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REVIEW

Current concepts and future strategies in the antimicrobial therapy of emerging Gram-positive spontaneous bacterial peritonitis

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Abstract

Spontaneous bacterial peritonitis (SBP) is the most common infection in end-stage liver disease patients. SBP is defined as an ascitic fluid infection with a polymorphonuclear leucocyte count $\geqslant$ 250/mm^3 without an evident intra-abdominal surgically treatable source. Several mechanisms contribute to SBP occurrence, including translocation of gut bacteria and their products, reduced intestinal motility provoking bacterial overgrowth, alteration of the gut's barrier function and local immune responses. Historically, Gram-negative enteric bacteria have been the main causative agents of SBP, thereby guiding the empirical therapeutic choice. However, over the last decade, a worryingly increasing prevalence of Gram-positive and multi-drug resistant (MDR) SBP has been seen. Recently, the microbiological spectrum of SBP seems to have changed in Europe due to a high prevalence of Gram-positive bacteria (48%-62%). The overall proportion of MDR bacteria is up to 22%-73% of cases. Consequently, empirical therapy based on third-generation cephalosporins or amoxicillin/clavulanic acid, can no longer be considered the standard of care, as these drugs are associated with poor outcomes. The

aim of this review is to describe, with an epidemiological focus, the evidence behind this rise in Gram-positive and MDR SBP from 2000 to present, and illustrate potential targeted therapeutic strategies. An appropriate treatment protocol should include daptomycin plus ceftaroline and meropenem, with prompt stepdown to a narrower spectrum when cultures and sensitivity data are available in order to reduce both cost and potential antibiotic resistance development.

Key words: Spontaneous bacterial peritonitis; Multi-drug resistant bacteria; End-stage liver disease; Cirrhosis; Critically ill patient

Core tip: Spontaneous bacterial peritonitis (SBP) is the most common infection in end-stage liver disease cirrhotic patients. Over the last decade, a worryingly increasing prevalence of Gram-positive and multi-drug resistant (MDR) SBP causative bacteria has been seen. Numerous driving factors have been proposed as associated with this epidemiological change. The aim of this review is to describe, with an epidemiological focus, the evidence behind this rise in Gram-positive and MDR SBP from 2000 to present, and illustrate potential targeted therapeutic strategies. Third-generation cephalosporins should be avoided in clinical settings with a high prevalence of MDR. An appropriate treatment protocol should include daptomycin plus ceftaroline and meropenem.

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INTRODUCTION

The development of abdominal ascites is the most frequent complication in cirrhotic patients[1], and infected ascites, better known as spontaneous bacterial peritonitis (SBP), is the most common infection in these patients, together with urinary tract infections[2]. SBP is defined as a polymorphonuclear (PMN) leucocyte count $\geqslant$ 250/mm^3, with or without positive ascitic culture and the absence of other sources of sepsis in the peritoneum or adjacent tissues[3]. SBP is a distinct clinical entity, as opposed to bacteriascites (positive ascitic culture with PMN < 250/mm^3, not needing therapy in cases of no accompanying symptoms) and secondary bacterial peritonitis, which are usually polymicrobial and linked to the inflammation or perforation of an abdominal organ[3].

Several mechanisms contribute to the occurrence of SBP, including translocation of gut bacteria and their products, reduction of intestinal motility provoking bacterial overgrowth, alteration of the gut's barrier function and local immune responses[4]. These premises explain why historically Gram-negative bacteria (GNB) have been the main causative agents of SBP, thereby guiding the empirical therapeutic choice[5]. However, over the last decade the prevalence of Gram-positive bacteria (GPB) and multidrug resistant (MDR) SBP has increased worryingly[6]. Important driving factors for this epidemiological change have been the extensive use of quinolones, as a prophylactic measure, and the increasing degree of instrumentalization of patients suffering from cirrhosis[7]. Consequently, empirical therapy based on third-generation cephalosporins (3GCs) or amoxicillin/clavulanic acid, especially within a healthcare setting, can no longer be considered the standard of care due to poor outcomes[8].

