Change in antibiotic regimen for emerging multidrug resistance in nosocomial ascitic fluid infection

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Received: 31 July 2019 / Accepted: 1 November 2019 / Published online: 21 November 2019
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Graphic abstract

Patients with portal hypertension-related ascites (defined as high serum ascites albumin gradient > 1.1 g/dL with 90% diagnostic accuracy) can develop spontaneous ascitic fluid infections (AFI) without pre-existent intra-abdominal source [1] AFI occurs in 10–30% of adult cirrhotic patients with ascites in a year's time with in-hospital mortality rate of 20–40%. It has been reported that the risk of dying of some major complications of cirrhosis has decreased over time, but that from sepsis has increased. Increasing spread

of multidrug-resistant (MDR) bacteria and the lack of new effective antibiotics are the likely reasons for this data. A due notice of this has been taken by World Health Organization who adopted an action plan to counteract the MDR strains in the 68th World Health Assembly. International Ascites Club planned a prospective, multicenter cross-sectional study which found the prevalence of MDR bacteria as 34% in 1302 cirrhotics across the globe and the same for India was 73% [2].

As per EASL and AASLD guidelines, SBP is diagnosed in patients with liver cirrhosis if polymorphonuclear cell count exceeds 250 cells/ μ L in ascetic fluid. It is recommended to initiate prompt antibiotic therapy without awaiting for bacterial culture report. About 50% of the AFI

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are culture positive and culturing ascitic fluid at bedside increases the sensitivity of the method in approximately 90%. Cases are usually defined as nosocomial if the diagnosis was made either after 48 h [3] of admission to hospital. The risk of developing AFI is greater in those with coexisting gastrointestinal bleed, previous episode of AFI or low ascitic protein levels as these patients have lower fluid complement levels and opsonin activity. In a study, the ascitic fluid protein concentration in the SBP group (0.72 ± 0.53 g/dL) was significantly lower than that seen in patients with sterile portal hypertension-related ascites (1.36 ± 0.89 g/dL) and was significantly lower than that of patients with ascites due to miscellaneous causes. Of those with sterile ascitic fluid protein concentration less than 1.0 g/dL, 15% developed SBP versus 1.5% of those whose sterile ascitic fluid protein concentration was greater than 1.0 g/dL. Hospitalization could also be a risk factor for SBP since SBP and CNNA in asymptomatic patients of outdoor clinic had a combined prevalence of 3.9%. One-year survival of 67% was better than historical data from hospitalized patients with SBP.

Literature on AFI in children with liver disease is limited, especially in terms of outcome in-hospital, multi-drug resistance organisms and follow-up. In this regard the study published in this issue of *Hepatology International*, by Singh et al. [4] provides much needed data from an Indian tertiary care center about AFI (30%). The authors report a cohort of 194 predominantly pediatric chronic liver disease with mean age of 85 months. More than half the AFI were nosocomial in origin presenting as fever (60%), pain in the abdomen (30%) and diarrhea (7%) and 40% were asymptomatic [4]. Most other studies in the Table 1 have reported fever and abdominal pain as the most prevalent clinical features of AFI [serial number 3, 4, 7, 10, 11]. In a report in 2017, from the same center as Singh et al. a total of 28.6% children with liver disease-related ascites had SBP/CNNA (serial number 4). The prevalence of this Indian center is comparable to that reported from elsewhere: varying between 28 and 43% in children with portal hypertensive ascites and/or end-stage chronic liver disease (serial number 3, 4, 7, 11). The prevalence of SBP decreased in Brazil from 29.06 to 13% in a decade (serial number 10 and 6), whereas around a decade back in Iran the prevalence varied between 20.06 and 36% in similar studies (serial number 8 and 9) and is 27.3% now (serial number 5). Signs of advanced liver disease such as low albumin, prolonged disease, cirrhosis, high Child–Pugh score and hepatic encephalopathy indicated higher likelihood of AFI as reported by Singh et al. [4] and others before (serial number 4, 6, 10). Elevated absolute neutrophil count and positive C reactive protein were also found to be good indicators of AFI (serial number 3 and 5). It has also been reported that total white cell

count declined to 30%, neutrophil count reduced to half and ascitic fluid cultures became negative after 48 h of antibiotic therapy (serial number 9).

