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Prevalence and Impact of Bacterial Infections in Children With Liver Disease—A Prospective Study

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Background and aims: **Risk of infections is increased in patients with acute liver failure (ALF) and decompensated chronic liver disease (DCLD). We evaluated the frequency, site, type and risk-factors for bacterial infections in children with ALF and DCLD and its effect on outcome.** ***Methods:*** **ALF or DCLD children were enrolled prospectively. Clinical and laboratory details were recorded. Cultures (blood, urine and ascites) and chest X-ray were done at admission followed by weekly surveillance cultures.** ***Results:*** **173 patients, 68 ALF and 105 DCLD were enrolled. Infections were more common in DCLD than ALF (60/105 [57.1%] vs. 27/68 [39.7%]; $P = 0.02$). Ascitic fluid infection, pneumonia, urinary tract infection and bacteremia were seen in 19%, 17.9%, 13.2% and 12.1% patients respectively. Healthcare-associated (HCA) infections were most frequent (39/87, 44.8%), followed by nosocomial (NC, 32%) and community-acquired (CA, 23%). Nearly 3/4th of bacterial isolates were resistant to cephalosporins and quinolones, 23% being multiresistant bacteria (MRB). DCLD patients with infection had higher Child–Pugh Score (10 [6–14] vs. 7 [6–14]; OR 3.2 [1.77–5.10]: $P = 0.007$), need for ICU care (26/60 vs. 3/45; OR 10.70 [2.98–38.42]: $P = 0.01$), in-hospital mortality (24/60 vs. 8/45;OR 3.08 [1.22–7.75]: $P = 0.04$) and mortality at 3 month follow-up (32/60 vs. 9/45; OR 4.57 [1.87–11.12]: $P = 0.00$). Infection did not affect the outcome in ALF.** ***Conclusion:*** **Infections develop in 40% ALF and 57% DCLD children. HCA and NC infections account for 77% of infections. Most culture isolates are resistant to cephalosporins and fluoroquinolones and 23% have MRB. Risk of infections is higher in DCLD patients with advanced liver disease. (J Clin Exp Hepatol 2017;xx:1–7)**

Bacterial infections are common in patients with acute liver failure (ALF) and decompensated chronic liver disease (DCLD)[1,2] and are often fatal either by itself or by precipitation of renal failure, shock or hepatic encephalopathy (HE).[3] Spontaneous bacterial peritonitis (SBP), urinary tract infection (UTI), pneumonia and bacteremia are the most frequently encountered infections.[4]

There are reports of increasing antibiotic resistance overall and specifically in patients with liver disease.[5] Antibiotics need to be used judiciously based on the likely organism and sensitivity pattern, to provide effective coverage and cost effective treatment while avoiding the development of resistance. Adult data cannot be extrapolated to children and unfortunately, data regarding infections in pediatric liver disease is scarce or unavailable.[6,7]

The objectives of our study were to evaluate (1) the frequency, site and risk factors for bacterial infections in children with ALF and DCLD, (2) nature of bacterial isolates, their sensitivity pattern and effect on in-hospital outcome.

PATIENTS AND METHODS

Prospective evaluation of bacterial infections occurring in children admitted with ALF or DCLD in our unit between March 2013 and November 2014 was done. ALF was defined as biochemical evidence of liver injury, no history of known chronic liver disease and coagulopathy not corrected by vitamin K administration i.e. INR > 1.5 in patients with hepatic encephalopathy [HE], or INR > 2.0 in patients without HE.[8] The diagnosis of CLD was based on clinical, laboratory, ultrasonographic and endoscopic [≥grade II esophageal varices] findings with or without liver histology. Decompensation was defined as the presence of ascites, encephalopathy and/or gastrointestinal bleeding. After admission a detailed history was taken

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Abbreviations: ALF: acute liver failure; CA: community acquired; DCLD: decompensated chronic liver diseases; GIB: gastrointestinal bleeding; GNB: gram negative bacilli; GPC: gram positive cocci; HCA: healthcare associated; HE: hepatic encephalopathy; ICU: intensive care unit; INR: international normalized ratio; MRB: multiresistant bacteria; NC: nosocomial; SBP: spontaneous bacterial peritonitis; UTI: urinary tract infection
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and clinical details including previous hospital admission and treatment given were recorded. The Child–Pugh score was calculated at admission.[9]

Cultures were drawn from blood, urine and ascitic fluid [if present]. Cultures were taken at admission prior to commencement of anti-microbial therapy. A chest X-ray was obtained if there was a clinical suspicion of pneumonia. Thereafter, surveillance cultures were sent on a weekly basis or earlier if there was a clinical suspicion of sepsis. In ventilated patients tracheal aspirates were taken on a weekly basis.

