Coquette, France), followed if necessary by the determination of free coagulase activity. *Enterobacteriaceae* and non fermenting bacilli were identified with API 20E and API 32GN strips, respectively (BioMérieux SA, 69 Marcy l'Etoile, France).

Antibiotic susceptibilities were determined using the disk diffusion technique, as recommended by the Antibiogram Committee of the French Society of Microbiology [9]. To detect methicillin resistance in *Staphylococcus aureus*, 5-μg oxacillin disks were used and plates were incubated for 24 h at 30 °C. Antibiotic resistance patterns of all isolates were studied and compared.

Staphylococcal carriage was defined as the presence of *Staphylococcus aureus* in nasal and/or stool cultures. Antimicrobial susceptibility testing was used

to distinguish methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) strains. RE/RNF stool carriage was defined by the presence of Gram-negative bacilli resistant to third-generation cephalosporins (enterobacteria or non-fermenting bacilli) in stools, as determined by culture on cefotaxime and ceftazidime-supplemented media; each strain detected on one or both supplemented medium was taken into account. Resistance was confirmed by further antimicrobial susceptibility testing.

All episodes of UTI, SBP and bacteraemia with positive culture occurring during the hospital stay in our unit were analysed.

UTI was defined by a leucocyte count exceeding 10 000/ml and bacteriuria, according the criteria of Kass, and regardless of clinical signs [10]. Patients with urinary catheters were excluded from the study.

The diagnosis of SBP was based on the combination of a positive ascitic fluid culture and a polymorphonuclear cell count of $> 250\ mm^3$, irrespective of clinical signs of SBP, or a positive ascitic fluid culture with no increase in the polymorphonuclear cell count but with abdominal pain and fever. This symptomatic form of bacterial ascites is considered to be a variant of SBP [11–15]. The diagnosis of bacteraemia was based on a combination of clinical signs (fever, hypothermia, encephalopathy and hypotension) and one or several positive blood cultures. Contaminants in ascitic fluid and blood cultures were excluded.

Quantitative variables are given as the mean $\pm$S.D. Comparison of variables among three groups of patients were performed using one-way analysis of variance (ANOVA). When ANOVA showed a significant difference, two groups were compared with Bonferroni-Dunn's test. Comparisons of percentages between groups were made with the χ^2 test, with Yates' correction when required. Multivariate analysis was done using a stepwise logistic regression model. The threshold for statistical differences was $P < 0{\cdot}05$. Data were analysed with Epi-Info software VS (CDC Atlanta) and Statview software.

RESULTS

Of the 748 patients studied, 125 were MRSA carriers on admission to the unit. MRSA carriage was found in stools and nose in 68 cases, in stools only in 25 cases and in nose only in 32 cases. The overall prevalence of MRSA carriage on admission was 16·7%. Of these 125 patients, 18 also carried RE/RNF in stools. Isolated carriage of RE/RNF in stools was found in a further 92 patients who made up the group of RE/RNF carriers. The overall prevalence of RE/RNF carriage was 14·7%. Numbers of patients colonized with various RE/RNF strains were as follows: *Enterobacter cloacae* 40, *Citrobacter freundii* 27, *Pseudomonas aeruginosa* 19, *Acinetobacter baumanii* 7, *Enterobacter aerogenes* 5, *Pseudomonas species* 4, *Stenotrophomonas maltophila* 4, *Klebsiella pneumoniae* 4, *Escherichia coli* 3, *Hafnia alvei* 3, *Klebsiella oxytoca* 2 and *Enterobacter sakasaki* 1. Two different strains of RE/RNF were isolated from the stools of 9 patients and one strain only from each of the remaining patients.

Carriage of MRSA and RE/RNF in relation to Child classification, mean patient age, Pugh score and duration of hospital stay is shown in Table 1. MRSA carriage was higher in Child C patients but the difference was not significant. Age, Pugh score and duration of hospital stay were significantly different among the three groups of patients. When compared with non-carrier patients, RE/RNF carriers were older ($P < 0{\cdot}03$) while MRSA carriers had a higher Pugh score and a longer duration of hospital stay in the unit ($P < 0{\cdot}01$).

