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RESEARCH ARTICLE

REVISED The need for antibiotic stewardship and treatment standardization in the care of cirrhotic patients with spontaneous bacterial peritonitis – a retrospective cohort study examining the effect of ceftriaxone dosing [v2; ref status: indexed, http://f1000r.es/3se]

Previously titled: Dosing of ceftriaxone and outcomes after spontaneous bacterial peritonitis

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Abstract

Background: Spontaneous bacterial peritonitis (SBP) is a common, often fatal affliction for cirrhotic patients. Despite all clinical trials of ceftriaxone for SBP using 2g daily, it is often given at 1g daily.
Aim: We evaluated survival after SBP as a function of ceftriaxone dosage.
Methods: A retrospective cohort of all patients who received ceftriaxone for SBP (greater than 250 neutrophils in the ascites).
Results: As opposed to 1 gram, median survival is longer for patients receiving 2 grams (228 days vs. 102 days (p = 0.26) and one year survival is significantly higher (p = 0.0034). After adjusting for baseline Model for End Stage Liver Disease (MELD) score, however, this difference was no longer significant. Similarly, there was a significantly shorter length of intensive care for patients receiving 2 g (0.59 ± 1.78 days vs. 3.26 ± 6.9, p = 0.034), odds ratio 0.11 (95% CI 0.02 - 0.65). This difference, too, was no longer significant after controlling for the MELD score - odds ratio 0.21 (95% CI 0.04 - 1.07). Additionally, 70% of patients received at least one additional antibiotic; over 25 different medications were used in various combinations.
Conclusions: Patients receiving 2 g of ceftriaxone may require fewer intensive care days and may enjoy an improved survival compared to those receiving 1 g daily. The complexity of antibiotic regimens to which cirrhotic patients are exposed must be studied further and rationalized. We recommend fastidious antibiotic stewardship for patients with cirrhosis. Efforts should be made to craft local standards for the treatment of SBP that include appropriate antibiotic selection and dose.

Open Peer Review

Invited Referee Responses

	1	2	3
version 1 published 14 Feb 2014	? report 1	? report 1	? report 1
version 2 published 14 Jul 2014 REVISED			✓ report

1 **José Castellote**, Hospital Universitari de Bellvitge Spain

2 **Manuela Merli**, Sapienza University of Rome Italy

3 **Andres Cardenas**, University of Barcelona Spain

Latest Comments

No Comments Yet

Corresponding author: Elliot B. Tapper (etapper@bidmc.harvard.edu)

Competing interests: No competing interests were disclosed.

Introduction

Ascites is the most common hepatic decompensation, occurring in 50% of cirrhotic patients followed for over a decade[1]. The development of ascites heralds a vulnerable time of sharply increased mortality for patients with liver disease – related in large part to spontaneous bacterial peritonitis (SBP)[2,3]. SBP is an infection of the ascitic fluid that occurs in 10–30% of patients with ascites[4]. Fatal in as many as 32.6% of cases, SBP can have a profound effect on the tenuous hemodynamics of patients with cirrhosis[5]. Exacerbating the arterial underfilling resulting from the splanchnic vasodilation of cirrhosis, SBP may lead to a decrease in cardiac output such that it can no longer satisfy the needs of a kidney that is already vasoconstricted[6]. The result is the hepatorenal syndrome which is often devastating. SBP with renal injury is fatal in 42% of patients[7].

SBP is caused by translocation of gastrointestinal organisms into the ascitic fluid, most commonly *Escherichia coli*, *Klebsiella pneumoniae* and *Streptococcus pneumoniae*. As such, third generation cephalosporins are amongst the best studied antibiotics in this setting, with ceftriaxone as the drug of choice where cefotaxime is not available. Studied as a treatment for SBP in clinical trials for 25 years, the doses employed have been either 1 g every 12 hours or 2 g every 24 hours given intravenously for 5 to 10 day courses[8–14].

At our center, we have found that ceftriaxone is often given at 1 g daily either in reference to online resources from other major teaching institutions or because 1 g is the general preset dose for this antibiotic as generated by the electronic ordering system[15]. (http://clinicalpharmacy.ucsf.edu/idmp/adult_guide/empiric_guide/intraabd_hosp_frame.htm, last accessed 1-12-2014). The outcomes of SBP as a function of ceftriaxone dosage – 1 g daily versus 2 g daily – have never been evaluated. It is unknown what effect the dosage of ceftriaxone has on the control of SBP or on mortality. Neither the American Association for the Study of Liver Disease (AASLD) nor the European Association for the Study of the Liver (EASL) guidelines on SBP management explicitly comment on the dosing of ceftriaxone for this indication[16,17].

