



Management of bacterial and fungal infections in cirrhosis: The MDRO challenge

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Summary

Bacterial infections are frequent in cirrhotic patients with acute decompensation or acute-on-chronic liver failure and can complicate the clinical course. Delayed diagnosis and inappropriate empirical treatments are associated with poor prognosis and increased mortality. Fungal infections are much less frequent, usually nosocomial and associated with extremely high short-term mortality. Early diagnosis and adequate empirical treatment of infections is therefore key in the management of these patients. In recent decades, antibiotic resistance has become a major worldwide problem in patients with cirrhosis, warranting a more complex approach to antibiotic treatment that includes the use of broad-spectrum antibiotics, new administration strategies, novel drugs and de-escalation policies. Herein, we review epidemiological changes, the main types of multidrug-resistant organisms, mechanisms of resistance, new rapid diagnostic tools and currently available therapeutic options for bacterial and fungal infections in cirrhosis.

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Keywords: Epidemiology; Prevalence; Prognosis; Antibiotic resistance; Antibiotic strategies.

Received 21 September 2020; received in revised form 9 November 2020; accepted 10 November 2020

Introduction

Bacterial infections are a frequent cause of acute decompensation in patients with cirrhosis^{1–3} and can complicate the clinical course of hospitalised patients. They can precipitate other decompensations (variceal haemorrhage and hepatic encephalopathy), may cause further decompensation (variceal rebleeding, acute kidney injury-hepatorenal syndrome [AKI-HRS]) and are major precipitants of acute-on-chronic liver failure (ACLF).^{4,5} Delayed diagnosis and inappropriate empirical treatments are associated with increased risk of ACLF and mortality in patients with acute decompensation and with poor clinical course and increased mortality in patients with ACLF.^{5–8} Bacterial infections are 5–6x more prevalent in patients with cirrhosis than in the general population, with an even higher prevalence in patients with ACLF.⁶ Moreover, cirrhosis increases the risk of developing severe sepsis and sepsis-related mortality. In contrast, fungal infections are quite infrequent and usually complicate the clinical course of patients with ACLF.^{1,2,6–11}

Therefore, early diagnosis and adequate empirical treatment of bacterial and fungal infections is of paramount clinical importance in advanced cirrhosis. The spread of antibiotic resistance has complicated treatment. Bacterial infections easily treated with simple antibiotic strategies (third-generation cephalosporins [TGC], amoxicillin-clavulanic acid or quinolones) in the past, now require a more complex approach that includes the use of broad-spectrum antibiotics, new administration strategies and de-escalation policies.¹² In

the current review, we describe epidemiological changes, the main types of multidrug-resistant organisms (MDROs), mechanisms of resistance, rapid diagnostic tools and currently available therapeutic options for bacterial and fungal infections in cirrhosis.

Bacterial infections

Bacterial infections are present in 32–40% of patients with decompensated cirrhosis: 32–50% of infections are community acquired, 25–41% are healthcare-associated (HCA) and 25–37% are nosocomial.^{7–11,13,14} Almost one-quarter of patients with cirrhosis and bacterial infections develop second infections, which further worsen the clinical course.^{8,11} In contrast, fungal infections are quite infrequent, representing 3–7% of culture positive infections in cirrhosis, and are mainly nosocomial.^{6,8–11}

Epidemiology and clinical types

The most common infection in patients with cirrhosis is spontaneous bacterial peritonitis (SBP). It accounts for 20–35% of all infections, frequently precipitates AKI and ACLF and is associated with high short-term mortality.^{15–17} Pathogens most commonly involved in SBP are Enterobacteriaceae and non-enterococcal streptococci,^{8,13,18} with enterococci increasingly involved in nosocomial episodes.^{19,20} Among other infections, the most common are urinary tract infections (UTIs; 14–41%), pneumonia (8–17%), primary/spontaneous bloodstream infections (BSIs; 8–21%) and

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Key points

MDR bacterial infections constitute a global and growing healthcare problem in decompensated cirrhosis and ACLF. These infections are associated with a high risk of septic shock, ACLF, and short-term mortality. Early diagnosis and adequate empirical antibiotic treatment are key to clinical management.



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<https://dx.doi.org/10.1016/j.jhep.2020.11.010>

skin and soft tissue infections (6–13%)^{7–14,16,19,21–24} Pathogens most frequently involved in UTIs are Enterobacteriaceae and enterococci, while those most frequently involved in primary BSI are Enterobacteriaceae and staphylococci.^{1,3,9} Other less common infections are cholangitis, endocarditis, catheter-related bloodstream infections, *Clostridium difficile* enterocolitis and secondary peritonitis.^{7,8,10,25} All non-SBP infections can trigger AKI and ACLF, although pneumonia and BSI are associated with the highest risk.^{10,17,25}

Microorganisms responsible for infections in the 80s and 90s were rarely multidrug resistant and therefore were easily treated with classical β -lactams or quinolones. However, in the last 25 years, antimicrobial resistance (AMR) has become a major public health threat worldwide, with particular implications for patients with decompensated cirrhosis. This population is highly susceptible to the development of infections caused by MDROs because of the concentration of several risk factors for antibiotic resistance, mainly repeated hospitalisations, and frequent exposure to antibiotics and invasive procedures.^{1,12} The greatly increased prevalence of MDROs observed in infections acquired in the healthcare environment, mainly in the nosocomial setting, but also in the community in patients with decompensated cirrhosis, demands the urgent implementation of new antibiotic strategies.¹²

Main MDROs and mechanisms of antibiotic resistance

According to CDC's Antibiotic Resistance Threats in the United States a total of 18 pathogens are considered urgent and major threats based on their capacity to develop new resistance mechanisms and their ability to spread rapidly through patients and patients' environment. This review will focus on resistant bacteria that are commonly isolated

amongst patients with cirrhosis. The main MDROs and their mechanisms of resistance are summarised in Table 1.

Enterobacterales

Bacteria of the Enterobacterales order are the most common in patients with cirrhosis. *Escherichia coli*, *Klebsiella pneumoniae* and other Enterobacteriaceae are responsible for up to 50% of bacterial infections in this setting.^{8,13,18} Classical β -lactams (TGC and amoxicillin-clavulanic acid) were considered the cornerstone of treatment of these bacteria in the past. However, the global spread of β -lactam resistance has significantly decreased the number of effective drugs. Enzymatic hydrolysis constitutes Enterobacteriaceae's main mechanism of resistance to β -lactams, although these microorganisms can utilise other mechanisms (porin deficit and drug efflux).²⁶ They produce β -lactamases capable of hydrolysing the β -lactam ring, rendering these antibiotics ineffective. β -lactamases can be classified according to structural or functional criteria. Their structural classification is based on protein sequencing and divides these enzymes into 4 different classes (Ambler's class A, B, C and D; Fig. 1) classified in turn into 2 groups: metalloenzymes (class B) and serine reactive hydrolases (A, B and D). The functional grouping correlates the properties of a specific enzyme with the observed microbiological resistance profile.^{27,28} Functional group 1 are cephalosporinases. They correspond to class C and are related to the expression of the AmpC gene. Several microorganisms may produce AmpC, among which *Citrobacter*, *Enterobacter* and *Serratia* species may exhibit low expression of AmpC that is increased by exposure to β -lactams.²⁹ Functional group 2 is a broader group of enzymes that correspond to class A and D β -lactamases; this group includes enzymes commonly classified as extended

Table 1. Main multidrug resistant organisms, resistant mechanisms, reservoir and therapeutic options.

MDRO	Gram-positive cocci		Gram-negative bacilli			
	Methicillin-resistant <i>S. aureus</i>	Vancomycin-resistant enterococci	ESBL-producing Enterobacteriaceae	Carbapenemase-producing Enterobacteriaceae	Carbapenem-resistant non-fermentative Enterobacteriaceae	
Main species	<i>S. aureus</i>	<i>E. faecium</i>	<i>E. coli</i> , <i>K. pneumoniae</i>	<i>E. coli</i> , <i>K. pneumoniae</i>	<i>Pseudomonas aeruginosa</i>	<i>Acinetobacter baumannii</i>
Resistance mechanism	Target modification	Target modification	β -lactam hydrolysis	β -lactam hydrolysis	Restricted outer permeability Efflux pumps β -lactam hydrolysis	β -lactam hydrolysis
Resistance genes	<i>mecA/mecC</i>	<i>vanA</i> , <i>vanB</i> , <i>VanC</i>	<i>bla</i> _{CTX-M} , <i>bla</i> _{TEM} , <i>bla</i> _{SHV}	<i>bla</i> _{KPC} , <i>bla</i> _{NDM} , <i>bla</i> _{OXA48} , <i>bla</i> _{VIM} , <i>bla</i> _{IMP}		
Reservoir	Oropharynx, nose, skin	Intestinal tract	Intestinal tract	Intestinal tract	Intestinal tract	Intestinal tract
Therapeutic options	Vancomycin, teicoplanin, daptomycin, linezolid, tedizolid, tigecycline, cef-taroline, 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

*Active only on KPC- or OXA-48-producing strains.