Of the 748 patients studied, 173 were treated with antibiotics (β-lactams, third generation cephalosporins, fluoroquinolones) for at least 10 days for sepsis and additionally, 183 patients were given norfloxacin for primary or secondary prophylaxis of SBP for at least 2 weeks before admission to the unit. If being given norfloxacin prophylaxis, patients took antibiotics until admission, then norfloxacin was withdrawn. The numbers and percentages of carrier and non-carrier patients receiving prior antibiotic therapy or norfloxacin prophylaxis are shown in Table 2. In comparison with non-carrier patients, MRSA and RE/RNF carriage was more common in patients who had received prior antibiotic therapy ($P < 0{\cdot}001$). A greater proportion of MRSA carriers had received norfloxacin prophylaxis than non-carrier patients ($P < 0{\cdot}05$), but there was no significant difference between RE/RNF carriers and non-carrier patients. Among the 43 MRSA carriers who had had previous norfloxacin prophylaxis, MRSA carriage was found in nose and stools in 27 cases, in stools only in 7 cases and in the nose only in 9 cases.

Sixty-three episodes of SBP, 45 episodes of bacteraemia and 114 episodes of UTI occurred in 60, 45 and 99 non-carrier patients respectively. Twenty-eight episodes of SBP, 30 episodes of bacteraemia and 50 episodes of UTI occurred respectively in 19, 22 and

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Table 1. *Carriers of MRSA and RE/RNF according to Child classification*

	MRSA carriers	RE/RNF carriers	Non-carriers	Total
Child A	9 (7·2)	7 (7·6)	73 (13·7)	89 (11·9)
Child B	45 (36·0)	36 (39·1)	200 (37·7)	281 (37·6)
Child C	71 (56·8)	49 (53·3)	258 (48·6)	378 (50·5)
Total	125	92	531	748
M/F	85/40	61/31	335/196	481/267
Age (years)	55·8 ± 11·4	56·7 ± 11·6*	53·8 ± 11·7*†	54·5 ± 11·7
PUGH score	9·9 ± 2·1**	9·8 ± 2·2	9·3 ± 2·4**††	9·5 ± 2·3
Hospital stay (days)	43·4 ± 39·6**	40·3 ± 28·8	35·2 ± 23·0**†††	37·1 ± 27·4

Means are given ± S.D. Percentages are in parentheses.
*$P < 0{\cdot}03$, ** $P < 0{\cdot}01$ (Bonferroni–Dunn's test).
†$P < 0{\cdot}05$, †† $P < 0{\cdot}02$, ††† $P < 0{\cdot}01$ (ANOVA).

Table 2. *Prevalence of patients receiving prior antibiotic therapy or norfloxacin prophylaxis in carrier and non-carrier groups*

	MRSA carriers ($n = 125$)	RE/RNF carriers ($n = 92$)	Non-carriers ($n = 531$)	Total ($n = 748$)	
Patients with previous antibiotic therapy	57 (45·6)	43 (46·7)	73 (13·7)	173	$P < 0{\cdot}001$
Patients with previous norfloxacin prophylaxis	43 (34·4)	22 (23·9)	118 (22·2)	183	$P < 0{\cdot}02$

Percentages are given in parentheses.

Table 3. *Prevalence of septic complications in carrier and non-carrier groups*

	MRSA carriers ($n = 125$)	RE/RNF carriers ($n = 92$)	Non-carriers ($n = 531$)	Total ($n = 748$)	
SBP*	19 (15·2)	14 (15·2)	60 (11·3)	93	n.s.
Bacteraemia	22 (17·6)	8 (8·7)	45 (8·5)	75	$P < 0{\cdot}01$
UTI†	34 (27·2)	26 (28·3)	99 (18·6)	159	$P < 0{\cdot}01$

Percentages are given in parentheses.
* SBP, spontaneous bacterial peritonitis; † UTI, urinary tract infection.

34 MRSA carriers. Fifteen episodes of SBP, 8 episodes of bacteraemia and 30 episodes of UTI occurred respectively in 14, 8 and 26 RE/RNF carriers.

The numbers and percentages of patients with septic complications in carrier and non-carrier groups are shown in Table 3. The percentage of patients with SBP was higher in MRSA and RE/RNF carriers but the difference was not significant. Bacteraemia was more frequent in MRSA carriers than in non-carriers ($P < 0{\cdot}01$), but there was no significant difference between bacteraemia rates in RE/RNF carriers and non-carrier patients. UTI was more frequent in both MRSA and RE/RNF carriers, in comparison with non-carriers ($P < 0{\cdot}01$).