Herein we present the results of a retrospective review of the outcomes of SBP stratified by dose of ceftriaxone. This study aims to determine the difference in overall survival and intensive care utilization after an episode of SBP treated with differing doses of ceftriaxone.

Methods

This is a retrospective, single center review of prospectively maintained medical records for all consecutive patients treated with ceftriaxone for SBP at the Beth Israel Deaconess Medical Center, Boston, USA, between January 2003 and December 2011.

We searched our clinical database for all patients that received ceftriaxone within 48 hours of a peritoneal fluid cell count and differential drawn in the emergency department or hospital ward. We then limited the population to those with 250 or more neutrophils in the ascites. Patient charts were then examined to exclude those with a prior liver transplant, evidence of intra-abdominal source of infection [abscess, perforation, recent (within 2 weeks) intra-abdominal surgery], peritoneal dialysis, ciprofloxacin or trimethroprim-sulfamethoxazole antibiotic prophylaxis, or documentation of a secondary infection (urinary tract infection, pneumonia, blood stream infection, cellulitis, meningitis) for which ceftriaxone was started prior to the peritoneal fluid collection. We collected data on age, sex, Model for End Stage Liver Disease (MELD) score (bilirubin, creatinine and PT/INR) at diagnosis, peritoneal white blood cell count and differential, blood and peritoneal culture data, dose of ceftriaxone, additional antibiotics, duration of antibiotic therapy, creatinine trends, intensive care utilization, length of hospital stay and mortality. Dates of death were confirmed in the medical record with reference to the Social Security Death Index. The cause of death was not collected as many patients died elsewhere. The primary outcome was overall survival after SBP diagnosis. Other outcomes included discharge creatinine, hospital length of stay and intensive care unit (ICU) length of stay.

Statistics were performed using SAS 9.2 and included student's t-test, multivariate regression analysis, and log-rank testing/survival analysis where appropriate. P-value of 0.05 was considered significant for all analyses. While no prior studies have examined the effect of ceftriaxone dosing in order to determine study power, prior studies of ceftriaxone for SBP may be instructive. For example, in comparing 2 g ceftriaxone to cefonicid, the in-hospital death rate during therapy was 13% versus 30% which, assuming an alpha of 0.05, a sample size of 91 gives an 80% power[13]. However, when examining the broader literature on ceftriaxone, regimens of variable duration (5 vs. 10 days) with 30% vs. 35% 30 day mortality would imply that studies require more than 1600 patients for adequate power[8–14].

Results

We found 138 patients with SBP treated with ceftriaxone. Of these, 91 patients met our inclusion criteria: 34 patients received 1 g daily and 57 received 2 g (total) daily. There was no significant difference between the groups with respect to age, gender, MELD score, peritoneal culture positivity or other infectious burden (Table 1). All patients had received a protocol of albumin infusion on days 1 and 3 after the diagnosis of SBP in accordance with best practice[18].

We next compared the hospital course for patients that received either dose of ceftriaxone (Table 2). While both groups were likely to be treated with at least one additional antibiotic during their hospitalization (74% of those treated with 1 g, and 61% of those treated with 2 g), this difference was not significant. The total course of antibiotics – ceftriaxone or otherwise – was also similar between groups. The group receiving 2 g ceftriaxone daily did have a trend towards a shorter hospital stay, although this did not meet statistical

Table 1. Patient characteristics for 1 g versus 2 g ceftriaxone dose, given as N (%) for categorical variables or mean ± SD for continuous variables.

	Ceftriaxone 1 g (N=34)	Ceftriaxone 2 g (N=57)	p-value
Patient age (years)	59.59 ± 11.24	55.10 ± 13.45	0.105
Female gender	9 (26%)	19 (33%)	0.527
MELD	20.55 ± 8.17	18.16 ± 6.48	0.125
Culture positive SBP	6 (18%)	6 (11%)	0.331
Other infectious source*	5 (14%)	9 (16%)	0.890

[[i]] *Looking at patients admitted to a floor service, excluding prior transplants and prior episodes of SBP.*]

[[ii]] *Patients with documented pneumonia or urinary tract infection]

[[iii]] *MELD = Model for End-Stage Liver Disease. SBP = Spontaneous Bacterial Peritonitis.*]

Table 2. Hospital course characteristics by ceftriaxone dose.