§Active only on KPC-producing strains.

*Choice for metallo- β -lactamase producers.

	Ambler Class	Enzymes	Drugs with <i>in vitro</i> activity						
			Classic β -lactam + β -lactamase inhibitors	Carbapenems	Ceftazidime-avibactam	Ceftolozane-tazobactam	Cefiderocol	Meropenem vaborbactam	Aztreonam-avibactam
β -lactamases	Serin	KPC			✓		✓	✓	✓
		CTX-M	+/-	✓	✓	+/-	✓	✓	✓
		TEM, SHV	+/-	✓	✓	+/-	✓	✓	✓
		C	AmpC	+/-	✓	✓	+/-	✓	✓
		D	OXA-48		✓		✓		✓
	Metallo	NDM					✓		✓
		B	VIM				✓		✓
		IMP					✓		✓

Fig. 1. β -lactamases types and *in vitro* activities of β -lactams/ β -lactamase inhibitors. Legend: ✓, active *in vitro*; +/-, intermediate activity *in vitro*.

spectrum β -lactamases (ESBL) such as CTX-M, TEM and SHV, and some carbapenemases including *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48. ESBL and carbapenemase-producing bacteria are resistant to penicillins/cephalosporins and carbapenems, respectively. Lastly, functional group 3 includes metalloenzymes (class B) such as New Delhi metallo- β -lactamase (NDM), Verona Integron-encoded Metallo- β -lactamase (VIM) and imipenem-resistant *Pseudomonas* (IMP).^{30–33} Antibiotics active against the different β -lactamases are shown in Fig. 1.

Pseudomonas aeruginosa

Pseudomonas aeruginosa exhibits both innate/intrinsic chromosomal and imported mechanisms of resistance that may be summarised as production of β -lactamase (both ESBL and carbapenemases),³⁴ overexpression of drug efflux pumps and porin modifications.

Porin loss is an important mechanism of resistance in *P. aeruginosa*. Porins are proteins of the outer membrane of gram-negative bacteria that act as a filter and are involved in passive diffusion of hydrophilic compounds into the cell, including some antibiotics. The loss of outer membrane protein D (OprD) is a major mechanism leading to carbapenem resistance. Decreased membrane permeability often acts together with efflux pumps that eject the antibiotic from the cytoplasm. Four pumps have been described in *P. aeruginosa*: MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY.^{35–37}

Finally, another known mechanism of resistance of *P. aeruginosa* is target modification, responsible

for resistance to aminoglycosides (methylation of 16S rRNA), β -lactams (modification of penicillin binding proteins [PBP]), fluoroquinolones (mutations of the DNA gyrase and topoisomerases IV) and polymyxins (alterations to the lipopolysaccharide).³⁸

Acinetobacter baumannii

Similar to other gram-negative bacteria, *A. baumannii* can develop resistance to antibiotics via production of β -lactamases, upregulation of multidrug efflux pumps, modification of aminoglycosides, permeability defects and alterations to target sites. Among β -lactamases, Ambler class B (IMP, VIM and NDM) and D (OXA-23, OXA-24, OXA-40 and OXA-51) are the most important.^{38,39}

Staphylococcus aureus

Several mechanisms of resistance are known for *S. aureus* including enzymatic inactivation of the antibiotic (penicillinase and aminoglycoside-modification enzymes), modification of the target to decrease affinity for the antibiotic (PBP2a in methicillin-resistant *S. aureus* [MRSA]), trapping of the antibiotic (for vancomycin and possibly daptomycin) and efflux pumps (fluoroquinolones and tetracycline). Bifunctional transglycosylase-transpeptidase PBP2 is the major inhibitory target for β -lactam antibiotics in *S. aureus*. MRSA becomes resistant to methicillin and oxacillin through the acquisition of the *mecA* gene that encodes a homologue of the PBP2 called PBP2a, enabling the bacteria to sustain cell-wall synthesis when other PBPs are inhibited.^{40–43}

Key points

The prevalence and type of MDROs vary markedly between countries and centres. Physicians caring for cirrhotic patients must know the epidemiology in their centre. Empirical antibiotic strategies should be tailored according to local epidemiology and severity of infection.

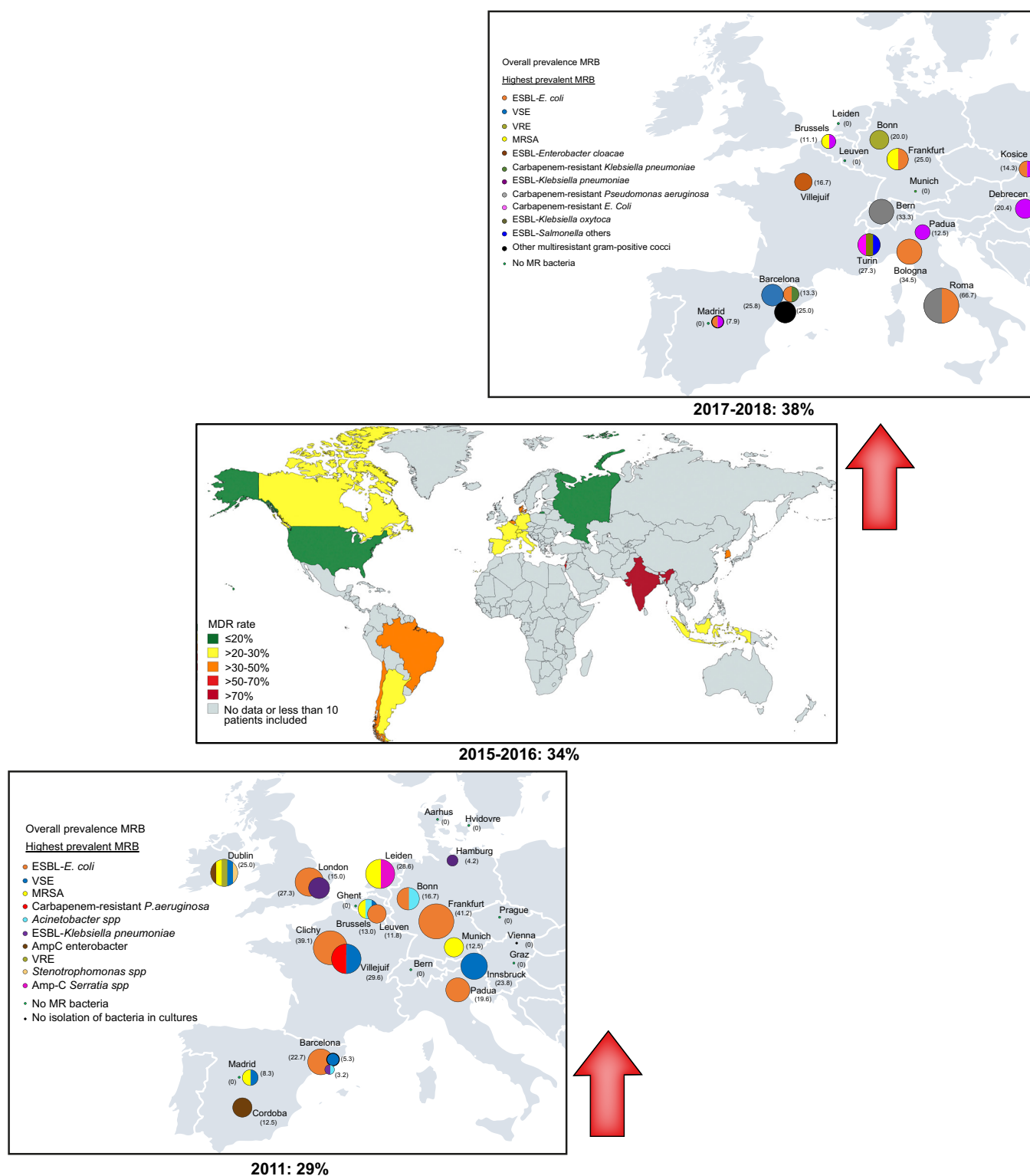


Fig. 2. Prevalence of MDROs in patients with cirrhosis in Europe and across the world.^{7,8} Different colours represent different MDRO prevalence rates (middle panel) or different MDROs (upper and lower panels). Prevalence markedly increased over time. Reproduced with permissions.⁸

