A broad spectrum antibiotic therapy as empirical treatment in Healthcare-Associated infections improves survival in cirrhotic patients: a randomized trial

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Abbreviations used in this paper:

spontaneous bacterial peritonitis (SBP), Multidrug resistant (MDR), Health-care associated (HCA), Model for End-stage liver disease (MELD), urinary tract infections (UTI), clinically documented infections (CDI)

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ABSTRACT

Early diagnosis and appropriate treatment of infections in cirrhosis are crucial due to their high morbidity and mortality. Multidrug-resistant (MDR) infections are on the increase in healthcare settings. Healthcare-associated (HCA) infections are still frequently treated as community-acquired with a detrimental effect on survival. We aimed to prospectively evaluate in a randomized trial the effectiveness of a Broad Spectrum antibiotic treatment in cirrhotic patients with HCA infections. Consecutive cirrhotic patients hospitalized with HCA infections were enrolled. After culture sampling, patients were promptly randomized to receive a Standard or a Broad Spectrum antibiotic treatment (NCT01820026). The primary endpoint was in-hospital mortality. Efficacy, side effects and the length of hospitalization were considered. Treatment failure was followed by a change in antibiotic therapy. Ninety-six patients were randomized and 94 were included. The two groups were similar for demographic, clinical and microbiological characteristics. The prevalence of MDR pathogens was 40% in the Standard vs 46% in the Broad Spectrum group. In-hospital mortality showed a substantial reduction in the Broad Spectrum vs Standard group (6 vs 25%, p=0.01). In a post-hoc analysis the reduction of mortality was more evident in patients with sepsis. The Broad Spectrum showed a lower rate of treatment failure than the Standard therapy (18 vs 51%, p=0.001). The length of hospitalization was shorter in the Broad Spectrum (12.3 ± 7 days) vs Standard group (18 ± 15 days) (p= 0.03). Five patients in each group developed a second infection during hospitalization with a similar prevalence of MDR (50% Broad Spectrum vs 60% Standard).

Conclusions: A Broad Spectrum antibiotic therapy as empirical treatment in HCA infections improves survival in cirrhosis. This treatment was significantly effective, safe and cost-saving.

Keywords: cirrhosis, bacterial infection, sepsis, antibiotic therapy, treatment failure
Introduction

Bacterial infections are a frequent and life-threatening complication in chronic liver disease; despite the improvement in diagnostic and therapeutic measures, infection-related morbidity and mortality still play a prominent role in these patients\(^1\text{-}^4\). The most likely explanation for this persistent high mortality is the growing spread of multi-resistant pathogens with a consequent reduction in the rate of treatment success with empirical standard antibiotic therapies. This problem has been raised by several authors in the last decade\(^5\text{-}^8\).

A timely initiation of antibiotic treatment is strongly recommended in these patients, particularly in the case of severe infections. This recommendation arises from the observation that a delay in starting empirical antibiotics is associated with an increase in mortality of more than 7% per hour even in the general population\(^9\text{-}^{10}\).

The choice of an appropriate and effective empirical antibiotic regimen is also crucial. Several studies have demonstrated that antibiotic treatment failure is related to a poorer outcome in cirrhotic patients\(^8\text{-}^{11}\text{-}^{12}\).

However there is a time lag between microbiological sampling and pathogen identification and, in addition, many infections are culture-negative in cirrhotic patients.

Since 2000 third-generation cephalosporins have been considered the gold standard in the treatment of most infections in cirrhotic patients due to their effectiveness against enterobacteriaceae and non-enterococcal streptococci and their low hepatic and renal toxicity. However, these recommendations are based on the results of trials carried out in the '80s and '90s, when the epidemiological and microbiological characteristics of the infections were very different. In the last decade, Gram positive and multi-drug-resistant (MDR) pathogens have become more prevalent, particularly in a nosocomial setting, due to the progressive shift in care from home to health-care facilities\(^11\text{-}^{13}\). It is also conceivable that the continuous antibiotic pressure, either for treatment or prophylaxis, may lead to more resistant pathogens.
As a result of these observations, it can be inferred that the choice of antibiotic treatment needs to be based on epidemiological class, the presence of risk factors for MDR and the local microbiological pattern.

