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ORIGINAL RESEARCH

A cost analysis of a broad-spectrum antibiotic therapy in the empirical treatment of health care-associated infections in cirrhotic patients

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Background: Early diagnosis and appropriate treatment of infections in cirrhosis are crucial. As new guidelines in this context, particularly for health care-associated (HCA) infections, would be needed, we performed a trial documenting whether an empirical broad-spectrum antibiotic therapy is more effective than the standard one for these infections. Because of the higher daily cost of broad-spectrum than standard antibiotics, we performed a cost analysis to compare: 1) total drug costs, 2) profitability of hospital admissions.

Methods: This retrospective observational analysis was performed on patients enrolled in the trial NCT01820026, in which consecutive cirrhotic patients with HCA infections were randomly assigned to a standard vs a broad-spectrum treatment. Antibiotic daily doses, days of treatment, length of hospital stay, and DRG (diagnosis-related group) were recorded from the clinical trial medical records. The profitability of hospitalizations was calculated considering DRG tariffs divided by length of hospital stay.

Results: We considered 84 patients (42 for each group). The standard therapy allowed to obtain a first-line treatment cost lower than in the broad-spectrum therapy. Anyway, the latter, being related to a lower failure rate (19% vs 57.1%), resulted in cost saving in terms of cumulative antibiotic costs (first- and second-line treatments). The mean cost saving per patient for the broad-spectrum arm was €44.18 (–37.6%), with a total cost saving of about €2,000. Compared to standard group, we observed a statistically significant reduction in hospital stay from 17.8 to 11.8 days ($p<0.002$) for patients treated with broad-spectrum antibiotics. The distribution of DRG tariffs was similar in the two groups. According to DRG, the shorter length of hospital stay of the broad-spectrum group involved a higher mean profitable daily cost than standard group (€345.61 vs €252.23; +37%).

Conclusion: Our study supports the idea that the use of a broad-spectrum empirical treatment for HCA infections in cirrhosis would be cost-saving and that hospitals need to be aware of the clinical and economic consequences of a wrong antibiotic treatment in this setting.

Keywords: profitability, diagnosis-related group, cost saving, antibiotic failure

Introduction

Bacterial infections occur in about one-third of hospitalized cirrhotic patients, with an incidence 4–5-fold higher than in hospitalized patients with other diseases.[1,2]

The main types of infections in those patients are spontaneous bacterial peritonitis (25%–31%), urinary tract infection (20%–40%), pneumonia (15%–21%), and bacteremia (12%).[2–4]

Bacterial infections in cirrhosis are associated with poor outcomes (mortality is higher about 4 times), accounting for about 30%–50% of deaths in cirrhotic patients.[5–8]

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The prognosis is particularly severe in the absence of prompt adequate therapeutic treatment.[9–11] Early diagnosis and appropriate empirical treatment of infections in cirrhosis are crucial; a delay in starting antibiotic therapy is associated with a relevant mortality increasing by the hour.[12,13]

Since 2000, third-generation cephalosporins have been considered the gold standard in the treatment of most infections in patients with cirrhosis because of their effectiveness against Enterobacteriaceae and non-enterococcus streptococcus and also because of their low hepatic and renal toxicity.

However, these recommendations were based on the results of trials carried out in the 1980s and 1990s, when the epidemiological and microbiological characteristics of the infections were very different. In the last decade, in fact, gram-positive and multidrug-resistant (MDR) pathogens have become more prevalent, particularly in the nosocomial setting, as a result of the progressive shift in care from home to health care facilities.[14–17]

In a large prospective study on cirrhotic patients with infections, multiresistant bacteria (18%) were isolated in 4% of community-acquired (CA) and 35% of hospital-acquired (HA) infections.[2] In the more recently individuated epidemiological class, including infections occurring in patients who had previous recent contacts with the health care system (health care-associated [HCA] infections), a rate of 14% of MDR was reported in cirrhotic patients.[14–16]

As a consequence, the efficacy of empirical antibiotic treatment progressively decreased from CA to HCA and HA infections.[9]

From these observations, it can be inferred that the choice of an antibiotic treatment needs to be more accurate and personalized 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 CA and HA infections.[12,17]

The high rate of antibiotic resistance (14%–50% in different countries) in HCA infections, and their poor prognosis has sparked off a debate about the possible advantages or disadvantages of using a broad-spectrum antibiotic as a first-line treatment in these infections.[9,12,15,16] No controlled trials were available on this matter, and HCA infections are still usually treated as CA with a detrimental effect on survival. No specific guidelines or indications are available at present for HCA infections.