In the study by Singh et al. [4], 40% of the children with chronic liver disease and AFI died in hospital and 7% had a 1-year AFI recurrence. Chronic liver disease with SBP was similar to CNNA except for higher in-hospital mortality. Area under ROC curve (AUC = 0.72) showed that Child–Pugh score cut-off 11 had 65% sensitivity and 71% specificity to determine in-hospital mortality [4]. Other studies have reported mortality of 25% and 40%, respectively, associated with AFI and SBP, respectively (serial number 4, 7). In a Brazilian study, the cumulative probability of native liver survival was 77.8% at 1 month, 27.8% at 3 months, and 11.1% at 6 months following the first episode of SBP resulting in mortality in 60% and liver transplant in 39% within a year (serial number 3). AFI follows an episode of bacteremia due to the constant exchange of fluids between the peritoneal and intravascular space. Bacterascites represents the transitory passage of bacteria through the ascitic fluid before lysis resulting from the bactericidal activity of ascites. So some patients may have bacterascites and later develop SBP. But it has also been suggested that the complement deficiency induced by chronic liver disease may be important in the pathogenesis of SBP. There should be immediate initiation of antibiotic treatment after AFI is diagnosed and so, a good knowledge of the local pathogens in the various centers as well as their sensitivity pattern is required. As is evident from table, most episodes of SBP are monomicrobial and due to Gram-negative bacteria, *Escherichia coli* being the most frequently isolated organism. Other frequently isolated bacteria include *Klebsiella*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *S. pneumoniae* and *Enterococci* (table). Some workers have suggested that pneumococcal vaccination may have a role to play in the prevention of SBP in children (serial number 9). In the light of the emergence of MDR bacteria as causative agents of AFI, it is imperative to relook at the first-line antibiotics. The present study by Singh et al. is the first pediatric study to report that 83% of the Gram-negative organisms causing AFI were MDR and 80% of these were nosocomial infections [4]. Similar results have been reported by a global study for isolates from Indian centers [2]. Moreover, in this global report, extensively drug-resistant (XDR) bacteria, which are defined as nonsusceptibility to at least 1 agent in all but less than 2 antimicrobial categories, were present in 33% of isolates from India as compared to other countries (0–16% isolates). Sensitivity to cefoperazone-sulbactam and carbapenem was present in 60% and 70%, respectively, in the present study by Singh et al. [4] which means that 30% of the isolates were carbapenem-resistant and these figures are comparable with the 22% XDR reported by the global study [2] for the isolates from India [2]. On univariate analysis, Singh et al.

Table 1 Studies done in childhood chronic liver disease with ascitic fluid infection

Serial no	Study year and journal references	Sample size	Median age (years)	Prevalence (%)	Risk factors	Death (%)	Gram –ve	Gram +ve	MDR
1	Singh 2019 India. Hepatol Int. 2019 Jul 9. https://doi.org/10.1007/s12072-019-09968-x	193	7	31	Longer duration of illness Higher CTP score	40	<i>E. coli</i> 38% <i>Klebsiella</i> 10% <i>Acinobacter</i> 5%	CONS 14% <i>S. pneumoniae</i> 10% <i>S. fecalis</i> 10%	83% of Gram –ve
2	Ghobrial 2018 Egypt PLoS One. 2018 Oct 5;13(10):e0203808	66	1	33	Fever, abdominal pain ANC and positive CRP	ND	<i>E. coli</i> 20% <i>Klebsiella</i> 20% <i>Pseudomonas</i> 10%	<i>S. aureus</i> 50% <i>S. viridians</i> 10% <i>Acinobacter</i> 10% <i>S. fecalis</i> 10%	ND
3	Veira 2018 Brazil Eur J Gastroenterol Hepatol. 2018 Mar; 30(3):323–327	18	1	ND	ND	60	<i>E. coli</i> 44% <i>Klebsiella</i> 22%	<i>S. viridans</i> 11% <i>Staph aureus</i>	Nil
4	Srivastava 2017 India J Pediatr Gastroenterol Nutr. 2017 Feb;64(2):194–199	262	7	28.6	Higher WBC HE Bacteremia	31.8	<i>E. coli</i> 37% <i>Klebsiella</i> 14.8%	CONS 14.8% <i>S. fecalis</i> 3.1%	ND
5	Kalvandi 2016 Iran. Hepat Mon. 2016 Jul 23;16(8):e38973	150	4.7	27.3	CRP	ND	<i>E. coli</i> 41% <i>Klebsiella</i> 11% <i>Acinobacter</i> 11%	<i>S. pneumoniae</i> 11% <i>Enterococcus</i> 18%	ND
6	Preto-Zamperlini 2014 Brazil J Pediatr Gastroenterol Nutr. 2014 Jan;58(1):96–98	152	2–18	13	CRP Lower albumin High WBC prolonged PT	ND	<i>Haemophilus influenza</i> <i>Bacteroides</i>	<i>S. pneumoniae</i> 44%	ND
7	El-Shabrawi 2011 Egypt Italian J Pediatr 2011;37(1):26–29	30	5.1	43	pH gradient at a cut off ≥ 0.1	23	<i>Bacteroides</i> (40%),	<i>S. aureus</i> (20%), <i>Streptococcus</i> (40%)	ND
8	Deghani 2007 Iran Pediatr Transplant. 2007;11:21–23	83	8 + 5.1	36.1	ND	ND	ND	ND	ND
9	Haghighat 2006 Iran World J Gastroenterol. 2006;12(36):5890–5892	63	5.5	20.6	ND	8	<i>E. coli</i> 15%	<i>S. pneumoniae</i> 38.5% <i>S. viridans</i> 15%	0%
10	Veira 2005 Brazil J Pediatr Gastroenterol Nutr. 2005 Mar;40(3):289–94	41	5.2	29.2	Cirrhosis Low albumin	ND	<i>Klebsiella</i> , <i>E. coli</i> and <i>Salmonella</i>	<i>S. aureus</i>	ND
11	Larcher 1985 J Pediatr. 1985 Jun; 106(6):907–12	11	–	ND	ND	ND	<i>Klebsiella</i> ,	<i>S. pneumoniae</i> 80%	ND

