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MINIREVIEWS

Antibiotic resistance in patients with liver cirrhosis: Prevalence and current approach to tackle

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Abstract

Regardless of etiology, complications with bacterial infection in patients with cirrhosis are reported in the range of 25%-46% according to the most recent data. Due to frequent episodes of bacterial infection and repetitive antibiotic treatment, most often with broad-spectrum gram negative coverage, patients with cirrhosis are at increased risk of encountering multidrug resistant bacteria, and this raises concern. In such patients, extended-spectrum beta-lactamase and AmpC-producing *Enterobacterales*, methicillin- or vancomycin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococci*, carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, all of which are difficult to treat, are the most common. That is why novel approaches to the prophylaxis and treatment of bacterial infections to avoid antibiotic resistance have recently been developed. At the same time, our knowledge of resistance mechanisms is constantly updated. This review summarizes the current situation regarding the burden of antibiotic resistance, including the prevalence and mechanisms of intrinsic and acquired resistance in bacterial species that most frequently cause complications in patients with liver cirrhosis and recent developments on how to deal with multidrug resistant bacteria.

Key Words: Cirrhosis; Bacterial complications; Antibiotics; Intrinsic resistance; Acquired resistance; Probiotics; Vaccines

Core Tip: This review presents current data on bacterial complications in patients with cirrhosis. A comprehensive analysis of the prevalence of antibiotic resistant isolates with a brief presentation of intrinsic and acquired resistance mechanisms was performed in the most prevalent pathobionts causing infections in cirrhosis. Current approved and developing options to treat bacterial complications to avoid resistance are also discussed.

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INTRODUCTION

Numerous clinical studies have revealed that, in patients with liver disease, bacterial complications manifest mainly in the advanced stage, as classified by Child-Pugh[1,2]. Their prevalence does not vary significantly depending on the etiology of cirrhosis[3] and is reported in the range of 25% to 46% according to the most recent data[4,5]; 44.4% of such patients suffer more than one episode[3].

The development of bacterial infection can accelerate the course of liver disease at any stage[6]. Regardless of the severity of liver disease itself, it can decompensate liver function and significantly increase the mortality rate[3,7-9]. The 30-mo survival rate in cases of cirrhosis with bacterial complications has been reported to be around half that of those without complications (34% *vs* 62%, respectively)[7]. Furthermore, lethal outcomes occurred more frequently when infection was caused by multidrug-resistant bacteria (MDR) than non-MDR bacteria (72% *vs* 28%, respectively)[10]. According to an international expert proposal, MDR was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories[11].

Due to frequent episodes of bacterial infection and repetitive antibiotic treatment, most often with broad-spectrum Gram negative coverage, patients with cirrhosis are at a higher risk of encountering MDR bacteria[5]. Due to the frequent need for invasive procedures, such as large-volume paracentesis or varices ligations, approximately 37% of patients with cirrhosis are readmitted to the hospital within 30 d[12], while hospitalization itself can be considered a risk factor since it can involve infection with bacteria spread in hospital units, including their MDR representatives[5].

Many research efforts have recently been directed towards developing strategies for the prevention of bacterial complications and demonstrating more efficient methods for the treatment of bacterial infections that avoid contributing to resistance. At the same time, our knowledge of resistance mechanisms is constantly updated. The above considerations led to this summary of the current situation with respect to the burden of antibiotic resistance in patients with liver cirrhosis.

In this review, the prevalence and mechanisms of antibiotic resistance in bacterial species that most commonly cause complications in patients with cirrhosis are discussed, alongside recent developments on how to cope with multidrug-resistant bacterial infections.

THE MOST COMMON BACTERIAL COMPLICATIONS IN PATIENTS WITH CIRRHOSIS

The prevalence of bacterial complications

Lymph fluid leakage into the peritoneal cavity (ascites) and bleeding of the esophageal varices are often diagnosed in patients with advanced cirrhosis. Ascites in combination with increased intestinal permeability and impaired venous blood flow comprise favorable conditions for bacterial growth. What is important to stress is that, in such patients, bacterial infection can manifest without an obvious source. Most often (around one third of patients with cirrhosis) spontaneous bacterial peritonitis (SBP) occurs[2]. When ascites is diagnosed, the 5-year survival rate is 30%-40%[13]. Acute decompensation is strongly associated with bacterial infection (22.3% of cases), especially when accompanied by acute-on-chronic liver failure (44% of cases)[14].

In addition to commonly diagnosed SBP, urinary tract infections (12%-25%) and pneumonia (15%-20%) are often present in patients with cirrhosis[3,4,15]. Less frequently, skin and soft tissue infections (5%-10%) and other miscellaneous infections (approximately 12%) can manifest[2-4]. In approximately 10% of patients, a life-threatening condition develops, such as spontaneous bacteremia[16,17]. The reported 30-day mortality rate of such patients is extremely high: 45%-53%[10,17]. Although rarely, spontaneous bacterial empyema (SBE) – an infection of preexisting hepatic hydrothorax fluid – most frequently caused by *Ecsherichia coli* or *Klebsiella pneumoniae* can occur[18].

The common sources of infection agents

Although infection agents are most commonly community-acquired (in 30% to 50% of cases)[4], due to the frequent need for various invasive procedures, such as peritoneocentesis, endoscopic ligations of the varices, intrahepatic transjugular shunt, percutaneous treatment, *etc.* – patients are at a higher risk of acquiring healthcare-associated or nosocomial infections. According to a study by Fernández *et al*[19], 35% of patients with cirrhosis were diagnosed with nosocomial

infections *vs* 5% of patients without cirrhosis. This finding has also been confirmed by others, suggesting that healthcare-associated infections develop in approximately one third of such patients[4,20].