Bacterial infections are the primary cause of death in patients with end-stage liver disease (ESLD), and require timely and appropriate treatment[9]. Thus, the aim of this review is to describe, with an epidemiological focus, the evidence behind this rise in Gram-positive and MDR SBP from 2000 to present, and illustrate potential targeted therapeutic strategies.

EPIDEMIOLOGY OF SBP: CHANGE OF PARADIGM

Globally, since 2000, there has been an increasing relevance of the role of GPB with respect to SBP (Figure 1). A description of this change follows, according to a geographical criterion.

Asia

Before 2000, GNB were, in consistency with the previous literature[10], the most prevalent etiologic cause of SBP in Asian cohorts of SBP patients. Then, changes occurred, but in a distinct fashion from country to country. In a retrospective study conducted in South Korea, which reviewed records of individuals diagnosed with SBP in 1995, 1998 and 1999, the rate of GPB was just 18.6% (44/237), with just 5 cases of infection by *Staphylococcus aureus* and 3 by *Enterococcus* spp., while the majority of GPB were represented by *Streptococcus* spp.[11]. These data were substantially confirmed by another South Korean retrospective study (episodes referring to the period from October 1998 to August 2003) that showed a proportion of GPB equal to 20.8% (22/106); no strains of *S. aureus* were detected, but there were 16 streptococci and 8 enterococci[12].

In a further South Korean retrospective study, which analysed cases from Janua ry 2002 to December 2004, the prevalence of GPB was also low; the bacterial isolates totalled 204 and *S. aureus*, *Enterococcus* spp. and *Streptococcus* spp. accounted for 3.9% (8/204), 3.9% (8/204) and 8.8% (18/204), respectively[13]. In addition, Heo *et al*[14] found a marginal proportion of GPB in their South Korean retrospective cohort (from June 2005

Figure 1 Worldwide prevalence of spontaneous bacterial peritonitis due to Gram-positive bacteria.

to May 2006), namely 16.7% (11/65). Interestingly, when keeping South Korean retrospective cohorts under consideration, the rate of GPB increases when data are split according to the onset of infection. Cheong *et al*[15] reviewing medical records from 1 January 2000 to 30 June 2007, found a relatively low number of GPB (22.9%, 54/236), but among nosocomial SBP (N-SBP; which occurred > 48 h after hospital admission), this rate was equal to 29.3% (37/126). At any rate, South Korea does not seem to be impacted by a remarkable increment of GPB. A recently published retrospective study, referring to a 10-year period (from 2005 to 2014) and comparing cases of culture-positive SBP with cases of culture-negative SBP, showed a rate of GPB equal to 25.5 (66/259), with a low number of *S. aureus* (2.7%, 7/259) and *Enterococcus* spp. (3.5%, 9/259)[16].

On the contrary, in China, the epidemiological shift towards GPB has been more apparent. In a retrospective study of 98 patients, 48 from 1996 to 2002, and 50 from 2003 to 2009, the proportion of GPB passed from 27% (13/48) to 53% (26/49); the rate of staphylococci also increased from 14% (7/48) to 37% (18/49), but with only 1 case of methicillin-resistant *S. aureus* (MRSA)[17]. More importantly, in-hospital mortality was greater among GPB-SBP than GNB-SBP cases (26% *vs* 11%, namely 7 deaths *vs* 2 deaths), although the result was not significant (P = 0.20)[17]. In a subsequent retrospective study conducted in China, which reviewed medical records from 2011 to 2013, Li *et al*[18] found a less prominent rate of GPB, equal to 27.8% (85/306), overlapping between nosocomial (27.3%, 27/99) and non-nosocomial episodes (28.0%, 58/207). Nonetheless, a worrisome percentage of MRSA stood out from this study: 37.5% (6/16) among non-nosocomial infections and, even worse, 85.7% (6/7) among nosocomial cases[18].