	1 g (N=34)	2 g (N=57)	p-value
Length of stay (days)	13.24 ± 21.5	10.28 ± 7.2	0.443
ICU days	3.26 ± 6.9	0.59 ± 1.78	*0.034**
Repeat paracentesis at index hospitalization (N, %)	14 (41)	32 (56)	0.167
Repeat paracentesis with >250 neutrophils (N, %)	7 (21)	11 (19)	0.881
30-day readmission (N, %)	11 (32)	16 (28)	0.665
Other inpatient antibiotics (N, %)	25 (74)	35 (61)	0.238
Total inpatient antibiotic days	8.4 ± 8.5	8.8 ± 6.3	0.821
Inpatient duration of ceftriaxone (days)	4.8 ± 3.1	5.3 ± 3.2	0.491
Creatinine at discharge	1.57 ± 1.04	1.41 ± 1.46	0.529

[[i]] ICU = intensive care unit. * Not significant after controlling for MELD score]

significance (13.24 days vs. 10.28, p = 0.44). We did see a statistically significant shorter average length of intensive unit (ICU) stay in patients who received 2 g ceftriaxone a day (0.59 ± 1.78 days), compared to those who received 1 g ceftriaxone daily (3.26 ± 6.9 days) (p = 0.034). The odds ratio for ICU utilization was 0.11 (95% CI 0.02–0.65). However, this difference was no longer significant after controlling for MELD score - odds ratio 0.21 (95% CI 0.04–1.07). Finally, we examined one-year survival for patients treated with 1 versus 2 g ceftriaxone, and found a significant improvement in survival associated with the 2 g dose (p 0.0034 log rank test)

(Figure 1). Median overall survival was greater for patients treated with the 2 g dose (228 days vs. 102 days, however it was not significant (p = 0.26).

Given the high prevalence of additional antibiotic treatment, we also examined the pattern of antibiotic use. Overall, 70% of patients were treated with at least one additional antibiotic. The duration of antibiotic use, as well as the number and type of antibiotics prescribed were highly variable (Table 3). While vancomycin was the most common concurrent antibiotic, used in 46% of patients, over
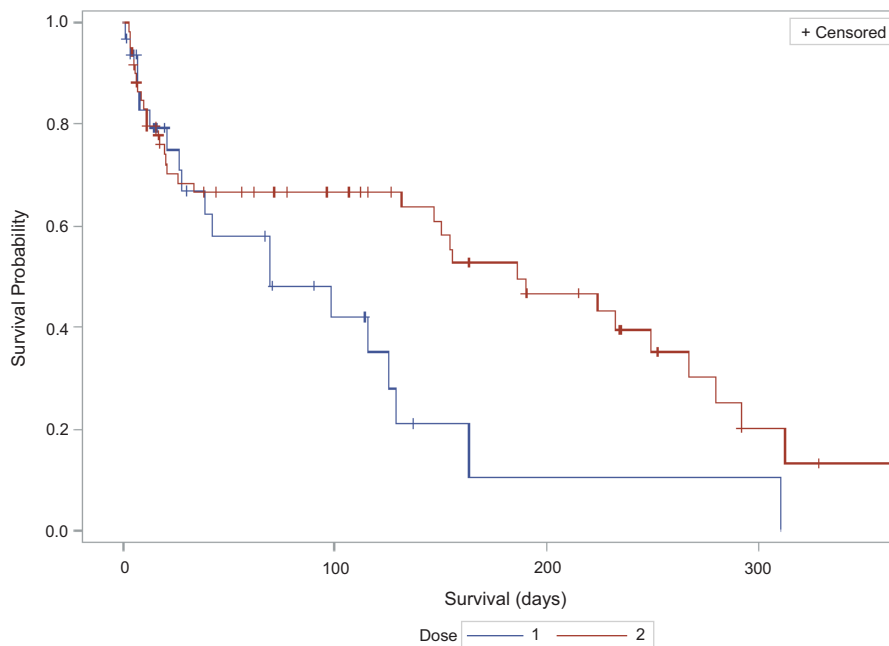
Figure 1. Kaplan-Meier survival curve after treatment of spontaneous bacterial peritonitis with 1 or 2 g ceftriaxone.