Recent international guidelines, updated in 2012, and an international position statement published in 2013 have suggested new therapeutic approaches to community acquired and nosocomial infections, although controlled studies are needed\textsuperscript{14-15}. Only a randomized, not blinded, controlled trial has been conducted recently in nosocomial Spontaneous Bacterial Peritonitis comparing a Standard therapy with a therapy that is active against MDR pathogens\textsuperscript{16}.

The growing evidence of a very high rate of antibiotic resistance (14-50\% in different countries) in HCA infections and their poor prognosis\textsuperscript{7,8,17-19} has sparked off a debate about the possible advantages or disadvantages of using a broader spectrum antibiotic treatment in these infections. To our knowledge, no controlled trials are available in this setting.

In the current study we tested, for the first time, the hypothesis that an empirical Broad Spectrum antibiotic treatment is better than the Standard therapy in the treatment of cirrhotic patients with HCA infections.

**Patients and methods**

**Eligibility criteria for participants**

After institutional review board approval and registration on clinicaltrial.gov (NCT01820026), patients were enrolled into the study after being informed and having given their written consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Our department has been part of a Hospital program of active research into infections since 2008\textsuperscript{3}. Eligible participants were cirrhotic patients consecutively admitted to our department,
a third referral centre, with a diagnosis of an HCA infection in September 2012. The diagnosis of cirrhosis was based on a liver biopsy, when available, and/or on clinical, biochemical, ultrasonography and endoscopic features. We classified the infections as HCA if the diagnosis was made at the time of hospital admission or within 48 hours of hospitalization in patients with any of the following criteria: a) the patient had attended a hospital or a haemodialysis clinic or received intravenous chemotherapy in the last 30 days, b) s/he was hospitalized for at least two days or had undergone surgery during the 90 days before infection or c) s/he had resided in a nursing home or a long-term care facility.20-21.

Exclusion criteria were age<18 years, advanced neoplasia (including hepatocellular carcinoma outside of the Milan criteria), a concomitant cause of immunosuppression (HIV, immunosuppressant therapy) or refusal to participate.

**Description of trial design**

**Baseline evaluation**

At admission, relevant baseline demographic, clinical and biochemical data were recorded. The severity of liver disease was assessed by using the Child–Pugh and the model of end-stage liver disease (MELD) scores. As far as the infectious screening on admission is concerned, all patients were investigated through: (a) their medical history and a physical examination focused on symptoms and signs of infection; (b) the measurement of blood pressure, heart rate, respiratory rate and body temperature; (c) laboratory tests including polymorphonucleated cell (PMNC) count, inflammatory markers, hepatic and renal function tests and urinalysis including fresh urine sediment; (d) analysis of biological fluids, when present (i.e. ascites, pleural effusion); (e) chest X-ray film; (f) abdominal ultrasound. Depending on the suspected site of infections, further investigations were carried out including cultures of blood, urine, sputum, ascitic and/or pleural fluid or purulent secretions.
SBP was defined as a polymorphonucleater cell count greater than 250/mm3 in the ascitic fluid ± a positive culture; pneumonia was defined as the presence of radiologic evidence of consolidation plus at least 2 of the following criteria: fever higher than 38°C or hypothermia less than 35°C, dyspnea, cough and purulent sputum, pleuritic chest pain or signs of consolidation on physical examination; urinary tract infections were diagnosed according to CDC/NHSN criteria without including asymptomatic bacteriuria\textsuperscript{22}; biliary tract infections, cellulitis and gastroenteritis were all diagnosed according to congruent symptoms and biochemical and imaging parameters following standard criteria\textsuperscript{3, 22} Evidence of a positive blood culture without a recognized site of infection was defined as spontaneous bacteremia.

Patients were considered to have systemic inflammatory response syndrome (SIRS) when they fulfilled the criteria established by international guidelines. Sepsis was diagnosed in the presence of SIRS and infection\textsuperscript{3}.

**Randomization**

After inclusion, patients were randomly assigned to one of two different empirical antibiotic treatments:

- **Standard Group**: mainly based on third generation- cephalosporins, depending on the site of infection (Table 1)

- **Broad Spectrum Group**: based on Imipenem/cilastatin, alone or in combination with other antibiotics, depending on the site of infection. (Table 1)

The antibiotic therapies had been established during the definition of the protocol of the study on the basis of:

1. a high safety profile in chronic liver disease
2. the recommended European guidelines for cirrhotic patients\textsuperscript{23} and for the treatment of hospital-acquired and/or HCA infections in the general population
3. availability and economic costs
The treatment was started within 24 hours from presentation at the emergency department and after culture sampling.