MDR multi drug resistance, CPT score Child Turcotte Pugh score, CRP C reactive protein, ND not described, ANC absolute neutrophil count, WBS white blood cell, PT prothrombin time, *E. coli* *Escherichia coli*, CONS coagulase negative *Staphylococcus*, *S. pneumoniae* *Streptococcus pneumoniae*, *S. fecalis* *Streptococcus fecalis*, *S. viridians* *Streptococcus viridans*

[4] found that the nosocomial acquisition of infection and history of antibiotics exposure prior to the index admission were significantly associated with development of antibiotics resistance. On multivariate analysis, history of antibiotics exposure independently predicted the development of resistant organism in AFI [OR (95% CI): 15.7 (1.42–174.20); $p=0.025$] [4]. Independent risk factors for MDR bacteria were infection in Asia (particularly in India), use of antibiotics in the 3 months before hospitalization and prior health care exposure in the global study [2]. Fernandez et al. in their hallmark work report that nosocomial origin, norfloxacin prophylaxis, previous infection with MDR bacteria and use of beta-lactams were risk factors for new MDR infections, treatment failure and poor survival in their cohort of decompensated cirrhosis among adults [5]. There have been many reports from across the world as well as India about emergence of MDR bacteria as a causative agent of AFI [2, 5]. The alarming increase in usage of injudicious antibiotic and the emergence of MDR isolates, emphasizes on careful use of antibiotics and an urgent need for early detection of these isolates for better treatment outcome.

The increasing emergence of MDR pathogens is causing the failure of traditional treatment regimens for nosocomial SBP, namely third-generation cephalosporins. According to the recent recommendations, third-generation cephalosporins should be restricted only to selected patients, particularly in case of community-acquired infections [6]. Singh et al. [4] suggested use of cefoperazone-sulbactam or carbapenems as first line of antibiotics in children with nosocomial AFI. Two recent studies showed that cefoperazone/sulbactam had a lower success rate and a higher 14-day mortality rate compared with carbapenems in bloodstream infections due to extended spectrum beta-lactamase producing *Enterobacteriaceae* [7, 8]. Hence cefoperazone/sulbactam could be considered as empirical therapy in less severe patients with nosocomial infections or as definitive therapy when antimicrobial susceptibility test is available. But the severe nosocomial infections should be treated with carbapenems as the first line of therapy. Finally, children with CLD and AFI should be listed for early liver transplantation to improve their survival. For insight into future strategies please see the graphical abstract.

Compliance with ethical standards

Conflict of interest I have no conflict of interest to declare.

References

1. Runyon BA, AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009;49:2087–2107
2. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, International Club of Ascites Global Study Group, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. *Gastroenterology* 2019;156(5):1368.e10–1380.e10
3. Alexopoulou A, Vasilieva L, Agiasotelli D, Siranidi K, Pouriki S, Tsiriga A, et al. Extensively drug-resistant bacteria are an independent predictive factor of mortality in 130 patients with spontaneous bacterial peritonitis or spontaneous bacteremia. *World J Gastroenterol* 2016;22:4049–4056
4. Singh SK, Poddar U, Mishra R, Srivastava A, Yachha SK. Ascitic fluid infection in children with liver disease: time to change empirical antibiotic policy. *Hepatol Int* 2019;9:45. <https://doi.org/10.1007/s12072-019-09968-x> (Epub ahead of print)
5. Fernández J, Acevedo J, Castro M, García O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012;55(5):1551–1561
6. Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: results of a randomized, controlled clinical trial. *Hepatology* 2016;63:1299–1309
7. Su J, Guo Q, Li Y, Wu S, Hu F, Xu S, et al. Comparison of empirical therapy with cefoperazone/sulbactam or a carbapenem for bloodstream infections due to ESBL-producing *Enterobacteriaceae*. *J Antimicrob Chemother* 2018;73(11):3176–3180
8. MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN). Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with *E coli* or *Klebsiella pneumoniae* bloodstream infection and ceftioxone resistance: a randomized clinical trial. *JAMA* 2018;320(10):984–994

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