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Infection prevention and control programme and COVID-19 measures: Effects on hospital-acquired infections in patients with cirrhosis

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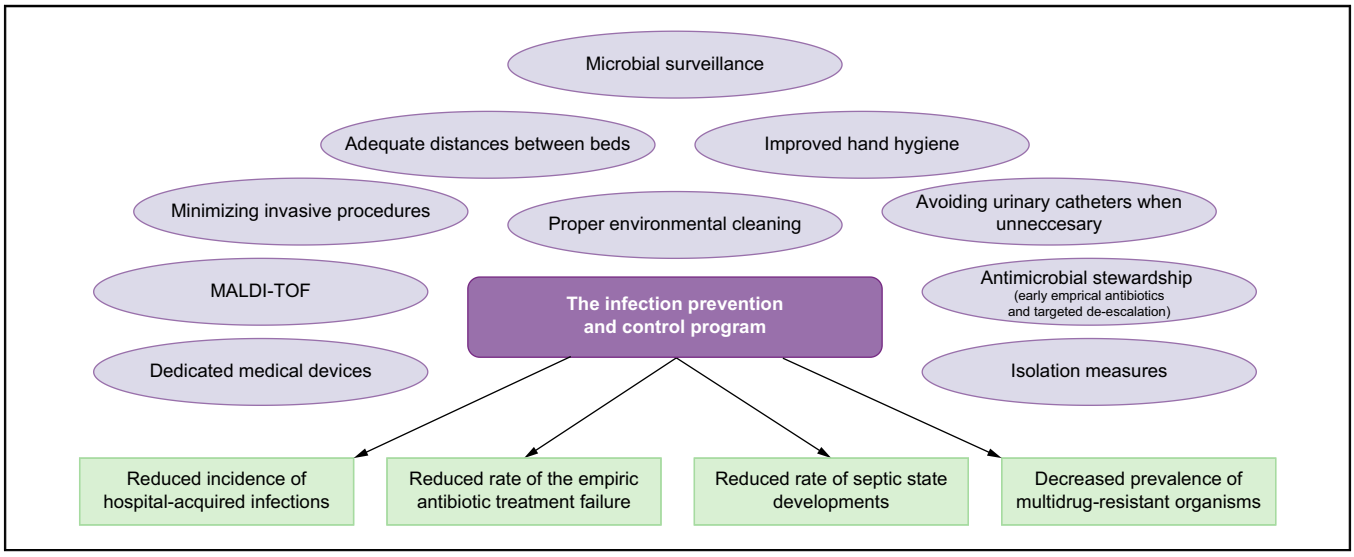
Graphical abstract



Highlights

- Hospital-acquired infections can be prevented by an infection and prevention control programme.
- COVID-19 measures alone are not able to significantly reduce the incidence of hospital-acquired infections.
- The infection prevention and control programme should be adopted in centres with a high prevalence of patients with cirrhosis.

Impact and implications

Infections are a life-threatening problem for patients with liver cirrhosis. Moreover, hospital-acquired infections are even more alarming owing to the high prevalence of multidrug-resistant bacteria. This study analysed a large cohort of hospitalised patients with cirrhosis from three different periods. Unlike in the first period, an infection prevention programme was applied in the second period, reducing the number of hospital-acquired infections and containing multidrug-resistant bacteria. In the third period, we imposed even more stringent measures to minimise the impact of the COVID-19 outbreak. However, these measures did not result in a further reduction in hospital-acquired infections.

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Infection prevention and control programme and COVID-19 measures: Effects on hospital-acquired infections in patients with cirrhosis

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Background & Aims: Bacterial infections affect survival of patients with cirrhosis. Hospital-acquired bacterial infections present a growing healthcare problem because of the increasing prevalence of multidrug-resistant organisms. This study aimed to investigate the impact of an infection prevention and control programme and coronavirus disease 2019 (COVID-19) measures on the incidence of hospital-acquired infections and a set of secondary outcomes, including the prevalence of multidrug-resistant organisms, empiric antibiotic treatment failure, and development of septic states in patients with cirrhosis.

Methods: The infection prevention and control programme was a complex strategy based on antimicrobial stewardship and the reduction of patient's exposure to risk factors. The COVID-19 measures presented further behavioural and hygiene restrictions imposed by the Hospital and Health Italian Sanitary System recommendations. We performed a combined retrospective and prospective study in which we compared the impact of extra measures against the hospital standard.

Results: We analysed data from 941 patients. The infection prevention and control programme was associated with a reduction in the incidence of hospital-acquired infections (17 *vs.* 8.9%, p <0.01). No further reduction was present after the COVID-19 measures had been imposed. The impact of the infection prevention and control programme remained significant even after controlling for the effects of confounding variables (odds ratio 0.44, 95% CI 0.26–0.73, p = 0.002). Furthermore, the adoption of the programme reduced the prevalence of multidrug-resistant organisms and decreased rates of empiric antibiotic treatment failure and the development of septic states.

Conclusions: The infection prevention and control programme decreased the incidence of hospital-acquired infections by nearly 50%. Furthermore, the programme also reduced the prevalence of most of the secondary outcomes. Based on the results of this study, we encourage other liver centres to adopt infection prevention and control programmes.

Impact and implications: Infections are a life-threatening problem for patients with liver cirrhosis. Moreover, hospital-acquired infections are even more alarming owing to the high prevalence of multidrug-resistant bacteria. This study analysed a large cohort of hospitalised patients with cirrhosis from three different periods. Unlike in the first period, an infection prevention programme was applied in the second period, reducing the number of hospital-acquired infections and containing multidrug-resistant bacteria. In the third period, we imposed even more stringent measures to minimise the impact of the COVID-19 outbreak. However, these measures did not result in a further reduction in hospital-acquired infections.