The nature of the bacteria responsible for SBP, bacteraemia and UTI in the three groups of patients is shown in Table 4. *Enterobacteriaceae* were isolated with a lower rate in bacteraemia and UTI in MRSA carriers in comparison with the two other groups (respectively 3·3% *vs.* 28·9% and 33·3% for bacteraemia, $P < 0{\cdot}05$; 46·0% *vs.* 71·9% and 80·0% for UTI, $P < 0{\cdot}01$). Conversely, infection with MRSA was found with a higher rate in MRSA carriers in SBP (46·4% *vs.* 11·1% and 0%, $P < 0{\cdot}001$), bacteraemia (53·3% *vs.* 6·7% and 0%, $P < 0{\cdot}001$), UTI (24·0% *vs.* 4·4% and 0%, $P < 0{\cdot}001$). Over four fifths (56/68, 82·4%) of *Staphylococcus aureus* strains isolated in the entire population were MRSA. The prevalence of total Gram-positive pathogens was comparable in the three groups for SBP and bacteraemia but was higher

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Table 4. *Bacteria cultured from ascitic fluid, blood culture and urine in carriers and non-carriers*

	Non-carrier†			MRSA carriers			RE/RNF carrier		
	A	B	U	A	B	U	A	B	U
Escherichia coli	13	11	60	3		13	6	2	10
Other *Enterobacteriaceae*	7	2	22	2	1	10	1		14
Total *Enterobacteriaceae*	20 (31·7%)	13 (28·9%)[a]	82 (71·9%)[b]	5 (17·9%)	1 (3·3%)[a]	23 (46·0%)[b]	7 (46·7%)	2 (33·3%)[a]	24 (80·0%)[b]
Non-fermenting Gram-negative bacilli	3	2	6	2	1	4			3
Bacteroides spp.	1				1				
Streptococcus spp.	17	9	2	6	4	1	3	1	1
Enterococcus spp.	12	2	11	2	1	8	4	1	2
MRSA	7 (11·1%) *	3 (6·7%) **	5 (4·4%) ***	13 (46·4%) *	16 (53·3%) **	12 (24·0%) ***	(0%) *	(0%) **	(0%) ***
MSSA	1	5	5			1			
Coagulase negative staphylococcus	1	11	2		6			4	
Clostridium spp.	1						1		
Total Gram-positive pathogens	39 (61·9%)	30 (66·7%)	25 (21·9%)[c]	21 (75%)	27 (90·0%)	22 (44%)[c]	8 (53·9%)	6 (66·6%)	3 (10%)[c]
Candida albicans			1			1			
Total	63	45	114	28	30	50	15	8	30

†A, Ascites; B, blood; U, urine.
[a] $P < 0{\cdot}05$; [b,c] $P < 0{\cdot}01$; * , **, *** $P < 0{\cdot}001$.

Table 5. *Risk of MRSA infection in carriers and non-carriers*

	MRSA carriers ($n = 125$)	RE/RNF carriers ($n = 92$)	Non-carriers ($n = 531$)	
SBP*	13 (10·4)	0 (0)	7 (1·3)	$P < 0{\cdot}001$
Bacteraemia	16 (12·8)	0 (0)	3 (0·6)	$P < 0{\cdot}001$
UTI*	12 (9·6)	0 (0)	5 (0·9)	$P < 0{\cdot}001$
Total	41 (32·8)	0 (0)	15 (2·8)	$P < 0{\cdot}001$

Percentages are given in parentheses.
* See footnote, Table 3.

in MRSA carriers in UTI (44·0% *vs.* 21·9% and 10·0%, $P < 0{\cdot}01$).

In MRSA carriers, MRSA strains were isolated from ascitic fluid, blood culture and urine after a mean interval following admission of 16 ± 26 days (extremes: 0–120 days, median: 13 days). The risk of infections related to MRSA in the three groups of patients is shown in Table 5. MRSA carriers had an increased risk of SBP, bacteraemia and UTI caused by MRSA in comparison with the two other groups, the overall risk was more than tenfold higher than in non-carriers.

Three patients carrying a resistant enterobacterial strain had episodes of infection caused by the same species and with the same antibiotic resistance pattern (UTI – two cases, bacteraemia – one case, *Citrobacter freundii* in one case, *Enterobacter cloacae* in two cases). Carriage and infection coincided in two cases.