More recently in a Chinese study, performed to compare the microbiological profiles of N-SBP and community acquired SBP (CA-SBP), 575 strains were isolated from January 2014 to December 2014. In the CA-SBP cases, the most frequently isolated pathogens were *Escherichia coli* (*E. coli*) (27.4%), coagulase-negative staphylococci (22%), *Klebsiella pneumoniae* (13.7%), *Enterococcus* spp. (9%) and *Streptococcus* (8.2%). In the N-SBP, the most frequently isolated pathogens were *E. coli* (25.9%), coagulase-negative staphylococci (23.4%), *K. pneumoniae* (2.5%), *Enterococcus* spp. (16.6%) and *Streptococcus* (6.2%). In the statistical analysis, there were no significant differences in the distributions of GPB between the CA and N-SBP. In contrast, compared with the CA-SBP, the distribution of enterococci was increased in the N-SBP (9.0% *vs* 16.6%, $P < 0.05$)[19].

Different results have come from studies in other Asian countries. In Iran, a prospective study (from November 2005 to December 2007) showed a proportion of GPB equal to 27.3% (12/44)[20]. A similar result (28.6%, 90/314) was found in another study conducted in Iran (from April 2005 to September 2011)[21]. A small cohort from Pakistan showed a relatively low percentage of GPB: 25% (3/12) in a 2007 prevalence study[22].

Africa

In an Egyptian prospective cohort, the burden of GPB turned out to be as high as 73.2%, namely 30

out of 41 episodes, including 10 cases by *Listeria monocytogenes*[23]. In contrast, a retrospective study conducted in Nigeria, which reviewed medical records from August 2009 to July 2010, showed a much smaller proportion of GBP, which although not marginal was equal to 31.8% (7/22)[24].

South America

In a Brazilian retrospective study referring to a 5-year period (from November 2001 to November 2006), a significant rate of GPB emerged despite the lack of a complete microbiological profile of 63 cases [*Streptococcus* spp. 23.8% (15/63), *S. aureus* 7.9% (5/63)][25]. A more recent and prospective multicentre study conducted in Argentina, from March 2011 to April 2012, showed a clear predominance of GPB over GNB [21/33 (63.6%)]; of note, the study, which aimed at investigating the potential association between proton pump inhibitors (PPIs) and SPB, showed no significant difference with regard to PPIs' consumption and duration between patients with and without SBP (as well as with and without other infections) nor with regard to the type of bacteria[26].

North America

A high number of GPB was found in a United States retrospective study, referring to medical records from July 2009 and November 2010: 80% (8/10), including two vancomycin-resistant enterococci (VRE)[27]. The high impact of GPB in SBP in North America has been further confirmed in a Canadian retrospective cohort that reviewed cases from February 2003 to May 2011; the data indicated that 57.1% (44/77) and 34.1% of these strains (15/44) were resistant to 3GCs (acquired or intrinsic resistance)[28].

Europe

In a prospective French study conducted from January 1996 to March 2001, GPB accounted for 68.3% (125/183) of ascitic fluid infections[29]. GPB cases were mainly explained by enterococci (43/125), streptococci (43/125) and *S. aureus* (36/125); the large majority of the latter (94.4%, 34/36) were MRSA[29]. In that study, the multivariate analysis showed that an infection provoked by *S. aureus* (while taking into account cases of bacteraemia) was independently linked to a higher mortality rate in cirrhotic patients (OR = 2.845, 95%CI: 1.421-5.695, P = 0.031)[29]. In France, Gram-positive cocci are today the predominant ascitic fluid microbes, with isolates ranging from 47.4%[30] to 56.1% of cases[31]. Data from a Spanish study, conducted from April 1998 to April 2000, demonstrated a low proportion of GPB (20.3%, 11/54)[32].