Introduction

Bacterial infections are one of the most important factors associated with the progression of liver failure and liver-related mortality in patients with cirrhosis.[1] The prevalence of bacterial infections is approximately 25–46% in patients hospitalised for acute decompensation of liver cirrhosis. Approximately two-thirds of infections are community-acquired and healthcare-associated, whereas the remaining third of infections are hospital-acquired.[2] Cirrhosis-associated immune dysfunction, the most critical factor that predisposes patients with liver cirrhosis to bacterial infections, has been extensively reviewed elsewhere.[3,4]

Hospital-acquired infections (HAIs) are of particular relevance. They are defined as infections that take place more than 48 h following admission. HAIs are highly prevalent in patients with cirrhosis and are associated with poor outcomes.[5] Furthermore, 'second infections', a specific subgroup of HAIs, have an even stronger association with mortality.[6] There are several widely recognised risk factors for HAIs in patients with

Keywords: Liver cirrhosis; Nosocomial infections; Antibiotic resistance; Bacterial infections; Antimicrobial stewardship; SARS-CoV-2; Empiric antibiotic failure; Multidrug-resistant bacteria.

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cirrhosis, such as admission with infection, history of lactulose, rifaximin or proton pump inhibitor use, low protein ascites, malnutrition, poor liver function, prior spontaneous bacterial peritonitis, invasive procedures, upper gastrointestinal bleeding, and recent hospitalisation.[5,7,8] Notably, HAIs are an independent risk factor for multidrug-resistant (MDR) infections, a growing cause of concern across Europe and worldwide.[5–7,9–12] Indeed, preventive measures have been repeatedly called for to prevent HAIs in patients with cirrhosis,[8,13] and guidelines have suggested more appropriate antimicrobial treatments in this setting.[4,7,14]

Despite the clinical and epidemiological impact of HAIs in patients with liver cirrhosis, there are no studies evaluating the effectiveness of hospital measures for their prevention in these patients. Based on international guidelines, the prevention of HAIs requires not only a programme that integrates multiple general measures, but also the application of specific antibiotic treatment in patients with cirrhosis.[4,14]

The primary aim of the study was to evaluate the impact of an infection prevention and control programme (IPCP) on the incidence of HAIs in a large cohort of patients with cirrhosis. The secondary aim of this study was to evaluate the impact of the IPCP on the failure of empiric antibiotic treatment, antibiotic resistance, development of sepsis, and hospital mortality in HAIs. However, owing to the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, the IPCP had to be modified, and further rules were implemented in hospital patient care. The new rules could also alter the incidence of HAIs; therefore, we added a small cohort of patients with cirrhosis hospitalised during the first COVID-19 lockdown to the present study to perform a three-series analysis comparing 'standard measures', 'IPCP', and 'COVID-19 measures'. The Supplementary information includes a special section dedicated to introducing different terms (Appendix S1).

Patients and methods

This combined retrospective and prospective interventional cohort study was performed in a tertiary liver care centre (Gastroenterology and Hepatology Unit, University Hospital – Policlinico Umberto 1, Rome, Italy). The local ethical committee approved the protocol of the study and retrospective and prospective data collection (ethical committee no. 3887, 20/11/15). All patients signed informed consent for participation in the study.

The IPCP was progressively introduced between November 2013 and March 2014 as a group of measures devoted to decreasing the incidence of HAIs in patients with cirrhosis. The IPCP included the following:

- Reduction in the number of beds per room and increase in their distance
- Improvement of hand hygiene practices, including positioning of alcohol-based antiseptic gel dispensers within patients' rooms
- Improvement in urinary catheter care (silicon-based and less prone to bacterial colonisation [Rüsch Teleflex Medical Srl, Varedo MB, Italy]) paired with their early removal
- Avoiding high frequency of invasive procedures whenever possible (*i.e.* care to perform one large volume instead of multiple smaller volume abdominal paracentesis or care to associate endoscopy for variceal screening with therapeutic band ligation in the same session when needed)
- Reduction of turnaround time for culture-based bacterial identification using novel tools MALDI-TOF MS (matrix-assisted laser desorption/ionisation–time of flight mass spectrometry)
- Isolation of patients who tested positive for MDR/extensively drug-resistant (XDR)/pandrug-resistant (PDR) organisms
- Active microbial surveillance of contacts of MDR/XDR/PDR organism-positive patients and dedicated medical devices for patients who tested positive for MDR/XDR/PDR organisms
- Proper environmental cleaning (accurate disinfection of the rooms after the discharge of patients who tested positive for MDR/XDR/PDR organisms)
- Antimicrobial stewardship is responsible for (1) early empirical antibiotic treatment guided by the severity of the infection and the presence of risk factors for MDR/XDR/PDR organisms and their local epidemiology according to guidelines (broad-spectrum antibiotics in cases of high risk of MDR/XDR/PDR organisms and high doses in cases of sepsis/septic shock)[4] and (2) early and targeted antibiotic de-escalation based on the infection evolution and results of microbiological tests and antibiotic resistance[4]

Regular audits and monthly multidisciplinary meetings were held to enforce the medical staff's adherence to the IPCP. Furthermore, the adherence of the medical staff to the IPCP was also monitored by a dedicated observer.

Owing to the spread of COVID-19 to the European continent, the IPCP had to be modified according to the Hospital and Health Italian Sanitary System recommendations (effective from 1 March 2020):

- Personal protective equipment is worn continuously by healthcare workers (doctors and nurses wearing disposable eye protection, disposable masks, disposable scrubs, disposable gloves, and disposable overshoes)
- Personal protective equipment is worn continuously by patients (disposable masks)
- Restriction of patients' movement on the ward
- Postponing all immediately unnecessary examinations
- Restriction of relatives' access to visit hospitalised patients

The hospital had to dedicate special wards to COVID-19-positive patients. However, all the measures mentioned above were implemented in non-COVID-19 wards as well. At the same time, there was only limited availability of infectious disease specialists for stewardship in the non-COVID-19 wards.

