Bacteriascites confers poor patient prognosis beyond MELD prediction

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Introduction:

Ascites is the most common complication of cirrhosis and subsequent portal hypertension. The development of ascites is associated with a poor prognosis and impairment of quality of life. (1, 2) Bacterial infection of the peritoneal cavity is rare in the absence of liver disease, however in cirrhotic patients with ascites bacterial infection is frequent and is recognised in two distinct forms, spontaneous bacterial peritonitis (SBP) and bacterial ascites (BA). SBP is a common bacterial complication of ascites in the absence of any intra-abdominally surgically treatable source of infection with a reported prevalence varying between 1.5-3.5% in the outpatient setting and 10% in hospitalised patients. (3-6) In SBP, peritoneal infection results in an inflammatory reaction and the diagnosis of SBP is made when the ascitic fluid neutrophil count exceeds 250/mm^3. Pathogens are identified in *circa* 60% of cases, comprising mainly of Gram-negative aerobic bacteria (*Enterobacteriaceae* and non-enterococcal *Streptococcus* spp.) and thus at diagnosis empirical antimicrobial therapy is commenced to target these pathogens, with adaptation if a pathogen is cultured. (7, 8) In those who survive an episode of SBP, recurrence rate at 1 year is 70% and reported survival at 1 year is 30-50%, falling to 25-30% at 2-years and thus it is guidance that patients recovering from an episode of SBP should be considered for Liver transplantation (LT). (2)

BA is a term used when ascitic fluid cultures are positive but in the context of an ascitic fluid neutrophil count of less than 250/mm^3. It is recognized as a different clinical entity to SBP with a reported prevalence of between 8-11% in patients with cirrhosis and ascites. BA is postulated to result from either spontaneous colonization of ascites (likely from gut translocation) or a secondary translocation from a concomitant extraperitoneal infection. In asymptomatic patients BA is thought to be a transient and potentially spontaneously reversible colonization of ascites. (9) Clinical guidance thus recommends that in patients exhibiting systemic inflammation or signs of infection should be

treated with antimicrobial therapy. (2) This creates a paradox for our management as whilst guidance states only to treat BA in the context of systemic symptoms, it is well recognized that SBP can occur without systemic symptoms suggesting that absence of systemic features should not in isolation dictate who receives antimicrobial therapy. In those without systemic symptoms, a repeat tap should be done at 72 hours and if neutrophil count >250/mm^3 they should be treated as per SBP. This recommendation is based on a historic series with small numbers of patients, where 62% of BA cases spontaneously resolved and 38% progressed to meet diagnostic criteria of SBP over 72 hours. (9, 10) More recently data has been published to suggest that whilst BA may spontaneously resolve, the occurrence of BA may still be a poor prognostic marker for survival with 1-year mortality rates of 66% reported. (11) No recommendations exist regarding the role of secondary prophylaxis in BA, nor regarding the significance of such an event on the patients overall prognosis.

We therefore hypothesized that BA is an important prognostic event and has the potential to negatively alter the natural history of a patient with cirrhosis. It was thus the aim of this study to compare the baseline patient characteristics in patients presenting with SBP and BA and characterize the bacterial pathogens identified in the two groups. We aimed to establish if survival, at different time points, differed for patients presenting with SBP and BA, and finally establish the predictors of poor outcome for SBP and BA and characterize any significant differences. The overall aim of the study was to improve understanding of the significance of an episode of BA on a patient's survival.

Methods

All consecutive microbiological samples coded as ascitic fluid at the Royal Free hospital, which provides tertiary hepatology services, from 2008 – 2018 were included in the study and retrospectively reviewed . Patients without cirrhosis were excluded. Patients were classified as having BA or SBP in keeping with the above published definitions. In patients who progressed from BA to SBP within 72 hours were classified for the purpose of the study as SBP (28 cases). For the purpose of this study, only

the index case of ascitic infection was recorded. Patients without cirrhosis were excluded. Baseline demographic, clinical, biochemical and microbiological data were collated. Transplant-free survival was recorded. Patients were censored at the point of death or censored alive at the time of liver transplantation (LT) or when lost to follow-up. All patients with SBP were treated as per best available evidence-based practice (including albumin administration) and according to local microbiological guidance; patients with BA only received antimicrobial therapy if other clinical or laboratory makers of infection were present (<5% of BA patients received antibiotics).

Descriptive statistics were used for quantitative variables (mean and standard deviation if the distribution was normal and median and interquartile range otherwise) and categorical variables (absolute frequencies and percentages). To determine whether significant differences existed between groups, the Student's t-test, or the Mann-Whitney U non-parametric method as appropriate was applied. Differences in nominal data were compiled either by the Chi-squared test or Fisher's exact test. Survival curves were generated using Kaplan-Meier survival analysis with follow-up started at the time of the index case of SBP/BA. Multivariate cox logistic regression models to predict mortality were generated from variables with $p<0.10$ in the univariate analyses, after excluding those with suspected collinearity.