Enterococcus

AMR is an important issue for *Enterococcus* spp. and intrinsic tolerance to several antimicrobials is common. All enterococci produce at least 5 different groups of PBPs and among them PBP5 seems to be associated with resistance to β -lactams and cephalosporines. Additionally, β -lactamase production has been described for both *E. faecalis* and *E. faecium*. Glycopeptide resistance, mainly seen among *E. faecium* isolates, is related to the alteration of the peptidoglycan synthesis pathway. Additionally, daptomycin and linezolid-resistant strains are increasingly reported.⁴⁴

Global and regional epidemiological differences in antibiotic resistance

The epidemiology of antibiotic resistance has relevant implications for the proper selection of empirical antibiotic treatment. Recently, 3 large epidemiological studies investigated the global and regional epidemiology of antibiotic resistance in patients with cirrhosis. In the GLOBAL study, a multicentre study including 1,302 patients with cirrhosis and bacterial infections in America, Asia and Europe, a striking heterogeneity was found in the prevalence of MDROs across the different countries⁸ (Fig. 2). Infections due to MDROs were more commonly observed in Asian centres: the percentage of infections due to MDROs exceeded 70% in Indian centres, compared to <20% in the USA, and 34% globally. Remarkably, the rate of extensively-drug resistant bacteria was 33% in India (mainly carbapenem-resistant *Enterobacteriaceae* and *A. baumannii*), while it ranged from 0–16% in all other countries. Notably, differences across geographic areas were maintained after adjusting for risk factors of MDROs such as nosocomial infections or previous antibiotic use. The BICHROME study assessed the prevalence of MDROs in patients with cirrhosis and BSI in 4 countries in Europe.⁹ The percentage of infections attributable to MDROs was highest in Italy (37%) and lowest in Spain (22%). Finally, Fernandez *et al.* analysed data on patients with cirrhosis and infections among those enrolled in the CANONIC study (2011) and the PREDICT study (2017–2018).⁷ Three relevant findings emerged from this study: a) MDROs were significantly more prevalent in infections occurring in Northern and Western Europe than in Southern Europe; b) from 2011 to 2017–2018 the prevalence of MDROs increased from 29% to 38% in culture-positive infections; c) the pattern of antibiotic resistance was highly heterogeneous, with marked differences in the type of MDROs among countries and centres (Fig. 2). The main messages from these studies are that: a) MDR bacterial infections constitute a global and growing healthcare problem in patients with decompensated cirrhosis and ACLF, with

international strategies focused on reducing antimicrobial selection pressure through the prevention of antibiotic misuse and overuse required to reduce antibiotic resistance; b) the prevalence of MDROs varies markedly among countries and centres, therefore, physicians caring for patients with cirrhosis must know the epidemiology in their centre; c) epidemiological scenarios could change over time and a periodic revision of local epidemiology (at least yearly) is mandatory.

These studies also showed that infections caused by MDROs are associated with lower resolution rates, higher incidence of septic shock and ACLF and higher short-term mortality compared to those caused by susceptible strains.^{7–9}

Diagnostic algorithm and new diagnostic tools

Current work-up

Early diagnosis and treatment of infection is paramount in patients with cirrhosis and acute decompensation or ACLF. Nowadays, diagnosis is based on clinical, analytical, imaging and microbiological assessments. A complete work-up including blood cell count and cultures, diagnostic paracentesis with ascitic fluid culture, urinary sediment and culture, sputum culture and chest X-ray should be carried out at admission and whenever a hospitalised patient deteriorates in order to rapidly detect and treat a possible infection.^{1–3}

The diagnosis of SBP is based on ascitic fluid analysis obtained by paracentesis. An ascitic polymorphonuclear count $\geq 250/\mu\text{l}$ is considered diagnostic of SBP and constitutes an indication to initiate an empirical antibiotic treatment immediately.^{45,46} Current EASL and British Society of Gastroenterology clinical practice guidelines state that in addition to ascitic fluid culture, blood cultures should also be performed in all patients with suspected SBP before starting antibiotic treatment. Only 40% of patients with SBP have positive cultures. Furthermore, it can take up to 5 days to identify the pathogen and its associated sensitivities, resulting in prolonged exposure to broad-spectrum antibiotics and the risk of antibiotic resistance.⁴⁷

New rapid techniques

Novel diagnostic tools are now being deployed to reduce the time-delay associated with culture-based pathogen identification and antibiotic sensitivity testing. Time delays affect the physician's ability to promptly de-escalate to targeted anti-infective therapy and apply judicious antibiotic stewardship to reduce the nosocomial generation of MDROs. These new methods can be categorised into those that facilitate shortened turnaround times for culture-based methods and those which are independent of culture-based methods (Table 2 and Fig. 3).

Key points

Mechanisms of antibiotic resistance differ among MDROs. β -lactam hydrolysis is frequently observed in gram-negative bacilli and target modifications predominate in gram-positive cocci.

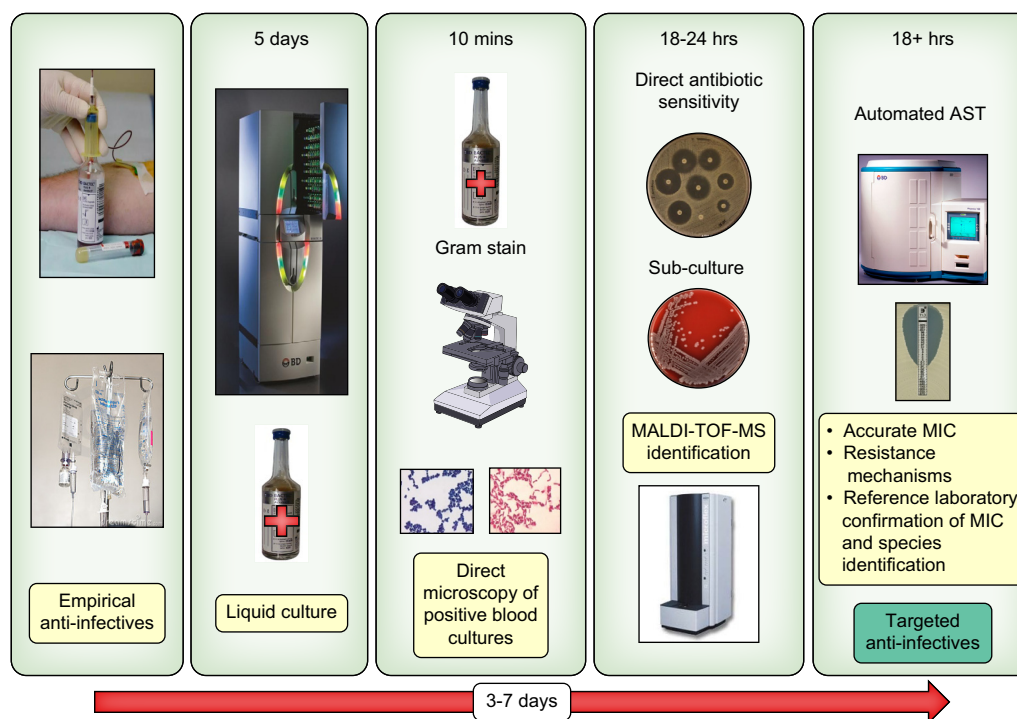
Table 2. New rapid diagnostic adjuncts for culture-based and non-culture-based identification deployed to reduce times of microbiological tests.