Patients

Patients with cirrhosis were included in the study if they were hospitalised between January 2009 and August 2013 (old control cohort following standard measures, therefore 'standard measures cohort' [SMC]), March 2014 to January 2018 (more recent cohort following the IPCP, therefore 'infection prevention and control cohort' [IPCC]), and March to July 2020 (5-month cohort during the COVID-19 period, therefore 'COVID-19 measures cohort' [C19MC]). None of the patients enrolled in this cohort were COVID-19 positive. We did not include patients hospitalised between November 2013 and February 2014 because the IPCP was gradually introduced during this period, and it achieved its full effect only by the end of February 2014. Patients were excluded if they were <18 years, had advanced neoplasia

(including hepatocellular carcinoma outside of the Milan criteria), and had concomitant HIV infection or corticosteroid or other immunosuppressive treatment.

The following infection screening algorithm was exercised at admission: (1) clinical assessment (medical history and physical examination with emphasis on symptoms/signs of infection, body temperature, blood pressure, and heart and respiratory rate), (2) blood test (liver and renal tests, an inflammatory panel including white blood cell [WBC] and neutrophil [NEU] counts, and urine analysis including urine sediment + microbiological assessment of other biological fluids, if present [*e.g.* ascites or pleural effusion]), and (3) imaging (chest X-ray and abdominal ultrasound examinations). The same algorithm was followed whenever a hospitalised patient deteriorated. Furthermore, the site of infection, isolated organisms, antibiotic susceptibility, empirical and culture-guided antibiotic treatment, and information regarding treatment failure were recorded.

Statistical analysis

Continuous variables are described by medians and IQRs unless stated otherwise. Categorical variables are expressed as absolute counts and percentages. The pairwise deletion was performed in cases of missing data to minimise the unnecessary removal of valid information and thus the introduction of bias. The Kruskal–Wallis test, the Mann–Whitney test, Fisher's exact test, and the χ^2 test were used to evaluate the significance of distribution differences in continuous and categorical variables. In the case of significant results, *post hoc* two-sample analyses followed to identify sources of differences. Simple logistic regression analyses were performed to investigate associations between independent variables and HAIs. A multivariable logistic regression analysis was performed to estimate the effect of the IPCP and COVID-19 measures while controlling for the confounding effect of other factors. We also performed a set of diagnostic tests of logistic regression model assumptions.

Results

General description of the three cohorts

The study sample (941 patients) consisted of three separate cohorts of patients, namely SMC (n = 428), IPCC (n = 425), and C19MC (n = 88). There were no differences among the three cohorts in age, but the IPCC included more male patients. Furthermore, the prevalence of alcoholic liver disease and non-alcoholic steatohepatitis increased in the more recent cohorts. In contrast, the prevalence of viral hepatitis and cryptogenic

Table 1. The baseline characteristics of patients together with the chronic treatment and median length of stay.

Characteristic	SMC (n = 428)*	IPCC (n = 425)*	C19MC (n = 88)*	*p* value
Age	62 (51, 73)	60 (54, 67)	60 (56, 68)	0.2†
Sex				0.022‡
Female	123 (29%)	88 (21%)	24 (27%)	
Male	305 (71%)	337 (79%)	64 (73%)	
Underlying chronic liver disease				<0.001‡
Viral	209 (49%)	153 (36%)	18 (20%)	
ALD	103 (24%)	124 (29%)	35 (40%)	
Viral + ALD	27 (6.3%)	47 (11%)	15 (17%)	
Cryptogenic	48 (11%)	34 (8.0%)	4 (4.5%)	
Another	30 (7.0%)	30 (7.1%)	4 (4.5%)	
NASH	11 (2.6%)	37 (8.7%)	12 (14%)	
SBP prophylaxis	14 (3.3%)	12 (2.8%)	0 (0%)	0.2§
BB	167 (39%)	182 (43%)	48 (56%)	0.015‡
Diuretics	320 (75%)	317 (75%)	59 (69%)	0.5‡
Lactulose	187 (44%)	201 (47%)	41 (48%)	0.5‡
PPI	288 (67%)	259 (61%)	49 (57%)	0.066‡
Rifaximin	50 (12%)	90 (21%)	24 (28%)	<0.001‡
Reason for admission				0.027‡
Acute	281 (66%)	241 (57%)	54 (61%)	
Elective	147 (34%)¶	184 (43%)**	34 (39%)††	
First (CA/HCA) infection	117 (27%)	79 (19%)	19 (22%)	0.009‡
MAP	85 (78, 93)	86 (77, 93)	87 (78, 96)	0.5†
CRP	0.91 (0.40, 3.00)	0.50 (0.17, 1.49)	1.31 (0.52, 3.78)	<0.001†
WBC count	4,970 (3,548, 7,342)	4,180 (3,190, 5,960)	3,920 (2,875, 6,470)	<0.001†
NEU	3,442 (2,240, 5,131)	2,512 (1,760, 3,700)	2,585 (1,588, 4,568)	<0.001†
MELD	13.0 (10.0, 17.0)	13.0 (10.0, 16.0)	12.0 (9.0, 15.0)	0.8†
Length of stay	10 (6, 18)	7 (5, 14)	10 (6, 19)	<0.001†