For this reason, in a recent study, for the first time, the hypothesis was tested that an empirical broad-spectrum antibiotic treatment would be more effective than the standard therapy in the treatment of cirrhotic patients with HCA infections. A randomized trial (NCT01820026) was performed in which 96 consecutive patients with cirrhosis hospitalized with HCA infections were randomized to receive a standard (48 patients) or a broad-spectrum (48 patients) antibiotic treatment.[18] In this study, the broad-spectrum therapy was associated to a lower rate of failure than the standard therapy (18% vs 51%; $p<0.001$). Compared with standard therapy, broad-spectrum therapy showed a substantial reduction in the rate of in-hospital mortality and in the length of hospital stay. Moreover, in a post hoc analysis, reduction of mortality was more evident in patients with sepsis.

Because of the higher daily cost of broad-spectrum antibiotics than standard antibiotics, we performed a cost analysis in order to evaluate the medical direct costs of the two antibiotic treatments. The primary aim of the cost analysis was the comparison of total drug costs and length of hospital stay upon using a broad-spectrum antibiotic therapy with respect to using standard antibiotic therapy. Secondarily, the profitability of hospital admissions (remuneration per inpatient day) with patients treated with broad-spectrum or standard therapy was estimated.

Methods

Clinical data

This retrospective observational cost analysis was performed on patients enrolled in the clinical trial approved by our institutional review board (Policlinico Umberto I Ethics Committee) and registered on clinicaltrial.gov (NCT01820026).[18] This trial considered patients with cirrhosis with a diagnosis of a HCA infection consecutively admitted to the referral center for advanced liver diseases, from September 2012 to February 2016. The diagnosis of cirrhosis was based on a liver biopsy, when available, and/or on clinical, biochemical, ultrasonography, and endoscopic features, and exclusion criteria were age <18 years; advanced neoplasia, including hepatocellular carcinoma outside of the Milan criteria (presence of a single HCC nodule with maximum size of 5 cm, or as many as three nodules with the largest not exceeding 3 cm and no macrovascular invasion); a concomitant cause of immunosuppression; or refusal to participate.

After obtaining written informed consent, 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) and broad-spectrum group (based on imipenem–cilastatin, alone or in combination with other antibiotics, depending on the site of infection).[18]

Patients selection

The present cost analysis was performed on 84 (42 for each group) out of 96 patients randomized in the clinical trial (NCT01820026) to obtain two comparable cohorts (ie, infectious sites, number of episodes). Table 1 reports the main characteristics (demographical, clinical, biochemical, and infective) of the two groups.

Definitions

Infections

Spontaneous bacterial peritonitis was defined as a polymorphonuclear cell count greater than 250/mm^3 in the ascitic fluid ± a positive culture; pneumonia was defined as the presence of radiologic evidence of consolidation plus at least two 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 in presence of leucocyturia and positive culture without including asymptomatic bacteriuria. The evidence of a positive blood culture without a recognized site of infection was defined as spontaneous bacteremia.

Comorbidities

A diagnosis of diabetes mellitus type 2 was done in case of one of the following: 1) fasting plasma glucose level of 126 mg/dL or higher, or 2) a 2-hour plasma glucose level of 200 mg/dL or higher during a 75-g oral glucose tolerance test, or 3) a random plasma glucose of 200 mg/dL or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.

The diagnostic criteria for organic chronic renal failure were the presence of either kidney damage or a decreased glomerular filtration rate of less than 60 mL/min/1.73 m^2 for at least 3 months.

Cost analysis

To perform the cost analysis, the following data were collected from the clinical trial medical records: antibiotic daily dose (number of vials), days of treatment, length of hospital stay, and DRG (diagnosis-related group).

The cost of antibiotics treatment was calculated multiplying the cost of vials by the related number of vials and days of treatment. The total cost of antibiotic therapy for each patient was the sum of costs calculated for all antibiotics received during the hospitalization period. The price of antibiotics was based on official ex-factory prices per vial in Umberto I Hospital.