Commensal gut bacteria can also be the cause of bacterial complications. Inflammatory-like abnormalities of the intestinal mucosa were found in two-thirds of patients with cirrhosis, and this effect becomes more pronounced with disease progression[21]. Patients with cirrhosis are also characterized by prolonged intestinal transit and bacterial overgrowth in the small intestine[22]. These abnormalities are aggravated by impaired immunity (so- called cirrhosis associated immune dysfunction), which is characterized by reduced leukocyte count due to hypersplenism, reduced production of innate immunity proteins such as complement, and general exhaustion of immune cells despite activation of their pro-inflammatory state[4,6,23]. Due to the synergistic effect of the aforementioned conditions, the intestinal barrier is compromised, and this facilitates the translocation of intestinal bacteria into the mesenteric lymph nodes, causing SBP, endotoxemia, or bacteremia[24,25]. The activation of pro-inflammatory cytokines and the tumor necrosis factor alpha facilitates secondary infections and contributes to sepsis-related organ failure[26]. Additionally, portosystemic collaterals slow down the clearance of bacteria and their metabolites from circulation[4,10].

Gram-negative intestinal bacteria are more likely to translocate than Gram-positive (approximately 60% *vs* approximately 40%)[3,22,27]. The most common Gram-negative pathobionts that cause infections in patients with cirrhosis belong to the *Enterobacterales* family (*Escherichia coli*, *Proteus spp.*, *Klebsiella pneumoniae*), while Gram-positive pathobionts belong to the *Enterococcaceae* or *Staphylococcaceae* families (*Staphylococcus aureus*, *Enterococci*)[4,10]. Fungal infections are less common (approximately 4%)[20,27].

ANTIBIOTIC RESISTANCE PATHWAYS AND MECHANISMS

Two antibiotic resistance pathways in bacteria

Because many antibiotics are naturally occurring compounds that bacteria are exposed to throughout their evolution, bacteria have evolved a series of structures and metabolic processes that allow them to survive in antibiotic-enriched environments. Many known antibiotics were mainly discovered as natural metabolites synthesized by Gram-positive bacteria or fungi. For example, *Amycolatopsis orientalis* synthesizes vancomycin; *Streptomyces spp*. – tetracycline; *Micromonospora purpurea* – gentamicin; *Amycolatopsis rifamycinica* – rifamycins; while carbapenems were developed from thienamycin – the naturally derived metabolite of *Streptomyces cattleya*[28]. Seventeen years after penicillin was isolated from the *Penicillium spp*. fungus, cephalosporin was discovered in *Acremonium spp*.[29].

Intrinsic or inherited antibiotic resistance pathways are usually encoded in the bacterial chromosome and passed on to their offspring (Table 1, Figure 1A)[30-33].

Under antibiotic pressure, a bacterium can enhance its resistance by mutations in existing genes. For example, in Gram-negative bacteria, resistance to multiple antibiotics has been developed by loss or mutation of the *oprD* gene, which encodes an outer membrane porin (Table 2, Figure 1B)[30-33]. This can be called acquired resistance[30,31]. Antibiotic resistance genes (ARGs) can also be carried out by plasmids. In this form, they can easily be transmitted between bacteria, whether of the same species or between different species. In general, plasmids, bacteriophages, and extracellular deoxyribonucleic acid (DNA) are the three main pathways of horizontal gene transfer in bacteria through the processes of conjugation, transduction, and natural transformation, respectively[34]. Conjugation is cell-to-cell contact through sexual pili, allowing bacteria to share plasmids or other mobile DNA elements, including ARGs. Bacteria can share genetic information through the transduction process, which is mediated by bacteriophages. Naturally transformable bacteria are able to take up short fragments of naked DNA from their environment.

Mechanisms and influencing factors of antibiotic resistance

Resistance to antibiotics can be achieved by decreasing the permeability of the bacterial wall, controlling the intracellular antibiotic concentration to a harmless level by accelerating the efflux pumps or by enzymatic modification of the antibiotic or its target[30,31]. In this article, a brief overview of intrinsic and acquired antibiotic resistance pathways is presented (Tables 1 and 2), while a detailed description of these mechanisms is well explored in several reviews[30-33].

The mechanisms of antibiotic resistance themselves cannot be significantly influenced by humans. What can be influenced is the selection of antibiotic resistant species under human-driven antibiotic pressures – either in the environment (such as through agricultural activity) or in the human organism (during antibiotic treatment). The use of oral or injected antibiotics for the treatment of any disease is associated with direct selection pressure on the commensal microbiota of any location in the body, primarily the digestive tract. Just one year after the introduction of semisynthetic penicillin, methicillin-resistant *S. aureus* (MRSA) emerged due to the selection of strains with the *mecA* gene, which is responsible for methicillin resistance[30]. After introducing vancomycin for the treatment of MRSA, vancomycin-resistant *S. aureus* (VRSA) was detected shortly thereafter[30].

Bacteria are not only capable of modifying an antibiotic target, but can also use target bypass strategies, as in the case of MRSA. Here, the conventional penicillin binding protein (PBP; an enzyme involved in peptidoglycan biosynthesis) changes to exogenous PBP – PBP2a that is homologous to the original target, but with a lower affinity for β-lactams[33].

Gram-positive bacteria in general are more susceptible to different antibiotics, but can acquire resistance through mutations in their genome or horizontal gene transfer[30]. For example, Boekhoud *et al*[35] have reported a *Clostridioides difficile* isolate resistant to metronidazole due to the plasmid pCD-METRO.