Values of p <0.05 are significant.
ALD, alcoholic liver disease; BB, beta blockers; C19MC, COVID-19 measures cohort; CA, community-acquired; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; HCA, health care-associated; IPCC, infection prevention and control cohort; MAP, mean arterial pressure; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; NEU, neutrophil; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; SMC, standard measures cohort; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell.
* Median (IQR) or n (%).
† Kruskal–Wallis rank sum test.
‡ Pearson's χ^2 test.
§ Fisher's exact test.
¶ 22 liver biopsies, 22 TIPS procedures, 47 local procedures for hepatocellular carcinoma (transarterial chemoembolisation or radiofrequency ablation), 45 banding of oesophageal varices requiring previous haemocomponents infusion, and 16 others (ERCP, polypectomy, and cardiac catheterisation).
** Twenty-six liver biopsies, 25 TIPS procedures, 53 local procedures for hepatocellular carcinoma (transarterial chemoembolisation or radiofrequency ablation), 56 banding of oesophageal varices requiring previous haemocomponents infusion, and 24 others (ERCP, polypectomy, and cardiac catheterisation).
†† Four biopsies, 5 TIPS procedures, 11 local procedures for hepatocellular carcinoma (transarterial chemoembolisation or radiofrequency ablation), 10 banding of oesophageal varices requiring previous haemocomponents infusion, and 4 others (ERCP, polypectomy, and cardiac catheterisation).

Table 2. Exposure to risk factors in the three cohorts.

Characteristic	SMC (n = 428)*	IPCC (n = 425)*	C19MC (n = 88)*	*p* value
More than (standard) two beds in a room	137 (32%)	8 (1.9%)	0 (0%)	<0.001†
Urinary catheter	67 (16%)	78 (18%)	20 (23%)	0.2†
Abdominal paracentesis	190 (44%)	119 (28%)	30 (34%)	<0.001†
Invasive procedures	1.69 (1.53)	1.44 (1.31)	1.44 (1.04)	0.041‡

Values of p <0.05 are significant.
C19MC, COVID-19 measures cohort; IPCC, infection prevention and control cohort; SMC, standard measures cohort.
* n (%) or mean (SD).
† Pearson's χ^2 test.
‡ Kruskal–Wallis rank sum test.

cirrhosis decreased. The use of beta blockers and rifaximin intensified between the SMC and the C19MC (*post hoc* two-sample analyses: p = 0.004 and p <0.001, respectively), and there was also a nonsignificant decreasing trend in the use of proton pump inhibitors (*post hoc* two-sample analyses: p = 0.07) (Table 1).

The SMC included fewer patients admitted electively compared with the IPCC, but there was no difference between the SMC and the C19MC (*post hoc* two-sample analysis: p = 0.007 and p = 0.4, respectively). Nevertheless, the severity of liver disease (model for end-stage liver disease [MELD] score) at admission was not significantly different between the three cohorts. The proportion of patients admitted as a result of ascites was roughly the same in the three cohorts: 122 (28.5%) in the SMC, 108 (25.4%) in the IPCC, and 18 (20.5%) in the C19MC (p = 0.25). Patients in the IPCC cohort had a shorter median length of stay than those in the SMC cohort (*post hoc* two-sample analysis: p <0.001) (Table 1). The all-cause in-hospital mortality was higher in the SMC (n = 46, 11%) than in the IPCC (n = 16, 3.8%) or C19MC (n = 5, 5.7%) (p <0.001; Supplementary information – Appendix S2).

The SMC had higher baseline values of inflammatory markers (C-reactive protein, WBC counts, and NEU counts) compared with the IPCC, which may be related to a higher proportion of patients admitted with community-acquired or healthcare-associated infection in the former cohort (*post hoc* two-sample analysis: p = 0.002) (Table 1).

Exposure to risk factors that might be linked to higher chances of HAIs was also evaluated[5,7,8] (Table 2). The presence of more than two beds in the same room, the overall number of abdominal paracenteses, and the number of invasive procedures generally decreased after the introduction of the IPCP (p <0.001, p <0.001, and p = 0.04, respectively). However, the frequency of the use of urinary catheters remained the same in all three cohorts (p = 0.2). The number of days during which the urinary catheter was used in each patient was not recorded.

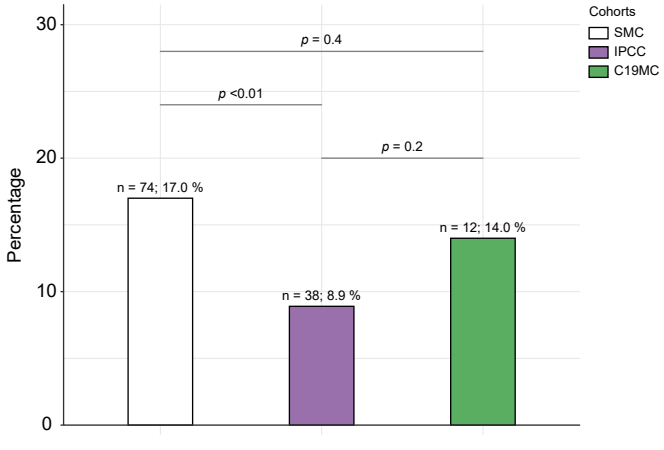

Fig. 1. The proportion of patients suffering from hospital-acquired infections in all three cohorts. The χ^2 test was used to evaluate the significance of distribution differences. Values of p <0.05 are significant. C19MC, COVID-19 measures cohort; IPCC, infection prevention and control cohort; SMC, standard measures cohort.

The effect of the IPCP and COVID-19 measures on the incidence of HAIs

The IPCP resulted in a significant reduction in the incidence of HAIs (Fig. 1). In the SMC and IPCC, the incidence of HAIs was 74 (17%) and 38 (8.9%), respectively (p <0.001). In the C19MC, however, the incidence of HAIs increased back to numbers more similar to those in the SMC (n = 12, 14%; p = 0.4).

