



Changing epidemiology in spontaneous bacterial peritonitis and challenging balance between new strategies in empirical antibiotics and emergence of resistant bacteria

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It has now been well described that bacterial infections are a common complication of liver cirrhosis and the most frequent precipitant of acute-on-chronic liver failure (ACLF). ACLF, in turn, is a major risk factor for developing nosocomial infections which have a major deleterious effect on prognosis (1). Spontaneous bacterial peritonitis (SBP) accounts for 25% of infections in these patients and carries significant mortality (2). A recent study has shown that inappropriate empirical antibiotic therapies for infection in ACLF actually increases 90-day mortality (2). However, there is also evidence that, over the years, improved timing and accuracy of the diagnosis of SBP as well as appropriate antibiotic therapy can reduce mortality from over 90% to 20% (3,4).

Historically, SBP was a condition typically caused by Gram-negative bacteria and the literature in the 1990s widely reported a predominance of enteric organisms such as *Escherichia coli* and *Klebsiella spp.* accounting for around 80% of all cases of SBP (5). At that time, Gram-positive bacteria (GPB) only accounted for 25% of SBP infections with a predominance of *Streptococci* (6). *Enterococci* accounted for 6–10% and *S. aureus* for only 2–4% of all SBP infections (7). As such, many local and international antimicrobial guidelines for its empiric treatment are designed to cover this spectrum of bacteria.

Since the turn of the millennium, however, there has been a growing awareness that the prevalence of GPB in liver cirrhosis has been on the increase, particularly in nosocomial infections. This is likely due to widespread use of prophylaxis with quinolones, increasing invasive procedures

and admissions to critical care units (8,9). Concurrently, due to over-exposure to antibiotics (10), there has also been an alarming rise in the worldwide incidence of multi-drug resistant (MDR) organisms in recent years, the trend of which is also pervasive in the cirrhotic population (9). Recognised risk factors for development of MDR infections in cirrhotic population are nosocomial origin or health care contact, previous treatment with beta-lactams, long-term prophylaxis with quinolones and recent infection with MDR bacteria (11). Resistance emergence is made more concerning by the lack of any recent or significant developments in novel anti-microbial therapy. As such, there has been a shift in focus towards anti-microbial stewardship and the judicious use of antimicrobials. The challenge in the current climate is therefore to be able to treat these high-risk, functionally immunosuppressed, end-stage liver disease patients promptly and appropriately, whilst minimising exposure to unnecessary or ineffective antibiotics.

It is in this context that Fiore *et al.* have sought to illustrate a) that there has been an epidemiological change in the profile of causative bacteria of SBP since 2000, specifically towards GPB and MDR, and b) that there is thus a need to update our empiric antibiotic guidelines accordingly (12).

Their review looked at a total of 29 studies from five continents, six of which were multi-centre studies. The retrospective and prospective studies, as well as the data from one randomised control trial, drew data from 1995 to 2016. The mean study size was 131 participants (median 77;

range, 10–575).

Retrospective analyses of pre-2000 data from South Korea, France and Greece showed rates of GPB that were consistent with early reports in the 1990s (18.6–25%). Post-2000 data varied widely between centres but on the whole supported a trend towards higher proportions of GPB.

In South Korea, Iran and Pakistan there was no marked increase in rates of Gram-positive bacteria after 2000 (prevalence 16.7–28.6%). In China, the studies were larger but showed mixed results with GPB being isolated in 27.8–53% of cases. The results from Africa (31.8–73.2% GPB), North America (57.1–80%) and South America (63.6%) appear to suggest a higher prevalence of GPB, however these results were drawn from small numbers of small studies. The studies from Europe more consistently showed higher rates of GPB post-2000 (35.8–68.3%) across France, Spain, Germany and Denmark.

There is also growing evidence in this review that the GPB profile is evolving, with an increasing proportion of GPB SBP being caused by *S. aureus* and *Enterococci*, particularly in the hospital setting. The authors raise the important clinical conundrum of how we determine whether *coagulase-negative staphylococcal* results are due to contamination of ascitic samples with skin commensal organisms or true pathogens. If we are to promote judicious use of antibiotics this will certainly be a question worth addressing.