Diagnostic technique	Species/strain identification	Antibiotic sensitivity identification	Antimicrobial resistance identification	Sample type	Turnaround time
Currently available in clinical practice					
Culture-based diagnostics					
MALDI-TOF-MS	✓			Positive blood or urine cultures, bacterial subcultures	< 1 hour
MAST diagnostics: CARBAPAcE (Chromogenic/colorimetric media)			✓	Bacterial subcultures	< 1 hour
Lateral flow assays			✓	Bacterial subcultures	< 1 hour
- NG-Test CARBA 5 [NG Biotech]					
- RESIST-4 O.K.N.V. plus IMP K-SeT [Coris BioConcept] (Immunochromatographic lateral flow assays)					
Accelerate Diagnostics (Real-time microscopy-based)	✓	✓		Positive blood culture	6 hours
Quantamatrix (Real-time microscopy-based)	✓	✓		Positive blood culture	6 hours
QuickFISH (Direct microscopy visualization of fluorophore)	✓			Positive blood culture	30 mins
IRS (Infrared spectroscopy)	✓			Bacterial subcultures	30 mins
BioFire (Multiplexed, syndrome-oriented PCR, Molecular, Film Array)	✓		✓	Positive blood culture	< 1 hour
Non-culture-based diagnostics					
T2 Biosystems – T2Dx/T2MR (Magnetic resonance nanotechnology)	✓			Whole blood	4 hours
Adjuncts for culture-based and non-culture-based diagnostics					
Curetis Unyvero™ BCU (Multiplex-PCR and bi-directional sequencing)	✓		✓	Positive blood cultures, bacterial subcultures/ clinical samples	4 hours
Cepheid GeneXpert (Multiplex real-time PCR)	✓		✓		1 hour
At research/development stage					
Culture-based diagnostics					
IRS (infrared spectroscopy)			✓	Bacterial subcultures	30 mins
Non-culture-based diagnostics					
Nanopore Diagnostics LLC (iNDxer, a nanopore sensor for detecting nucleic acid biomarkers directly in minimally processed samples)	✓	✓	✓	Bacterial subcultures	3 hours
Oxford Nanopore Technologies (Long read WGS)	✓	✓	✓	Bacterial subcultures	3 hours
Adjuncts for culture-based and non-culture-based diagnostics					
MALDI-TOF-MS/MS (SRM/MRM)		✓	✓	Bacterial cultures/clinical samples	3 hours

FISH, fluorescent *in situ* hybridization; MALDI-TOF MS, matrix-assisted laser desorption ionization-time of flight mass spectrometry; MRM, multiple reaction monitoring methods; SRM, single reaction monitoring method; WGS, whole-genome sequencing.

Entries in brackets describe the basis of the diagnostic test.

Current BSI diagnostic workflow and management



Potential future BSI diagnostic workflow and management

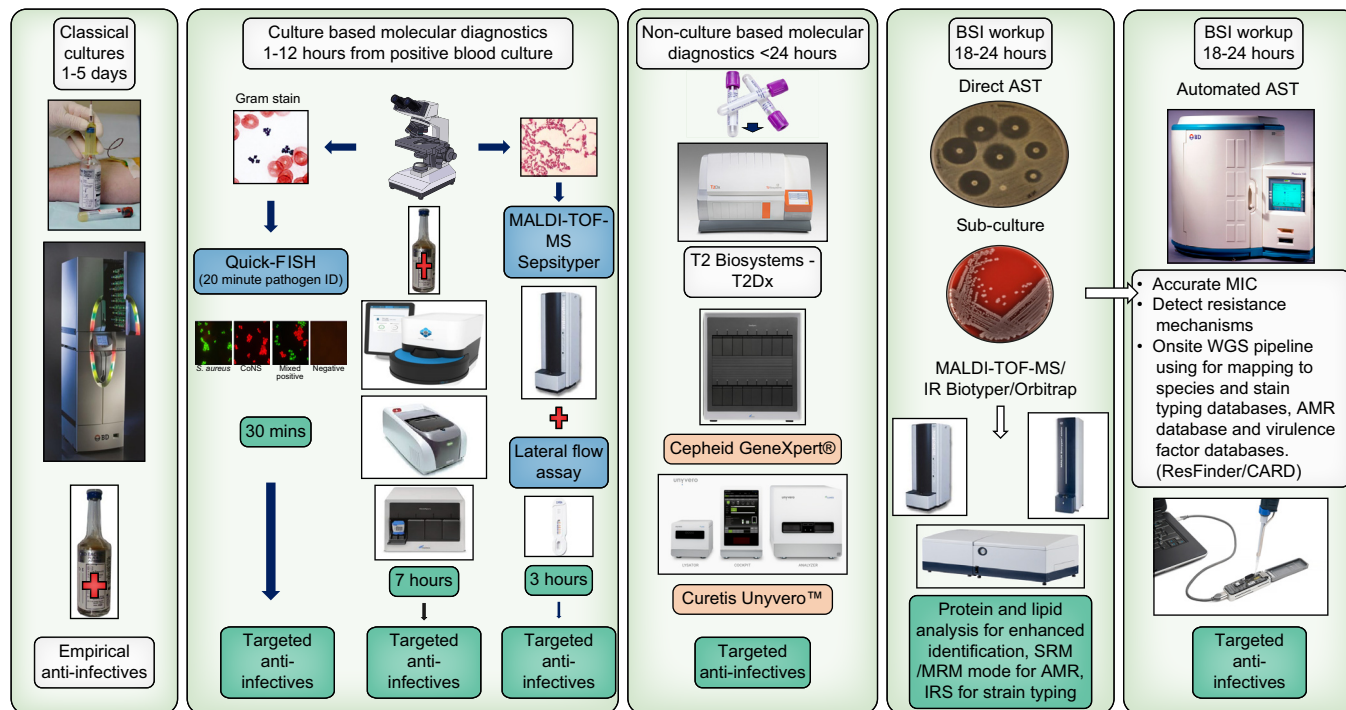


Fig. 3. Diagnostic microbiological workflow for blood stream infections. Current (upper panel) and potential future diagnostic workflow (lower panel) and management for blood stream infections: to identify the organism, perform antibiotic sensitivity testing and determine antimicrobial resistance mechanisms. Adapted from the original figure: Rapid molecular diagnostics with permission from Dr R L Gorton,¹ and Ms K J Roulston;^{2,3} ¹Health Service Laboratories LLP; ²Royal Free London NHS Trust; ³Centre for Clinical Microbiology, Division of Infection & Immunity, UCL

Key points

New rapid microbiological techniques (MALDI-TOF-MS, multiplex real-time PCR and others) are currently available in clinical practice and markedly reduce the time required for pathogen identification and antibiotic sensitivity testing. They facilitate prompt de-escalation policies.

Culture-based techniques

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) utilises the ribosomal proteins released from cultured bacterial cells and compares the spectra generated to a database of organisms. For positive blood cultures, MALDI-TOF-MS can quickly identify bacterial growth, accelerating the overall process of antibiotic sensitivity testing.⁴⁸ This technology can be deployed on blood culture bottle fluid and urine before the isolation of colonies on solid agar for species identification.

Colorimetric assays such as CARBAPAcE are used to detect carbapenemase-producing phenotypes in the Enterobacterales directly from cultured colonies. NG-Test CARBA 5 and the RESIST-4 O.K.N.V. plus IMP K-SeT are lateral flow complementary assays that employ immunochromatographic technology for the detection of KPC, OXA-48, NDM, VIM and IMP (the 'Big 5') carbapenemases in Enterobacterales, *P. aeruginosa* and *A. baumannii*.⁴⁹

Accelerate Diagnostics PhenoTM and Quanta-matrix are new automated antibiotic sensitivity testing approaches that utilise real-time microscopy. They identify and give phenotypic results direct from positive blood cultures in <7 hours. QuickFISH® (OpGen, USA) is a fluorescent *in situ* hybridisation method used for the whole-cell analysis of bacteria and yeasts within a blood culture. This technique can be used to identify species in <30 min with high sensitivity/specificity.

The Curetis UnyveroTM platform and the Cepheid GeneXpert can be deployed for rapid species identification and reporting of AMR directly on blood culture samples, sub-cultured isolates and from non-cultured direct patient specimen samples. The Curetis UnyveroTM blood culture unit can detect bacterial and fungal pathogens and antibiotic resistance genes with turnaround times of 4 hours. The Cepheid system utilises a modular platform multiplex PCR. It can be used to differentiate between methicillin-susceptible

Staphylococcus aureus and MRSA directly from blood cultures. The non-blood culture modules are utilised to identify a variety of bacterial and viral pathogen and AMR markers. Finally, the BioFire FilmArray BCID array panel uses an automated nested multiplex PCR with a panel of 23 bacterial species, 6 candida species and 10 resistance genes direct from positive blood cultures.

Non-culture-based techniques

The T2 biosystems T2Dx platforms can be used for the detection of Bacteria (T2Bacteria): *E. faecium*, *S. aureus*, *K. pneumoniae*, *P. aeruginosa*, *E. coli* and for the detection of Candida species (T2Candida). Detection is directly from whole blood (K EDTA 5 ml vacutainer tube BD) with no purification or extraction required. Turnaround times are between 3–5 hours.