As shown in Table 3, simple logistic regression analyses confirmed the association of the IPCP with a decreased incidence of HAI (odds ratio [OR] 0.47, 95% CI 0.31–0.71). However, they also revealed several other associations. MELD (OR 1.11, 95% CI 1.07–1.14), urinary catheter (OR 7.23, 95% CI 4.81–10.90), abdominal paracentesis (OR 2.64, 95% CI 1.80–3.89), invasive procedures (OR 1.67, 95% CI 1.48–1.89), and length of stay (OR 1.10, 95% CI 1.08–1.11) were all positively associated with HAI. By contrast, beta blockers (OR 0.57, 95% CI 0.38–0.85) and elective admission (OR 0.21, 95% CI 0.12–0.35) were negatively associated with HAI. Weak positive associations with HAI were also confirmed in cases of baseline WBC (after rounding decimals: OR 1.00, 95% CI 1.00–1.00) and NEU (after rounding decimals: OR 1.00, 95% CI 1.00–1.00). There was also a nonsignificant trend in the first infection, increasing the chance of a HAI (OR 1.46, 95% CI 0.95–2.21).

A multiple logistic regression analysis was performed to control for potential confounding effects and estimate the true effect of the IPCP on the incidence of HAI (Table 4). Potential confounders identified in simple analyses (Table 4) or in previously published work[1] were introduced into the multivariable model. After the removal of NEU (variance inflation factor >10), the variance inflation factor values of the rest of the variables were less than 1.73 (the remaining results of the set of diagnostic tests for logistic regression model assumptions are presented in the Supplementary information – Appendix S3). Finally, in the multivariable model, the IPCP remained associated with a decreased incidence of HAIs (OR 0.44, 95% CI 0.26–0.73). There was a similar nonsignificant trend in the case of the C19MC (OR 0.51, 95% CI 0.20–1.20) (Table 4). Furthermore, both invasive procedures and urinary catheters remained associated with HAIs. In addition, the first (community-acquired or healthcare-associated) infection was associated with a decreased incidence of HAIs (OR 0.43, 95% CI 0.24–0.75).

Table 3. Simple logistic regression analyses estimating the relationship between various variables and hospital-acquired infection.

	n	OR	95% CI	*p* value
Group	941			
SMC		–	–	
IPCC		0.46973	0.30701, 0.70828	<0.001
C19MC		0.75533	0.37444, 1.41239	0.40
Sex	941			
Female		–	–	
Male		0.82426	0.54473, 1.27060	0.37
BB	939	0.56910	0.37542, 0.84857	0.007
SBP prophylaxis	941	1.59264	0.52394, 3.99415	0.36
Lactulose	939	0.88602	0.60239, 1.29658	0.54
PPI	939	1.12718	0.76050, 1.69198	0.56
Rifaximin	938	1.11219	0.66869, 1.78419	0.67
Reason for admission	941			
Acute		–	–	
Elective		0.21412	0.12193, 0.35433	<0.001
First (CA/HCA) infection	941			
No		–	–	
Yes		1.45810	0.94720, 2.20652	0.080
CRP	757	1.00005	0.9999, 1.00017	0.45
WBC count	939	1.00009	1.00004, 1.00013	<0.001
NEU	937	1.00012	1.00007, 1.00018	<0.001
MELD	936	1.10536	1.07035, 1.14190	<0.001
Urinary catheter	940	7.22951	4.80912, 10.9035	<0.001
Abdominal paracentesis	941	2.64078	1.80223, 3.88895	<0.001
Invasive procedures	941	1.66500	1.47631, 1.88619	<0.001
Length of stay	941	1.09543	1.07823, 1.11413	<0.001

Values of p <0.05 are significant (Wald test).
BB, beta blockers; C19MC, COVID-19 measures cohort; CA, community-acquired; CRP, C-reactive protein, HCA, healthcare-associated; IPCC, infection prevention and control cohort; MELD, model for end-stage liver disease; NEU, neutrophil; OR, odds ratio; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; SMC, standard measures cohort; WBC, white blood cell.

Table 4. Multiple logistic regression estimating the relationship between individual measures on one side and hospital-acquired infections on the other (after controlling for the confounding effect of other risk factors).

	OR	95% CI	*p* value
Group			
SMC	–	–	
IPCC	0.44	0.26, 0.73	0.002
C19MC	0.51	0.20, 1.20	0.14
BB	0.81	0.49, 1.33	0.4
Reason for admission			
Acute	–	–	
Elective	0.51	0.25, 0.97	0.044
First (CA/HCA) infection			
No	–	–	
Yes	0.43	0.24, 0.75	0.004
WBC count	1.00	1.00, 1.00	0.3
MELD	1.03	0.99, 1.07	0.13
Urinary catheter	3.70	2.16, 6.32	<0.001
Abdominal paracentesis	0.70	0.38, 1.28	0.3
Invasive procedures	1.21	1.01, 1.45	0.038
Length of stay	1.07	1.05, 1.09	<0.001

Values of p <0.05 are significant (Wald test).
BB, beta blockers; C19MC, COVID-19 measures cohort; CA, community-acquired; HCA, healthcare-associated; IPCC, infection prevention and control cohort; MELD, model for end-stage liver disease; OR, odds ratio; SMC, standard measures cohort; WBC, white blood cell.