Patients were randomized using sealed opaque envelopes containing the treatment assignment in a 1:1 ratio.

Data collected during the study included: demographic information, origin of liver disease, clinical data about severity of liver cirrhosis and complications, biochemical parameters, comorbidities, site of infection, microbiological results (gram strains, type and antibiotic resistance, primary inflammatory markers, clinical events during hospitalization, duration of antibiotic treatment (days), side effects of the antibiotic therapy, length of hospital stay. All data were collected prospectively.

**Primary outcome**

The primary outcome of the study was hospital mortality. For this purpose all episodes of death and their causes were carefully recorded during hospitalization and factors associated with a higher mortality risk were investigated.

**Secondary outcomes**

Secondary outcomes were treatment failure, length of hospital stay and the occurrence of side effects.

Criteria for the definition of treatment failure were: (1) persistence of clinical signs of infection as well as positive biomarkers of infection including C-reactive protein and procalcitonin; 2) in cases of culture positive infections, antibiotic resistance to the antimicrobial susceptibility test and/or persistence of culture positive after 72 hours of antibiotic treatment; 3) in cases of culture negative infections conventional criteria were adopted according to Mandell et al; 4) in all cases of SBP, if the ascitic fluid neutrophil count failed to decrease to less than 25% of the pre-treatment value after 2 days of antibiotic treatment.
Following the diagnosis of treatment failure, the physician was allowed to change the antibiotic therapy in line with the microbiological data or the opinion of the consultant in infectious diseases.

**Statistical Analysis**

This is a prospective, not-blinded, randomized, clinical trial comparing two different antibiotic treatments. The primary end point of the study was in-hospital survival and this was used for sample size calculation. Considering an in-hospital mortality rate of 36% in patients with HCA infections\(^3\), we hypothesized that the use of Broad Spectrum antibiotics as the empirical first-line therapy could reduce the in-hospital mortality rate to 10% . As a result, forty eight patients were required in each group to guarantee a power of at least 80% with a probability of Type I error of 5%. The results in the Tables and text are presented as median ± IqR for continuous data and as proportions for categorical ones. The continuous numeric variables were examined by the parametric or non-parametric (Kruskall-Wallis test) ANOVA for independent samples, whilst association among categorical data was analysed by the Chi squared test. Binary outcomes were analysed by means of univariate and multivariate logistic regression. All tests were two tailed. P< 0.05 was considered to be statistically significant. The statistical analysis was made using the statistical software NCSS.

**Results:**

**Patients**

We considered 113 cirrhotic patients *in whom a HCA infection was suspected on admission*. Nine patients were excluded for hepatocellular carcinoma outside of the Milan criteria: 2 patients for recurrence of liver cirrhosis after organ transplantation following immunosuppressive therapy, 2 patients for steroid treatment for alcoholic hepatitis, 3 for non-liver advanced neoplasia and low life expectancy and one refused randomization. We,
therefore, randomized 96 patients with HCA infections. Two patients were randomized, but it was found afterwards that they failed to meet the eligibility criteria (two patients with neoplastic ascites). They were considered as a deviation from the study protocol and were excluded from the analysis. The study was, therefore, based on 94 patients, 48 in the Standard and 46 in the Broad Spectrum group. A flowchart of the patients assessed for eligibility and included in the study is given in Figure 1.

The mean age of the patients was 58 ± 12.6 years, the majority (71%) were males. The main origin of liver disease was hepatitis C in 46%, hepatitis B in 6% and alcohol abuse in 25%. The majority of patients had decompensated liver disease (53% Child-Pugh B, 36% Child-Pugh C) and a MELD median score of 15 (6-32). Twenty-six patients had a diagnosis of hepatocellular carcinoma that met the Milan criteria.

The patients included in the two randomized groups had similar demographic, clinical and biochemical characteristics. There was a prevalence of chronic kidney disease and a Child-Pugh score that tended to be higher in the patients randomized to the Standard therapy, but the difference was not statistically significant (Table 2).

Infections

Urinary tract infections (UTI) (n=33; 46%), spontaneous bacterial peritonitis (SBP) (n=21; 22%) and pneumonia (n=18; 19%) were the more prevalent infections.