Blood cultures were routinely obtained from peripheral veins. Central line cultures were taken for suspected line sepsis or if unable to obtain peripheral cultures. Aseptic precautions were taken and an adequate blood volume was ensured.[10] Urine samples were mid-stream clean catch or catheterized as per standard recommendations.[11] Ascitic fluid was inoculated into the culture bottle at the patient's bedside as per guidelines.[12] Blood and ascitic fluid cultures were inoculated into BACTEC culture media [Becton Dickinson Diagnostics, New Jersey, USA]. Urine cultures were inoculated on Crome media [HiMedia, Mumbai, India]. Isolated organisms were identified by standard methods and tested for antimicrobial susceptibility by both the disk-diffusion method and the BD Phoenix automated ID system [Becton Dickinson Diagnostics, New Jersey, USA] according to the recommendations of the Clinical and Laboratory Standards institute.[13] Organisms were labeled as multiresistant [MRB] if they were resistant to 3 different antibiotic families, including β-lactams.[14]

Infections were diagnosed on the basis of standard criteria. Presence of ascitic fluid infection and its type i.e. spontaneous bacterial peritonitis [SBP], culture negative neutrocytic ascites and mono-microbial non-neutrocytic bacteriascites were defined as per standard definitions.[12] Blood stream infection was diagnosed in presence of positive blood culture and urinary tract infections [UTI] in the presence of both pyuria and a positive culture with a colony count of $\geq 10^5$ organisms/ml. Pneumonia was diagnosed in patients with clinical features and suggestive chest X-ray.[5]

Infections diagnosed at admission or within 48 h of admission were classified as healthcare associated [HCA] if the patient had a history of hospitalization for at least 2 days in the previous 90 days or community acquired [CA] if no history of hospitalization in the previous 90 days was present.[15] Infection was labeled as nosocomial [NC] when the diagnosis of infection was made beyond 48 h of admission. A patient was labeled to have had a "recent" antibiotic exposure if he had received antibiotics for a period of >48 h in the preceding 90 days prior to admission.[15] Urinary catheterization, ascitic fluid paracentesis, pleural tap, central line insertion, endoscopic sclerotherapy or band ligation or invasive ventilation were classified as invasive procedures for this study.

The Institute's Ethics Committee approved the study. Written informed consent was obtained from the parent or guardian of all participants.

Statistical Analysis

Data is represented as median [range] and percentages. SPSS [version 20.0; SPSS, Inc., Chicago, IL] was used for statistical analysis. Inter-group comparisons were performed using Mann–Whitney *U* test, Fisher's exact test or a one-way ANOVA. Odd's ratio was calculated where appropriate. Differences were considered significant at the level of 0.05.

A multivariate logistic regression model was used to predict the risk of infections in DCLD patients with the significant factors ($P < 0.05$) identified by univariate analysis. Main effects logistic regression model was used and scoring systems were not included in it because a score comprises of many parameters.

RESULTS

A total of 173 patients, 68 ALF [48 boys, age 72 [0.5–192] months] and 105 DCLD [70 boys, age 84 [3–204] months] were enrolled in the study. The etiology of liver disease in both the groups is illustrated in Figure 1.

Prevalence and Site of Infection

In the ALF group [$n = 68$], a total of 249 [4 (2–14) per patient] culture specimens [blood = 96, urine = 104, ascitic fluid = 44, tracheal aspirate = 5] were obtained (Figure 2). Twenty-seven [39.7%] patients had bacterial infection; 24 [35.2%] patients had single site and 3 [4.4%] had multiple site infection. UTI [11/68, 16.1%] was the most common site followed by pneumonia [10, 14.7%], ascitic fluid infection [8, 11.7%] and blood stream infection [6, 8.8%]. Bacterial infections were documented in 16/27 [59.2%] patients within 48 h of admission at our hospital [12 (75%) HCA and 4 (25%) CA]. Patients with HCA infections had a median hospital stay of 4 [2–24] days prior to coming to our center. NC infections were observed in 11 [40.7%] patients and were identified after 9 [7–14] days of hospitalization. UTI was the commonest HCA and CA infection seen in 8/12 [67%] and 4/4 [100%] patients respectively while pneumonia was the commonest NC infection [8/11 children].

In the DCLD group [$n = 105$], 424 [5 (3–22) per patient] culture specimens [blood = 180, urine = 184, ascites = 59, tracheal aspirate = 1] were obtained. Sixty [57.1%] DCLD patients had bacterial infection: ascitic fluid infection [25, 23.8%], pneumonia [21, 20%], blood stream infection [15, 14.2%] and UTI [12, 11.4%]. Single site infection was present in 46 [43.8%] patients and 14 [13.3%] had infections at multiple sites. Majority of the infections were HCA [27/60, 45%] with a median hospital stay of 6 [4–11] days prior to coming to our center. In patients with NC infections

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