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Management of multidrug-resistant infections in cirrhosis

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Abstract

The World Health Organization describes antimicrobial resistance (AMR) as one of the biggest threats to global health, food security, and development with indiscriminate use of antimicrobials globally driving the emergence of multidrug-resistant bacteria, resistant to 60% of antimicrobials in some countries. Infections with multi-drug resistant organisms (MDROs) have increased in recent decades in patients with cirrhosis, who are frequently prescribed antibiotics, regularly undergo invasive procedures such as large volume paracentesis and have recurrent hospitalizations, posing a particular risk in this already immunocompromised cohort of patients. In this review, we explore mechanisms underlying this vulnerability to MDRO infection; the effect of bacterial infections on disease course in cirrhosis; prevalence of MDROs in patients with cirrhosis; outcomes following MDRO infection; fungal infections; antibiotics and their efficacy; and management of MDRO infections in terms of detection, antimicrobial and non-antimicrobial treatments, prophylaxis, antibiotic stewardship, the gut microbiome, and technological interventions.

Main concepts and learning points

Antimicrobial resistance (AMR) is a worldwide and growing problem
Patients with cirrhosis are particularly vulnerable to infection with multidrug-resistant organisms (MDROs) and associated complications
Best practice centres on: • Aggressive and systematic screening for infection • Antibiotic and non-antibiotic prophylaxis • Appropriate broad-spectrum empirical antibiotic therapy (particularly in unwell patients and in those with risk factors for MDROs) in the case of infection • Use of commercially available technologies to rapidly diagnose pathogens and their resistance profiles, followed by immediate optimization (typically de-escalation) of empiric therapy, and avoidance of unnecessarily prolonged therapy, in keeping with antimicrobial stewardship principles

Introduction

Antimicrobial resistance (AMR) poses a global threat of morbidity, mortality (conservatively estimated at 700,000 annual deaths globally in 2014), and economic impact.[1,2] If rates of multidrug-resistant (MDR), extensively drug-resistant (XDR), and pandrug-resistant (PDR) infections increase (see Table 1 for definitions),[3] these consequences will intensify.

In recent decades, AMR has become a significant global problem in patients with cirrhosis.[4] A large US study found that patients with cirrhosis' risk of dying from sepsis increased by 28% between 2002 and 2010,[5] and it has been proposed that this may be related to the increasing spread of multidrug-resistant organisms (MDROs).[6]

Cirrhosis and vulnerability to infection

Patients with cirrhosis are more vulnerable to infection than the general population for multiple reasons.

The gut microbiome in cirrhosis tends towards dysbiosis and small intestinal bacterial overgrowth,[7] with decreased microbial diversity and increased pathogenic species,[8] damage to gut-associated lymphoid tissue,[9] and with the development of portal hypertension and advancing cirrhosis, increased bacterial translocation from the gut to the systemic circulation.[10] Unfortunately, the gut microbiome is also an important reservoir of MDROs.[8,11]

Processes such as intestinal bacterial translocation, which results from damage to the intestinal mucosal barrier, leads to translocation of pro-inflammatory pathogen-associated molecular patterns (PAMPs), and necrosis of liver cells, which causes release of damage-associated molecular patterns (DAMPs), resulting in a state of abnormal inflammation.[12,13]

There is neutrophil and monocyte dysfunction, and reduced protein synthesis which further perturbs the innate immune system.[14,15] The immune surveillance role of the liver, via damage to the reticuloendothelial system, is impaired. Albumin, which reduces prostaglandin-E2 (PGE_2) bioavailability and appears to have a role in modulating PGE_2-mediated immune dysfunction, has reduced serum levels in advanced cirrhosis.[16]

These and other factors contribute to cirrhosis-associated immune dysfunction (CAID), which refers to a syndrome of immunodeficiency and systemic inflammation, resulting in an increased vulnerability to bacterial infection.[9] Ongoing excessive alcohol consumption and malnutrition, if present, also have deleterious effects on immune function.[17,18] The prevalence of bacterial infections in patients with cirrhosis is 5-6 times that of the general population.[4]

Community-acquired versus healthcare-associated versus. nosocomial infections

European colleagues, on review of multiple studies, reported that 32-50% of infections in decompensated cirrhosis are community-acquired (CA), 25-41% are healthcare-associated (HCA), and 25-37% are nosocomial. The proportion of infections attributable to MDROs increases across these three groups.[4]

Effect of bacterial infection on disease course in cirrhosis

Bacterial infections (BI) may precipitate variceal hemorrhage, variceal rebleeding, hepatic encephalopathy (HE), hyponatremia, acute kidney injury/hepatorenal syndrome, and acute-on-chronic liver failure (ACLF).[4,19] In a multi-center European study, BI was the most frequent precipitant of acute decompensation (AD) with ACLF (AD-ACLF) (proven BI 44%, suspected BI

5.9%), and was likely the most frequent precipitant of AD without ACLF (AD-No ACLF) (proven BI 22%, suspected BI 6.9%), followed closely by alcoholic hepatitis.[20]

In a multi-centre North American study of patients with cirrhosis who were admitted with an infection, or developed an infection during their hospitalization, the occurrence of a second infection during hospitalization was associated with a 30-day mortality rate of 49%.[21]

A 2010 systematic review reported a fourfold increase in mortality following infection in patients with cirrhosis (pooled odds ratio (OR), 3.75; 95% confidence interval (CI), 2.12 to 4.23), with mortality at 1, 3 and 12-months of 28.6%, 44% and 63%, respectively.[22]

Increasing prevalence of MDROs in patients with cirrhosis

Pre-operative carriage of extended-spectrum beta-lactamase *Enterobacteriaceae* (ESBLE) on rectal screening in French liver transplantation (LT) patients increased from 0% during 2001-2003, to 10.6% during 2009-2010. This corresponded with an increased risk of ESBLE infection within 4 months of LT from 1.6% to 12.8%. ESBLE carriage was also identified as an independent predictor of post-LT infection overall, this occurring in 48% of ESBLE carriers, versus. 6.7% of non-ESBLE carriers ($p<0.001$).[23]

In a large, multi-centre 2011 series of patients in Northern, Southern, and Western Europe hospitalized with decompensated cirrhosis, 50.8% of infections were culture-positive, of which 29.2% were caused by MDROs (corresponding to 15.4% of all infections). ESBLE was the most frequently isolated MDRO (isolated in 3.7% of all infections), followed by vancomycin-sensitive *Enterococcus* (VERSUSE, 2.9%) and methicillin-resistant *Staphylococcus aureus* (MRSA, 2.3%).[24] In a linked 2017-2018 series from Eastern, Southern and Western Europe, 55.9% of infections were culture-positive, of which 37.9% were caused by MDROs

(corresponding to 23.3% of all infections). ESBLE was again found to be the most isolated MDRO (isolated in 7.0% of all infections), followed by VERSUSE (4.2%), then by ESBL-producing *Klebsiella pneumoniae* (3.9%).[24]