Despite accepted diagnostic criteria for SBP is an ascitic fluid with PMN>250/mm3, defining SBP as ascitic fluid with PMN>500 or WBC>1000 cells/uL correlates with better positive likelihood ratios. (12) Therefore, outcomes were also evaluated with these defining criteria.

Statistical analysis was performed using SPSS version 23.0 (IBM Statistics) and R (v.3.5.1, R Core Team).

In view of the retrospective nature of the study, permission from patients and ethic committee review were not required.

Results

Population and baseline demographic data

A total of 8890 samples labelled as "ascitic fluid" were received by the microbiology laboratory over the study period. Following review of all cases, 1918 samples were excluded as they were unsuitable for analysis and not further processed (sample clotted/leaked/unable to perform WCC/wrongly labelled fluid), and further 6132 samples were excluded from further analysis as they were negative for both SBP and BA on microbiological evaluation (ascitic fluid neutrophil count <250cells/mm^3 and culture negative). This resulted in 840 ascitic fluid samples which potentially met the diagnostic criteria for SBP or BA. From the 840 samples, a further 99 cases were excluded as disease aetiology was non-cirrhotic portal hypertension, and 352 cases excluded as there were recurrent/duplicate samples from the same patient. This resulted in 176 cases of SBP and 213 cases of BA which were included in the study.

Baseline demographic data was similar between patients diagnosed with SBP when compared to those with BA. Specifically, gender distribution (males 64% vs 68%, respectively p=0.47), distribution of cirrhosis aetiology and mean age at presentation was similar between groups (55 vs. 56 years, p=0.34). Alcohol related liver disease was the commonest underlying aetiology accounting for 83/176 (47%) of those with SBP and 115/213 (54%) of those with BA. (Table1) Location of the patient when the ascitic tap was taken (out-patient, ward, accident and emergency, or ITU) was not significantly different in those cases of SBP compared to BA. Univariate analysis of laboratory parameters at the time of ascitic tap revealed that patients with SBP had significantly higher blood total WCC (10.2 vs 6.0, p<0.01) and neutrophil count (8.4 vs 4.9, p<0.01) when compared to those with BA. Furthermore, in cases of SBP, INR was higher (1.7 vs 1.5, p<0.01) and serum sodium was lower (134 vs 136, p=0.04) when compared to those with BA. No significant differences were found between serum bilirubin (56 vs 52 p=0.54), albumin (28 vs 30 p=0.10) or creatinine (92 vs 86, p= 0.44) at the time of the ascitic tap in cases of SBP compared to BA. Neutropenic patients were more frequent in the BA group (10/176= 6% vs 33/213=16%). Both the Model for end stage liver disease score (MELD)

(21 vs 18, p<0.01) and United Kingdom end stage liver disease score (UKELD) (55 vs 53, p<0.01) calculated at the time of the ascitic tap were significantly higher in patients who had SBP when compared to those with BA. (Table 1)

Microbiological Evaluation

There were significant differences between the organisms and pathogens cultured in patients with SBP compared to BA. Overall 49% (86/171) of SBP samples were culture positive. Pathogenic organisms were classified as those belonging to one of the following groups: the bacterial order *Enterobacterales*; the bacterial genus *Enterococcu*s; Lancefied group *streptococci* and *streptococcus* anginosus group; bacterial species *Pseudomonas aeruginosa, Staphylococcus aureus, Clostridium perfringens;* the fungal genus *Candida* (Supplementary Table 1). Pathogenic organisms accounted for 83% (71/86) of those identified in patients with SBP compared to 42% (89/213) of the BA cases (p<0.01). Of the pathogens identified, the percentage identified as bowel flora in origin were similar between the two groups (SBP 65/71 vs. BA 78/89, p=0.45), as were extended-spectrum beta-lactamase species (ESBL) (SBP 11/50 vs BA 5/40, p=0.27). Interestingly the *Enterobacteriaceae* contributed to a significantly higher proportion in the SBP group (SBP 50/81 vs. BA 40/89, p<0.01) and the prevalence of multi-drug resistant pathogens (defined as acquired resistance to more than two antimicrobial classes) was significantly higher in the SBP group (SBP 14/71 vs BA 5/89, p=0.01). The above is summarized in Table 2.