In a retrospective study by Ariza *et al*[33], reviewing medical records related to a subsequent period from 2001 to 2009, GPB rate was again relevant [35.8% (88/246)]. Surprisingly, the lowest percentage was among nosocomial infections (27.3%, 18/66) in comparison with community-acquired (36.5%, 18/85) and healthcare-related infections (41.1%, 39/95); however, the highest rate of MDR-GPB was found among nosocomial cases (27.8%, 5/18)[33]. In Italy, interesting data stem from a recently published randomized clinical trial (RCT), conducted from 2011 to 2014. The aim of that RCT was to compare ceftazidime to the combination of daptomycin plus meropenem, applied as an empirical treatment of N-SBP (in this case, defined if it occurred > 72 h after hospital admission); in particular, 62.5% (10/16) of culture-positive cases were due to GPB (8 enterococci)[34]. Of note, the broad-spectrum regimen proved to be significantly more effective with regard to the primary outcome, namely the resolution of SBP after 7 d of treatment (86.7% *vs* 25%; P < 0.001); that finding did not come as a surprise, in the light of the total rate of MDR bacteria [37.5% (6/16)][34].

In Germany, the growing number of GPB was already a touted issue, more than a decade ago. In a prospective cohort from 2002 to August 2006, Umgelter *et al*[35] found a GPB rate equal to 45.4% (20/44, 10 *E. faecium*). Again, in Germany, a retrospective cohort covering a 12-year period (from January 2001 to November 2011) found a predominance of GPB (53.7%, 65/121), where *Enterococcus* spp. (28 out of 65 GPB) played a highly relevant role[36]. In the multivariate analysis, use of antibiotics (OR = 3.875, 95%CI: 1.189-12.631, P = 0.025) and nosocomial infection (OR = 3.287, 95%CI: 1.311-8.243, P = 0.011) were the independent predictors of enterococcal infections, which were associated with higher mortality (12% probability of 90-d survival *vs* 50% in non-enterococcal cases, P = 0.022 by log-rank test) in case of treatment with a 3GC or a quinolone[36]. Also, in a more recent German prospective cohort, followed from March 2012 to February 2016, and focusing only on nosocomial and healthcare-related SBP, GPB were relevant [*Staphylococcus* spp., *Enterococcus* spp. and *Streptococcus* spp. accounted for 40% of cases (20/50)][37].

Greece was one the first countries to warn about the increasing importance of GPB-SBP. Cholongitas *et al*[38], in a retrospective evaluation, observed that the rate of GPB went from 25% (5/20) to 59.1% (13/22%) in two subsequent periods of time, from 1998 to 1999 and from 2000 to 2002, respectively. This trend in Greece was confirmed by another retrospective study, including cases from 2008 to May 2011, with 26 episodes out of 47 (55%) due to GPB, most of all streptococci (10 isolates), followed by 6 *E. faecalis*, 3 *E. faecium* and 2 *S. aureus*; neither VRE nor MRSA were detected[6].

In Denmark, a retrospective review of medical records from 2000 to 2006 showed a proportion of Gram-positive cocci, without considering other GPB, equal to 45.9% (86/187)[39].

CONTROVERSIES RELATED TO THE DIAGNOSIS OF SBP BY GRAM-POSITIVE BACTERIA

Although some authors have previously considered the isolation of coagulase-negative staphylococci within ascitic

culture as skin contamination[15,40,41], today the clinical significance of such a finding appears relevant in both nosocomial[19,34] and community acquired infections[19]. More than 40 years ago, MacGregor and Beaty[42] proposed guidelines to differentiate contamination from significant positive blood cultures in bacteraemic patients; nowadays guidelines, however, are still lacking in their ability to differentiate contamination from significant positive ascitic cultures.