A large, intercontinental 2015-2016 study of hospitalized patients with cirrhosis and bacterial or fungal infections isolated MDR bacteria in 34% with a positive culture, and XDR bacteria in 8%. ESBLE infections accounted for 12% of positive cultures, followed by carbapenem-resistant *Enterobacteriaceae* (CRE, 5%), *Acinetobacter baumannii* (3%), vancomycin-resistant Enterococci (2%) and MRSA (2%).[25] MDR and XDR bacterial infections were very common in India, comprising 73% and 33% of isolates, respectively. In contrast, the corresponding figures for the United States were 16% and 3%. The US had the lowest proportion of MDR isolates of the countries studied, and Belgium, Canada, Indonesia, Israel, Russia, and Switzerland all had zero XDR isolates.[25]

Considering the latter two European series, taking account of culture-positive infections, and accepting that there are some differences in the populations studied, an upwards trend in occurrence of infection with MDROs is noted, from 29% in 2011, to 38% in 2017-2018.[4]

Risk factors for AMR in patients with cirrhosis

In the large, intercontinental 2015-2016 study of hospitalized patients with cirrhosis and bacterial or fungal infections mentioned above, risk factors for MDR BI were geographic area (India, and Asia in general), younger age, antibiotic treatment in the previous 3-months, invasive procedures in the previous month, higher Child-Turcotte-Pugh score, higher MELD-Na score, and having an HCA or nosocomial infection. MDR infections were more commonly observed in urinary tract infection (UTI), pneumonia, and skin and soft tissue infections, than in those with spontaneous bacterial peritonitis (SBP) or spontaneous bacteremia. Risk factors

for XDR BI were similar, except that geographic area was a risk factor for India alone, and site of infection only for UTI and pneumonia. If a second infection occurred during hospitalization, the percentage of positive cultures that were MDR and XDR rose (50% versus 34%; p<0.001; and 17% versus 8%; p<0.001, respectively).[25]

In the above large, multi-centre European study, nosocomial infection, ICU admission, and recent hospitalization were identified as independent predictors of MDR infection.[24]

Exposure to a beta-lactam agent in the month preceding LT has been found to be an independent predictor of ESBLE fecal carriage, as has a history of SBP.[23]

Whether or not quinolone antibiotic prophylaxis is a risk factor for infection with MDROs or not is debated. In the intercontinental study mentioned, it was not found to be a risk factor, although it should be noted that only 10% of the patients in this study were on quinolone prophylaxis.[25] Studies have shown conflicting results on this particular issue,[26,27] with most suggesting that quinolone prophylaxis is a driver of the spread of infections with MDROs.[25] Given the established clinical benefit of quinolones in patients with ascites meeting criteria for prophylaxis, however, they should not be avoided based on concerns regarding AMR.[25]

Clinical outcomes following infection with MDROs

BI with MDROs is associated with a longer duration of antibiotic treatment and hospital stay, a lower rate of resolution of infection, a higher incidence of septic shock, requirement for critical care, mechanical ventilation, renal replacement therapy, and higher in-hospital and 28-day mortality.[25]

Fungal infections

In the large, intercontinental study mentioned, 4% of positive cultures were fungal. However, if a second infection developed during hospitalization, the rate of fungal infections increased to 11% ($p<0.001$).[25] Similarly, in a North American study of 2864 patients with cirrhosis admitted non-electively, fungal infections were more likely to be nosocomial (definition used: infections diagnosed 48 hours or more into admission which were not unresolved previous infections) than non-nosocomial (fungal infection was present in 14% of patients with nosocomial infections versus 2% of patients with non-nosocomial infections, $p<0.0001$).[28]

In a 2014-15 European study of 312 patients with cirrhosis and confirmed bloodstream infection (BSI), *Candida* spp. were isolated in 7% of cases. Of the 21 *Candida* BSIs, 18 were nosocomial, 2 were HCA, and 1 was CA. Of note, *Candida* BSI was strongly associated with inappropriate antimicrobial treatment in the first 24 hours, and 30-day mortality was 43% (in 9 out of 21 patients), which was second only to carbapenem-resistant *Enterobacteriaceae* BSI (44%, in 4 out of 9 patients).[29]

In a European study of 642 cirrhotic patients with either AD or ACLF published in 2018, fungal infections were seen only in the ACLF cohort (2% of ACLF patients) and were associated with a 90-day-mortality of 71%.[13]

Invasive fungal infections tend to occur in the severely immunocompromised. Invasive candidiasis/candidemia is the most common (70-90% of cases), followed by invasive aspergillosis (10-20%).[4]

Major risk factors for fungal infection – as described mainly in the general population – include abdominal surgery, recent broad-spectrum antibiotics, central venous catheters, total parenteral nutrition, AKI-renal replacement therapy, prolonged ICU stay, and diabetes mellitus, for invasive candidiasis; and prolonged steroid therapy, poor liver function, and

prolonged ICU stay, for invasive aspergillosis. Potential risk factors include multifocal colonization by *Candida*, ACLF, steroid therapy, and malnutrition, for invasive candidiasis; and ACLF, renal replacement therapy, and malnutrition, for invasive aspergillosis.[4]

In an Italian study of patients with cirrhosis and who developed candidaemia (n=90), risk factors were ACLF within 30 days (p=0.046), gastrointestinal endoscopy within 30 days (p=0.014), antibiotic treatment for at least 7 days within 30 days (p=0.049), presence of central venous catheter (p=0.011), total parenteral nutrition at infection onset (p=0.002), and length of in-hospital stay >15 days (p<0.001). Conversely, rifaximin treatment with a total daily dose of at least 1200 mg was associated with a lower rate of candidaemia, although this benefit was only seen in patients without central venous catheters (p=0.016).[30]

Fungal infection should be considered where patients presumed to have infection have negative bacterial cultures, particularly in patients with renal insufficiency, and in those who have had multiple courses of antibiotics.[31]

Blood cultures are estimated to be around 50% sensitive for invasive fungal infection and may take several days to grow *Candida*.[32] Beta-D-glucan and galactomannan testing, as well as culture-based and non-culture-based rapid diagnostic tests (see 'Technological interventions') therefore play an important role in the diagnosis of invasive fungal infections, as does imaging.[4]

In the US Centers for Disease Control and Prevention (CDC) report, *Antibiotic Resistance Threats in the United States, 2019, Candida auris* is described as an urgent threat (323 cases in 2018), and drug-resistant *Candida* as a serious threat (estimated 34,800 cases and 1,700 deaths), with azole-resistant *Aspergillus fumigatus* on the watch list. Fluconazole-resistant

Candida was first identified in 1988, caspofungin-resistant *Candida* in 2004, and amphotericin B-resistant *Candida auris* in 2016.[33]

In a 2012-16 US series, 7% of *Candida* BSIs were resistant to fluconazole, and 1.6% to echinocandins.[34] *Candida albicans* is the commonest *Candida* BSI, with non-albicans *Candida* strains being more likely to be resistant.[34,35] In most patients, an echinocandin, rather than fluconazole, is the most appropriate initial treatment for candidemia.[36]

In the CDC data, 90% of *C. auris* isolates were resistant to at least one antifungal, with 30% resistant to at least two antifungals. Some strains are resistant to all three available classes of antifungal (azoles, echinocandins, and amphotericin B). *C. auris* spreads easily and can cause outbreaks in healthcare facilities.[33]

ANTIBIOTICS AND THEIR EFFICACY

Changes in hepatological practice in recent decades have altered the epidemiology of the bacterial infections seen in patients with cirrhosis.