Survival Analysis

The median follow-up time from ascitic fluid sampling was 59 months in both patients with SBP and BA. Out of the 176 patients with SBP there were 95 deaths (54%) and 23 patients (13%) underwent LT (censored as alive at the time of OLT). In the 213 patients with BA there were 111 deaths (52%) and 36 underwent LT (17%) over the follow-up period. The cause of death was due to liver

related complications in >90% cases of BA and SBP. As we don't perform living donor transplantation, all the transplanted patients had to wait for an organ to be allocated as per current national allocation system. Median time to death was shorter in patients with SBP compared to BA (30-days vs. 92-days) resulting in patients with SBP having a significantly lower survival at 1 month (120/167=72% vs 174/205=84%, p<0.01) and 3 months (99/164=60%vs 149/200=75%, p<0.01) when compared to patients with BA. The survival difference disappeared after 3-months with no significant differences in patient survival when calculated at 6-months, 1, 3 and 5-years. (Table 3 & Figure 1a and b)

Applying ascitic fluid PMN>500 or WBC>1000 cells/uL as criteria to define an episode of SBP, reduced the number of SBP cases to 125. Of these, 64 episodes (51%) either died or required a LT over the follow-up period. LT-free survival was re-calculated and similar findings were obtained, with significantly lower survival in the newly defined SBP episodes at 1 month (73% vs 82%, p<0.01) and 3 months (62% vs 71%, p<0.01) when compared to patients with BA. Again the survival difference disappeared afterwards, with no significant difference in patients survival after 3 months between the two groups. (Supplementary Table 2 & Figure 2)

To test whether an episode of BA is an independent predictor of adverse outcome if the initial episode of infection is successfully treated, analysis was restricted to patients who were alive, without LT, after 30 days of ascitic fluid testing. This excluded those who died in hospital from sepsis related to the infectious event. Ninety-five patients died or underwent LT within 30-days from index presentation (SBP n=56, BA n=39). Survival after exclusion of the above cases at 3-months, 6-months and 12-months was 85%, 75% and 65% respectively for SBP and 88%, 76% and 61% for BA. (p=NS across all groups).

Given the accepted paradigm that an episode of SBP increases mortality beyond that which the MELD score predicts, patients were grouped into MELD categories ≤9, 10-19, 20-29, 30-39 and ≥30 and 3-month mortality in patients with SBP and BA were compared to published data. (13-16)

Mortality was substantially higher across all MELD groupings for both SBP and BA when compared to the predicted mortality calculated by MELD score alone. (Table 4)

Predictors of outcome

In the SBP group, predictors of death using cox regression univariate analysis included older age ($p<0.08$), creatinine ($p<0.01$), bilirubin ($p=0.01$), INR ($p<0.01$), WCC ($p<0.01$) and neutrophil count ($p<0.01$) alongside MELD ($p<0.01$), UKELD ($p=0.03$) score and the culture of enterobacteriaceae in ascitic fluid ($p=0.08$). On multivariate analysis inputting variables of age, WCC, MELD and enterobacteriaceae, independent predictors of an event were older age ($p<0.01$), higher peripheral blood WCC ($p<0.01$) and higher MELD scores ($p<0.01$). (Table 5).

In the BA group predictors of an event (death or LT) on cox regression univariate analysis included older age ($p=0.01$), platelets ($p<0.01$), INR ($p<0.01$), MELD score ($p=0.02$), UKELD score ($p=0.01$) and the culture of enterobacteriaceae on ascitic fluid ($p=0.04$). On multivariate analysis inputting variable of age, platelet count, MELD score and enterobacteriaceae, independent predictors of an event were older age ($p<0.01$), platelet count ($p<0.01$) and MELD score ($p<0.01$). (Table 5)

Discussion

In this study we have shown that BA is a clinically significant event associated with high patient mortality. Overall transplant free survival at 6 and 12-months demonstrated no significant differences between patients with SBP and BA and the predictors of poor prognosis on multivariate analysis (age, and MELD) were similar in both groups, even when SBP episodes were filtered for PMN>500 or

WBC>1000. Despite these similarities patients with SBP had significantly higher index MELD scores, rates of enterobacteriaceae and multi drug resistant organisms when compared to patients with BA.

The MELD score which was initially developed to predict 3-month mortality in patients undergoing a transjugular intrahepatic portosystemic shunt insertion (TIPSS) has now been incorporated widely into clinical practice to predict mortality in patients with liver cirrhosis and guide organ allocation in LT. (13, 17, 18) Despite its wide spread clinical use, its prognostic accuracy lacks specificity. It is acknowledged that in specific patient groups the MELD's predictive accuracy of mortality can be improved by additional aspects such as adding frailty and hepatic encephalopathy scores. (19, 20) In the context of SBP it is accepted and incorporated into clinical practice guidelines that an episode of SBP is a poor prognostic marker both in the short and long term beyond the mortality that MELD predicts. The EASL clinical practice guidelines acknowledges this and recommends secondary prophylaxis and transplant evaluation in any patient who has an episode of SBP irrespective of the MELD score. (2) There is no such recommendation for BA. In this study 3-month mortality across patients in the BA group was substantially higher than that which the MELD score alone would predict. Furthermore overall 1-year survival was not significantly different between SBP and BA (44% as 50%, $p=0.27$), despite those with BA having a significantly lower MELD score at index presentation (21 vs. 18, $p<0.01$). These two novel findings in BA suggest that the clinical significance of such an event on prognosis is similar to that of SBP and should not be underestimated.