Perhaps the most worrisome findings, however, relate to the emergence and prevalence of multi-drug resistant organisms in Asia, North America and Europe. In China, subgroup analysis according to community versus nosocomial onset showed a worryingly high rate of MRSA (85.7%, 6/7 patients) in the latter group. The cases from the United States also identified vancomycin-resistant *Enterococci* in SBP ascites and, in Canada, the rates of resistance to 3rd generation cephalosporins (3GC) in GPB were as high as 34.1% (intrinsic) to 57.1% (acquired). In one Spanish study of 246 patients, GPB made up 35.8% of cases and, within the nosocomial cohort, 27% were MDR-GPB. A randomised clinical trial in Italy, looking at the treatment of nosocomial SBP, identified GPB in 62.5% and a total MDR rate of 37.5%. A French study of 183 patients also showed that *S. aureus* isolates, which accounted for 36/125 GPB cases, was made up of MRSA strains in 94.4% of those cases, and it was independently and significantly associated to a higher mortality in cirrhotic patients.

Based on these findings, Fiore et al suggest that the current widely accepted use of 3GC empirical treatment is now outdated as it does not adequately cover GPB or

emerging MDR. This suggestion is in agreement with epidemiological findings (11,13) and is clinically significant following a recent study showing that inappropriate antibiotic treatment of bacterial infections in patients with ACLF is associated with poorer outcome including higher critical care requirements, worse evolution of ACLF disease course and higher 28- and 90-day mortality rates (2).

Taking into account the altered physiology in end-stage liver disease patients, Fiore et al advise the avoidance of aminoglycosides, linezolid, teicoplanin, and tigecycline due to the risk of nephrotoxicity, thrombocytopenia, poor bioavailability in ascites and the need to dose adjust in liver failure, respectively. They propose an early empiric approach for SBP with daptomycin, ceftaroline and meropenem where there is a high prevalence of MDR organisms such as VRE, MRSA or ESBL or to continue using 3GC (i.e., ceftriaxone or cefotaxime) when the risk of MDR is low. Empirical treatment should be followed by early de-escalation of antimicrobial therapy once sensitivities are known, in order to reduce development of resistance. It is worth considering that up to 50% of ascites with a polymorph count $>250/\text{mm}^3$ go on to have negative cultures but should nevertheless be treated as per culture-positive SBP as it follows a similar clinical course (14). In these cases it would obviously not be possible for any antibiotic de-escalation to be informed by sensitivities and therefore it is likely that many of these patients will complete their course of treatment on empirical antibiotics.

The most pertinent point raised from this paper is that there is clear inter-centre variability and the clinical challenge is therefore to fully understand both the regional prevalence of SBP micro-organisms as well as individual risk factors for MDR [such as nosocomial or healthcare-related setting, previous quinolone or -lactam exposure, or previous MDR infection (8)] in order to instigate appropriate and judicious antimicrobial therapy. Obviously, a blanket change in antimicrobial practice to cover MDR will only further drive the emergence of even more resistant bacteria.

Finally, the issue of SBP prophylaxis remains unaddressed in light of the changing epidemiology. Current guidelines recommend that patients at risk of SBP [i.e., ascitic protein concentration $<15 \text{ g/L}$ along with liver failure or renal dysfunction (15)] should be considered for primary prophylaxis and all patients following a single case of SBP should be started on secondary prophylaxis due to the high risk of recurrence (14,15). However, there is growing consensus that quinolone exposure is associated

with the development of resistant strains (8) and any long-term prophylactic antibiotic use will certainly contribute to the evolution of MDR.

Fiore *et al* review adds further weight to the emerging worldwide trend towards high frequency of GPB in SBP and the rise in MDR, particularly in nosocomial SBP. A change in antimicrobial practice to reflect this is necessary for optimisation of both antimicrobial stewardship and patient outcomes. Thus, new strategies of empirical antibiotic treatment should be tailored according to the local patterns of antibiotic resistance. MDR pathogens differ hugely not only between different countries but also between different areas within the same country. Ideally, every single area should identify its own pattern of resistance along with risk factors and thus, the use of effective empirical antibiotic treatment against MDR could be narrowed to those with high risk of MDR infection only, keeping the employment of new antibiotics to the minimum necessary.

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