Patients with cirrhosis are now subject to more invasive procedures than in the past, with increased critical care admissions and associated line and tube placements, interventional radiology procedures, the advent of endoscopic variceal ligation, and an expanded liver transplantation program, all of which provide a potential portal of entry for bacteria and may be associated with infections.[37]

Historically, approximately 70-80% of isolated organisms in cirrhotic patients with BI were Gram-negative bacilli.[37,38] Since 1990, the use of quinolones such as norfloxacin for SBP prophylaxis has become established (this has since been found to reduce mortality, infections

overall, and the risk of developing hepatorenal syndrome also).[27,39,40] Of note, second-generation quinolones, which include norfloxacin and ciprofloxacin, have expanded Gram-negative and atypical coverage, but limited Gram-positive coverage.[41] A Spanish prospective study of BI in patients with cirrhosis admitted to a liver unit between 1998 and 2000 showed a marked increase in the proportion of Gram-positive cocci infections compared with historical norms, these now accounting for 53% of bacterial infections. Gram-positive cocci infection was associated with ICU admission and having had invasive procedures, whilst an increased rate of infection with quinolone-resistant Gram-negative bacilli was associated with being on norfloxacin prophylaxis.[37]

The widespread use of third-generation cephalosporins (TGCs) has also been linked to the increase in *Enterococcal* infections seen in patients with cirrhosis.[6] In a German study of culture-positive ascitic fluid samples taken between 2000 and 2011, Gram-negative organisms were isolated in 46% of SBP cases, and Gram-positive bacteria in 58% of cases (sum > 100% due to polymicrobial infections), with *Enterococcus* accounting for 24% of total cases. *Enterococcus* has intrinsic resistance to TGCs, and in subjects with monomicrobial SBP, 90-day survival was 12% in the case of *Enterococcal* infection versus 50% in non-*Enterococcal* infection (p=0.022).[42]

Taking a global perspective, in the large, intercontinental 2015-16 study previously discussed, 57% of positive cultures were Gram-negative bacteria, 38% Gram-positive bacteria, and 4% fungal.[25]

The incidence of MDROs has been increasing in patients with cirrhosis. Figure 1 shows the main MDROs, their mechanisms of resistance, and reservoir, and Table 2 their therapeutic options.[4]

Mechanisms of antibiotic resistance

Mechanisms of antibiotic resistance are various. The most common mechanism of antibiotic resistance in Gram-negative bacteria is through beta-lactamase production – beta-lactamases hydrolyze susceptible beta-lactam antibiotics, rendering them ineffective.[43]

The Ambler classification divides beta-lactamases into 4 classes (A to D) based on their amino acid sequences – class A (which includes most extended-spectrum beta-lactamases), class C (the 'AmpC beta-lactamases') and class D (the 'OXA beta-lactamases') have a serine residue at the active site, whilst class B (the 'metallo-beta-lactamases') beta-lactamases require a bivalent metal ion (usually zinc) for their activity.[44,45]

Given the importance of carbapenems (which retain activity against the cephalosporinases and extended-spectrum beta-lactamases found in many Gram-negative pathogens) in the hepatologist's antibiotic armory, carbapenem-resistant Gram-negative bacilli are of particular concern.[46] Antibiotic resistance to carbapenems can be through carbapenemases and/or through non-carbapenemase resistance mechanisms (e.g., a porin gene mutation may limit the ability of carbapenems to penetrate the bacterial cell wall).[47] Carbapenemases are discussed below.

Carbapenemases

These belong to Ambler classes A, B and D.[48]

Major families of class A carbapenemases include NMC/IMI, SME, and KPC enzymes. All can hydrolyze a wide range of beta-lactams, including carbapenems, cephalosporins, penicillins, and aztreonam, though all are inhibited by clavulanate and tazobactam.[48]

Class B beta-lactamases are characterized by their ability to hydrolyze carbapenems and by their resistance to beta-lactamase inhibitors such as clavulanate and tazobactam. Most of these enzymes hydrolyze cephalosporins and penicillins, in addition to carbapenems, but lack the ability to hydrolyze aztreonam.[48]

Class D beta-lactamases have a preferential ability to hydrolyze oxacillin, rather than penicillin. They have variable carbapenemase activity and are variably resistant to beta-lactamase inhibitors, though all are inhibited more efficiently by tazobactam than by clavulanate.[49]

As of 2020, English guidelines recommend that frontline diagnostic laboratories implement molecular or immunochromatographic assays for the detection of KPC, OXA-48-like, NDM (New Delhi metallo-beta-lactamase) and VIM (VIM-type metallo-beta-lactamase) carbapenemase families (the current most-prevalent CPE enzymes in the UK) to complement culture-based testing.[50]

MANAGEMENT OF MULTIDRUG-RESISTANT INFECTIONS IN CIRRHOSIS

Detection of MDROs

Microbiological surveillance

Screening for MDROs via nasal and rectal swabs aims to reduce patient-to-patient transmission, and positive results should trigger not just infection control precautions, but also an awareness in the physician that decolonization, or more potent antimicrobial prophylaxis/treatment may be required for that patient. Taking the example of CRE, groups in whom screening should be performed in acute-care hospitals include patients admitted from long-term acute care facilities, or other long-term care facilities with known endemicity,

or patients who are transferred from another acute-care hospital. The additional groups in whom screening should be considered are various,[51] and best practice is for all patients with cirrhosis to be screened for MDROs with rectal and nasal swabs on hospitalization.

Screening of unwell patients with cirrhosis for infection

Detecting infection in patients with cirrhosis is more challenging than in the general population. As a result of their impaired immunity, most patients with decompensated cirrhosis are unable to mount a febrile response to infection; on the other hand, patients with alcoholic hepatitis may have fever, tachypnoea, and leukocytosis in the absence of infection.[31]

Due to the high prevalence of SBP in cirrhotic inpatients with ascites, and its frequently non-specific presentation, the practice of performing a routine diagnostic ascitic tap on admission for any patient with cirrhosis and ascites admitted to hospital is long-established.[52] Other occasions for diagnostic ascitic tap include on presentation with new-onset ascites, the development of gastrointestinal symptoms, symptoms or signs of systemic inflammation, altered white blood cell count, HE, worsening liver or renal function, to assess response to treatment of SBP, and in gastrointestinal hemorrhage. It is important to send ascitic fluid in blood culture bottles (10 mL per bottle), in addition to a standard ascitic fluid microscopy, culture and susceptibility testing (MCS) sample, as this markedly increases sensitivity (93% versus 43%, $p<0.0001$) and reduces time to diagnosis.[53–56] Allowing for their established limitations in liver disease, C-reactive protein and procalcitonin can also be used to help detect infection and assess its severity, and may have an additional role in antibiotic stewardship.[19,56]

A 2012 European review advises culture of ascites, blood, and urine on admission of patients with cirrhosis to hospital and upon subsequent clinical deterioration. In the case of bacterial

infection, detailed physical examination (*e.g.*, for cellulitis), sputum Gram stain, cultures of urine, blood, ascites, sputum, and pleural fluid, chest radiograph, and in the case of severe sepsis, abdominal ultrasound, are recommended.[57]

In the United Kingdom, patients admitted with decompensated cirrhosis are recommended to undergo a full septic screen, including diagnostic paracentesis, blood cultures, urine dip/MCS, full blood count, C-reactive protein, chest radiograph, and ultrasound abdomen.[54] A recent Italian paper makes similar recommendations on the requirement to rule out infection in patients admitted with an acute decompensation of cirrhosis, advising paracentesis, chest radiograph, urinalysis and cultures be performed on hospitalization, in the case of worsening liver or renal function, and if further complications or organ failures develop.[6]

In the case of bacterascites (ascites neutrophil count <250/mm^3 but positive bacterial culture), EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis recommend treatment with antibiotics if signs of systemic inflammation or infection are present. Otherwise, repeat sampling and ascitic fluid culture is recommended, with antibiotic treatment started regardless of neutrophil count if bacterascites is again demonstrated on the repeat culture.[56]

The role of newer rapid diagnostic tests for antimicrobial species identification and susceptibility testing/resistance gene identification is discussed later.