In our opinion, the absence of recommendations based on solid evidence does not justify concluding isolation of coagulase-negative staphylococci as contamination[15]. Future studies are required to establish the hypothetical difference between the contaminants or pathogens.

CURRENT THERAPEUTIC STRATEGIES FOR SBP BY GPB

The current guidelines rely on outdated epidemiology[43-45] and take into account neither the increasing prevalence of GPB nor the emerging phenomenon of MDR bacteria as aetiological agents of SBP[46]. Opinion leaders recommend 3GCs[47] or piperacillin/tazobactam, meropenem ± glycopeptide[1] for patients at risk of MDR SBP. The role of piperacillin/tazobactam in the treatment of life-threatening infections due to extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* is a controversial issue[47-49]; moreover, meropenem is active against ESBL-producing *Enterobacteriaceae* but is weakly active against Gram-positive cocci[50,51]. Glycopeptides are active against Gram-positive cocci, as well as MDR, but their use is not advisable because of their nephrotoxicity. Acute kidney injury is higher in ESLD patients, it could be related to hemodynamic instability and/or hepatorenal syndrome[52]. Furthermore, the minimum inhibitory concentration (MIC) of vancomycin appears to be shifting upwards in some institutions, a phenomenon known as MIC creep; and, where the MIC increase occurs, treatment failure is common[53,54]. Teicoplanin MIC creep has also been described; but, regardless, when it is administered intravenously it does not achieve therapeutic concentration in the ascitic fluid[55].

Antibiotics active against VRE are linezolid, tigecycline, and daptomycin. Linezolid is not recommended in the majority of ESLD and SBP patients because of high frequency thrombocytopenia[56]. A tigecycline dose adjustment is requested in patients with severe hepatic impairment[57,58]. Daptomycin is a lipopeptide active against MDR GPB, including drug-resistant and drug-susceptible *S. aureus* and VRE[59]. Decreased susceptibility to daptomycin has been reported in drug-resistant *S. aureus*; it is frequently accompanied by a paradoxical decrease in beta-lactam resistance, a process known as the "see-saw" effect. Despite the observed discordance in resistance phenotypes, the combination of daptomycin/beta-lactams has been proven clinically effective for the prevention and treatment of infections due to daptomycin-resistant *S. aureus* strains[60,61]. Therefore, daptomycin monotherapy should not be used for the treatment of SBP due to MRSA, unless the isolate is likely to be fully susceptible[62]. The combination of daptomycin plus ceftaroline is highly active against MRSA, the potent bactericidal activity appears to be sufficiently robust to allow rapid de-escalation to single ceftaroline with daptomycin sparing[63]. Furthermore, ceftaroline in combination with daptomycin restores daptomycin activity against daptomycin-resistant VRE strains[64]. Aminoglycoside antibiotics, especially gentamicin, are used in combination with ampicillin for the treatment of enterococcal systemic infections[65]. Despite rigorous patient monitoring, nephrotoxicity appears in 10%-25% of therapeutic courses[66]. Therefore, their use is not advisable in cirrhotic patients. In recent years, an alternative treatment with ampicillin plus ceftriaxone has proved to be safer than gentamicin in combination with ampicillin[67]. In ESLD patients, the combination of ampicillin plus ceftriaxone should be used for SBP due to enterococci, regardless of aminoglycoside resistance-level status.

FUTURE PERSPECTIVES

The 20th century has been characterized by the dramatic effect of the large-scale use of antibiotics after their discovery, saving millions of lives[68]. Unfortunately, natural selection and misuse of antibiotics, both in human beings and in animals, have led to the development of difficult-to-treat infections by MDR bacteria, also known as superbugs, the nightmare of the new century[69]. Research efforts by pharmaceutical companies are not keeping pace with the worldwide spread of superbugs and this has prompted new strategies to optimize existing resources, such as the reviving of old antibiotics[70], the implementation of antimicrobial stewardship programs[71,72], and the judicious use of new anti-infective agents[73]. However, the epidemiology of bacterial infections has a huge inter-centre variability and the therapeutic approach should be inspired by the principle of "one size does not fit all", which obviously also applies to SBP[74]. In other words, the current challenge is to accurately identify patients with SBP for whom empirical broad-spectrum therapy would be appropriate, with special attention to MDR-GPB in contexts where their prevalence is relevant[74].