The effect of the IPCP and COVID-19 measures on the incidence of MDR and XDR/PDR organisms, rate of empiric antibiotic treatment failure, development of septic states, and mortality among patients with HAIs

A higher rate of empiric antibiotic treatment failure (60 *vs.* 21%, p <0.001) and a higher rate of septic states (68 *vs.* 32%, p <0.001) were reported in the SMC than in the IPCC. The prevalence of MDR organisms was also higher (65 *vs.* 35%, p = 0.02) in the SMC. In-hospital mortality was not different between the two cohorts: n = 25 (34%) in the SMC cohort and n = 9 (24%) in the IPCC cohort (Fig. 2). The absolute counts of secondary outcomes were low in the C19MC cohort, which precludes us from reaching any reliable results. Finally, sepsis was the most frequent cause of death in all three cohorts (n = 20 [80%] in the SMC, n = 6 [67%] in the IPCC, and n = 4 [100%] in the C19MC).

Description of the HAIs

The characteristics of HAIs are presented in Table 5. The success of bacterial isolation and the Gram spectrum of bacteria did not change significantly among the three cohorts. The most common sites of infections were the urinary and respiratory tracts and spontaneous bacterial peritonitis (alone or in combination). There was an increasing use of piperacillin–tazobactam (alone or in combination with glycopeptides) as empiric antibiotic therapy in the more recent cohorts. Fluoroquinolone and cephalosporin use correspondingly decreased. Apart from HAIs, we also provide a comprehensive review of the empiric antibiotic treatment of community-acquired and healthcare-associated infections (Supplementary information – Appendix S2).

Discussion

Recently, encouraging improvements have been made in the management of decompensated cirrhosis. However, the mortality from bacterial infection remains a difficult challenge to overcome. In addition, HAIs are a significant threat owing to the high prevalence of MDR organisms in patients with cirrhosis and the lack of new antibiotic molecules to face worsening antibiotic resistance. These circumstances have led many authors to study

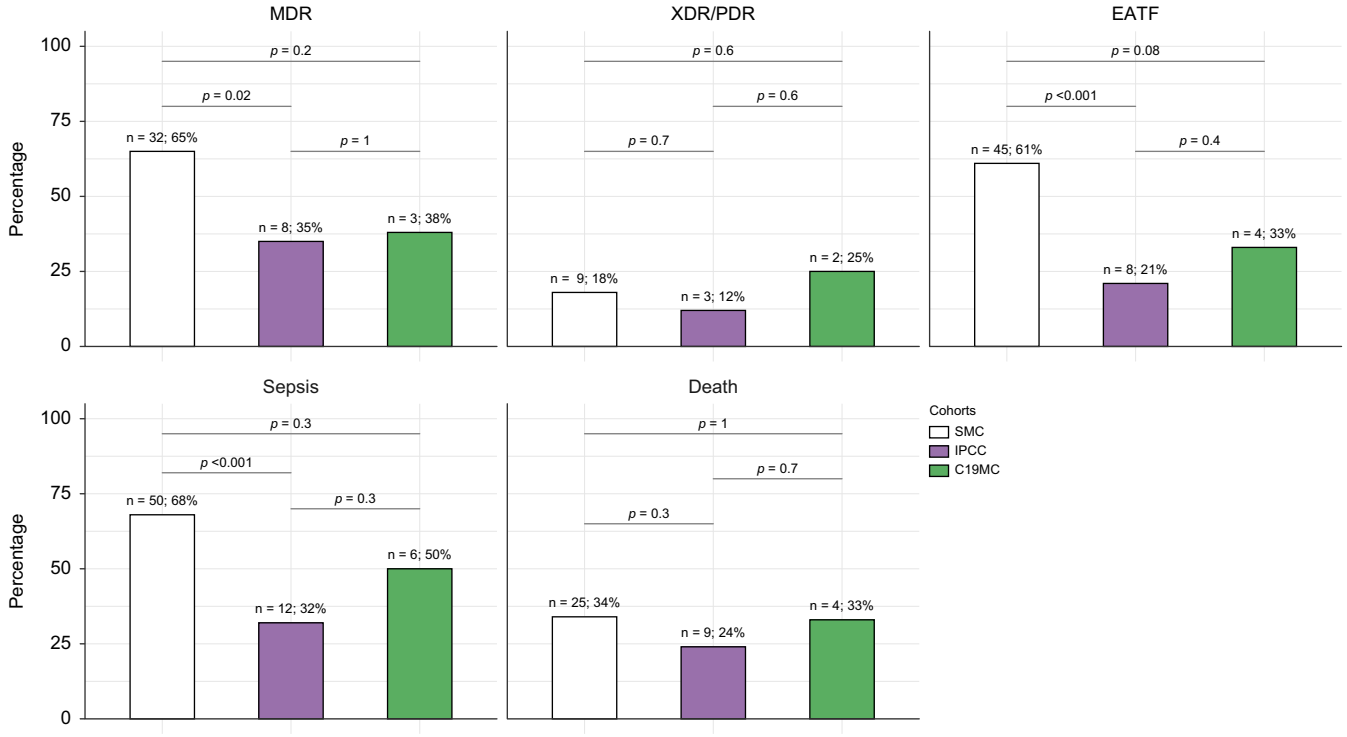

Fig. 2. The incidence of secondary outcomes among patients with hospital-acquired infections. MDR and XDR/PDR proportions are calculated only from populations of patients with successful bacterial isolation. The χ^2 test was used to evaluate the significance of distribution differences. Values of p <0.05 are significant. C19MC, COVID-19 measures cohort; EATF, empiric antibiotic treatment failure; IPCC, infection prevention and control cohort; MDR, multidrug resistance; SMC, standard measures cohort; XDR/PDR, extreme drug resistance/pandrug resistance.

and highlight the importance of preventing infections in patients with cirrhosis, especially in hospital settings.[11,13,15,16]