Table 3. Types of inpatient antibiotics prescribed in addition to ceftriaxone, with number of patients and percentage of total population (n=138) and range of duration of inpatient antibiotic coverage (days).

Antibiotic	Number of patients N (%)	Duration range (days)
Vancomycin	63 (46)	1–22
Metronidazole	39 (28)	1–113
Piperacillin-tazobactam	26 (19)	1–23
Levofloxacin	21 (15)	1–43
Ciprofloxacin*	20 (15)	1–14
Cefepime	13 (9)	1–14
Meropenem	8 (6)	1–10
Ampicillin-sulbactam	6 (4)	1–37
Ceftazidime	6 (4)	1–9
Ampicillin	4 (3)	2–7
Azithromycin	4 (3)	1–6
Fluconazole	4 (3)	1–37
Nafcillin	3 (2)	2–6
Clindamycin	3 (2)	2–6
Gentamycin	2 (1)	6–9
Daptomycin	2 (1)	5–7
Amoxicillin	2 (1)	3–6
Trimethoprim-sulphamethoxazole*	1 (<1)	3
Ertapenem	1 (<1)	2
Clarithromycin	1 (<1)	3
Caspafungin	1 (<1)	11
Micafungin	1 (<1)	1
Aztreonam	1 (<1)	2
Moxifloxacin	1 (<1)	2
Linezolid	1 (<1)	9
Cefotaxime	1 (<1)	1
Cefazolin	1 (<1)	3

[[i] *Recorded as treatment. This analysis excluded patients continued on ciprofloxacin or trimethoprim-sulphamethoxazole for prophylaxis.]

25 different medications were used in a variety of combinations. To further understand the antibiotic regimens observed, we next examined the available culture data. Of 91 patients diagnosed with SBP on neutrophil criteria, 13 were culture-positive. Of these, one patient had a documented infection resistant to ceftriaxone. This patient was excluded from the analysis. 14 patients had evidence of a secondary infection (Table 1). These included pneumonia (diagnosed with chest x-ray), urinary tract infection (>100,000 colonies on urine dipstick with positive urine culture), and cellulitis (clinical diagnosis documented in chart).

Conclusion

Our study of ceftriaxone dosage for SBP yielded three core findings. First, there was a trend towards improved mortality with the 2 g dosage, however we did not detect a difference between the groups receiving either dose of ceftriaxone and the rate of in-hospital mortality or the rate of persistent renal injury. Second, a total ceftriaxone dose of 2 g daily over 1 g daily exhibited a non-significant reduction of intensive care utilization by cirrhotic patients with SBP, after adjusting for MELD score. Prospective studies in a larger cohort are indicated to explore the true significance of these results. While it could explain our results, whether the pharmacodynamics of intravenous ceftriaxone are such that the peritoneal drug concentration following a 1 g infusion results in slower control of infection is unclear from our study[19]. Third, the number, duration and complexity of antibiotic regimens that cirrhotic patients experience is highly variable. The reasons for this finding are unclear and deserve further study in order to understand both the physician and patient factors that increase antibiotic regimen complexity as well as the effect on outcomes including mortality, morbidity and future infection with resistant organisms. Ultimately, we feel that the complexity of antibiotic regimens speaks to clinical uncertainty and the urgent need to improve the yield of ascitic cultures and tailor therapy for SBP with consideration of local microbiological data.

This study emphasizes the need for antibiotic stewardship and treatment standardization in the care of cirrhotic patients. We feel this can be easily achieved by computer programming. For centers that use electronic provider order entry, a preset dose of 2 g of ceftriaxone when prescribing for a diagnosis of SBP can ensure standardized and appropriate dosing. Beyond that, we have programmed a prompt into ceftriaxone orders that asks the physician to specify whether the medication is intended to treat SBP. This selection results in an automatic 2 g daily dose (Figure 2). This has two purposes. First, by selecting an indication for the antibiotic, we are effectively able to track our patients treated for SBP prospectively for quality assurance purposes. Second, while our findings are inconclusive, they are suggestive of a benefit from a higher ceftriaxone dose, which the study may have ultimately been underpowered to detect. Cirrhotic patients can be admitted to any service of the hospital, including those staffed by hepatologists, internists, surgeons and intensivists. By standardizing care delivery, the healthcare system can ensure that the medications cirrhotic patients receive are dosed appropriately for their needs. Furthermore, by programming a menu-selection for SBP, our hospital - or any hospital with similar capabilities - may track the disease indications for each antibiotic allowing for audits and outreach.