The profitability of hospitalizations was calculated considering the related DRG tariffs. In particular, for each group, the total amount (DRG tariff) reimbursed for the hospitalizations was divided by the length of hospital stay (days of hospitalization) reported in medical records. The DRGs considered in the present analysis were DRG202

Table 1 Demographic, clinical, and infectious characteristics of patients treated with standard vs broad-spectrum therapy

Main characteristics	Standard group (n=42)	Broad-spectrum group (n=42)	*p*-value
Age (years), mean (range)	57.5 (53–60)	58 (53–65)	n.s.
Male, n (%)	31 (74)	31 (74)	n.s.
Diabetes mellitus, n (%)	16 (38)	14 (33)	n.s.
Organic renal failure, n (%)	5 (12)	3 (7)	n.s.
Active alcohol abuse, n (%) (>3 alcohol units/day for man; >2 alcohol units/day for woman)	8 (19)	9 (21)	n.s.
Child–Pugh score, mean ± SD	8.8+1.6	8.3+1.4	n.s.
MELD score, mean ± SD	16.6+5.5	15.3+4.6	n.s.
Hepatocellular carcinoma, n (%)	16 (33)	10 (22)	n.s.
Urinary tract infections, n	22	21	n.s.
Pneumonia, n	9	9	n.s.
Spontaneous bacteremia, n	1	1	n.s.
Spontaneous bacterial peritonitis, n	10	11	n.s.
Sepsis, n (%)	22 (53)	19 (44)	n.s.
C-reactive protein (mg/dL), mean (range)	2.1 (1.6–2.9)	1.9 (1.4–3)	n.s.
Positive cultures, n (%)	27 (64)	28 (67)	n.s.
Gram negative, n (%)	19 (70)	18 (64)	n.s.
Gram positive, n (%)	8 (30)	10 (36)	
Multidrug resistant, n (%)	11 (41)	12 (43)	n.s.

Abbreviations: n.s., not statistically significant; MELD, Model for End-Stage Liver Disease; SD, standard deviation.

"Liver cirrhosis and alcoholic hepatitis" and DRG203 "Malignant hepatobiliary or pancreatic neoplasia," as indicated in medical records. For a hospital stay within 27 days, the reimbursement for DRG202 was €4,013, and when the threshold was passed an additional cost per day of €185 was added to the tariff. The tariff reimbursed for DRG203 was €4,085, considering a length of hospital stay of 35 days, and the additional cost per day over the threshold was €173.

Statistical analysis

Continuous data are expressed as means ± standard deviations or medians with ranges according to the distribution of the variables. Categorical data are expressed as numbers and percentages. The significance of the differences between groups was evaluated by the Kruskal–Wallis test or χ^2 test. All tests were two-tailed. A p-value<0.05 was considered statistically significant. The statistical analysis was made using the statistical software NCSS.

Results

Eighty-four patients were considered. The mean age of the patients was 57.7±12.6 years; the majority (74%) were males. The main origin of liver disease was hepatitis C in 49%, hepatitis B in 7%, and alcohol abuse in 28%. The majority of patients had decompensated liver disease (82% Child–Pugh B-C) and a Model for End-Stage Liver Disease median score of 15.7 (range, 6–31). Twenty-six patients had a diagnosis of HCC that met the Milan criteria.

As shown in Table 1, the patients included in the two randomized groups had similar demographic, clinical, biochemical, and infectious characteristics.

Primary endpoint: costs evaluation of antibiotic treatments

Table 2 shows the results of the cost comparison between standard and broad-spectrum treatment groups. The results are reported as mean cost per patient treated and total cost per group, separately for first line of treatment (randomization), second line of treatment (subsequent treatment in case of failure), and total antibiotic treatment. As shown in Table 2, the standard therapy allowed to obtain a first-line treatment cost lower than in the broad-spectrum therapy; however, the latter, being related to a lower rate of treatment failure (19.0% vs 57.1%), resulted in cost saving by considering also the costs of second-line treatments. The mean cost saving per patient for the broad-spectrum arm was €44.18 (–37.6%), with a total cost saving (42 patients) of about €2,000.