Antimicrobial treatment of multidrug-resistant infections in cirrhosis [Table 2]

In cirrhosis, it is recommended that ascitic fluid, blood and urine cultures are taken prior to antibiotic administration, being mindful that each hour of delay in antibiotic administration in severe sepsis/septic shock is associated with a linear increase in mortality.[58,59]

In the previously described intercontinental study, administration of a microbiologically effective empirical treatment (as determined *in vitro* by sensitivity testing) improved in-hospital and 28-day survival in bacterial MDRO by 40-50% and was the only modifiable predictor of mortality. Microbiological efficacy was significantly higher in patients who received a treatment adherent to the protocols recommended in the *European Association for the Study of the Liver (EASL) Clinical Practice Guideline for the management of patients with decompensated cirrhosis*. It is worth noting, however, that bacteria isolated in Asian centers were less likely to be sensitive to the antibiotics recommended by EASL than bacteria isolated at the other centers (50% versus 80%).[25,56]

Initial empirical antibiotic treatment should virtually target all the bacteria potentially responsible for the infection;[6] empiric broad-spectrum therapy (in an Italian population of cirrhotic patients with HCAs, and a prevalence of MDROs of 40%-46%) has been shown to reduce mortality, treatment failure, and length of stay.[56,60] The optimal choice of empirical antibiotic therapy will vary according to site of infection, origin of infection (CA versus HCA versus nosocomial), severity of infection, and local microbial epidemiology.[19] For example, in a 2021 Korean RCT, empirical carbapenem (versus TGCs) use for treatment of SBP was found to reduce mortality only in a sub-group of patients who were critically ill (Chronic Liver Failure-Sequential Organ Failure Assessment score of 7 or more).[61]

HCA and nosocomial SBP are more likely be caused by resistant organisms than CA SBP, and empiric treatment with TGCs is not recommended due to poor effectiveness.[56,62] EASL

guidelines recommend empiric piperacillin/tazobactam in areas with a low prevalence of MDROs, whilst carbapenems are recommended in areas with a high prevalence of ESBLE. The addition of a glycopeptide, daptomycin, or linezolid to carbapenem therapy is recommended in areas with a high prevalence of Gram-positive MDROs.[56]

Given the heterogeneity in MDROs seen at various centers (see Table 3),[25] empiric local antibiotic protocols should be optimized according to local AMR characteristics.

An optimal duration of antibiotic treatment to treat infection in patients with cirrhosis has not yet been established, except in the case of SBP (minimum 5-day course advised).[6,63] For most other infections, a 7-day course is adequate.[6]

The longer that commensal bacteria in the skin and gut are exposed to antibiotics, the greater the pressure on opportunistic pathogens (such as *Escherichia coli*) to select for antibiotic resistance, and these resistant organisms may then subsequently cause clinical infection.[64,65] This 'collateral selection' of commensal organisms is the dominant driver of the important forms of antibiotic resistance affecting patients. These resistant opportunistic pathogens are transmitted between asymptomatic carriers, and many resistance-conferring genes can pass easily between bacterial strains/species.[65]

A 2019 European multicenter observational study found that continuous/extended infusion of piperacillin-tazobactam or carbapenems was associated with a significantly lower mortality than intermittent infusion of these drugs (adjusted hazard ratio, 0.41; 95% CI, 0.11 to 0.936; p=0.04) in patients with cirrhosis and BSI.[66] Inadequate antibiotic dosing schedules may result in suboptimal exposure at the site of infection, increasing the risk of both therapeutic failure and the selection of resistant bacteria.[67] Extended infusion strategies are beneficial in that

they are more likely to maintain serum drug levels above the minimum inhibitory concentration and the mutagenic window.[4]

Clinicians are encouraged to consult their local, national, and international guidelines (such as the relevant American Association for the Study of Liver Diseases (AASLD) (2021) or EASL (2018) guidelines),[56,68] and consult with microbiology/infectious diseases colleagues as necessary, for advice on choice of antimicrobial protocols. Knowledge of one's own center's epidemiology is essential,[4] and breadth of empiric antimicrobial cover should also be influenced by the severity of an individual patient's infection, and their risk factors for MDROs.[69]

Whilst balancing the need for adequate broad-spectrum cover and thereby minimizing the risk of a delay in patients receiving microbiologically effective treatment, clinicians should always look towards rapid de-escalation of antibiotics as a key strategy when required.[25,59] This avoids driving AMR unnecessarily through the prescription of excessively broad and prolonged courses of antibiotics. Technological solutions and intensive antimicrobial stewardship have an important role here and are discussed further below.

Antibiotic and non-antibiotic prophylaxis of infections in cirrhosis

Antibiotic prophylaxis

The role of quinolone prophylaxis in patients with ascites is discussed above. To benefit from primary prophylaxis, such patients should have low-protein ascites (<15 g/L). Unlike UK guidelines, EASL guidelines advise that to justify norfloxacin prophylaxis in primary prevention, patients with low-protein ascites should also have Child-Turcotte-Pugh score ≥9 and serum bilirubin level ≥3 mg/dL, with either impaired renal function or hyponatraemia.[56,70]

AASLD guidelines are similar, recommending quinolone primary prophylaxis in patients with low-protein ascites and renal dysfunction, serum sodium <130 mmol/L, or liver failure.[68] Prevention of spontaneous bacterial empyema has not been studied.[68]

There are two further scenarios of note where antibiotic prophylaxis is recommended in cirrhosis (other than in the cases of prophylaxis for invasive procedures, and rifaximin in the treatment of HE): in secondary prevention of SBP (again, with quinolones, and less convincingly with trimethoprim-sulfamethoxazole),[55,68] and in prophylaxis of bacterial infection in gastrointestinal bleeding. The choice of agent in gastrointestinal bleeding should be guided by the factors discussed in *'Appropriate antimicrobial therapy'* above. First-choice agents as per EASL are ceftriaxone or norfloxacin (depending on both patient factors and prevalence of quinolone-resistant infections) for up to 7 days; AASLD recommends ceftriaxone 1 gram/24 h as first choice, for a maximum of 7 days, with consideration of discontinuation once haemorrhage has resolved and vasoactive drugs have been discontinued.[56,71]

Peri-liver transplantation antibiotic prophylaxis

In a study of pre-operative carriage of ESBLE in LT patients, the authors recommended ESBLE-targeted intra-operative antibiotic prophylaxis in patients with previous ESBLE infection, exposure to a beta-lactam agent in the month preceding LT, or a history of SBP, as well as consideration of empiric post-operative antimicrobial treatment.[23]