Our conclusions are limited in a few ways. First, our study is retrospective and therefore we cannot comment on the impact of other

Figure 2. Modified provider order entry standardizes treatment of spontaneous bacterial peritonitis. A. When an ordering physician chooses ceftriaxone, an indication must be chosen. **B**. When spontaneous bacterial peritonitis is the chosen indication, the preset dose is 2 g daily.

treatment decisions that may or may not be associated with the dose of ceftriaxone chosen. We can speak only to the association of ceftriaxone dose with mortality, not causation. Furthermore, given the fragmented nature of clinical care, it is impossible to know the cause of death in all patients. Additionally, we cannot exclude the possibility that our study was underpowered to detect a difference between treatment groups. Second, the microbiology of our patients' SBP is unclear given the low rate of culture positivity so we cannot comment on the impact of antimicrobial resistance. Third, follow-up paracenteses to confirm resolution of the SBP after antibiotic treatment were infrequent and thus we cannot comment on the rate of resolution of neutrophilia as function of ceftriaxone dose.

In order to prevent unwanted practice variation, we recommend standardizing the treatment of SBP by automating the dose of ceftriaxone in the provider order entry system. Further research must be aimed at rationalizing the antibiotic regimens employed in the treatment of cirrhotic patients. Programs to this end include fastidious antibiotic stewardship facilitated by computerized audits of indication-based antibiotic usage and improved microbial culture and detection techniques.

Data availability

figshare: Spontaneous bacterial peritonitis outcome and ceftriaxone dosage data, doi: http://dx.doi.org/10.6084/m9.figshare.931754[20]

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    Data Source

Open Peer Review

Current Referee Status: ☐? ☐? ☑

Referee Responses for Version 2

☑ **Andres Cardenas**
Institut Clinic de Malalties Digestives i Metaboliques, Hospital Clinic, University of Barcelona, Barcelona,
Spain

Approved: 21 July 2014

Referee Report: 21 July 2014
doi:10.5256/f1000research.4910.r5502
The article now looks good and I do not have any further comments.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that
it is of an acceptable scientific standard.**

Competing Interests: No competing interests were disclosed.

Referee Responses for Version 1

☐? **Andres Cardenas**
Institut Clinic de Malalties Digestives i Metaboliques, Hospital Clinic, University of Barcelona, Barcelona,
Spain

Approved with reservations: 10 April 2014

Referee Report: 10 April 2014
doi:10.5256/f1000research.3447.r3998
This is an interesting retrospective study where the authors review the effectiveness of ceftriaxone dosing
for patients with SBP. I like the article and the principles behind the analysis.

Major points:
1. The aim of the study should be better explained - what did the authors set out to study? Cure,
   outcomes, prognosis?

2. The title should reflect the retrospective nature of the analysis.

3. Were any patients on antibiotic prophylaxis (i.e norfloxacion or cipro) prior to the dx of SBP or other
   bacterial infections?

4. There is a trend of differences in mortality. Why is this so - do the authors have the causes of death in both groups?

The authors' message should be that there seems to be a difference and that this analysis paves the way for future randomized studies that take local microbiological data from each institution into account.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

1 Comment

Author Response

Elliot Tapper, Department of Medicine, Beth Israel Deaconess Medical Center, USA
Posted: 18 Jun 2014

We appreciate Dr. Cardenas' comments. As regards to his major points, the first three were easily addressed. First, the title, abstract and introduction have been changed substantially to clarify the aims with the principle focus being patient outcomes. Second, the title has been changed. Third, we clarified that patients on antibiotic prophylaxis were excluded.