Secondary endpoint: profitability of hospital admissions

Compared to standard group, we observed a statistically significant reduction in hospital stay from 17.8 to 11.8 days (p<0.002) for patients treated with broad-spectrum antibiotics. The distribution of DRG tariffs was similar in the two groups (standard therapy: DRG202 69.0% DRG203 31.0%; broad-spectrum therapy: DRG202 71.0% DRG203 29.0%). Table 2 shows the profitability of hospital admissions (mean profitable daily cost) for standard and broad-spectrum groups. According to the DRG tariffs considered, the shorter length of hospital stay associated with the broad-spectrum group involved a higher mean profitable daily cost in comparison to the standard group (€345.61 vs €252.23; +37.0%).

Discussion

The identification of an adequate empirical antibiotic treatment for bacterial infections in cirrhosis is important because of the high mortality related to this complication. This problem is particularly relevant in the setting of HCA infections because of their high rate of MDR given the usual practice to treat them similarly to CA.[10,11,16,19]

The lack of a prompt and adequate empirical treatment significantly increases mortality, need of further treatments,

Table 2 Costs, length of hospitalization, and profitability of first- and second-line standard vs broad-spectrum antibiotic treatments

Variables	Line of treatment	Standard (A)	Broad-spectrum (B)	Difference B–A
Mean cost per patient	First line	€8.78	€85.00	€76.22
	Second line	€152.81	€32.43	–€120.39
	Total	€161.59	€117.43	–€44.17
Overall costs	First line	€368.72	€3,570.00	€3,201.28
	Second line	€6,418.20	€1,361.90	–€5,056.30
	Total	€6,786.90	€4,931.90	–€1,855.00
Total days of hospitalization		746	495	–251
Total amount of DRG tariffs		€188.20	€171.10	–€17.1
Mean length of hospital stay (days)		17.8	11.8	–6
Mean profitable daily cost		€252.20	€345.20	–€93

Abbreviations: DRG, diagnosis-related group.

rate of complications, and length of hospital stay. No specific indications exist for antibiotic treatment of HCA bacterial infections in cirrhotic patients.

A clinical trial was performed to compare standard antibiotic therapy with broad-spectrum empirical antibiotic therapy in cirrhotic patients with HCA infections. The broad-spectrum approach significantly reduced in-hospital mortality vs standard therapy (12% vs 31%; $p<0.01$). The improvement in survival was the result of the lower therapeutic failure (broad spectrum 19%; standard 57%), with infection resolution for all infectious sites. The need of a second-line treatment and the length of hospital stay were lower in the broad-spectrum group. As a consequence of the above reported clinical results, we performed a cost analysis focused on antibiotic treatment (broad-spectrum therapy vs standard therapy) and hospitalization costs (DRG tariffs).

The cost savings per each patient treated with the broad-spectrum therapy, compared with the standard therapy, were attributable to the lower failure (second-line treatment), which represents the main driver in the reduction of treatment costs. The mean cost per patient treated was €117.43 with broad-spectrum therapy and €161.59 with standard therapy. The total cost to treat all patients in broad-spectrum group (n=42) was 4,931.90, and it was 6,786.92 to treat all patients in standard group (n=42). Although standard therapy led to treatment costs lower than the broad-spectrum one in terms of first-line treatment, the latter, being related to a lower rate of treatment failure, was cost saving, considering the treatment costs of second-line treatments. The broad-spectrum therapy cost saving for total antibiotic treatment (first and second line) was 37.6%.

The profitability of hospital admissions, calculated on DRG tariffs, for patient treated with broad spectrum was higher than standard therapy (€345.61 vs €252.23). The lower length of hospital stay of broad-spectrum therapy (11.8 days vs 17.8 days) determined a 37% higher "hospital admissions daily-profitability" compared with standard group.

Unfortunately, since similar analyses are currently not available in the medical literature, and so it is not possible to compare the results obtained in this cost analysis with the results from other studies.

A possible limitation in the current analysis could be attributed to the use of DRG tariffs as a "proxy" for the hospitalization costs. However, data obtained through DRG tariffs represents a valid source for carrying out a cost analysis on the profitability of hospital admissions. Another limitation is that the present results cannot be fully generalized, since the clinical trial we referred to was monocentric and conducted in a country with a high prevalence of MDR bacteria.

Conclusion

This study supports the idea that the use of a broad-spectrum empirical treatment for HCA infections in cirrhosis would be cost-saving and that hospitals need to be aware of the clinical and economic consequences of a wrong antibiotic treatment of these diseases.

Disclosure

The authors report no conflicts of interest in this work.

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