The mortality rate during hospital stay was higher in MRSA carriers (29·6%, 37/125) and in RE/RNF carriers (25·0%, 23/92) than in non-carrier patients (14·1%, 75/531) ($P < 0{\cdot}001$). A septic complication was the direct cause of death in 45% of MRSA carriers, 47·8% of RE/RNF carriers and 34·7% of non-carrier patients (n.s.). The cause of death was liver failure in the remaining patients. Pugh score and age at admission were higher in patients who died during hospital stay than in surviving patients

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(respectively $11{\cdot}1 \pm 1{\cdot}8$ *vs.* $9{\cdot}1 \pm 2{\cdot}3$, $P < 0{\cdot}001$; $60{\cdot}8 \pm 10{\cdot}9$ *vs.* $53{\cdot}2 \pm 11{\cdot}4$ years, $P < 0{\cdot}001$). In multivariate analysis with mortality as the dependent variable, Pugh score (OR: 1·669 CI_{95} 1·485–1·876, $P < 0{\cdot}0001$), age (OR: 1·083 CI_{95} 1·060–1·105, $P < 0{\cdot}0001$), MRSA carriage (OR: 2·305, CI_{95} 1·363–3·897, $P = 0{\cdot}0018$) and bacteraemia (OR: 2·99, CI_{95} 1·507–5·918, $P = 0{\cdot}0017$) were associated with mortality.

DISCUSSION

In this study series of cirrhotic patients, we chose for practical reasons to detect MRSA carriage on admission only. We showed that carriage is a strong predictor of subsequent infections caused by this strain. We were also able to document the prevalence of the different micro-organisms involved in hospital-acquired SBP, bacteraemia and ITU in cirrhotic patients, since all the patients included in the study were hospitalized before admission to our unit and were then exposed to a long hospital stay. *Enterobacteriaceae* and especially *Escherichia coli* have been reported to be the main agents responsible for SBP [15], but these data refer principally to community-acquired infections. The prevalence of different bacteria involved in hospital-acquired infections in cirrhotic patients has not been extensively studied as yet. We have shown previously changes in the nature of bacteria causing SBP over a 20 year period with a decrease in the prevalence of *Enterobacteriaceae* from 78·7% to 60·3%. Moreover, resistance of bacteria increases as shown by the emergence of enterobacterial strains resistant to third generation cephalosporins since 1993 [16]. In this study, of a total of 106 episodes of SBP (in 93 patients) the overall prevalence of *Enterobacteriaceae* was only 30·2% with a prevalence of 20·8% for *Escherichia coli*. In contrast, the prevalences of *Streptococcus* spp., *Enterococcus* spp. and *Staphylococcus* spp. were respectively 24·5, 17·0 and 19·8%. We found a high prevalence of *Staphylococcus aureus* in SBP, with most of the strains isolated being methicillin resistant. *Staphylococcus* spp. predominated in bacteraemia, again with a high prevalence of MRSA. Conversely, *Enterobacteriaceae* predominated in UTI, with a prevalence of 66·5%, compared with a prevalence of *Staphylococcus aureus* of 11·3%. Most *Staphylococcus aureus* strains were MRSA. We found a high prevalence of *Staphylococcus aureus*, mainly MRSA, whatever the site of infection. Carriage of MRSA at time of admission was the main contributory factor.

Today, MRSA is recognized as a major nosocomial pathogen, causing nosocomial infections in community and referral hospitals, as well as in long-term care facilities throughout the world [17, 18]. Two previous studies have assessed the prevalence of carriage of staphylococcal strains in cirrhotic patients, but only by sampling of the anterior nares and without sampling stools. Chapoutot et al. found a prevalence of MRSA carriage of 5·8% on admission while Chang et al. found a prevalence of 16·6% [19, 20]. The latter result was very close to that observed in our study (16·7%). The ecological niche of staphylococci is the anterior nares and previous studies have shown that the nares are the most consistent site from which the organism can be isolated [18]. We have also studied the carriage in stools and we have shown that though both sites are colonized in most cases (54%), the organism is isolated from stools only in 20% of cases, demonstrating that assessing nasal carriage only may underestimate the true prevalence of carriage.