Sixty episodes (64%) were microbiologically documented. Gram negative pathogens were isolated in 39 cases (65% of the culture-positive episodes) and a MDR pathogen was identified in 26 cases (43% of isolates). Ten patients (12% of group 1 and 9% of group 2) developed a second episode of infection during hospitalization with a similar prevalence of MDR (60% in Standard vs 50% in Broad Spectrum). The epidemiological and microbiological characteristics of the two groups of patients are shown in Table 3.
Empirical treatment and outcomes

Primary endpoint

Fifteen patients died during hospitalization (9 for sepsis, 4 for a deterioration in the liver function and 2 for variceal bleeding). In-hospital mortality was significantly higher in the Standard than in the Broad Spectrum Group (25 vs 6%; p=0.01). Higher mortality in the Standard group was observed for all sites of infection (UTI 21 vs 0%, pneumonia 30 vs 20%, PBS 33 vs 11%).

In the univariate analysis, in-hospital mortality was higher in patients with sepsis (71 vs 38%, p=0.02) and in those with MELD >15 (15 ± 4.9 vs 18.2 ± 5.7; p=0.04), but not in those with a higher Child-Pugh score (7.9±1.4 vs 8.6 ± 1.3; p=0.3) or comorbidities (chronic renal disease or diabetes). For the series of patients as a whole, a multivariate analysis confirmed that the Standard antibiotic therapy (p=0.03; OR 4.6; IC 1.15-18.5) and a diagnosis of sepsis (p=0.039; OR 3.8; IC 1.1-13.9), but not the MELD score (p=0.25, OR 1.06; IC 0.9-1.2), were independent negative prognostic factors.

In the group of patients randomized to the Standard therapy, according to the latter results, the presence of sepsis showed a negative prognostic relevance irrespective of the site of infection: in-hospital mortality was 57% vs 0% for UTI, 40% vs 0% for SBP and 43% vs 28% for pneumonia in patients with and without sepsis, respectively.

When the infection was not complicated by sepsis, the benefit derived from the use of Broad Spectrum antibiotics was blunted. The mortality rate was, in fact, generally low in both groups (6% vs 0% for UTI, 25% vs 15% for SBP and 0% vs 0% for pneumonia in patients randomized in the Standard and Broad Spectrum groups, respectively).

Secondary endpoints
As far as the response to the empirical antibiotic treatment is concerned, we observed a higher treatment failure in the Standard than in the Broad Spectrum Group (51 vs 18%; p=0.001). The higher rate in the Standard group was similar for all sites of infections (UTI 50 vs 22%, pneumonia 40 vs 22%, SBP 40 vs 20%).

In the subgroup of patients with a culture-positive infection, the rate of therapeutic failure was 56% in the Standard vs 19% in the Broad Spectrum Group (p=0.0002), while in the subgroup of patients who were not microbiologically documented, the rate of therapeutic failure was 63% vs 20%, respectively (p=0.0007).

The length of hospitalization was also longer in the Standard Group (18 ± 15 days) than in the Broad Spectrum Group (12.3 ± 7 days) (p= 0.03).

Only one patient showed a side effect of the antibiotic treatment: this was a patient whose renal function deteriorated following the administration of vancomycin, but showed a prompt recovery after discontinuation.

**Discussion**

The individuation of adequate empirical antibiotic treatment for bacterial infections in cirrhosis is important because of the high mortality related to this complication. It is a continuous challenge due to the progressive evolution of pathogens and their antibiotic resistances. An increase in the prevalence of multi-resistant pathogens has been documented in the last decades in HA and in HCA infections in several countries. This microbiological pattern explains the increasing rate of therapeutic failure and the poor prognosis when these patients are treated with first line Standard antibiotic treatment. Based on these observations, a different therapeutic approach (with broad spectrum antibiotics) has been
suggested for patients with HA infections\textsuperscript{14,16,23}. To our knowledge, no specific indications exist for the antibiotic treatment of HCA bacterial infections in hospitalized cirrhotic patients.

The present study compares for the first time a Standard vs a Broad Spectrum empirical antibiotic therapy in cirrhotic patients with HCA infections. The proposed new therapeutic approach significantly reduced in-hospital mortality in these patients. The improvement in survival was the result of the higher therapeutic success, with infection resolution for all sites of infection. The advantage of the Broad Spectrum antibiotic therapy was probably related to their efficacy on MDR pathogens; in fact, this effect was well documented in the culture positive infections.