Many bacteria carry multiple MDR efflux pump genes in their chromosomes and can acquire them as plasmids. A tripartite resistance nodulation division pump has been found to be carried by a plasmid, with genes encoding the antibiotic-targeting enzyme New Delhi metalo-beta-lactamase 1 (Table 2)[30]. Although overproduction of the MDR

Table 1 Examples of intrinsic (natural) antibiotic resistance pathways in bacteria

Resistance mechanism	Molecule/process involved	Resistance to antibiotic	Primary host	Genome-encoded	Plasmid-encoded
Decrease in bacterial wall permeability	Reduced porin expression	Different antibiotics	Gram-negative bacteria	*oprD* gene	No
Increase in efflux	Tripartite RND pump family	Different antibiotics	Gram-negative bacteria	Yes	Yes
Antibiotic inactivation by chemical group transfer	Modification	Aminoglycosides	Gram-negative and Gram-positive bacteria	Yes	Yes
	Oxidation	Tetracyclines	Many bacteria	*Tet(X)* genes	Yes
Antibiotic hydrolysis	AmpC beta-lactamases	Broad-spectrum beta-lactams	Gram-negative bacteria: *Enterobacteriaceae*	Yes	Yes
	Carbapenemases	A variety of beta-lactams	*Enterobacteriaceae*	Yes	Yes
Modification of antibiotic target	Modification of peptidoglycan precursors	Glycopeptides: vancomycin	Gram-positive cocci: *Enterococcaceae*	*vanC*, *vanD* operons	*vanA* gene claster
	Alteration of LPS	Polymyxins: colistin	Gram-negative: *Enterobacteriaceae*	Yes	Yes
	Exchange of conventional PBP to PBP2a	Beta-lactams	*Staphylococcaceae*	*mecA* gene	Yes

RND: Resistance-nodulation-division pump family; LPS: Lipopolysaccharide; PBP: Penicillin binding protein.

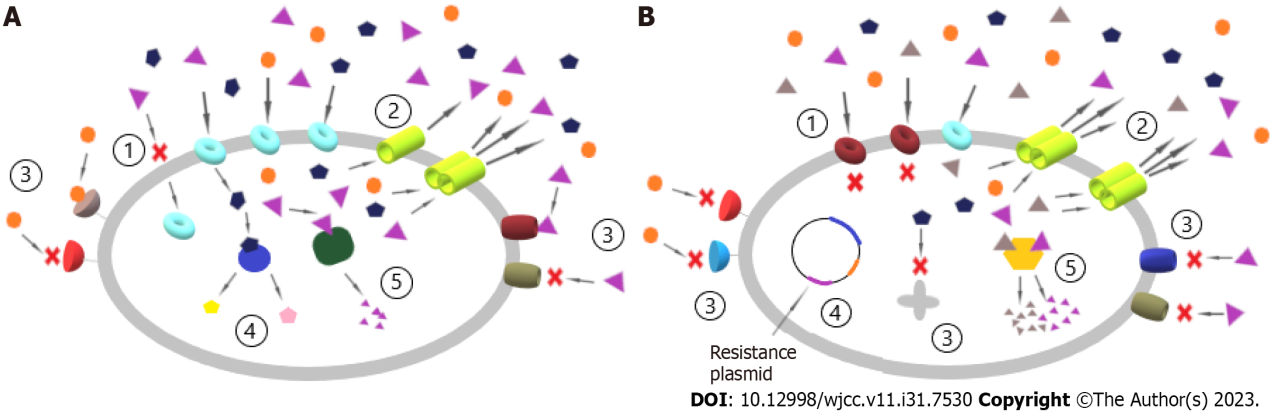

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Figure 1 Antibiotic resistance pathways in bacteria. A: Intrinsic resistance mechanisms. 1: Decrease in bacterial wall permeability: suppression of porin expression, 2: Increase in efflux: activation of efflux pumps, 3: Alteration of antibiotic targets, 4: Antibiotic inactivation by enzymatic modifications, 5: Antibiotic hydrolysis; B: Acquired resistance mechanisms. 1: Decrease in bacterial wall permeability: mutations of porin-coding genes, 2: Increase in efflux: enhance efflux pump gene expression by acquiring additional genes *via* external DNA, 3: Alteration of antibiotic targets: mutations of genes that encode antibiotic targets, 4: Acquisition of additional ARGs *via* external DNA (plasmids and others), 5: Antibiotic hydrolysis: broadening of the substrate specificity of hydrolyses.

efflux pump is a less effective way to diminish the toxic effect of antibiotics compared to enzymatic alteration of antibiotics or their target, bacteria can achieve resistance to a whole class of antimicrobial molecules through multiple biochemical pathways involving different resistance mechanisms[36].

Resistance to antibiotics is not always associated with ARGs

To survive in an antibiotic-enriched environment, bacteria can engage a mechanism of switching between metabolic stages – from the normal, susceptible cell type to the tolerant or persister state[37]. The ability of a bacterium to survive high concentrations of bactericidal agents to which it is fully susceptible is called antibiotic persistence[30]. Unlike resistant strains, which can grow under antibiotic pressure, persisters do not grow. Instead, they switch to a stringent response stage, minimizing metabolic processes that include blockage of transcription and DNA replication[37]. Although in different proportions (from 0.001% to 1%), persister cells have been identified in almost all examined bacterial species, including Gram-negative and Gram-positive bacteria[37]. Antibiotic persistence is thought to be involved in developing resistance to antibiotics and maintaining chronic bacterial infections. Chronic infection is assumed to be unresolved by a host's immune system due to a population of persisters[30].