Whilst we have convincingly demonstrated an increased patient mortality following an episode of BA, it can also be concluded that this is not exclusively due to the acute "infective" episode. After exclusion of all patients that died or underwent LT within 30-days of diagnosis of BA, mortality remained significantly reduced with 1 in 4 patients dying over the next 5 months and was equivalent to those patients who had survived an episode of SBP. This data suggests that an episode of BA confers increased longer-term mortality even if the index infection resolves. This is not a unique concept in cirrhosis, it is recognized that bacterial infection can change the natural history of cirrhosis and

increase the risk of death 4-fold independent of the MELD score. (21-23) It is worthy of note that no patients with BA were included in these studies. Moreover, the published literature also suggests that the increased risk of death remains even if patients survive the first infective episode again independent of their underlying liver disease prognostic scores. (21, 22) This published data is supported by the findings in this current study with the novel addition that BA, like SBP appears to have a similar impact on the natural history of a patient with cirrhosis.

The role of antibiotics in BA remains unclear and lack of data regarding their use and impact on patient outcomes are lacking. We do not routinely treat patients with BA with antibiotics in our unit, therefore <5% of our patients received antibiotics. Historic data suggests that approximately 60% of patients with BA will spontaneously clear the infection. (9) Guidelines based on expert opinion state that microbial therapy should be reserved for those with systemic features of infection, however it is also widely accepted that patient with SBP may have no systemic signs of infection, thus indicating that this may be a poor discriminator to guide the use of antimicrobial therapy in BA. (2) One may postulate that the impaired survival in BA highlighted in this study may be either due to untreated infection in the short term (although this is unlikely as the 1-month mortality was significantly lower observed in SBP) and/or lack of longer-term prophylactic antibiotics. On univariate analysis, culture of a pathogen and particularly culture of enterobacteriaceae was associated with a significant risk of overall mortality in BA. The pathogenesis of SBP is related to bacterial translocation from the intestinal lumen to ascites as a result of changes in gut flora, intestinal permeability, alongside defects in host immunity with the family enterobacteriaceae the most frequently detected pathogen. (24-26) It is not unreasonable to postulate that gut pathogens cultured in ascitic fluid in BA have a similar aetiology and cases of BA with cultured gut pathogens would benefit from targeted secondary prophylaxis; this requires further prospective evaluation.

On multivariate analysis predictors of survival differed only on a higher peripheral WCC being predictive in SBP and a lower platelet count being predictive in BA, with both a higher MELD and age

being independent predictors of mortality in both groups. However patients with SBP had a significantly higher baseline MELD scores (21 vs 18, $p<0.01$). The platelet count as a predictor of mortality in BA is of interest, as it could potentially suggest that the BA cohort may have a more severe portal hypertension phenotype but less severe baseline impaired synthetic function as demonstrated by significantly lower MELD scores at the time of infection. This would need to be further evaluated out-with of this study as may help understand the pathophysiology and target future therapies.

The presence of more neutropenic patients in the BA group suggests that ascitic fluid results may be falsely negative and initiation of treatment in this category should be considered even if not meeting criteria for SBP.

Few papers have been published in the past 5 years on the impact of an episode of BA on transplant-free survival. (11, 27-30) Oey et al, report on 123 patients with BA and reported transplant free 1-month survival of 68% and 1-year survival of 40% and report survival rates, like in our study, comparable to SBP. (11) Ning et al report on 192 patients with BA, with a 1-month survival similar to that reported in this study of 86.5%. (27) Li et al report on 418 with ascites-positive cultures, with a 28-day transplant free mortality significantly higher in the SBP group in patients with Acute on Chronic Liver Failure (ACLF) (41.3% vs 65.5%; P = .015), but comparable 28-day transplant-free mortalities in patients without ACLF (13% vs 13.9%; p = .822), and significantly higher 28-day mortality than within the control group (18.4% vs 8.6%; P = .010). (28)

The current study has limitations, the major being that it is a retrospective data collection with non-standardized management protocols over a protracted time period.

In conclusion we feel this study highlights the negative impact of an event of BA on survival. The implication of this being unrecognized in routine clinical practice is that patients with BA are potentially disadvantaged; firstly, by not being considered for LT evaluation, and secondly if listed,

mortality being underestimated by conventional liver severity scores which currently guide organ allocation worldwide.

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