Some risk factors are well established. The setting of acquisition (nosocomial or healthcare-related *vs* community-acquired) and the history of exposition to antibiotics, such as beta-lactams and/or quinolones, are probably the main ones[75,76]. Exposure to quinolones, largely used to prevent SBP in cirrhotic patients, is a significant risk factor for MRSA infections[77,78]. Moreover, antibiotics administered within the past 30 d before SBP diagnosis and a lower sepsis-related organ failure assessment (commonly known as SOFA) score proved to be significantly associated with SBP by GPB in a cohort of 77 patients[79]. The impact of MDR-GPB on SBP patient mortality is not well investigated; recently, we performed a systematic review aimed at summarizing the evidence from the literature concerning

Table 1 Characteristics of the studies

Ref.	Journal	Publication year	Observation time span	Study design	Country, clinical setting	Proportion of infections by GPB (%)
Asia - South Korea						
Park *et al*[11]	*J Gastroenterol Hepatol*	2003	1995, 1998, 1999	RC, single centre	South Korea, University Hospital	44/237 (18.6)
Song *et al*[12]	*J Korean Med Sci*	2006	1998 (October) - 2003 (August)	RC, single centre	South Korea, University Hospital	22/106 (20.8)
Cho *et al*[13]	*Scand J Infect Dis*	2007	2002-2004	RC, single centre	South Korea, University Hospital	34/204 (16.6)
Heo *et al*[14]	*Gut Liver*	2009	1998 (June) - 2003 (May)	RC, multicentre	South Korea	11/65 (16.7)
Cheong *et al*[15]	*Clin Infect Dis*	2009	2000 (January) - 2007 (June)	RC, single centre	South Korea, University Hospital	54/236 (22.9)
Na *et al*[16]	*Scand J Infect Dis*	2017	2005-2014	RC, single centre	South Korea, University Hospital	66/259 (25.5)
Asia - China						
Gou *et al*[17]	*Saudi Med J*	2010	1996-2009	RC, single centre	China, University Hospital	39/97 (42.2)
Li *et al*[18]	*World J Gastroenterol*	2015	2011-2013	RC, single centre	China, University Hospital	85/306 (27.8)
Shi *et al*[19]	*Sci Rep*	2017	2014	RC, single centre	China, Tertiary Hospital	293/575 (50.9)
Asia - Other countries						
Kamani *et al*[20]	*BMC Gastroenterol*	2008	2005 (November) - 2007 (December)	PC, single centre	Iran, University Hospital	12/44 (27.3)
Sheikhbahaei *et al*[21]	*Int J Hepatol*	2014	2005 (April) - 2011 (September)	PC, single centre	Iran, University Hospital	90/314 (28.6)