Table 2 Examples of acquired antibiotic resistance in bacteria

Metabolic process	Molecule/reaction involved	Resistance to antibiotic	Host	Genome encoded	Plasmid encoded
Decrease in bacterial wall permeability	Modified porins	Many antibiotics	Gram-negative bacteria	Loss or mutated *oprD* mutations in porin operon	
Increase in efflux	RND pump family	Many antibiotics	Gram-negative bacteria; *S. aureus*	Mutations in *mtr* region, mexEF-oprN	RND with NDM-1
	Efflux pump	Fluoroquinolones	*S. aureus*	Amplification of *norA* gene	
Enzymatic antibiotic inactivation	Oxidation	Tetracyclines	Many bacteria		Mobile *Tet(X)*
Antibiotic hydrolysis	ESBLs	Broad-spectrum beta-lactams	Gram-negative bacteria	Yes	Yes
Modification of antibiotic target	RNA polymerase RpoB	Rifampicin	*S. aureus*	Mutated *RpoB* gene	
	DNA gyrase GyrA and topoisomerase IV ParC	Quinolones Fluoroquinolones	*S. aureus*; *K. pneumoniae*	QRDR	Yes
	DHPS and DHFR	Trimethoprim–sulfamethoxazole	Gram-negative bacteria	Mutated *dfrA* gene	Yes
	Altered rRNA	Macrolides: erythromycin, Oxazolidinones: linezolid	*Staphylococcus spp.*; *Streptococcus spp.*	Mutated rRNA operon	Yes
	Modification of peptidoglycan precursors	Vancomycin	*Enterococcaceae*, *Staphyloccaceae*	Mutated *van* genes, *van*R/*van* S controls	Yes
	Enoyl-ACP reductase	Triclosan	*P. aeruginosa*	Alternative *fab*V gene	
	Addition of moieties to LPS	Colistin	*Enterobacter spp.*	Mutated TSC genes	*mcr*
	Transpeptidase moiety of PBP	Methicillin and other beta-lactams	*Staphylococcus spp.*	*mecA* gene	SCC*mec*
	Dihydropteroate synthase	Sulphonamides		Mutated *sul1/2* gene	

RND: Family of resistance–nodulation–division efflux pumps; NDM-1: New Delhi metalo-beta-lactamase 1; ESBLs: Extended spectrum of beta-lactamases; QRDR: quinolone resistance determine region; DHPS: Dihydropteroate synthase; DHFR: Dihydrofolate reductase; TSC: Two-component system; mcr: Mobile colistin resistance; LPS: Lipopolysaccharide; PBP: Penicillin binding protein; SCCmec: Staphylococcal cassette chromosome.

Another known mechanism, originally discovered in bacteria as a plasmid maintenance tool[38], is the toxin-antitoxin system (TA), which potentially contributes to both the transition to the persister stage and the development of antibiotic resistance[39]. A toxin is usually a protein that is capable of inhibiting or modifying essential cell processes – such as mRNA transcription and translation, DNA replication, or cell wall functioning – in response to threatening conditions. An antitoxin (usually noncoding RNA) inhibits the cognate toxin or degrades its mRNA when there is no need for a stringent response. The antitoxin is encoded in the same TA module as the toxin. Bacteria can possess several different TA modules encoded in their genome or plasmids, and they are activated under specific stresses, such as the appearance of a bactericidal agent in the environment. Conjugative plasmids carrying ARGs and TAs are considered to have the most efficient pathway for the dissemination of antibiotic resistance between bacteria[39]. A recent comprehensive genetic study of the most prevalent MDR bacteria, *Escherichia coli* and *Klebsiella pneumoniae*, elucidated the complexity of the resistance acquisition process, in which the adoption of ARG-carrying plasmids is facilitated by mutation in the core metabolic genes[40]. Advanced genomic approaches will undoubtedly shed light on other options for bacteria to survive in a toxin-enriched environment.

RECENT RECOMMENDATIONS FOR PROPHYLAXIS AND TREATMENT OF BACTERIAL COMPLICATIONS IN CIRRHOSIS

Antibiotics, having antibacterial and germicidal effects, can not only effectively prevent and treat bacterial infection, but can also decrease the incidence of further decompensation of cirrhosis[41]. The most common recommendation for the treatment of patients with advanced liver disease aggravated by bacterial complications is the use of broad-spectrum antibiotics such as penicillin derivatives (amoxicillin-clavulanate) and cephalosporin derivatives (cefotaxime, ceftriaxone), quinolones (norfloxacin, ofloxacin), or, less commonly, aminoglycosides (neomycin) and trimethoprim/sulfamethoxazole

[26].

Third-generation cephalosporins (ceftriaxone, cefotaxime) are recommended to be started empirically (before obtaining culture results) in all patients with suspected SBP or SBE when the polymorphonuclear cell count in the ascites or pleural fluid is > 250/mm^3, however, the risk of MDR isolates must be considered, as cephalosporins have become less effective in settings where MDR bacteria are prevalent[42].

Although there is a risk of the emergence of isolates resistant to quinolones, the most recent recommendation for the primary prophylaxis of SBP in patients with ascites is the use of oral norfloxacin[6,42]. Norfloxacin or ciprofloxacin is also recommended for secondary prophylaxis[42]. When ascites is accompanied by gastrointestinal hemorrhage, ceftriaxone, cefotaxime, and piperacillin-tazobactam, along with albumin injections are recommended[42,43]. Third-generation cephalosporins are also the drug of choice for the treatment of bacteremia, pneumonia, and soft tissue infections in conjunction with penicillin derivatives and macrolides[4,42]. In the case of nosocomial infection, treatment with a broader spectrum antibiotic (piperacillin-tazobactam, vancomycin, carbapenems, tetracyclines or trimethoprim/sulfamethoxazole) is recommended since the third-generation cephalosporins, quinolones, and amoxicillin/clavulanic acid are ineffective in these patients[4,15,26,42].

