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MANAGEMENT OF CIRRHOTIC PATIENT (A CARDENAS AND P TANDON, SECTION EDITORS)

Multidrug-Resistant Bacterial Infection in Patients with Cirrhosis. A Review

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Abstract

Purpose of Review The burden of multidrug resistance has become one of the world's most urgent public health problems. Patients with infection caused by multidrug-resistant organisms (MDROs) have an increased risk for worse outcomes and death.

Recent Findings Cirrhotic patients, mostly decompensated, are prone to developing infections caused by MDROs, particularly because they are in close contact with healthcare settings. During the last two decades, the first-line therapies recommended to treat infections in cirrhotic patients have become progressively less effective. Early identification of patients at high risk of MDRO infection is essential.

Summary Considering the emergence and spread of MDROs, empirical first-line antibiotic treatment must be tailored according to the local prevalence of MDROs and risk factors for MDRO infection. New empirical strategies must include antibiotics that are active against MDROs followed by a well-standardized early de-escalation policy. Appropriate use of broad-spectrum antibiotics, restriction of antibiotic prophylaxis to high-risk populations, promotion of infection-control measures, and support of research into the development of new antibiotics are needed to control the worrisome spread of MDROs.

Keywords Cirrhosis · Bacterial infection · Multidrug-resistant organism · Antibiotic · Carbapenem · Glycopeptide

Abbreviations

ACA	amoxicillin-clavulanic acid
ACLF	acute-on-chronic liver failure
AKI	acute kidney injury
CRE	carbapenem-resistant *Enterobacteriaceae*
ESBL	extended-spectrum β-lactamase
GNB	Gram-negative bacillus
GPC	Gram-positive coccus
HCA	healthcare-associated
HRS	hepatorenal syndrome
ICU	intensive care unit
MDRO	multidrug-resistant organism
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
PDR	pan-drug-resistant
RCT	randomized controlled trial
SB	spontaneous bacteremia
SBP	spontaneous bacterial peritonitis
TGC	third-generation cephalosporins
UTI	urinary tract infection
VSE	vancomycin-susceptible *Enterococcus*
VRE	vancomycin-resistant *Enterococcus*
XDR	extensively drug-resistant

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Introduction: Impact of Infection in Chronic Liver Disease

Cirrhosis is characterized by an increased susceptibility to infection, particularly bacterial infection [1]. The pathophysiological

mechanisms of this susceptibility are numerous and complex and include impaired innate and adaptive immunity, dysbiosis, intestinal bacterial overgrowth, and translocation from the gastrointestinal tract [2]. An episode of infection constitutes a milestone in the clinical course of cirrhosis, precipitating clinical decompensation (hepatic encephalopathy, variceal bleeding, hepatorenal syndrome (HRS)) or worsening a pre-existing decompensated state [3••]. Moreover, bacterial infection is the most common identifiable precipitating event of acute-on-chronic liver failure (ACLF) [4, 5]. In patients with cirrhosis, the cumulative incidence of infection during hospitalization ranges from 25 to 35% [6, 7]. In comparison, the prevalence reported in the general population for healthcare-associated infection is between 4 and 7% [8, 9]. Among compensated and decompensated cirrhosis patients, bacterial infection is associated with a four- to fivefold increase in in-hospital mortality [10]. Mortality rates among infected cirrhosis patients reach 30 and 63% at 1 and 12 months, respectively [10]. Patients with cirrhosis have a higher risk of developing sepsis, septic organ failure, and septic shock [11, 12]. Moreover, severe sepsis and septic shock are associated with higher in-hospital mortality in cirrhotic patients than in non-cirrhotic patients (for severe sepsis 40% vs. 30% and for septic shock 70% vs. 50%, respectively) [13]. Recognized risk factors for the development of infection are severe liver dysfunction, gastrointestinal bleeding, low protein in ascites fluid, prior spontaneous bacterial peritonitis (SBP), and hospitalization [6, 14]. The two leading sites of infection in cirrhotic patients are SBP and urinary tract infection (UTI), followed by pneumonia (common in the intensive care unit (ICU)), cellulitis, and primary bacteremia [13–15]. Historically, *Enterobacteriaceae* and non-enterococcal *Streptococci* dominated the epidemiology of bacterial infection in cirrhosis.