A consensus as to the optimal duration of peri-LT antibiotic/antifungal prophylaxis has yet to be established. A randomized controlled trial (RCT) of 102 patients, randomized to receive intra-operative antibiotics only or a 72-hour course of perioperative antibiotics, found no significant difference between the two groups in rates of surgical site infection or nosocomial

infection, though – as the authors point out – the study was under-powered (60%) and should be seen as a pilot study.[72]

Non-antibiotic prophylaxis

Administration of non-selective beta-blockers (NSBB) is associated with a reduced occurrence of SBP.[73] NSBB have been shown to ameliorate gastrointestinal permeability and reduce bacterial translocation.[74]

In a placebo-controlled RCT of combined granulocyte colony-stimulating factor (G-CSF) and darbopoietin-alpha therapy in patients with decompensated cirrhosis, the intervention group had improved survival, Child-Turcotte-Pugh score, MELD score, need for large-volume paracentesis, and septic shock rates at 12 months.[75] However, in a more recent, larger RCT of ACLF patients, G-CSF therapy was not associated with increased 90-day transplant-free survival.[76]

Other candidate strategies for the prevention of BI in cirrhosis include prokinetics (by targeting intestinal dysmotility), bile acids and farnesoid X receptor agonists (by improving the intestinal barrier), and statins (by targeting immune dysfunction).[77]

International cooperation

At the 68th World Health Assembly in 2015, the World Health Organization (WHO) adopted a Global Action Plan on AMR, which set out to improve awareness and understanding of AMR, strengthen knowledge through surveillance (e.g. through its Global AMR Surveillance System) and research, reduce the incidence of infection, optimize the use of antimicrobial agents, and ensure sustainable investment in tackling AMR.[78]

Antimicrobial stewardship

The CDC advise that hospital prescribers and pharmacists can improve antibiotic prescribing by optimizing antibiotic selection, re-assessing antibiotic treatment when the results of diagnostic testing are available, and using the shortest effective duration of therapy.[79] Hospitals are recommended to have dedicated antimicrobial stewardship teams.[69]

The WHO Global Action Plan on AMR states that systematic misuse and overuse of antimicrobial drugs in human medicine and food production has put every nation at risk from the consequences of AMR.[78]

Considering the case of India, which has a particularly high rate of AMR, the root causes are multiple, with health system factors and environmental factors contributing. Addressing the relevant drivers is not straightforward, but public health recommendations have included the prevention of powerful antibiotics being sold over the counter, public and physician education campaigns about the dangers of uncontrolled antimicrobial use, ending financial compensation of physicians for the issuing of antibiotic prescriptions, ending the use of relevant antimicrobial growth promoters in livestock, regulations governing the discharge of antimicrobial waste into the environment, and robust, national data collection on AMR to drive policy.[80]

Targeting the gut microbiome

Prebiotics, probiotics, non-absorbable antibiotics such as rifaximin, a dietary regimen which includes complex carbohydrates and phenols, fecal microbiota transplantation (FMT), and bacteriophage therapy have been proposed as potential treatments for AMR, via modulation of the gut microbiome [Figure 2].[8]

Rifaximin

Oral rifaximin, a non-absorbable (systemic absorption is <0.4%) semisynthetic rifamycin derivative, which selectively decontaminates the gut, has been shown to be an efficacious treatment for HE.[81] It is bactericidal against a range of gut pathogens, including *Escherichia coli*, *Salmonella*, *Shigella* and *Campylobacter*.[82]

In a small placebo-controlled RCT, those treated with rifaximin were less likely to develop infection (OR, 0.21; 95% CI, 0.05 to 0.96) over 90 days.[83] In a prospective study of a selected cohort of patients with refractory ascites not on norfloxacin prophylaxis, rifaximin improved mortality, and was also associated with significant subsidence of ascites, however, this study had methodological flaws such as a lack of blinding.[84] In a large retrospective study, rifaximin administration was associated with a reduced incidence of infections overall in cirrhotic patients not already on norfloxacin prophylaxis (it is not clear what proportion of these patients had refractory ascites).[85] Another large retrospective study found that rifaximin was associated with decreased SBP risk in both hepatocellular carcinoma (HCC) and non-HCC cohorts, and a reduced risk of SBP, variceal bleeding and death in the non-HCC cohort, though these patients were not on norfloxacin prophylaxis.[86] In a further retrospective study in patients listed for LT at our institution, patients treated with rifaximin had a reduced incidence of SBP, variceal bleeding and all-cause admissions (prevalence of ciprofloxacin prophylaxis in the rifaximin and rifaximin-naïve cohorts was 15% and 20% respectively, which was not a statistically significant difference).[87] In an RCT of rifaximin versus norfloxacin for secondary prophylaxis of SBP, rifaximin outperformed norfloxacin, significantly reducing SBP recurrence and mortality, however, other studies have not shown a benefit, and EASL guidelines do not advocate the use of rifaximin for this indication.[56,88,89]

Rifaximin has been reported to have a low risk of inducing bacterial resistance.[90–92]. Rifaximin therapy is associated with reduced rates of *Clostridium difficile* infection (CDI) in patients with cirrhosis, though it is associated with *C. difficile* rifaximin-resistance should CDI develop.[93,94] Rifaximin-resistant staphylococci have been isolated on the skin following rifaximin administration in cirrhotic patients.[95] However, the consequences in terms of clinically relevant AMR are uncertain.

Fecal microbiota transplantation

FMT is the transfer of fecal microbiota from a healthy donor, providing exogenous bacterial flora as a therapeutic intervention.[96] There is level 1a evidence for the efficacy of FMT in treating recurrent *Clostridium difficile* infection.[97]

Given the known association of gastrointestinal MDRO colonization with clinical infection, MDRO decolonization with FMT is a logical potential therapy.

A systematic review and meta-analysis of FMT for the decolonization of MDROs in the gut found low quality evidence that decolonization was achieved in half of the cases one month after FMT, with 70% of successful cases occurring within the first week after FMT, and few temporary adverse events identified. The study indicated a potential benefit of FMT as a decolonization intervention, with future well-designed RCTs advised to confirm this.[98] A prospective, randomised placebo-controlled feasibility trial of FMT to eradicate gastrointestinal carriage of MDROs is ongoing.[99] Exploration of targeted drugs that act on microbial targets, that mimic or modulate microbial metabolites, or that interfere with interactions between microbes and the host may offer an exciting therapeutic paradigm.

Technological interventions

More advanced diagnostic tools are being used to reduce the time taken to diagnose pathogens and discern their sensitivities, compared with traditional culture and antimicrobial sensitivity testing techniques. The potential benefits of such techniques for patient outcomes, reduced healthcare costs, and improved antimicrobial stewardship (*e.g.*, through rapid de-escalation of broad-spectrum strategies where appropriate) are enormous.

These technologies can be categorized into those that facilitate shorter turnaround times for culture-based methods, and those which work independently of culture-based methods.[4] The below list of products is not exhaustive.

Culture-based technologies

Matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF MS: Bruker Daltonics, Fremont, California, USA) works by analyzing the spectra of ribosomal proteins released by cultured bacteria and matching this against a database to identify organisms.