Zaman *et al*[22]	*J Ayub Med Coll Abbottabad*	2011	2007	PC, single centre	Pakistan, University Hospital	3/12 (25)
Africa						
El Sayed Zaki *et al*[23]	*J Infect Public Health*	2011	Not provided	PC, single centre	Egypt, University Hospital	30/41 (73.2)
Oladimeji *et al*[24]	*Pan Afr Med J*	2013	2009 (August) - 2010 (July)	RC, single centre	Nigeria, University Hospital	7/22 (31.8)
South America						
Reginato *et al*[25]	*Sao Paolo Med J*	2011	2001 (November) - 2006 (November)	RC, single centre	Brazil, Tertiary Hospital	20/63 (31.7)
Terg *et al*[26]	*J Hepatol*	2015	2011 (March) - 2012 (April)	PC, multicentre	Argentina	21/33 (63.6)
North America						
Tandon *et al*[27]	*Clin Gastroenterol Hepatol*	2012	2009 (July) - 2010 (November)	RC, single centre	United States, University Hospital	8/10 (80)
Chaulk *et al*[28]	*Can J Gastroenterol Hepatol*	2014	2003 (February) - 2010 (May)	RC, single centre	Canada, Tertiary Hospital	44/77 (57.1)
Europe						
Campillo *et al*[29]	*Clin Infect Dis*	2002	1996 (January) - 2001 (March)	PC, single centre	France, Tertiary Hospital	125/183 (68.3)
Piroth *et al*[31]	*BMC Infect Dis*	2014	2010-2011	PC, multicentre	France, University Hospitals	32/57 (56.1)
Thévenot *et al*[30]	*Am J Gastroenterol*	2016	2014 (March) – 2015 (August)	PC, multicentre	France	40/84 (47.4)
Fernández *et al*[32]	*Hepatology*	2002	1998 (April) - 2000 (April)	PC, single centre	Spain, University Hospital	11/54 (20.3)
Ariza *et al*[33]	*J Hepatol*	2012	2001-2009	RC, single centre	Spain, University Hospital	88/246 (35.8)
Piano *et al*[34]	*Hepatology*	2016	2011-2014	RCT, multicentre	Italy	10/16 (62.5)
Umgelter *et al*[35]	*Infection*	2009	2002 (January) - 2006 (August)	PC, single centre	Germany, University Hospital	20/44 (45.4)
Reuken *et al*[36]	*Aliment Pharmacol Ther*	2009	2002 (January) - 2011 (November)	RC, single centre	Germany, Tertiary Hospital	65/121 (53.7)
Lutz *et al*[37]	*Eur J Clin Invest*	2017	2012 (March) - 2016 (February)	PC, single centre	Germany, University Hospital	20/50 (40)
Cholongitas *et al*[38]	*Liver Int*	2005	1998-200	RC, single centre	Greece, University Hospital	18/42 (42.9)
Novocic *et al*[39]	*Scand J Gastroenterol*	2012	2000-2006	RC, multicentre	Denmark, University Hospitals	86/187 (45.9)