MDR BACTERIA BURDEN IN PATIENTS WITH CIRRHOSIS

Delayed antibiotic treatment is associated with an increased risk of mortality, in particular in patients with septic shock [4]. On the other hand, conventional strategies of antibiotic use carry the danger of selection of resistant commensal bacteria in the gut or elsewhere in the body. Currently, in patients with cirrhosis, approximately 30%-40% of infections are caused by MDR bacteria[27]. Among the main sources of bacterial infection in patients with cirrhosis, healthcare-associated and nosocomial origins are characterized by the highest prevalence of antibiotic-resistant species – 35% and 14%, respectively – while among community-acquired species only 4% appear to be MDR[19].

To avoid resistance, new and existing antibacterial regimens are constantly being developed for the treatment of bacterial infections and prophylaxis. In case of suspected SBP, recent AASL guidelines for the management of ascites strongly recommend narrowing the coverage of antibiotics as soon as the culture results are available, and restricting the primary prophylaxis of SBP with antibiotics to patients with very advanced cirrhosis[42]. Considering the risk of bacterial complications originating from the intestinal microflora, non-absorbable oral antibiotics are chosen more frequently for the prophylaxis of infections and can improve short-term survival in high-risk patients[24,44]. However, resistance can also develop to such antibiotics. For example, after rifaximin prophylaxis of overt hepatic encephalopathy, *Staphylococcus spp.* resistant to rifaximin was detected in 50% of patients[45]. Rifaximin *per os* can also modify intestinal microflora: a significant increase in *Eubacteriaceae* and *Propionibacterium* and a decrease in the abundance of *Veillonellaceae*, *Roseburia*, and *Blautia* have been reported[46].

In contrast, a study reported that rifaximin treatment led to an increase in the abundance of potentially beneficial taxa and a decrease in *Klebsiella spp.* resistomes (resistome – a set of genes responsible for antibiotic resistance), as well as antibiotic-resistant Gram-negative bacteria[47].

Use of broad-spectrum antibiotics diminishes the diversity of the gut microbiota, promotes changes in the proportion of bacterial communities, and decreases the total abundance of fungi[47,48]. Bajaj *et al*[49] reported a significant reduction in *Sclerodermataceae*, *Dothideomycetes*, and *Saccharomyces boulardii* and a substantial increase in *Candida* in patients with cirrhosis after treatment with broad-spectrum antibiotics. They also detected a decrease in the *Basidiomycota/Ascomycete* ratio and concluded that broad-spectrum antibiotics can alter the balanced bacterial and fungal communities. This is one of the main risk factors for fungal infections.

In a recent study by Shamsaddini *et al*[47] among 163 outpatients with cirrhosis and 40 healthy control subjects, the abundance of ARGs in the gut microbiota was found to be higher than in the control samples and worsened with the severity of the cirrhosis. Furthermore, the abundance of ARGs predicts a poor prognosis and increases the mortality rate. In the patients enrolled, resistome-associated pathobionts belonging to *Enterobacterales*, *Streptococcus spp.*, *Enterococcus spp.* and *Acinetobacter spp.* had already been detected at admission. The resistome pattern included genes resistant to β-lactamases, macrolides, quinolones, aminoglycosides, tetracyclines, fosfomycin, and rifamycin. During hospitalization, three patients became infected with methicillin-resistant *Staphylococcus aureus*, three with *Candida spp*. and one with *Streptococcus viridans*. In this study, treatment with rifaximin only minimally affected the prevalence of resistome[47].

The extensive use of broad-spectrum antibiotics in healthcare settings has established conditions under which MDR bacteria have spread. The most common of these are extended-spectrum beta-lactamase producing *Enterobacterales*; non-fermentative Gram-negative bacilli (*i.e.*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii*); carbapenemase-producing *Enterobacterales*; methicillin-resistant (MRSA) or VRSA *Staphylococcus aureus*; vancomycin-susceptible or resistant *Enterococci* (VSE or VRE); and extensively drug-resistant (XDR) *Mycobacterium tuberculosis*[26]. XDR was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (*i.e.* bacterial isolates remain susceptible to only one or two categories)[11].

In frequently hospitalized patients with cirrhosis, extended spectrum beta lactamase and AmpC-producing *Enterobacterales* (that is, *Escherichia coli*, *Klebsiella pneumoniae*), methicillin- or vancomycin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococci*, all of which are difficult to treat, are the most common[4]. XDR bacteria such as carbapenemase-producing *Enterobacterales*, carbapenem-resistant *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are also found as causative agents of bacterial complications in such patients[4].

In a study by Milovanovic *et al*[10] involving 85 patients with cirrhosis and bacteremia, the most common pathogen was *Enterococcus spp.* (32%), followed by methicillin-susceptible *Staphylococcus aureus* (15%) and *Escherichia coli* (14%), and

37% of all isolated bacteria appeared to be multidrug resistant. Specifically, 73% of MDR bacteria were resistant to ampicillin, 70% to amoxicillin, and 51% to amoxicillinclavulanic acid. Resistance to third- and fourth-generation cephalosporins was detected in 44% to 49% of MDR bacteria. This group exhibited unexpectedly high resistance to amikacin (54%) and trimethoprim/sulfamethoxazole (51%). Resistance to meropenem was 20%, and 15% for imipenem, resistance to glycopeptide vancomycin was 15.4%, and 45% for teicoplanin. MDR bacteria was an independent predictor of mortality (OR = 6.2), and the proportion of MDR isolates increased with disease progression[10]. The authors emphasized that, even in developed countries with well-established healthcare systems, MDR bacteria significantly increased the mortality rate in patients with cirrhosis[10].