Risk factors and preventive strategies

Risk factors for bacterial infection and antibiotic resistance

Poor liver function, upper gastrointestinal bleeding, low protein ascites, prior SBP and hospitalisation (especially if associated with invasive procedures and intensive care unit [ICU] admission) are all well-known clinical risk factors for the development of bacterial infections in cirrhosis.^{1–3} Active alcohol consumption and poor nutritional status have also been suggested as factors that predispose individuals to infection.⁵⁰ Some genetic polymorphisms (NOD2 variants, mannose-binding lectin deficiency and toll-like receptor 2 polymorphisms) also increase the risk of SBP through immune dysfunction.⁵¹

Recent contact with the healthcare system, especially nosocomial infection, recent use of systemic antibiotics (1–3 months), prior invasive procedures, ICU admission and infection by MDROs in the last 6 months have been described as risk factors for antibiotic resistance in cirrhosis (Table 3).^{7–9,12–14,18} Mechanical ventilation has also

Table 3. Risk factors for infections caused by MDRO and fungi in cirrhosis.

	Major risk factors	Potential risk factors
Bacterial infection by MDROs	Nosocomial episode Recent hospitalisation (3 months) Recent systemic antibiotics exposure (1 to 3 months) Recent invasive procedures (1 month) ICU admission Recent infection or colonisation by MDROs (6 months)	Long-term norfloxacin prophylaxis Health care-associated infections ACLF Diabetes mellitus
Invasive candidiasis*	Abdominal surgery Recent broad-spectrum antibiotic exposure Central venous catheter, total parenteral nutrition AKI-Renal replacement therapy Prolonged stay in the ICU Diabetes mellitus	Multifocal colonization by <i>Candida</i> ACLF Steroid therapy Malnutrition
Invasive aspergillosis*	Prolonged steroid therapy Poor liver function Prolonged stay in the ICU	ACLF Renal replacement therapy Malnutrition

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; ICU, intensive care unit; MDROs, multidrug-resistant organisms.

*Described mainly in the general population.

Table 4. Current indications for antibiotic prophylaxis in decompensated cirrhosis.

Indication	Antibiotic and dose	Duration
Secondary prophylaxis of SBP	Norflloxacin 400 mg/day or ciprofloxacin 500 mg/day PO	Long-term: until LT
Upper gastrointestinal bleeding	Norflloxacin 400 mg/12 h or ciprofloxacin 500 mg/12 h PO in compensated cirrhosis IV ceftriaxone 1 g/day in patients with: - Ascites, jaundice, hepatic encephalopathy or malnutrition - Those already on quinolone prophylaxis - In areas with a high prevalence of quinolone-resistant bacteria - Active bleeding IV ertapenem 1 g/day in patients colonised by ESBL- <i>Enterobacteriaceae</i>	Short-term: 5-7 days
Primary prophylaxis of SBP	Norflloxacin 400 mg/day or ciprofloxacin 500 mg/d PO	Long-term: until LT or clinical improvement
Patients with low protein ascites (<15 g/L) and advanced cirrhosis*		

LT, liver transplantation; SBP, spontaneous bacteria peritonitis.

*Child-Pugh C or Child-Pugh ≥9 points with serum bilirubin ≥3 mg/dl and/or serum creatinine ≥1.2 mg/dl, blood urea nitrogen ≥25 mg/dl, serum sodium ≤130 mEq/L.

been reported as independently associated with MDR infection in nosocomial episodes.⁷ The role of long-term quinolone prophylaxis as a predisposing factor for AMR in cirrhosis is unclear. Single-centre studies reported on this association in the past,¹³ but recent large epidemiological and interventional studies, evaluating long-term norfloxacin prophylaxis for the prevention of SBP in patients with advanced cirrhosis, do not confirm this association.^{7,8,52}

Current prophylactic strategies

Antibiotic prophylaxis in cirrhosis must be restricted to selected patients at a very high risk of developing SBP or other spontaneous infections in order to prevent the development of antibiotic resistance. Current indications and types of antibiotic prophylaxis are shown in Table 4.^{12,45,53} Despite the increase in quinolone resistance observed over time, this antibiotic family continues to be the main drug prescribed in the prophylaxis of bacterial infections in cirrhosis. Two main reasons explain this paradox: first, there are no effective antibiotic or non-antibiotic alternatives;⁵³ second, quinolones are still effective in the prevention of SBP in this complex epidemiological scenario.⁵²

Some studies suggest that rifaximin could be effective in preventing SBP in cirrhosis.^{54–56} This antibiotic induces few changes in the stool microbiome and appears not to increase antibiotic resistance.⁵⁷ However, other studies have failed to show any benefit of rifaximin in the prevention of SBP.⁵⁸ As a consequence, current EASL guidelines do not recommend rifaximin as an alternative to norfloxacin for SBP prophylaxis. No recommendation was given to guide primary or secondary prophylaxis of SBP among patients already on rifaximin for the prevention of recurrent hepatic encephalopathy.⁴⁵

Among non-antibiotic measures suggested to prevent MDROs, faecal microbiota transplantation appears promising.⁵⁹

Two recent randomised clinical trials (RCT) suggest that albumin administration can prevent

SBP and non-SBP infections in patients with decompensated cirrhosis.^{60,61} Attenuation of inflammatory response by albumin treatment could at least partially explain this finding. In contrast, a recent open label RCT performed in the UK in 828 hospitalised patients with cirrhosis and hypoalbuminemia reported no beneficial effects of albumin administration on the prevention of bacterial infections in the short-term.⁶² Haematopoietic factors could also be effective in the prevention of infections in cirrhosis by improving cirrhosis-associated immune dysfunction. In a small placebo RCT, the administration of granulocyte colony-stimulating factor (G-CSF) plus darbopoietin-α prevented the development of septic shock and improved 1-year survival in patients with decompensated cirrhosis.⁶³ In contrast, a recent European RCT including 163 patients with ACLF failed to show any beneficial effect of G-CSF on the prevention of bacterial infections or on survival.⁶⁴

Prophylactic bundles should also be implemented to prevent ventilator-associated pneumonia and catheter-related infections in critically ill patients with cirrhosis.^{12,53}

Measures to prevent the spread of antibiotic resistance

The emergence and spread of AMR in cirrhosis requires the implementation of measures aimed to prevent its exacerbation. Prevention strategies include not only the restriction of antibiotic prophylaxis to high-risk populations but also strict infection control policies, investigation of non-antibiotic prophylaxis, stewardship programmes on adequate antibiotic prescription, early de-escalation strategies based on rapid microbiological tests and probably, epidemiological surveillance programmes.^{12,53}

Infection control policies

Decreasing the risk of cross-transmission between MDRO carriers and other patients during hospitalisation is key in the prevention of antibiotic resistance. Colonised and infected patients should

Key points

Restriction of antibiotic prophylaxis to high-risk populations, strict infection control policies, stewardship programmes on adequate antibiotic prescription, early de-escalation strategies and short duration of antibiotic treatments are measures that prevent antibiotic resistance.

be isolated and treated with strict infection control directives that include hand hygiene, proper environmental cleaning, barrier/contact precautions (use of disposable gloves and gowns), and if possible dedicated staff.^{12,53}

Epidemiological surveillance

Regular assessment and detection of potential carriers of MDROs through periodical rectal and nasal swabs, the main reservoirs of resistant strains, could prevent antibiotic resistance in cirrhosis. Detection of MDR colonisation should be followed by prompt isolation of the patient, thereby limiting the spread of resistant strains in the healthcare environment. Colonisation data could also guide empirical antibiotic strategies, avoiding antibiotic overuse.^{12,53,65} Studies performed in non-cirrhotic patients show that MDRO carriage increases the risk of subsequent infection by the colonising organism.^{66–68} The prevalence of ESBL-*Enterobacteriaceae* faecal carriage in patients with cirrhosis seems to be at least similar to that observed in the general population of the same area, ranging from 6.5 to 15% in Europe.^{69,70} Importantly, patients with cirrhosis and pre-transplant ESBL-*Enterobacteriaceae* rectal carriage are more likely to have an infection caused by this resistant strain than non-carriers.⁷⁰ Nasal MRSA carriage is also associated with an increased risk of subsequent infections by the same MDRO in cirrhosis.⁷¹

Key points

Strategies aimed at optimizing the antibiotics' pharmacokinetic/pharmacodynamic (use of high doses within the first 48–72 hours and of continuous/extended infusions for β -lactams) are currently recommended in the treatment of patients with decompensated cirrhosis and severe infections.