Investigators in Houston, Texas, USA were able to reduce time to bacterial pathogen identification and discernment of relevant antibiotic sensitivities, and communication of these data to prescribers, facilitating earlier optimization of antibiotic therapy when they trialed integrated MALDI-TOF MS of Gram-negative early-positive blood culture isolates, rapid antimicrobial susceptibility testing, and near-real-time antimicrobial stewardship practices against preintervention care.[100] Mean blood culture time-to-positivity (TTP) was 15.6 +/- 12 hours for both groups and was not significantly different. However, the average time from blood culture TTP to final species identification and antimicrobial susceptibility results was 47.1 +/- 13.7 hours in the preintervention group, versus 24.4 +/- 11.4 hours in the intervention group ($p<0.001$). Combined with near-real-time antimicrobial stewardship practices, this

resulted in efforts to adjust and optimize antimicrobial management (de-escalation/escalation of antibiotic therapy, dosing/route modifications, and/or discontinuation of unnecessary Gram-positive coverage) at on average 75 hours from TTP in the preintervention group (in 80% of eligible patients) versus 29 hours in the intervention group (in 94% of eligible patients; p=0.004). Most importantly from an individual patient perspective, average time from BSI onset to initiation of an active agent fell from 73.2 hours in the preintervention group, to 36.5 hours in the intervention group (p<0.001). Despite the labor-intensive nature of the intervention, the intervention group had significantly reduced hospital costs (p=0.009) and length of stay (p=0.01). MALDI-TOF MS can also be used to identify yeast (and bacteria) grown on agar media.[100]

Colorimetric assays such as CARBA PAcE (Mast Group Ltd, Bootle, England) can be used to detect carbapenemase-producing bacteria (CARBA PAcE can be used for *Pseudomonas*, *Acinetobacter* and *Enterobacterales*). In CARBA PAcE, a sample of a pure culture growth is mixed with a solution and processed before being incubated for 10 minutes, then the result is read. Overall sensitivity and specificity for CARBA PAcE on testing was 72% and 91%, although with optimization of agar, extrapolated sensitivity improved to 89% for all carbapenemases, and 96% for the four major carbapenemases.[101]

Rapid immunochromatographic assays are available that provide results from clinical isolates or positive blood culture results in no more than 15 minutes, test 4-5 major carbapenemases (the fifth is uncommon in Western countries) and demonstrate concordance with the reference standard of up to 100%.[102]

Other culture-based technologies that give results in minutes-to-hours from blood cultures turning positive include dRAST (direct and Rapid Antimicrobial Susceptibility Testing:

QuantaMatrix, Seoul, South Korea), which outperformed MALDI-TOF MS in guiding optimal antibiotic choice;[103] Sepsityper (Bruker Corporation, Billerica, Massachusetts, USA), VITEK 2 (bioMérieux, Marcy-l'Étoile, France) and Accelerate Pheno (Accelerate Diagnostics, Inc., Tucson, Arizona, USA), which have been found to have pathogen identification and susceptibility testing accuracy ranging from 89.5%-96.6%;[104] and QuickFISH (OpGen, Inc., Rockville, Maryland, USA), which uses fluorescent in situ hybridization to identify bacteria and yeast pathogens in positive blood cultures and – provided the relevant organism is tested for – concordance with the reference standard approaches 100%.[105,106]

Non-culture-based technologies

Unyvero (Curetis, Holzgerlingen, Germany) is a rapid molecular diagnostic (PCR-based) technology which has been trialed mostly in the context of pneumonia and joint infections. It delivers results in 4-5 hours and does not require prior culture before the test can be run. In a multicenter trial of patients with lower respiratory tract infections, bronchoalveolar lavage fluid samples were tested and overall concordance with routine culture was 82.1%, with sensitivity and specificity for bacteria detection of 84% and 98%, respectively. Concordance in detection of MDROs was good for MRSA and carbapenem-resistant isolates (87.5-100%) but was poor for *Pseudomonas aeruginosa*.[107]

T2Dx (T2 Biosystems, Lexington, Massachusetts, USA) uses T2 magnetic resonance technology to analyze whole blood samples, without the requirement for prior culture, detecting bacterial and fungal species within 3-5 hours with robust accuracy.[108,109] A meta-analysis of prospective and retrospective trials, including one RCT, found significant benefits of its use on time to targeted antimicrobial therapy, time to de-escalation from empiric therapy, length of intensive care stay, and length of hospital stay.[110]

Combined culture- and non-culture-based technologies

A technique combining nucleic acid purification and real-time PCR detection facilitates a range of detection capabilities for viruses and bacteria (including Mycobacteria),[111] can detect AMR, and again has shown good performance against reference tests.[112–115] It can be used on positive blood cultures to shorten time to identification of pathogens and their resistance profiles, and has non-culture-based applications also.[4,116] Results take from around 50 minutes to 2 hours.

FILMArray Blood Culture Identification Panel (BioFire Diagnostics, Salt Lake City, Utah, USA) uses a PCR strategy to screen for a panel of 24 bacterial and fungal pathogens, and 3 antibacterial resistance genes, from positive blood cultures, with strong performance against reference standards and a turnaround time of around one hour.[4,117–119] It has also been used to directly examine CSF and bronchoalveolar lavage samples, without the need to wait for positive cultures.[118,120]

DISCUSSION

Clinicians have a dual responsibility – to treat the patient in front of them with effective and timely antimicrobials, usually empirically at first, whilst minimizing the risk of driving AMR through unnecessary, excessively broad-spectrum, or excessively prolonged antimicrobial prescribing.

Infection control precautions in healthcare settings should be optimized. For example, instances of the nursing of patients infected with MDROs in open bays, and the sharing of bathroom facilities, should be minimized, as should the number of staff entering the patient's environment. Hand hygiene, environmental cleaning and barrier nursing are essential.

Avoidance of unnecessary instrumentation and implementation of relevant bundles to prevent, for example, ventilator-associated pneumonia and catheter-related infections are also important.[69] In settings with a higher prevalence of MDROs, the use of separate diagnostics areas, such as radiology services (as became common during the COVID-19 pandemic), should be trialed.

Alternatives to antibiotic prophylaxis should be sought where possible, and further studies should identify more precisely which patient cohorts benefit from antibiotic prophylaxis.[6,69]

Robust screening for infection in patients with cirrhosis on admission to hospital, and on subsequent deterioration, should be performed, particularly if decompensation is present. In those with severe sepsis/septic shock, urgent sampling of ascites, blood and urine followed by immediate empiric broad-spectrum antibiotic therapy is required. Fungal infection, though uncommon, should be considered in patients who develop a second infection during hospitalization, in ACLF, and in at-risk patients who fail to respond to appropriate broad-spectrum antibiotics.

Screening protocols for MDROs via nasal and rectal swabs should be optimized based on evidence of benefit.