A worldwide study of 1302 hospitalized patients with cirrhosis from 46 centers in Asia, Europe, and North and South America also found that up to 34% of bacterial infections were caused by MDR species[2], with the highest prevalence in patients from India[2]. The most common species were extended-spectrum beta-lactamase-producing *Enterobacterales*, MRSA, vancomycin-resistant *Enterococci*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*[2].

In a prospective study conducted almost 10 years ago by Fernández *et al*[19] among 233 patients with cirrhosis, only 18% of bacterial infections (most commonly SBP, urinary tract infections and pneumonia) were caused by MDR species. Again, the most common were extended-spectrum beta-lactamase-producing *Enterobacterales* followed by *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecium*. MDR bacteria caused septic shock and mortality twice as often as non-MDR bacteria. In particular, when the authors repeated this study 4 years later, they obtained the same results[19].

During recent decades, the prevalence of infections due to MDR and XDR bacteria among patients with cirrhosis has increased[20,50]. The CANONIC Study group reported an increase in MDR infections in patients with cirrhosis in Europe –from 29% in 2011 to 38% in 2017 and 2018[50]. Long-term quinolones for the prophylaxis of SBP have been found to be strongly associated with continuously increasing rates of MDR pathobionts (approaching 40%), and carry an inherent risk of SBP breakthrough[51]. An increase in the proportion of Gram-positive MDR bacterial infections has also been observed [4]. The widespread use of third-generation cephalosporins has contributed to the emergence of nosocomial and healthcare-associated enterococcal infections resistant to cephalosporins[4].

CURRENTLY APPROVED ANTIBIOTIC-FREE PROPHYLAXIS OF BACTERIAL COMPLICATIONS

Because bacteria are so powerfully equipped with survival tools to help them when faced with antibiotics, the best way to avoid the selection of antibiotic-resistant bacteria is by reducing antibiotic use. This is difficult to implement if the infection has already manifested, while antibiotic prophylaxis should be restricted to the subgroup of patients who are at a very high risk of infection based on the availability of evidence[5,6,42,52]. For example, previously recommended for the treatment of hepatic encephalopathy[53], non-absorbable rifaximin has been proposed for SBP prophylaxis as an alternative to norfloxacin to avoid selection of isolates resistant to quinolones. Rifaximin has been shown to reduce the risk of SBP in patients with hepatic encephalopathy, but prophylaxis has not yet been confirmed[4].

By reducing portal hypertension, non-selective beta-blockers contribute to diminishing the risk of variceal bleeding and ascites formation[6]. Beta-blockers have also been shown to reduce intestinal bacteria translocation and therefore lower the risk of SBP, but they have no influence on urinary or respiratory tract infections[4].

To prevent refractory septic shock in patients with acute decompensation stage cirrhosis, a low-dose steroids prescription has been shown to be appropriate to monitor adrenal insufficiency that often appears in such patients[4].

Human albumin is not only the main regulator of blood oncotic pressure but is also characterized by scavenging and immunomodulatory activity. Albumin treatment has been shown to restore immune dysfunction in cirrhosis[4]. Along with antibiotics, albumin injections are recommended for SBP treatment, especially for patients with kidney dysfunction [6,42]. Furthermore, since albumin binds to some antibiotics, which keeps them in circulation longer, hypoalbuminemia promotes the clearance of antibiotics from plasma[26]. For example, ceftriaxone is 83%-96% bound to albumin, flucloxacillin 95%, cephalothin 55%-75%, aztreonam 60%, carbapenems 85%-95% (ertapenem) and 96%-99%(faropenem) and vancomycin 30%-60%[54]. Therefore, even when faced non-MDR bacteria characterized by a low minimal inhibitory concentration, hypoalbuminemia can prevent patients from maintaining an effective antibiotic concentration in the blood over time and thus can decrease the therapeutic effect of antibiotics[26]. In this case, a higher-than-routinely-prescribed dose of antibiotics is required.

However, the therapeutic effect of time-dependent antibiotics, such as those belonging to the ß-lactams family, strongly depends on the clearance rate. Due to the disruption of blood flow through the liver caused by fibrosis and portosystemic shunts, the drugs metabolized in the liver remain in the bloodstream for a longer period of time, leading to higher concentrations of antibiotics, which persist for longer. For this reason, in addition to hypoalbuminemia, blood flow and kidney impairment should also be taken into account when prescribing a particular antibiotic course to a patient[54]. Since empirical dosing regimens of medications are usually derived from studies of healthy populations, optimizing the antibacterial dosage for patients with cirrhosis is mandatory, considering hypoalbuminemia, hepatic blood flow impairment, the presence of portosystemic shunts, and renal dysfunction, according to Zoratti *et al*[26].

FECAL MICROBIOTA TRANSPLANTATION (FMT) TO REDUCE THE BURDEN OF MDR BACTERIA

Currently, fecal microbiota transplantation (FMT) has been approved for the treatment of recurrent *Clostridioides difficile* infection that does not respond to metronidazole or vancomycin. In two recent clinical trials, it was found that FMT reduced the abundance of antibiotic resistance genes in the microbiota of patients with cirrhosis[55]. After one single administration of an FMT capsule, a lower abundance of vancomycin, beta-lactamase, and rifamycin ARGs was detected after 4 wk, compared to baseline and placebo levels[55]. These findings suggest that FMT offers a promising therapy that may reduce the population of multidrug resistant organisms. However, it is too early to implement FMT therapy to reduce the risk of MDR infections because several important issues remain unsolved.