The present study was performed in a tertiary referral centre for liver diseases. The IPCP was based mainly on decreasing the patients' exposure to HAI risk factors and on cooperation with a dedicated specialist in infectious diseases to ensure antibiotic stewardship. To our knowledge, the impact of such a programme has not been previously evaluated in patients with liver cirrhosis in real clinical settings. Furthermore, we enrolled a cohort of patients with cirrhosis hospitalised during the COVID-19 lockdown, a period characterised by further restrictions imposed by the Hospital and Health Italian Sanitary System to minimise the spread of COVID-19. Therefore, we took this opportunity and investigated whether the COVID-19 measures further reduced the incidence of HAIs, as previously reported in populations of both patients with cirrhosis and those without cirrhosis.[17,18]

In our study, we were able to decrease the patients' exposure to risk factors previously linked to HAIs.[19–21] First, we effectively reduced the number of patients per room in accordance with hospital governance. This strategy increases the distance between patients and minimises the possibility of airborne, droplet, or contact pathogen transmission. However, we failed to limit the use of urinary catheters. The urinary catheter was frequently positioned in the emergency department before the patient was sent to our ward. However, we tried to remove urinary catheters as soon as they were unnecessary. We also adopted an upgraded type of catheter (Rush Teleflex Medical San BnD) associated with a lower risk of urinary tract infections. Finally, we also promoted improved bedside hand hygiene standards (the handwashing technique and the positioning of antiseptic gel dispensers within each patient room). Although we did not quantify the quality of the handwashing technique *per se*, we performed monthly audits to verify the healthcare personnel's compliance with it. It has also been reported that the positioning of antiseptic gel dispensers alone increased healthcare personnel compliance.[20] Importantly, none of these measures deviates from the standards of care recommended by the EASL Clinical Practice Guidelines.[14]

The most important finding of this study is that the implementation of the IPCP was associated with a lower incidence of HAIs. The proportion of patients with an HAI was 17% in the SMC cohort, whereas it significantly decreased in the IPCC cohort to as low as 8.9% (p <0.01). The baseline MELD was comparable in all three cohorts despite differences between them (such as the proportion of patients admitted with an infection or different reasons for admission). Notably, the effect of the IPCP remained significant even after controlling for these differences (confounding factors) in the multivariable logistic regression analysis (OR 0.44, 95% CI 0.26–0.73). Furthermore, the IPCP also decreased the prevalence of MDR organisms, the rate of empiric antibiotic treatment failure, and the development of septic states (p = 0.02, p <0.001, and p <0.001, respectively; Fig. 2). The less frequent empiric antibiotic treatment failure and the resulting low incidence of septic state developments were likely caused by the change in the antibiotic strategy itself: carbapenem and piperacillin–tazobactam were the empirical antibiotic treatments for HAIs. This strategy was also suggested in the most recent EASL Clinical Practice Guidelines.[14] Conversely, the IPCP was not associated with a decreased prevalence of XDR/PDR organisms or in-hospital mortality. However, these findings must

Table 5. Hospital-acquired infection characteristics and empirical antibiotic treatment.

Characteristic	SMC (n = 74)*	IPCC (n = 38)*	C19MC (n = 12)*	*p* value†
Successful bacterial isolation	50 (68%)	23 (61%)	10 (83%)	0.4
Gram stain				0.9
Gram-negative	25 (50%)	14 (64%)	5 (56%)	
Gram-positive	22 (44%)	7 (32%)	4 (44%)	
Gram-positive and gram-negative	3 (6.0%)	1 (4.5%)	0 (0%)	
Site of the infection				
UTI	27 (36%)	10 (26%)	4 (33%)	
Pneumonia	12 (16%)	10 (26%)	2 (17%)	
SBP	12 (16%)	2 (5.3%)	1 (8.3%)	
Spontaneous bacteraemia	3 (4.1%)	8 (21%)	2 (17%)	
Another	10 (14%)	1 (2.6%)	1 (8.3%)	
Colitis	1 (1.4%)	4 (11%)	2 (17%)	
Pneumonia + UTI	5 (6.8%)	1 (2.6%)	0 (0%)	
Cholangitis	3 (4.1%)	0 (0%)	0 (0%)	
Cholangitis + SBP	1 (1.4%)	0 (0%)	0 (0%)	
Pneumonia + SBP	0 (0%)	1 (2.6%)	0 (0%)	
UTI + SBP	0 (0%)	1 (2.6%)	0 (0%)	
Empiric antibiotic treatment				
Piperacillin-tazobactam	15 (20%)	14 (37%)	3 (25%)	
Fluoroquinolone	21 (28%)	1 (2.6%)	0 (0%)	
Carbapenem	9 (12%)	12 (32%)	0 (0%)	
Cephalosporine	17 (23%)	2 (5.3%)	0 (0%)	
Beta-lactam	8 (11%)	1 (2.6%)	0 (0%)	
Glycopeptide	3 (4.1%)	4 (11%)	1 (8.3%)	
Other	0 (0%)	3 (7.9%)	2 (17%)	
Carbapenem + glycopeptide	0 (0%)	1 (2.6%)	2 (17%)	
Piperacillin–tazobactam + glycopeptide	0 (0%)	0 (0%)	3 (25%)	
Cephalosporine + another	0 (0%)	0 (0%)	1 (8.3%)	
Cephalosporine + carbapenem	1 (1.4%)	0 (0%)	0 (0%)	

Values of p <0.05 are significant.
C19MC, COVID-19 measures cohort; IPCC, infection prevention and control cohort; SBP, spontaneous bacterial peritonitis; SMC, standard measures cohort; UTI, urinary tract infection.
* n (%).
† Fisher's exact test.

be interpreted with caution owing to small counts of events resulting in the low statistical power of tests.