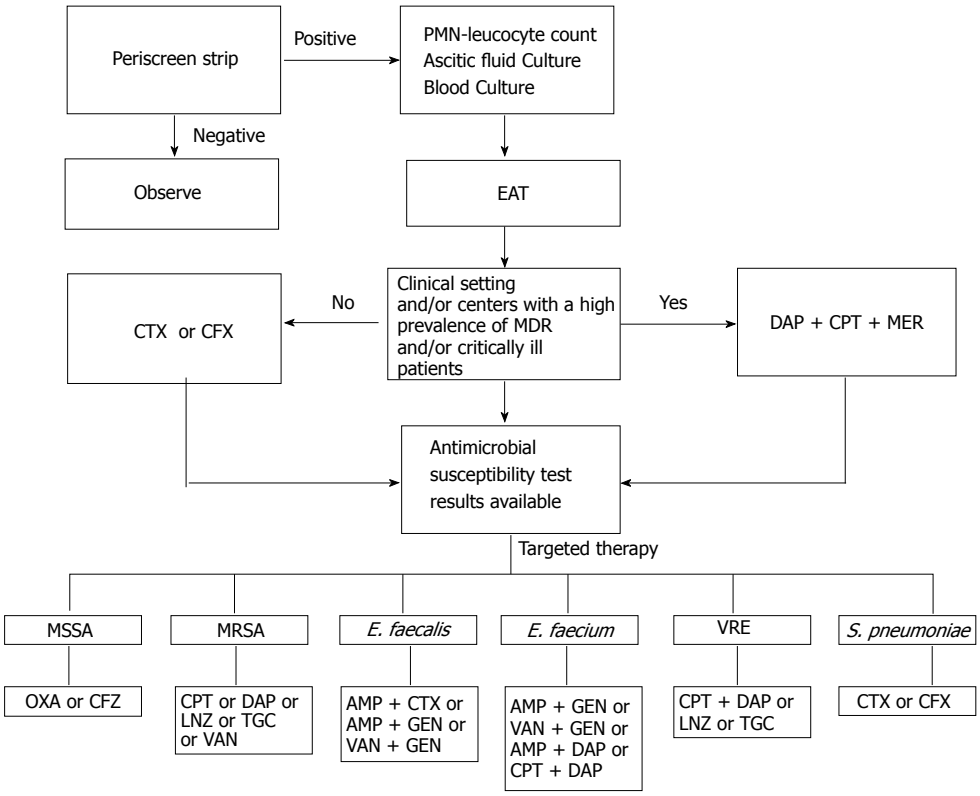

Figure 2 Infection management algorithm of spontaneous peritonitis due to Gram-positive bacteria[45,46,51,54,61,62,65,72,80,82-84]. AMP: Ampicillin; CFX: Cefotaxime; CFZ: Cefazolin; CPT: Ceftaroline; CTX: Ceftriaxone; DAP: Daptomycin; EAT: Empiric antibacterial therapy; GEN: Gentamicin; LNZ: Linezolid; MDR: Multidrug resistant; MER: Meropenem; MRSA: Methicillin-resistant *S. aureus*; MSSA: Methicillin-susceptible *S. aureus*; OXA: Oxacillin; PMN: Polymorphonuclear; TGC: Tigecycline; VAN: Vancomycin; VRE: Vancomycin-resistant enterococci.

the epidemiology of nosocomial cases of SBP, in order to highlight the importance of MDR bacteria outcome; of the initial 2556 manuscripts retrieved, only 9 were included in the qualitative analysis, and a quantitative analysis on mortality was not possible[80].

Risk factors could be integrated into predictive models of mortality in individuals with SBP so as to further help identify patients in need of more aggressive therapeutic strategies from the very start of the infective process[81].

CONCLUSION

GPB are increasingly important as causative agents of SBP. In some contexts, they even supersede GNB as the main cause of this infection (Table 1 describes the main features of included studies). In parallel with this phenomenon, physicians have to face the rise of superbugs, both among GNBs and GPBs. In presence of particularly worrisome epidemiological data and other risk factors for superbug infections, a broad-spectrum empirical approach is required, encompassing antibiotics with well-established activity against pathogens, such MRSA and VRE, pending the results of microbiological tests that would allow a de-escalation strategy whenever possible.

On the basis of the current literature, we propose a treatment algorithm for SBP due to GPB (Figure 2). If an ESLD patient with ascites is "symptomatic" for SBP (temperature above 38 ℃ or below 36.5 ℃, chills, abdominal tenderness, arterial hypotension, developing or worsening hepatic encephalopathy, gastrointestinal bleeding within the previous 15 d) it is necessary to perform a Periscreen strip on the ascitic fluid[30]. If the Periscreen strip is positive the patient requires immediate hospitalization with comparison of this result with cytology and immediate microbiological cultures. A culture of ascitic fluid and blood should systematically be carried out at the bedside[34]. Empiric antibacterial therapy (EAT) should be initiated after obtaining *a*ppropriate cultures. 3GCs should not be used in clinical settings and/or centres with a high prevalence of MDR bacteria. ESLD patients with SBP in clinical settings and/or centres with a high prevalence of VRE, MRSA and ESBL should immediately receive broad-spectrum EAT[82]. An appropriate treatment protocol should include daptomycin plus ceftaroline and meropenem[83]. When the culture is positive and susceptibility data are available, an antibiotic with a narrower spectrum should be promptly initiated (early de-escalation strategy); this strategy limits the selection of antibiotic resistances and saves on costs[83].

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