First, FMT safety issues have not yet been fully addressed. Since patients with cirrhosis have compromised intestinal barriers, it is necessary to ensure that only the "healthy" microbiota is transplanted. Therefore, a methodology is needed to select donors. It would be desirable to know which composition of the donor microbiota performs the most effective therapeutic function and then standardize the supply of donor material. A methodology for screening the donor microbiota for potential pathobionts and their metabolites should be established to avoid transplantation of MDR bacteria and other dangerous pathobionts to the recipient. Even if this were to be the case, there would be a risk of transplanting potentially pathogenic microbes for which screening techniques are not yet available, or some undefined molecules presented in donor feces which could trigger an adverse immune response. For example, in a study by Bajaj *et al*[55], MDR *Escherichia coli* was transplanted from one donor to two recipients during the FMT procedure.

Second, it remains unclear what administration route (enemas, capsules, *etc.*) and dosage of FMT is necessary to achieve a therapeutic response, how many treatment courses should be applied and how long it is necessary to wait between courses[55].

PREBIOTICS AND PROBIOTICS CAN REDUCE THE BURDEN OF MDR BACTERIA

In many studies, although usually without strong evidence-based argumentation due to methodological flaws, it has been proven that high-fiber foods such as whole grains and various vegetables maintain the intestine microbiota in healthy shape due to the abundance of prebiotics in their composition[56]. Prebiotics promote an increase in the proportion of beneficial gut bacteria such as *Bifidobacterium longum*. At the same time, fermentation of prebiotics by the gut microbiota produces short-chain fatty acids such as acetate, butyrate, and propionate. In particular, butyrate has an anti-inflammatory effect and promotes the reestablishment of the intestinal barrier[57]. A randomized perspective study of healthy adults has shown that a diet enriched with prebiotics improves intestinal microbial diversity and relieves the pro-inflammatory immune response[58]. Short-chain fatty acids also have a positive effect on liver lipid metabolism. Treatment with oligosaccharides such as inulin-type fructans considerably improves liver steatosis in patients with cirrhosis[59].

The beneficial effects of probiotics on the gut microbiota have been widely known for a considerable period of time. This is why probiotic-rich foods such as kefir, kimchi, kombucha, pickles, buttermilk, cottage cheese, tempeh, sauerkraut, and miso soup are widely recommended as components of a healthy diet[57]. Pharmaceutical forms of probiotics, such as *Lactobacillus plantarum*, *Lactobacillus brevis*, *Leuconostoc mesenteroides*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*, are often prescribed in combination with prebiotics to restore a bacterial community after antibiotic treatment. However, because of the different composition of such preparations, not only at the species level but also at the strain level, their efficacy can vary considerably. This circumstance makes it very difficult to assess and compare the results of clinical trials on such products, therefore, the confidence level of evidence of such trials is still low[60].

It is assumed that probiotics reduce the ability of pathological bacteria to interact with the intestinal epithelium, and thus prevent the translocation of bacteria and their products through the intestinal barrier. Synbiotic treatment (a pharmaceutical form of combining prebiotics and probiotics) has been shown to ensure intact intestinal permeability by maintaining immunoglobulin A (IgA) production, promoting the integrity of gut lining cells with fully functioning tight junctions, promoting *Lactobacillus spp.* growth and inhibiting the overgrowth of potentially pathogenic *Escherichia coli* and *Staphylococcal* species[61]. The above-mentioned effect of synbiotics has a general beneficial effect on liver and intestinal function, and therefore can contribute to reducing the damage caused by MDR bacteria. The meta-analysis conducted by Cai *et al*[62], involving 826 patients with cirrhosis in total, revealed that probiotics had better efficacy than FMT in the prevention of hepatic encephalopathy, decreasing serum levels of ammonia, endotoxemia levels, and hospitalization rates. However, a randomized clinical trial with 116 participants enrolled concluded that they were not effective against the intestinal microbiota resistome[63]. While *in vitro* and animal studies demonstrate the promising effects of *Lactobacilli* and *Bifidobacterium* on the decrease of pathogenic bacteria in the intestine and urinary tract, including *Helicobacter pylori*, *Salmonella* and some MDR bacteria such as *Escherichia coli* and *Klebsiella pneumoniae*[64,65]. Through the secretion of antibacterial chemicals, including lactic acid and hydrogen peroxide, probiotics in combination with antibiotics have been shown to enhance the therapeutic effects of the latter[66,67].

OTHER PERSPECTIVES ON COPING WITH MDR BACTERIA

Nanoparticles may serve as an imperative tool for fighting antibiotic resistance because they bypass toxin-resistant bacteria systems. In particular, silver and gold nanoparticles in combination with metal oxide nanoparticles demonstrate promising, although nonspecific, bactericidal effects on Gram-positive and Gram-negative bacteria *in vitro*. This includes different MDR and XDR bacteria such as *Mycobacterium tuberculosis*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*,

MRSA, *Escherichia coli*, *Enterococcus faecalis*, *Streptococcus pyogenes*, *Salmonella typhi* and *Klebsiella pneumoniae*, bearing NDM-1, VRE, and VRSA[66].

Currently, there are no single published study or ongoing clinical trial on nanoparticle treatment or its use in the prophylaxis of bacterial complications in cirrhosis. In the experimental study by Yang *et al*[68], a biliary stent coated with silver nanoparticles was not only characterized by antibacterial activity but also served longer without obstruction. Metallic and metal oxide nanoparticles have been externally studied for their use in combating nosocomial bacteria, which are highly resistant to antibiotics in clinical settings[69].

Because of their small dimensions, nanoparticles anchor and easily penetrate the bacterial wall, alter the permeability of the cell membrane, promote free radical production, destroy bacterial DNA and operate in other ways to disrupt the metabolism of a bacterium, ultimately causing cell death[66]. However, due to many toxicological issues that remain unsolved, the treatment of bacterial infections with nanoparticles remains a theoretical prospect[70,71]. Although, if designed with specific surface functions to enhance their therapeutic effect and diminish toxicity, nanoparticles can be effective at least externally for antibiotic-resistant oral and wound biofilms treatment[71].