The rate of in-hospital mortality with the Standard therapy (25\%) was comparable to our initial assumption (30\%) based on a previous study\textsuperscript{3}; the Broad Spectrum antibiotic therapy reduced mortality to 6\%, thus reaching the target that had been set initially (66\% reduction).

In addition to the antibiotic treatment, sepsis was selected as an independent predictor of in-hospital mortality in our series. The prognostic relevance of sepsis was documented for all sites of infections. In fact, when sepsis coexisted, mortality was significantly increased. In a post-hoc analysis the beneficial effect of the Broad Spectrum antibiotics was evident in patients with sepsis.

As a relevant secondary end-point of the study, we can also report on a reduction in the length of hospitalization in patients treated with Broad Spectrum antibiotics which represents significant cost saving.

The results of the present study suggest how to optimize the empirical antibiotic therapy in HCA infections in cirrhotic patients; this is a crucial point as the main relevant infections in these patients (pneumonia and SBP) are often culture negative (approx 50\% in our series) which does not allow a targeted therapy. Furthermore, any delay in the start of the therapy during a bacterial infection may prove to be detrimental.
We believe our study shows very relevant results with an important message, though it does have some limitations: (1) the study was monocentric. We originally planned for a multicenter study but, as it was an unsponsored interventional study, other Hospitals refused to take part in it. In fact, despite the inclusion of antibiotics that are readily available in hospital settings, with a similar economic impact, further economic coverage was frequently required. (2) the study was not double blind. (3) The findings of our study cannot be fully generalized, particularly since this study was conducted in a country with a high prevalence of MDR bacteria (in terms of ESBL-producing bacteria, carbapenemases producing Gram negative bacilli, and MRSA) both in the community and in hospital settings. Thus, further multicenter studies are probably needed to assess the risk factors associated with a MDR etiology in cirrhotic patients developing a healthcare-associated infection.

Some concerns may arise from the possibility that empirical Broad Spectrum antibiotic treatment in cirrhotic patients may be a cause of further antibiotic resistance by selecting “carbapenemasi producing bacteria”. Although the problem of overusing broad-spectrum antibiotics is real, the risk-benefit ratio needs to be taken into account. In our series we observed a similar rate of second infection during hospitalization for both groups. In second infections antibiotic resistance was similar in patients who had received either Standard or Broad Spectrum antibiotic therapy, supporting the fact that the latter regimen was not implicated in causing further antibiotic resistance. Moreover, as recently proposed, a prompt de-escalation of antibiotic therapy with broad spectrum antibiotics to a non carbapenem-beta lattamic antibiotic in the case of the individuation of non MDR could also help to limit the selection of antibiotic resistances.27

In conclusion, our study has shown that a broad spectrum antibiotic therapy as empirical treatment in HCA infections improves survival in cirrhotic patients. This treatment proved to be significantly effective, safe and cost-saving.
References


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Table 1. Empirical antibiotic protocol for HCA infections: Standard vs Broad Spectrum.

(Doses were always adjusted according to renal function).

<table>
<thead>
<tr>
<th>Sites</th>
<th>Standard treatment</th>
<th>Broad Spectrum treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous peritonitis</td>
<td>Cefotaxime (2 g/8 h IV)</td>
<td>Imipenem/cilastatin (500 mg/6h IV) + Vancomycin (1 g/12 h IV)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous bacteremia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Amoxicillin/clavulanic acid (2.2 g /8h IV) or Ciprofloxacin (500 mg/12h PO) (if no quinolone prophylaxis)</td>
<td>Imipenem/cilastatin (500 mg /6 h IV)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Amoxicillin/clavulanic acid (2.2 g /8h IV) + Azitromycin (500mg /24h PO)</td>
<td>Imipenem/cilastatin (500 mg iv/6 h) + Vancomycin (1 g/12h IV) + Azitromycin (500 mg/24h PO)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Amoxicillin/clavulanic acid (2.2 g /8h IV)</td>
<td>Imipenem/cilastatin (500 mg/6h IV) + Tygecillin (50 mg/12 h IV after a load dose of 100 mg)</td>
</tr>
</tbody>
</table>
Table 2. Demographical, clinical, biochemical and infective characteristics of the 2 groups of patients.