As for his fourth, unfortunately it is extremely difficult to determine causes of death when patients often die at other institutions. We do not feel that this is a major limitation for three main reasons. First, we confirm that the patients are alive or dead using a national database. Second, the available prognostics in liver disease, namely the MELD, are capable of predicting all-cause mortality and we adjust for MELD. Third, the causes of death in decompensated cirrhosis are fairly circumscribed and typically closely related to the patients' antecedent clinical course. SBP can result in mortality via sepsis, and renal failure but also, potentially, variceal bleeding, if say the clinician held beta-blockade to preserve renal function.
Competing Interests: No competing interests were disclosed.

Manuela Merli
Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy

Approved with reservations: 08 April 2014

Referee Report: 08 April 2014
doi:10.5256/f1000research.3447.r4389
This is a retrospective study aimed at evaluating the relationship between dosing of ceftriaxone (1 or 2 grams) and outcome in SBP.

This issue is certainly of interest however, as the authors stated in the discussion, the study is inconclusive due to several limitations which derive from the retrospective approach. For this reason I

would also suggest that the title should be changed to underline the point that the main finding in the study is that uneventfully these patients may receive different antibiotic dosages for the same indication. A possible title could be "*Need for antibiotic stewardship and treatment standardization in the care of cirrhotic patients*"

The answer to the question "*should we use 1 or 2g ceftriaxone*?" can only be derived from a prospective randomized study. On the other hand it is unlikely that one year mortality (Figure 1) could have been influenced by the treatment of the index episode. In fact these patients had a similar length of stay, a similar in hospital mortality and a similar rate of 30 days readmission. From this point of view, one could even derive that the therapy with 1g ceftriaxone was not inferior to 2g ceftriaxone. I suggest these observations be taken into account in the text.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

1 Comment

Author Response

Elliot Tapper, Department of Medicine, Beth Israel Deaconess Medical Center, USA
Posted: 18 Jun 2014

The reviewers' points are well taken and have been adopted in the manuscript. Language reinforcing the statistically equal efficacy of ceftriaxone doses has been inserted at critical points. The notion that 1g is non-inferior to 2g however cannot be included as the study design does not allow for claims regarding inferiority. Furthermore, we believe that though the power calculation based on prior works suggested our sample size was sufficient, it is likely the case that when comparing 1g to 2g, the study was underpowered to confirm the trends toward improved outcomes with 2g.
Competing Interests: No competing interests were disclosed.

José Castellote
Gastroenterology Department, Hepatology Unit, Hospital Universitari de Bellvitge, Barcelona, Spain

Approved with reservations: 25 February 2014

Referee Report: 25 February 2014
doi:10.5256/f1000research.3447.r3731
This is an interesting retrospective study but I have the following comments:
1. The title is appropriate. I think that the abstract provides an adequate summary but the conclusions may need to be changed. The first sentence is a recommendation and the differences in one-year survival are difficult to explain purely on the basis of 7 days of antibiotic therapy.

2. In the method section the clinical endpoints that the authors are going to study should be explained and the following should be added: in-hospital mortality, infection cure rate, bacterial resistance and super-infections. Ascitic culture method should also be detailed.

3. What are the reasons for different mortality rates at one-year in both groups? This point is crucial and must be discussed in the discussion.

4. Lastly, I think that the study shows no differences in hospital mortality rate, infection control rate, renal failure, or hepatorenal syndrome between both groups and this should be pointed out in the conclusions.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

1 Comment

Author Response

Elliot Tapper, Department of Medicine, Beth Israel Deaconess Medical Center, USA
Posted: 18 Jun 2014

The reviewer's comments are well taken.

1. The language used in the conclusions has been moderated for less sweeping claims. The use of 1 year mortality after one clinical event is frequently described in the literature on cirrhosis. While SBP and 1 year mortality seem disconnected, SBP is a watershed moment for patients with ascites, the prognostic effects of which are well described.

2. Endpoints have been clarified. Mortality has been included. Infection cure rate is incompletely captured as very few patients received follow up paracentesis; patients with resistant species (very few) and super-infections were specifically excluded from the study. The ascitic culture method is standard.

3. We add a specific comment on the causes of mortality. Please see our response to Dr. Cardenas. We regret that we cannot provide actual causes of death. However, as the primary outcome was all-cause mortality and we controlled for factors that are validated to predict all-cause mortality, we feel that this outcome is legitimate.

4. Agreed.

Competing Interests: No competing interests were disclosed.