Host defense peptides, the cationic amphipathic peptides like difensins and cathelicidins, and antimicrobial peptides such as polylysine are currently under investigation as potential agents against MDR bacteria. These peptides are naturally synthesized in many organisms, including humans, in response to infection. Having low cellular toxicity, they are active against gram-negative and gram-positive bacteria, including MDR representatives. Furthermore, they are effective against fungi and biofilms, which are difficult to treat with antibiotics[66].

Another promising strategy for combating MDR bacteria is bacteriophage therapy. Bacteriophages are a natural component of the intestinal microflora. They infect bacteria, causing cell lysis when in their virulent state, or they can switch to a temperate state *via* incorporation of their genome into the bacterial chromosome or by forming a self-replicating plasmid[12,72]. The therapeutic potential of bacteriophages is due to their affinity for specific bacteria species. Therefore, its action can be accurately predicted to target a specific bacterium. However, the clinical implementation of bacteriophage therapy faces a number of challenges. First, bacteriophages have been shown to trigger a pro-inflammatory immune response[73]. Second, due to their narrow host range, bacteriophages have limited therapeutic utility in the event of encountering an infection caused by a number of different bacteria, although this can be overcome through the use of phage cocktails. Finally, bacteriophages can carry genes that are harmful to human cells. Hence, the preparation of a safe bacteriophage cocktail for clinical applications is a considerable challenge[66,72]. Additionally, phages can be ineffective [74].

However, progress in biotechnologies allows for the production of recombinant phage products, genomic-editing tools can be used to construct genetically manipulated phages, or engineered phages with the required traits in mind[74]. For example, phage lysins have been found to be solely capable of lysing bacterial cells. In experimental studies, the use of phage lysins in combination with antibiotics appeared to be more effective in eradicating bacterial infections than antibiotics alone[72].

New natural antimicrobials are also constantly sought that are effective against MDR bacteria[75].

As vaccines do not develop resistance, the invention of vaccines against MDR bacteria is also considered an option to reduce the burden of MDR bacteria[76]. Especially effective vaccines would be greatly appreciated against such notorious bugs as *Staphylococcus aureus* (MRSA and VRSA), MDR and XDR isolates of *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Clostridioides difficile*.

Especially challenging is developing vaccines against representatives of the commensal flora, as they are in constant contact with the human immune system. Given that the physiology of an *ex vivo* bacterium may differ from its behavior *in vivo*, this makes the task even more complicated. Furthermore, some bacteria, such as *Staphylococcus aureus*, an ubiquitous and in general inoffensive colonizer of human skin and nasal passage, can escape immune attack and remain viable even if it is ingested by neutrophils or macrophages[77]. To date, all candidate vaccines against this pathogen have been discontinued at or before Phase 3 clinical development due to ineffectiveness or side effects[78-80].

The worldwide spread of carbapenem resistant and even colistin resistant *Klebsiella pneumoniae* isolates is stimulating the development of a vaccine against this pathogen, but recombinant and other vaccine candidates have been tested in experimental models and remain in the preclinical or early clinical phases so far[81,82]. The same is true regarding a vaccine against extraintestinal pathogenic *Escherichia coli*[79,80].

Acinetobacter baumannii and *Clostridioides difficile* are ubiquitous in the environment but are not part of normal human flora. Therefore, a vaccine against these pathogens is technically feasible, but no vaccine has been approved for clinical use to date[79,80].

Therapeutic monoclonal antibodies against commensal flora such as *Staphylococcus aureus*, *Pseudomonas aeruginosa,* and others are also being investigated. The function of such antibodies is to neutralize bacterial toxins and thus reduce the pathological effects of certain bacteria[83]. Molecules such as virulence factors secreted by staphylococci (enterotoxin serotype B, alpha-hemolysin, *etc.*) are promising candidates for the development of therapeutic antibodies, but none have yet been approved for clinical use[83]. For example, a chimeric murine/human monoclonal antibody Pagibaximab has been developed to prevent staphylococcal sepsis in low-birthweight infants and showed > 90% efficacy against the most prevalent CoNS isolates in preclinical studies, however, appeared ineffective in the randomized, double-blind, multicenter, placebo-controlled clinical trial (ClinicalTrials.gov Identifier: NCT00646399).

A method of developing a vaccine that does not target a specific bacterium but enhances mucosal immunity in general has shown promise. Uromune, a sublingual vaccine for the prophylaxis of recurrent urinary tract infections, has shown tangible benefits over antibiotics in clinical trials and is already on the market[84,85]. Taking into account the experience gained in vaccine development and the use of modern biotechnological methods, more effective vaccines can be expected to become available in the near future[86].

CONCLUSION

Recent data on the development of MDR bacterial complications in cirrhotic patients prompt the use of antibiotic-free prophylaxis strategies. Some, such as the combination of probiotics/prebiotics and human albumin injections, appear promising. Effective vaccines and therapeutic antibodies can also be expected in the near future.

Currently, there is no effective alternative for the treatment of bacterial infections, and antibiotics remain the first choice. However, there is room to improve existing regimens by applying a personalized approach. The selection of MDR bacteria can occur not only as a result of the activity of ARGs, but also as a result of inadequate therapeutic concentrations of antibiotics in the body of a patient. This may occur due to hypoalbuminemia, hepatic blood flow disturbances, portosystemic shunts, renal impairment, or a combination of the above factors. Thus, individualized regimens and monitoring of antibiotic concentration according to patient conditions can significantly improve the effectiveness of antibiotic treatment and can reduce the selection of MDR bacteria during the treatment of patients with cirrhosis.

FOOTNOTES

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