Several factors may account for this high prevalence of carriage. All these patients had been exposed to long prior hospital stay since they were inpatients before admission to our unit. Many had end-stage liver diseases with a high risk of septic complications and extensive prior use of antibiotic therapy. Little is known about the risk of infection related to this organism in carrier cirrhotic patients. We found an increased prevalence of MRSA strains not only in bacteraemia as expected but also in SBP and UTI in carrier patients. The presence of MRSA in anterior nares and stools suggests that multiple sites may often be colonized, facilitating episodes of bacteraemia. In this study, nasal and stool culture were performed only on admission and were not repeated later during the hospital stay. It is therefore possible that the prevalence of carriage increased during hospitalization, which may account for the 15 cases of infection due to MRSA that were observed in the non-carrier patients.

Infections are a major cause of morbidity and a significant contributor to death in patients with cirrhosis. The mortality rate was high in our patient population including many patients with end-stage liver disease. One third to one half of deaths were directly caused by sepsis and we found that bacteraemia was a independent predicator of mortality. MRSA carriers had more advanced disease

liver disease, while RE/RNF carriers were older than non-carriers, which may account for their higher mortality rate. However MRSA carriage was an independent predictor of mortality, and the higher prevalence of bacteraemia in MRSA carriers is likely to be a contributory factor to the adverse prognostic impact of MRSA carriage.

In our study MRSA carrier patients had received prior antibiotic therapy to a greater extent than non-carrier patients [17]. As expected, previous antibiotic therapy had been also given to a greater extent in RE/RNF carrier patients. Norfloxacin is a widely used drug for long term selective intestinal decontamination in cirrhotic patients because it is incompletely absorbed from the intestine, is highly active against Gram-negative bacilli, has low activity against anaerobic bacteria and reduces dramatically the risk of infections carried by Gram-negative bacilli [21–23]. We showed in a previous study that long-term norfloxacin administration carries a risk of disturbing the bacterial ecology of patients with emergence of enterobacterial strains highly resistant to quinolones and the occurrence of *Staphylococcus aureus* and *Staphylococcus* spp. in the stools [24]. All the staphylococcal strains were methicillin resistant. More recently, we have shown that long-term norfloxacin administration in cirrhotic patients promotes staphylococcal SBP and bacteraemia and increases the risk of carriage of the methicillin resistant phenotype [7]. Because of this risk of emergence, we have chosen to stop administering prophylactic norfloxacin to patients admitted to our unit. In this study, we have shown that norfloxacin is a risk factor for carriage of MRSA. MRSA was found in stools in carrier patients taking norfloxacin, suggesting that changes in intestinal bacterial ecology may have a role in colonization. These data suggest that the increased risk of staphylococcal infections due to administration of norfloxacin is related to carriage of this strain. Regarding the different patterns of resistance to quinolone in different pathogens, the most striking has been the rapid emergence of a high prevalence of quinolone resistance ($> 90\%$) among methicillin-resistant but not methicillin-susceptible strains of *Staphylococcus aureus* in many parts of the world [25].

We also found a high prevalence of carriage of RE/RNF strains (14·7%) in patients exposed to a long hospital stay. However, unlike MRSA carriage, RE/RNF carriage was not associated with an increased risk of infection caused by RE/RNF strains since only three cases of infection caused by the same RE strain which was found in the stools were observed. Norfloxacin prophylaxis was not given to a greater extent in RE/RNF carrier patients than in non-carrier patients showing that norfloxacin prophylaxis does not seem to increase the risk of carrying these strains; this finding is in agreement with studies showing that *Escherichia coli* resistant to norfloxaxin isolated in patients receiving this antibiotic are not resistant to third-generation cephalosporin [26].

In conclusion, we have shown that cirrhotic patients with advanced disease necessitating long hospital stay have a high prevalence of MRSA carriage which is a main factor predisposing to infections caused by this bacterial strain. Thus, MRSA carriage has important clinical consequences and is a poor prognostic factor as shown by the higher mortality rate of carrier patients. Staphylococcal infections contribute in greater part to the epidemiology of infections in cirrhotic inpatients when compared to that observed in community infections. Previous antibiotic therapy and norfloxacin prophylaxis increases the risk of MRSA carriage. Carriage should be assessed in patients submitted to frequent or long term hospitalization because approaches to the elimination of carriage based on disinfectants and local antibiotics are available. Also, use of norfloxacin should be limited in these patients because of the risk of emergence of MRSA infections [27].

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