<table>
<thead>
<tr>
<th></th>
<th>Standard group (48)</th>
<th>Broad Spectrum group (46)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 (54-60)</td>
<td>58.5 (54-65)</td>
<td>0.8</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>31 (65)</td>
<td>36 (78)</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>18 (37)</td>
<td>16 (35)</td>
<td>0.8</td>
</tr>
<tr>
<td>Chronic Kidney Disease, n (%)</td>
<td>8 (17)</td>
<td>3 (6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Origin of liver disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol, n (%)</td>
<td>15 (31)</td>
<td>9 (20)</td>
<td>0.3</td>
</tr>
<tr>
<td>HCV-related, n (%)</td>
<td>21 (44)</td>
<td>22 (48)</td>
<td></td>
</tr>
<tr>
<td>HBV-related, n (%)</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>8 (17)</td>
<td>13 (28)</td>
<td></td>
</tr>
<tr>
<td>Active alcoholabuse, n (%)</td>
<td>9 (19)</td>
<td>11 (24)</td>
<td>0.54</td>
</tr>
<tr>
<td>Gastrointestinal bleeding n, (%)</td>
<td>3 (6)</td>
<td>5 (10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Ascites, n (%)</td>
<td>40 (83)</td>
<td>36 (78)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hepaticencephalopathy, n (%)</td>
<td>16 (33)</td>
<td>18 (39)</td>
<td>0.5</td>
</tr>
<tr>
<td>Child Pugh Score</td>
<td>9 (8-9)</td>
<td>8 (7-8)</td>
<td>0.08</td>
</tr>
<tr>
<td>MELD Score</td>
<td>15.5 (14-17)</td>
<td>15 (13-16)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hpatocellular carcinoma, n (%)</td>
<td>16 (33)</td>
<td>10 (22)</td>
<td>0.2</td>
</tr>
<tr>
<td>Seruomalbumin (mg/dL)</td>
<td>3 (2.7-3.2)</td>
<td>3.15 (2.8-3.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>International Normalized Ratio</td>
<td>1.33 (1.26-1.6)</td>
<td>1.4 (1.29-1.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1 (0.8-1.1)</td>
<td>1 (0.9-1.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hyponatremia, n (%)</td>
<td>10 (21)</td>
<td>8 (17)</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Table 3. Characteristics of the infections in the 2 groups of patients.

<table>
<thead>
<tr>
<th></th>
<th>Standard Group (48)</th>
<th>BroadSpectrum Group (46)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infections, n (%)</td>
<td>22 (46)</td>
<td>21 (46)</td>
<td>0.98</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>9 (19)</td>
<td>9 (20)</td>
<td>0.92</td>
</tr>
<tr>
<td>Spontaneous bacteraemia, n (%)</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>0.6</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis, n (%)</td>
<td>10 (21)</td>
<td>11 (24)</td>
<td>0.7</td>
</tr>
<tr>
<td>Cholangitis, n (%)</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>0.7</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>23 (47)</td>
<td>19 (41)</td>
<td>0.5</td>
</tr>
<tr>
<td>C-Reactive protein (mg/dL)</td>
<td>2.2 (1.5-3)</td>
<td>1.8 (1.2-3)</td>
<td>0.43</td>
</tr>
<tr>
<td>Positive cultures, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. Coli</td>
<td>15</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>K. Pneumoniae</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>P. Mirabilis</td>
<td>1</td>
<td>0</td>
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<tr>
<td>P. Aeruginosa</td>
<td>0</td>
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</tr>
<tr>
<td>Enterococcus</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>S. Aureus</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Multidrugresistant, n (%)</td>
<td>12 (40)</td>
<td>14 (47)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Legend of Figure

Figure 1. Study flow-chart

Figure 1. Flowchart of the study
Assessed for eligibility (n=113)

Excluded (n=17):
- Declined to participate (n=1)
- Not meeting inclusion criteria (n=16):
  - Hepatocellular carcinoma out of Milan criteria (n=9)
  - Non liver advanced neoplasia (n=3)
  - Immunosuppressive therapy (n=4)

Randomized (n=96)

Allocated to Standard antibiotic therapy (n=48)
- Analyzed (n=48)

Allocated to Broad Spectrum antibiotic therapy (n=48)
- Excluded for deviation of protocol (n=2): neoplastic ascites (n=2)
  - Analyzed (n=46)