During the pandemic, strict behavioural and hygiene precautions were imposed on hospital wards. Only one doctor or nurse could be present in a patient room at one time; the overall number of personnel in the ward was also severely limited, and visits from the outside were banned entirely. All healthcare personnel and patients wore masks, and contact was limited to what was necessary and was always carried out wearing disposable gloves. Furthermore, diagnostic procedures had to be strictly essential or even life-saving to be performed to reduce contact among patients.

There was no further reduction in the incidence of HAIs in the C19MC. This finding is not in accordance with studies demonstrating a significantly decreased incidence of HAIs during the COVID-19 outbreak.[15,16] One possible explanation of this finding is that many protective measures had already been applied in our ward (through the IPCP) before the COVID-19 measures were implemented in the Italian hospitals. Therefore, the additional value of COVID-19 measures was not statistically significant. Second, one of the critical measures of the IPCP – *i.e.* the continuous presence of a specialist in infectious diseases – had to be terminated to allocate them to individual COVID-19 departments. Third, no external nonpharmacological measures reduce the intensity of pathological bacterial translocation, which is one of the most important origins of bacterial infections in patients with cirrhosis. Last, although not analysed in our study, we can hypothesise that during the pandemic period, owing to the unavailability of caregivers and the sedentary lifestyle, the nutritional status of individuals with cirrhosis could have worsened, leading to a greater sensitivity to infections.

Interestingly, according to Bajaj *et al.*,[5] admission with infection is associated with a higher risk of HAI in patients with cirrhosis (OR 2.93, 95% CI 2.33–3.68). In our rather large series, there were 52 HAIs (42%) in patients already admitted with an infection, whether community-acquired or healthcare-associated. We demonstrated a similar nonsignificant trend in the univariable analysis (OR 1.46, 95% CI 0.95–2.21). However, multivariable analysis results show contradictory information concerning this relationship (OR 0.43, 95% CI 0.24–0.75). We can only hypothesise about the reason for such a discrepancy. From a statistical point of view, it could have resulted from model underspecification.[22] Bajaj *et al.*[5] included admission with infection, baseline WBC and MELD, and history of diabetes and lactulose use in their model to predict HAIs (area under the receiver operating characteristic curve = 0.70, 95% CI 0.67–0.73). Our model did not consider the history of diabetes and lactulose use because of nonsignificant results in univariable regression models. However, we included several other well-recognised risk factors, such as acute admission, instrumentation (abdominal paracentesis, urinary catheters, and other invasive procedures), the use of beta blockers, and the length of hospital stay. This multivariable analysis might have theoretically revealed the hidden relationship between admission with infection and the development of HAI. From a clinical point of view, this unexpected observation could have resulted from several different aspects. We think that rapid resolution of the first infection may result in a reduction in circulating pro-inflammatory molecules,

transiently improving immune system function and thus guaranteeing patients with cirrhosis 'a recovery period' during which they are less susceptible to bacterial infections. Another potential explanation is that patients admitted with community-acquired or healthcare-associated infections are at a greater risk of death and can die even before they develop a HAI. The true relationship between admission with infection and the development of a second HAI should be investigated in future research.

The present study has several potential limitations. We report a single-centre experience; therefore, further external studies are required to validate our results. Although we collected the data mostly prospectively, the SMC data collection was retrospective, which, without any mitigation measures, introduces a certain risk of bias. Third, the present study assessed in-hospital outcomes only. Patients were not followed up after discharge, which might have also introduced a potential bias. Furthermore, although adherence to most of the measures was not systematically measured, we are afraid that we are not able to determine which IPCP components are the most important in preventing HAI. However, this pilot study included a large number of patients with cirrhosis (almost a thousand). The strength of our findings comes from the demonstration that the incidence of HAI decreased during later periods (the IPCP and COVID-19 periods) and from the confirmation that the effect of the IPCP remained significant even after accounting for the effect of confounding variables in the multivariable regression analysis.

Conclusions

HAIs are frequent and severe complications that affect survival in patients with liver cirrhosis. HAIs present a growing healthcare problem because of the increasing prevalence of MDR organisms, which extends through all industrialised countries. The IPCP is a multiple strategy based mainly on antimicrobial stewardship and the reduction of patient exposure to risk factors. In summary, the IPCP decreased the incidence of HAIs in real life by nearly 50% in patients with liver cirrhosis. Furthermore, it resulted in a lower prevalence of MDR bacteria and a lower rate of empirical antibiotic treatment failure. Notably, the results were achieved without any deviations from the standards of care recommended by the EASL Clinical Practice Guidelines, and for the first time, they confirmed the importance of adopting these recommendations in real life. COVID-19 measures did not further reduce the incidence of HAIs. Based on the present findings, we encourage other liver centres to adopt the IPCP.

Abbreviations

ALD, alcoholic liver disease; BB, beta-blockers; C19MC, COVID-19 measures cohort; CA, community acquired; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; EATF, empiric antibiotic treatment failure; HAI, hospital-acquired infection; HCA, healthcare-associated; IPCC, infection prevention and control cohort; IPCP, infection prevention and control programme; MAP, mean arterial pressure; MDR, multidrug-resistant; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; OR, odds ratio; PDR, pandrug-resistant; PPI, proton pump inhibitor; SBP, spontaneous bacterial peritonitis; SMC, standard measures cohort; UTI, urinary tract infection; WBC, white blood cell; XDR, extensively drug-resistant.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: SDC, LL, MM. Acquisition of data: SDC, LL. Analysis and interpretation of data: SDC, JG, LL, GC, MM. Drafting of the article: SDC, JG, LL, MM. Critical revision of the manuscript for important intellectual content: MM. Approved the final version of the article: all authors

Data availability statement

The database used in this study will be made available from the corresponding author based on a reasonable request and respecting the European Privacy Law.

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Supplementary data

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Author names in bold designate shared co-first authorship.

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