Treatment of infections

Antibiotic stewardship principles should be implemented at the time of antibiotic prescription in each liver unit and should include prevention of antibiotic overuse and well-defined early de-escalation policies.^{12,45,53} These initiatives will probably require hospitals to have specifically dedicated teams.

Empirical schedules, duration of antibiotic therapy and de-escalation policies

Currently recommended antibiotic schedules

Several studies proved that an early administration of appropriate antibiotic treatment is associated with a reduction in mortality rate in patients with cirrhosis and bacterial infections.^{6,8,10,13,72} Any delay in the initiation of a proper antibiotic treatment is associated with an increase in mortality, particularly in patients with septic shock.⁷² Empirical antibiotic treatment should cover all of the potential pathogens but should balance this against the risk of selecting further antibiotic resistance.^{3,12,53} A proper empirical antibiotic protocol should first consider the severity of infection and local epidemiology and then the type of infection and the presence of risk factors for MDROs (Fig. 4). Patients with sepsis, severe sepsis or shock should receive empirical strategies covering all potential pathogens.^{12,73}

Key points

Treatment of MDR bacterial infections may require the use of new drugs active against resistant gram-negative bacilli (ceftazidime-avibactam, ceftolozano-tazobactam, cefiderocol, etc.) or gram-positive cocci (ceftaroline, ceftobiprole, tedizolid, etc.).

The rate of bacteria resistant to classic β -lactams now exceeds 50% in many centres. Consequently, they are only recommended for community-acquired SBP, BSIs and UTIs, without sepsis, while their combination with antibiotics active against intracellular pathogens (azithromycin or quinolones) is recommended in pneumonia. For nosocomial infections, broad-spectrum antibiotic regimens covering ESBL-*Enterobacteriaceae*, *E. faecium* and MRSA are suggested (e.g. carbapenems $\pm$ glycopeptides/lipopeptides). Piperacillin/tazobactam can be prescribed in patients with UTIs due to ESBL-*Enterobacteriaceae* but is discouraged in patients with BSI or SBP caused by ESBL-*Enterobacteriaceae*, because it is less effective than carbapenems in the general population.⁷⁴ Empirical antibiotic treatment for HCA infections should be adapted to local epidemiology and the presence of other risk factors (e.g. prior antibiotic use). Recent EASL practice guidelines summarise these recommendations (Table 5), underlying that in any case, empirical antibiotic protocols must be tailored to local epidemiology.⁴⁵ Adherence to EASL recommendations is associated with lower mortality.⁸

Pharmacokinetic optimisation of antibiotic schedules

Beyond the *in vitro* activity of antibiotics, several other factors contribute to their effectiveness. In critically ill patients, antibiotic therapy cannot be optimised based only on susceptibility, according to mean inhibitory concentration (MICs). Pharmacokinetic (PK) variability is also a major contributor to therapeutic failure. Timely administration of the right dose (and the right treatment schedule) is required to guarantee the correct exposure to antibiotics in critically ill patients.⁷⁵ Patients with cirrhosis frequently present with hypoalbuminemia and expansion of the third space, feature (volume of distribution related variations) that could affect serum concentrations of the antibiotic and jeopardise its ability to reach its optimal PK/pharmacodynamic (PK/PD) target.^{76,77} In addition, drug PKs may be altered in patients with shock, resulting in highly variable drug exposure and the possibility of both failure and emergence of antibiotic resistance.^{77–79} All these factors may affect the efficacy of standard dosages of hydrophilic antibiotics (e.g. β -lactams, aminoglycosides, glycopeptides, lipopeptides). β -lactams exhibit time-dependent PD characteristics and their optimal killing effect depends on the percentage of the dosing interval in which drug free (f) serum concentrations remain above the MIC of the pathogen ($\%fT_{>MIC}$).^{80,81} An acceptable $\%fT_{>MIC}$ for β -lactams is 40–60% of the dosing intervals, but most authors prefer dosing regimens that surpass the $\%fT_{>MIC}$ for 100% of the dosing interval in critically ill patients.⁸²

Given the short half-life of most frontline β -lactams, extended infusion strategies are more

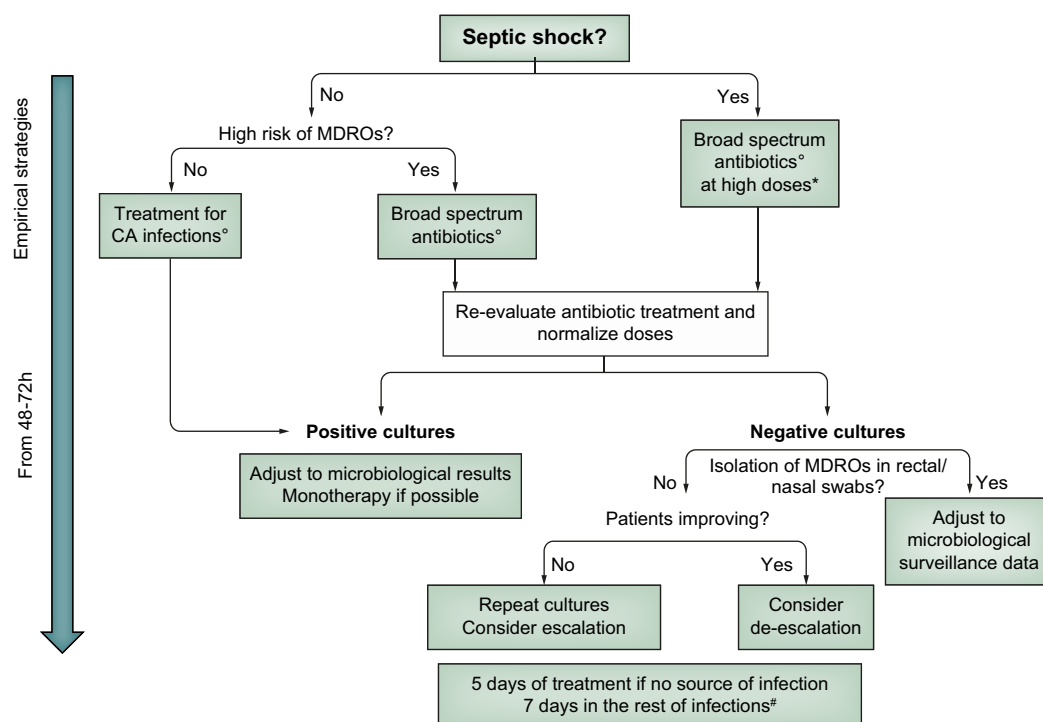


Fig. 4. Suggested algorithm for the management of patients with cirrhosis and severe sepsis or shock. Empirical treatment is guided by the severity of infection, the presence of risk factors for MDROs and local epidemiology. Broader spectrum antibiotics at high doses are used in the most severe infections covering all possible pathogens. Antibiotic schedules are re-evaluated after completing 48–72 hours of therapy. At which point, de-escalation can be considered based on microbiological isolations in clinical and epidemiological surveillance samples, and clinical evolution. °See Table 5 for specific antibiotic strategies. *See Table 6 for high-dose strategies. #Short-term treatments are recommended in the majority of patients, except for infections caused by *S. aureus*, intracellular strains, fungal infection, abscesses, parapneumonic empyema, biofilm formation or infections with predefined duration of treatment. GPC, gram-positive cocci; MDROs, multidrug-resistant organisms; TGC, third-generation cephalosporins.

likely to maintain serum drug levels above the MIC compared to standard bolus administration. These strategies – aimed at optimising the antibiotics' PK/PD – are currently recommended for the treatment of patients with cirrhosis and severe infections.

They consist of the use of high antibiotic doses within the first 48–72 hours after the diagnosis of infection and of the administration of time-dependent antibiotics (β -lactams) in continuous or extended infusions. This therapeutic strategy

Table 5. Recommended empirical antibiotic treatment for bacterial infections in cirrhosis.