Given the marked heterogeneity in the prevalence and characteristics of MDROs between centers, empirical antibiotic regimens should be tailored to local bacterial epidemiology. AMR patterns change over time, and local epidemiology should be monitored frequently (annual monitoring has been suggested as a minimum standard).[4]

New biomarkers and risk prediction models should be developed to help identify the presence or absence of infection in patients with cirrhosis more reliably.[121] Such biomarkers should

have as rapid a turnaround time as possible, to help reduce inappropriate administration or non-administration of antimicrobials.[6]

Rapid microbiological diagnostic and resistance tests should be used more widely and optimized further.[69] Hospitals should take a medium and long-term view when considering the acquisition costs of these technologies, which have been demonstrated on multiple occasions to not only improve patient outcomes but to reduce hospital costs. They also play a key role in antimicrobial de-escalation, which is essential for reducing selective pressure and AMR. Antibiotic administration regimens should be optimized, e.g., through extended infusion protocols.[66]

International strategies to reduce AMR through prevention of antibiotic misuse/overuse, and associated selective pressure, are required.[4] Governments and transnational organizations should use their influence to drive development of new antimicrobial drugs. Education campaigns, such as on the importance of rapid de-escalation of antibiotics, should be undertaken. The WHO recommend a root and branch education strategy on AMR, involving the public, schoolchildren, as well as those working in health, veterinary and agriculture sectors.[78]

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TABLES

Table 1: Definitions of multidrug-resistant, extensively drug-resistant, and pandrug-resistant bacteria

(NB when a species has intrinsic resistance to an antimicrobial agent or to the whole category, that agent or category is not counted when calculating the number of agents or categories to which the bacterial isolate is non-susceptible)[3]

Category	**Definition**
Multidrug-resistant bacteria	Non-susceptibility to at least one agent in three or more antimicrobial categories
Extensively drug-resistant bacteria	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)
Pandrug-resistant bacteria	Non-susceptibility to all agents in all antimicrobial categories

Table 2: Therapeutic options for treating multidrug-resistant organisms in patients with cirrhosis

MDRO	**Gram-positive cocci**		**Gram-negative bacilli**			
	Methicillin-resistant S. aureus	*Vancomycin-resistant enterococci (Main*	*ESBL-producing Enterobacteriacaea (Main species: E. coli*	*Carbapenemase-producing Enterobacteriacaea (Main species: E. coli*	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*

		species: E. faecium)	*K. pneumoniae)*	*K. pneumoniae)*		
Therapeutic Options	Vancomcycin Teicoplanin Daptomycin Linezolid Tedizolid Tigecycline Ceftaroline Ceftobiprole Razupenem Dalbavancin Oritavancin	Daptomycin Linezolid Tedizolid Tigecycline Razupenem	Carbapenems Temocillin Ceftolozane-tazobactam	Ceftazidime-avibactam Aztreonam-avibactam Meropenem-vaborbactam Cefiderocol	Ceftolozane-tazobactam Cefiderocol Eravacycline	Tigecycline Colistin Cefiderocol Eravacycline

(Adapted from J Hepatol, Vol 75, Supplement 1, Fernández J, Piano S, Bartoletti M, Wey EQ, Management of bacterial and fungal infections in cirrhosis: The MDRO challenge, S101-S117, Copyright 2021, with permission from Elsevier.)

Table 3: Prevalence of MDR and XDR Bacteria Across Different Countries[a]

Country		MDR	XDR	ESBL *Enterobacteriaceae*	CRE	*Acinetobacter baumannii*	MRSA	VRE
Overall, n (%)		253 (34)	62 (8)	89 (12)	35 (5)	19 (3)	14 (2)	16 (2)
Asia, n (%)		97 (51)	33 (17)	26 (14)	20 (11)	14 (7)	6 (3)	5 (3)
	India	63 (73)	28 (33)	18 (21)	19 (22)	11 (13)	2 (2)	3 (4)
	Indonesia	3 (25)	0 (0)	1 (8)	0 (0)	1 (8)	0 (0)	0 (0)
	South Korea	31 (33)	5 (5)	7 (8)	1 (1)	2 (2)	4 (4)	2 (2)
Europe, n (%)		104 (29)	20 (6)	31 (9)	13 (4)	4 (1)	8 (2)	6 (2)
	Belgium	5 (33)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)
	Denmark	6 (50)	2 (17)	2 (17)	2 (17)	0 (0)	1 (8)	0 (0)
	France	3 (30)	1 (10)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
	Germany	5 (26)	1 (5)	2 (11)	1 (5)	0 (0)	0 (0)	0 (0)
	Israel	4 (57)	0 (0)	3 (43)	0 (0)	0 (0)	0 (0)	0 (0)
	Italy	57 (30)	14 (7)	15 (8)	7 (4)	2 (1)	5 (3)	6 (3)
	Russia[b]	1 (17)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)
	Spain	16 (23)	2 (3)	4 (6)	2 (3)	1 (1)	2 (3)	0 (0)
	Switzerland	6 (26)	0 (0)	2 (9)	0 (0)	0 (0)	0 (0)	0 (0)
America, n (%)		52 (27)	9 (5)	32 (17)	2 (1)	1 (1)	0 (0)	5 (3)
	Canada	4 (24)	0 (0)	3 (18)	0 (0)	0 (0)	0 (0)	0 (0)
	United States	6 (16)	1 (3)	4 (11)	0 (0)	0 (0)	0 (0)	1 (5)
	Argentina	22 (27)	2 (3)	14 (17)	0 (0)	0 (0)	0 (0)	2 (11)
	Brazil	10 (31)	5 (16)	4 (13)	2 (6)	1 (3)	0 (0)	1 (4)
	Chile	9 (3)	1 (4)	6 (26)	0 (0)	0 (0)	0 (0)	1 (3)

CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended spectrum beta-lactamase producing; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
[a]Only patients with positive cultures (n = 740) were included in this analysis.
[b]European Russia. Only countries with at least 10 patients included were reported.

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FIGURES

Figure 1

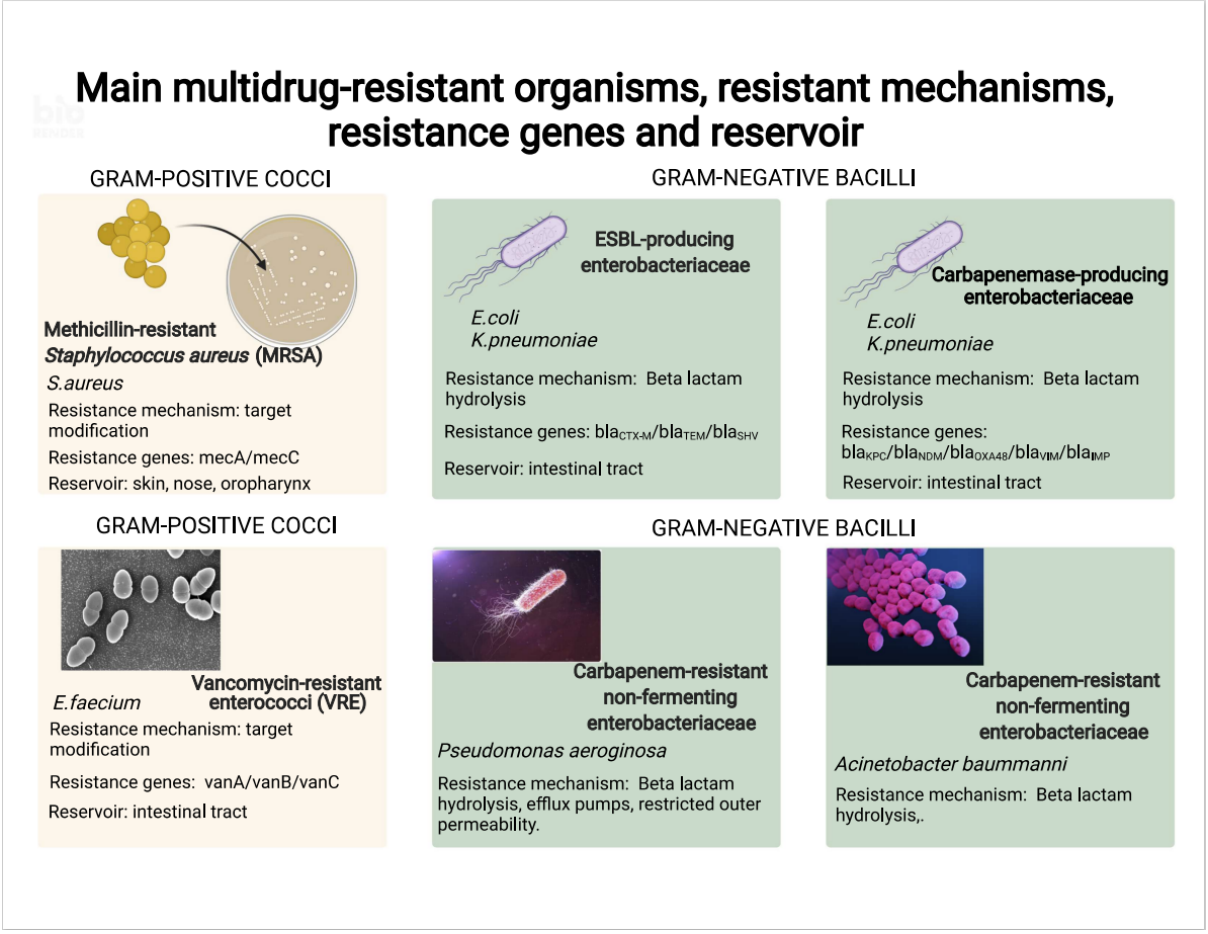

Figure 2

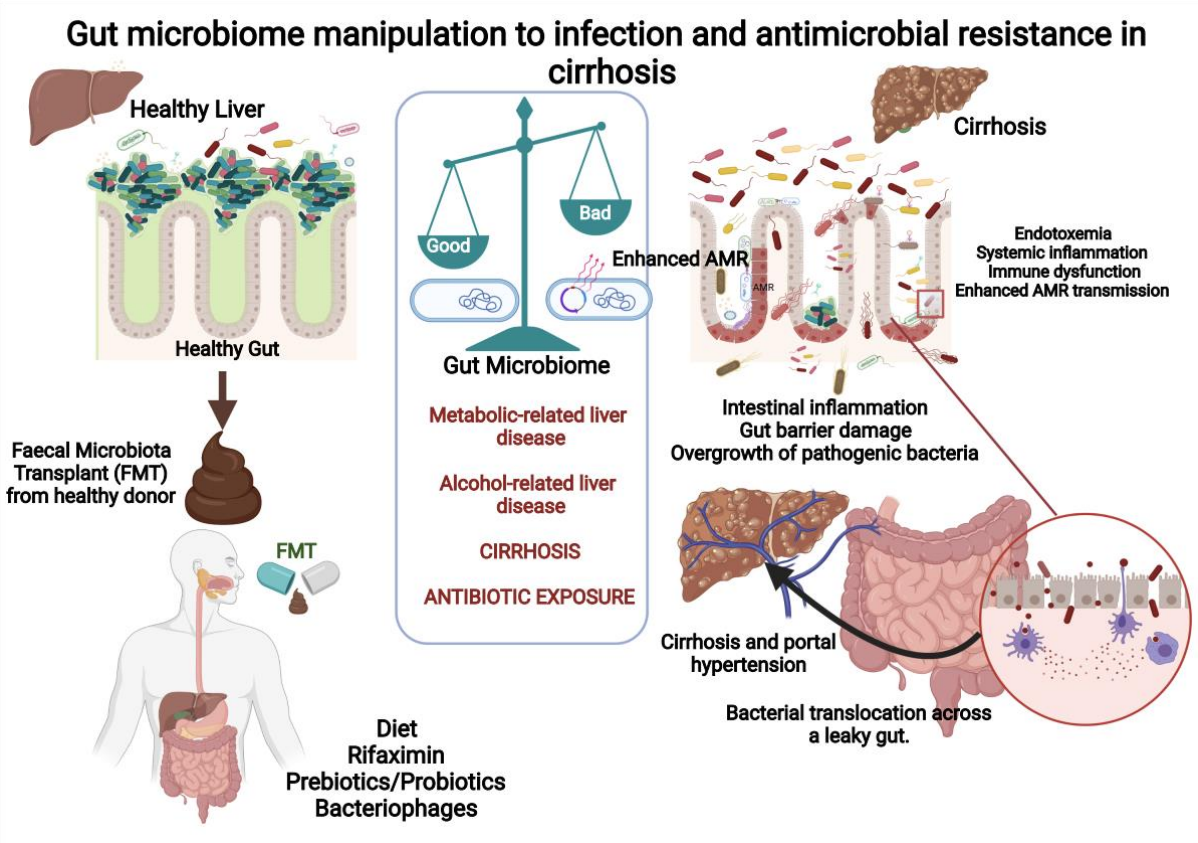
Gut microbiome manipulation to infection and antimicrobial resistance in cirrhosis
Healthy Liver
Healthy Gut
Faecal Microbiota Transplant (FMT) from healthy donor
FMT
Diet
Rifaximin
Prebiotics/Probiotics
Bacteriophages
Good
Bad
Gut Microbiome
Metabolic-related liver disease
Alcohol-related liver disease
CIRRHOSIS
ANTIBIOTIC EXPOSURE
Enhanced AMR
Cirrhosis
Endotoxemia
Systemic inflammation
Immune dysfunction
Enhanced AMR transmission
Intestinal inflammation
Gut barrier damage
Overgrowth of pathogenic bacteria
Cirrhosis and portal hypertension
Bacterial translocation across a leaky gut.

FIGURE CAPTIONS

Figure 1

A summary of the main multidrug-resistant organisms, mechanisms of resistance, and reservoir. (Adapted from J Hepatol, Vol 75, Supplement 1, Fernández J, Piano S, Bartoletti M, Wey EQ, Management of bacterial and fungal infections in cirrhosis: The MDRO challenge, S101-S117, Copyright 2021, with permission from Elsevier. Created on Biorender.com with licence for publication.)

Figure 2

Gut microbiome manipulation to treat infection and antimicrobial resistance in cirrhosis.

The gut microbiome of patients with cirrhosis becomes 'dysbiotic', characterised by an overall decrease in bacterial diversity, with an overabundance of pathogenic species such as *Enterococcus faecalis*, that cause liver injury and intestinal barrier damage. The microbiota is by far the largest reservoir of multi-drug-resistant organisms and antimicrobial resistance (AMR) genes known as the 'resistome'. Intestinal inflammation and barrier damage have been found to increase AMR carriage and vertical transmission. Targeting the gut-liver axis with treatments such as Faecal Microbiota