Type of infection	Community-acquired infections	Nosocomial infections*
SBP, spontaneous bacterial empyema and spontaneous bacteremia	Cefotaxime or ceftriaxone or amoxicillin/clavulanic acid Uncomplicated: fosfomycin or cotrimoxazole	Piperacillin/tazobactam or meropenem $\pm$ vancomycin or daptomycin or linezolid [®] Uncomplicated: nitrofurantoin or fosfomycin
UTI	If sepsis: cefotaxime or ceftriaxone or amoxicillin/clavulanic acid	If sepsis: piperacillin/tazobactam or meropenem $\pm$ glycopeptide [#]
Pneumonia	Amoxicillin/clavulanic acid or ceftriaxone + macrolide or levofloxacin or moxifloxacin	Piperacillin/tazobactam or meropenem/ceftazidime + ciprofloxacin $\pm$ glycopeptides or linezolid should be added in patients with risk factors for MRSA [§]
Skin and soft tissue infections (SSTI)	Amoxicillin/clavulanic acid $\pm$ clindamycin If necrotizing fasciitis: Meropenem + daptomycin + clindamycin	Meropenem or piperacillin/tazobactam + glycopeptides or daptomycin or linezolid [¶] $\pm$ clindamycin

HCA, healthcare associated; MRSA, methicillin-resistant *Staphylococcus aureus*; SBP, spontaneous bacterial peritonitis.

*Recommended empirical treatment also for HCA, urinary infections and pneumonia. Empirical antibiotic treatment of spontaneous HCA infections and skin and soft tissue infections will be decided on the basis of the severity of infection (patients with severe sepsis should receive the schedule proposed for nosocomial infections) and on the local prevalence of MDROs in HCA infections.

[®]In areas with a low prevalence of MDROs.

[®]linezolid in areas with a high prevalence of vancomycin-resistant enterococci. Alternative choice in case of bacteraemia.

[#]IV vancomycin, teicoplanin or daptomycin in areas with a high prevalence MRSA and vancomycin-susceptible enterococci. Vancomycin must be replaced by linezolid in areas with a high prevalence of vancomycin-resistant enterococci.

[§]Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage.

[¶]Clindamycin is suggested in case of severe skin and soft tissue infections because of anti-toxin activity. A similar activity is provided by linezolid.

Table 6. Proposed empirical doses and ways of administration of the main antibiotics in patients with septic shock.

Antibiotic and initial dose*	Doses during the first 48-72 hours and mode of administration	De-escalation after 72 hours ^c
Ceftriaxone 2 g	1 g/12 hours	1 g/12-24 hours
Cefotaxime 2 g	6-8 g/day in continuous infusion ^b	1-2 g/8 hours
Ceftazidime 2 g	6 g/day in continuous infusion ^b	1-2 g/8 hours
Meropenem 2 g	6 g/day in continuous infusion ^b	1-2 g/8 hours
Piperacillin-tazobactam 4 g-0.5g	16-2 g/day in continuous infusion ^b	4 g/6-8h
Ceftazidime-avibactam 2.5 g	7.5 g/day in continuous infusion ^b	7.5 g/day in continuous infusion ^b
Ceftolozane-tazobactam 1.5g (3 g in case of pneumonia)	4.5 or 9 g in continuous infusion ^b	4.5 or 9 g in continuous infusion ^b
Levofloxacin 1,000 mg	500 mg/12 hours	500 mg/24 hours
Ciprofloxacin 600 mg	400 mg/8 hours	400 mg/12 hours
Tigecycline 200 mg [#]	100 mg/12 hours [#]	50 mg/12 hours [#]
Metronidazole 1,000 mg	500 mg/6 hours	500 mg/8 hours
Clindamycin 900 mg	600 mg/6 hours	600 mg/6 hours
Vancomycin 20 mg/kg	15-20 mg/kg/12 hours	Adjust by TDM
Teicoplanin 12-15 mg/kg	8-12 mg/kg/day	8 mg/kg/day
Linezolid 600 mg	600 mg/12 hours	600 mg/12 hours
Daptomycin 10-12 mg/kg [§]	8-12 mg/kg/day	6-12 mg/kg/day
Amikacin 25 mg/kg	20 mg/kg/day	Consider stopping or adjust by TDM
Gentamicin 7-9 mg/kg	7 mg/kg/day	Consider stopping or adjust by TDM
Tobramycin 7-9 mg/kg	7 mg/kg/day	Consider stopping or adjust by TDM
Fosfomycin 4 g	200-300 mg/kg/day in continuous infusion ^b	2 g/6 hours
Colistin 6-9 MIU	4.5 MIU/12 hours	3 MIU/12 hours

MIU, million international units; TDM, therapeutic drug monitoring.

*First dose is independent of renal function.

^bDoses recommended in patients with glomerular filtration rate >60 ml/min. Consider maintaining high doses after 72 hours in patients with septic shock, especially if there is an improvement in renal function to avoid sub-therapeutic plasma levels.

^cIf continuous infusion is not possible administer the drug every 6-8 hours in extended infusions (within 3-4 hours).

[#]half doses in patients with advanced cirrhosis (Child-Pugh class C). Tigecycline should be never used alone.

[§]12 mg/kg in infections caused by enterococci.

[^]Adjusted body weight. Aminoglycosides and colistin should be used only when no other option is available.

achieves high and sustained concentrations of the drug at the source of infection. The concentrations achieved are several times higher than the MIC and the mutagenic window, increasing the likelihood of therapeutic success and decreasing the risk of resistance selection (Fig. 4, Table 6).^{12,53,83} A recent prospective multicentre study in patients with cirrhosis and BSI showed that a loading dose followed by continuous infusion of β -lactams improves 30-day survival compared to traditional dosing schedules.⁸⁴ Most high-dose antibiotic strategies are off label and their safety profile needs to be proven in patients with cirrhosis.

Duration of antibiotic therapy and de-escalation policies

Early de-escalation policies and shortened durations of antibiotic treatment are other key measures to prevent antibiotic resistance. The use of broad-spectrum empirical antibiotics must be followed by early de-escalation policies (narrow the spectrum of antibiotics) to reduce the risk of selecting resistant strains. De-escalation is easy once the pathogen has been identified and an antimicrobial susceptibility test is available. This strategy is associated with good clinical outcomes.⁸ De-escalation is more problematic in culture-negative infections. PK de-escalation (normalisation of dosing strategies) on day 3 after the initiation of therapy has been proposed as a way to de-escalate and prevent antibiotic resistance. Hopefully, new rapid microbiological

tests will guide de-escalation policies in the near future.¹²

Long durations of antibiotic therapy are also a key determinant of antibiotic resistance. A 5-day antibiotic course is as effective as a 10-day course in patients with SBP.⁸⁵ Although the duration of antibiotics has not been specifically investigated in non-SBP infections, data from the general population suggest that short antibiotic courses (e.g. 7-day) are feasible for most infections.⁸⁶ Exceptions include infections caused by *S. aureus* (for which a 10-day course is recommended), intracellular strains, fungal infection, abscesses, parapneumonic empyema, biofilm formation or infections with a predefined duration of treatment.

Novel antibiotics for the treatment of MDROs

Ceftazidime-avibactam is a novel drug that combines a TGC with a β -lactamase inhibitor.¹² Importantly, ceftazidime-avibactam can inactivate KPC carbapenemases and most OXA-48. Several observational studies have confirmed its efficacy in the treatment of these infections.^{87,88}

Vaborbactam is a β -lactamase inhibitor with high affinity for serine proteases. Its addition to meropenem restores its activity against KPC but not against OXA-48- or metallo- β -lactamase-producing strains.⁸⁹

Ceftolozane-tazobactam is a new β -lactam/ β -lactamase inhibitor combination similar in structure to ceftazidime. However, compared to ceftazidime it shows higher affinity for PBPs of *P. aeruginosa* and higher stability against hydrolysis

by the chromosomal AmpC β -lactamase of *P. aeruginosa*. In addition to its activity against *P. aeruginosa* it may be considered a promising carbapenem-sparing treatment regimen against ESBL-producing *Enterobacteriaceae*.⁹⁰

Cefiderocol is a novel siderophore cephalosporin. Like other β -lactams, it inhibits bacterial cell wall synthesis by interacting with PBPs. However, it has the unique characteristic of entering the periplasmic space using the bacteria's iron transport system, enabling it to avoid efflux pumps. In addition to eluding this resistance mechanism, this characteristic confers enhanced stability against hydrolysis by many β -lactamases, including ESBLs such as CTX-M, and carbapenemases such as KPC, NDM, VIM, IMP, OXA-23, OXA-48-like.^{91,92} Table 1 summarises the activity of these novel therapeutic options against the main MDROs.

Other novel drugs that are currently under evaluation for MDROs include imipenem-relebactam, plazomycin, everacycline, aztreonam-avibactam, ceftaroline-avibactam, cefepime-zidebactam, meropenem-nacubactam.¹²

Fungal infections

Prevalence and prognostic impact

Invasive fungal infections (IFIs) are reported in 3–7% of culture-positive infections in cirrhosis and are more frequently observed as secondary/nosocomial infections complicating the course of ACLF.^{6,8,9} Invasive candidiasis/candidemia is the most frequent IFI (70–90%) followed by invasive aspergillosis (IA; 10–20%). *Pneumocystis jirovecii*, *Cryptococcus spp* and *Zygomycetes* infections are rare.

IFIs tend to occur in deeply immunocompromised patients. There is an inverse relationship between the number of functional circulating neutrophils and the risk of IFI.⁹³ Functional defects in neutrophil function and paresis of the adaptive immune response associated with cirrhosis⁹⁴ increase the risk of IFIs caused by *Candida spp* and *Aspergillus spp*.^{6,95} Also, the associated supportive therapy for ACLF which may include vascular accesses, broad-spectrum antibiotic exposure, corticosteroids, ICU stay and renal replacement therapy among others increases the risk of IFI in this very sick population. Risk factors for invasive candidiasis and IA in the general population and in patients with liver disease are described in Table 3.^{50,96–99}

Generally, IFIs are associated with an extremely poor prognosis in patients with decompensated cirrhosis. Candidemia and other invasive candidiasis lead to 28-day mortality rates of around 45–60%.^{6,10,96} The prognosis of ACLF complicated by IA is even worse, with just exceptional cases of survival despite adequate antifungal treatment.⁵⁰

Diagnostic tools

Appropriate diagnosis of IFIs is critical because of their impact on mortality and the substantial economic

burden they generate. The current diagnostic criteria for proven IFIs requires microbiological and/or histopathological evidence of fungal infection. The gold standard for the diagnosis of candidemia is a positive blood culture. However, this technique has relatively low sensitivity¹⁰⁰ and long incubation times, requiring several days for identification of the *Candida* species. Two diagnostic techniques have been deployed to decrease the time to identification from blood cultures. The first is MALDI-TOF MS that can result in identification within minutes and can distinguish MDRO *C. auris* from other *Candida* species. The second is peptide nucleic acid-FISH which can distinguish *C. albicans* from *C. glabrata/krusei* within an hour of a blood culture bottle becoming positive.¹⁰¹

Beyond fungal cultures, some tests can detect fungal-specific antigens in clinical samples. BDG (1,3- β -D-glucan) is present in the cell wall of many fungi and can be detected in an antigen-based assay; although it is not specific for *Candida*, when combined with epidemiologic risk factors, microbiologic colonisation data, imaging and risk stratification scoring, it adds diagnostic value. More importantly, this biomarker has good negative predictive value when combined with clinical risk stratification and can therefore be used to rule out IFIs in clinical practice.¹⁰² Another cell-wall marker of IFI is galactomannan (GM). GM is produced by *Aspergillus spp*, *Penicillium spp* and *Histoplasma spp*. Its determination is routinely used in the diagnosis of IA in haemato-oncological and in immunosuppressed critically ill patients (serum or bronchoalveolar lavage samples; BAL). Detection of GM in BAL samples is 56–73% sensitive and 89–94% specific for the diagnosis of IA. Serum GM testing shows lower sensitivity (33–38%) but similar specificity (87–97%).^{103,104}

With respect to new diagnostic tests, the T2Candida panel can detect targets from whole blood. It can diagnose BSI caused by *C. albicans*, *C. tropicalis*, *C. parapsilosis*, or *C. glabrata/C. krusei* with a sensitivity of 91% and negative predictive value approaching 99%. Moreover, 2 new assays have become available for the diagnosis of IA. LFA utilises an *Aspergillus*-specific monoclonal antibody. The second is the development of standardised PCRs for the identification of *Aspergillus spp* directly from whole blood and BAL samples.¹⁰⁴

Regarding radiological investigations, it is important to remark that imaging of pulmonary IA in patients with cirrhosis or severe alcoholic hepatitis reveals mainly non-specific lung infiltrates on chest CT and rarely shows cavitated nodules or 'classical' features with a halo sign.⁵⁰

Antifungal treatments

Invasive candidiasis

The diagnosis of invasive candidiasis requires the prompt initiation of an echinocandin in severely ill patients with cirrhosis. Fluconazole should not be used as first-line therapy in this setting due to the

Key points

Invasive fungal infections are reported in 3–7% of culture-positive infections in cirrhosis and are more frequently observed as second/nosocomial infections complicating the course of ACLF.

Key points

The diagnosis of an invasive fungal infection requires the prompt initiation of antifungal therapy. First-line options are echinocandins for invasive candidiasis and voriconazole for invasive aspergillosis. Therapeutic drug monitoring of voriconazole is recommended to minimize the risk of toxicity.

emergence of fluconazole-resistant organisms, such as *Candida glabrata* and *C. krusei*. In contrast to caspofungin that requires dose adjustment in patients with advanced cirrhosis, anidulafungin and micafungin PKs are not affected by liver dysfunction and classical doses are appropriate.^{105,106} Early removal (within 48 hours) of any intravenous catheter is required. Antifungal treatment should be maintained for a minimum of 2 weeks from the first set of negative blood cultures. It may be stopped once funduscopy and echocardiography have excluded retinal or valvular infection. Where visceral infection is suspected, the ability to establish source control will determine the duration of therapy.¹⁰⁵

Invasive aspergillosis

Voriconazole is the first-line treatment for IA in haemato-oncological patients.¹⁰⁷ Isavuconazole is also recommended as a first-line agent for IA by the IDSA and has a more benign side effect and PK/PD profile. Some experts suggest a combination of voriconazole and an echinocandin for severely ill immunocompromised patients and a combination of antifungals is a recognised option for salvage therapy.¹⁰⁸ Liposomal amphotericin B is an alternative treatment when voriconazole is not tolerated or is contraindicated. Voriconazole frequently induces transient self-limited hepatotoxicity but cases of acute liver failure have been reported.¹⁰⁹ Therapeutic drug monitoring of voriconazole is recommended as a way of optimising antifungal therapy while minimising the risk of toxicity. Duration of therapy will depend on the anatomical site of the IA and the degree, length and cause of any ongoing immune paresis.

Antifungal prophylaxis

Given the poor prognosis associated with IFIs in patients with liver disease, some experts advocate for the initiation of antifungal prophylaxis in selected populations at high risk of infection (i.e. patients with ACLF requiring organ support while on the transplant waiting list or individuals with severe alcoholic hepatitis receiving steroids). The type and duration of antifungal prophylaxis have not been defined.

Areas of controversy

The emergence and spread of AMR in cirrhosis requires the immediate implementation of effective preventative measures at local, regional and international levels. However, rapid diagnostic tests, epidemiological surveillance and stewardship programmes on antibiotic prescription are costly initiatives in terms of health economics. Cost-effectiveness studies are therefore needed. The safety and efficacy of high-dose antibiotics for

septic shock and the utility of antifungal prophylaxis for high-risk populations, also deserve further evaluation.

Abbreviations

ACLF, acute-on-chronic liver failure; AKI-HRS, acute kidney injury-hepatorenal syndrome; AMR, antimicrobial resistance; BAL, bronchoalveolar lavage; BSI, bloodstream infections; ESBL, extended-spectrum β -lactamase; G-CSF, granulocyte colony-stimulating factor; GM, galactomannan; HCA, healthcare-associated; IA, invasive aspergillosis; ICU, intensive care unit; IFI, invasive fungal infection; KPC, *Klebsiella pneumoniae* carbapenemase; MALDI-TOF MS, matrix-assisted laser desorption ionization-time of flight mass spectrometry; MDROs, multidrug-resistant organisms; MIC, mean inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; PBP, penicillin binding protein; PK/PD, pharmacokinetic/pharmacodynamic; RCT, randomised clinical trials; SBP, spontaneous bacterial peritonitis; TGC, third-generation cephalosporins; UTI, urinary tract infection.

Financial support

No financial support has been received to write this review.

Conflict of interest

Javier Fernandez has received grant and research support from Grifols and speaker honorarium from MSD and Grifols. Javier Fernandez and Salvatore Piano advise Mallinckrodt. Michele Bartoletti and Emmanuel Q. Wey have nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JF decided the structure of the chapter. JF, SP, MB and EW are co-first authors of the article and wrote the manuscript.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2020.11.010>.

Transparency declaration

This article is published as part of a supplement entitled New Concepts and Perspectives in Decompensated Cirrhosis. Publication of the supplement was supported financially by CSL Behring. The sponsor had no involvement in content development, the decision to submit the manuscript or in the acceptance of the manuscript for publication.

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Author names in bold designate shared co-first authorship

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