The Global Burden of Multidrug-Resistant Organisms in the General Population

Multidrug-resistant organisms (MDROs) are already widespread across the globe [16]. In 2013, the Centers for Disease Control and Prevention (CDC) published a report stating that each year in the USA, at least two million people develop an antibiotic-resistant infection and at least 23,000 people die [17]. In another publication from the European Centre for Disease Prevention and Control (ECDC), the authors reported that 25,000 patients die each year in the EU from multidrug-resistant bacteria [18]. However, adverse outcomes associated with MDROs are also economic, with an estimated cumulative loss of USD 2.9 trillion by 2050 for OECD countries (compared to a world without MDROs) [19]. The mechanisms underlying the emergence of multidrug-resistant bacteria include antibiotic overuse, inappropriate prescribing, extensive agricultural use of antibiotics, and a critical shortage in the development of new antibiotics [20–22]. Bacterial resistance is associated with a twofold increase in adverse outcomes compared with susceptible strains [23]. Moreover, patients with infections caused by MDROs are more prone to treatment or prophylaxis failure, prolonged hospitalization, longer ICU stays, invasive procedures, and death [24]. For instance, patients infected by carbapenem-resistant *Enterobacteriaceae* (CRE) with bacteremia have a three to five times higher mortality rate than those infected with susceptible strains [24, 25]. In addition, the poor outcomes attributable to MDRO-related infection have multiple causes (more severe underlying illness, more comorbidities, and in some cases, lack of effective therapy) and are not just attributable to treatment delays [24, 26]. During the past few years, the definitions in the medical literature for MDROs have varied widely, resulting in a poor understanding of the extent of the problem of antimicrobial resistance. In 2011, an expert group, in collaboration with CDC and ECDC, published the first standardized international terminology to be used to describe acquired resistance profiles [27]. Based on this standardized terminology, a bacterial strain is defined as MDR when it is non-susceptible to at least one agent in three or more antimicrobial categories available for empirical treatment [27]. Extensively drug-resistant (XDR) is defined as non-susceptibility to at least one agent in all except two (or fewer) antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories), and pan-drug-resistant (PDR) is defined as non-susceptibility to all available antimicrobial agents [27]. The three leading common MDROs in Europe are *Staphylococcus aureus*, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*. Two-thirds of the deaths that are directly attributable to MDROs are due to these three organisms [18]. Among Gram-negative bacilli (GNB), the situation has become particularly alarming with the emergence of strains that are developing resistance to all drugs available with very few therapeutic options in progress from current research [28]. The most serious concerns among the resistant GNBs encountered in healthcare facilities are *Enterobacteriaceae* (mostly *Klebsiella pneumoniae*), *P. aeruginosa*, and *Acinetobacter* spp. [17, 28, 29]. In 2017, the European Antimicrobial Resistance Surveillance System Network (EARS-Net), which includes 30 countries, reported on the problematic resistance situation for GNBs, citing high rates of extended-spectrum beta-lactamase (ESBL)-producing strains of *Escherichia coli* and *K. pneumoniae* [30]. In the EU, a quarter (25.7%) of *K. pneumoniae* and 12.4% of *E. coli* strains were resistant to third-generation cephalosporins (TGCs). The majority of TGC-resistant bacteria were ESBL-positive (88.4 and 88.5% for *E. coli* and *K. pneumoniae*, respectively) [30]. ESBL production was commonly associated with polyresistance to several key antimicrobials. Therefore, antibiotic options are extremely limited, and carbapenems are the treatment of choice. Accordingly, there is intensive use of carbapenems as the first-choice antimicrobial, resulting in a burden of CRE isolates within countries with high rates of ESBL-producing strains

(e.g., in Greece, > 50% of *K. pneumoniae* strains are carbapenem-resistant) [30, 31]. Unfortunately, therapies available for multidrug-resistant GNB, including CRE, are limited to a few options (e.g., colistin and tigecycline). *P. aeruginosa* and *Acinetobacter* species are two challenging pathogens to control in healthcare settings that are intrinsically resistant to most available antimicrobial agents and are spreading acquired resistance to last-line therapies (4% of *Acinetobacter* spp. are colistin-resistant) [30]. Large variations were noted in the EARS-Net report between countries, with generally lower resistance in the northwest and increasing resistance towards the southeast region of Europe [30].

Among multidrug-resistant Gram-positive cocci (GPC), *S. aureus* and *Enterococcus* species remain the biggest control challenge and are associated with rapid global spread [17, 28, 30]. Since 2013, CDC has ranked methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enteroccocus* spp. (VRE) as serious public threats [17]. MRSA is among the deadliest of all antibiotic-resistant organisms, with 11,285 deaths per year in the USA [17]. MRSA-related bloodstream infections (BSI) are clearly associated with higher mortality rates (OR, 1.93; 95% CI, 1.54–2.42) than methicillin-susceptible *S. aureus* (MSSA)-related infections [32]. Patients carrying MRSA have a fourfold increased risk of developing an infection [33]. In Europe and the USA, surveillance data have shown a decline in rates of invasive MRSA since 2005, particularly in the healthcare setting due to preventive measures [17, 30, 34]. However, in the last decade, community-acquired MRSA infections are increasingly caused by MRSA clones similar to those already described in nosocomial settings [35]. In Europe, 17% of invasive isolates of *S. aureus* reported to EARS-Net are MRSA, with large differences between national percentages (1 to 44%) [30]. *Enterococcus* species (dominated by *E. faecalis* and *E. faecium*) are a major cause of nosocomial infections and are characterized by high levels of antimicrobial resistance. *E. faecalis* and *E. faecium* have high rates of resistance to gentamicin (30.5% for faecalis in EU/2016), while only *E. faecium* has been reported to have high rates of VRE (11.8% in EU/2016) [30]. This situation is particularly worrisome because this trend is significantly increasing in the USA and in EU countries [30, 36]. Moreover, *Enterococcus* species can transfer vancomycin-resistant genes to other species, such as *S. aureus*, causing the emergence of vancomycin-resistant *S. aureus* (VRSA) [37].

Multidrug-Resistant Organisms in Cirrhosis

Epidemiology

Patients with advanced liver disease, particularly decompensated cirrhosis, are at high risk of developing MDRO infections. They are more likely to undergo repeated hospitalizations and are frequently exposed to antibiotic therapy as well as antibiotic prophylaxis (long-term primary and secondary for SBP and short-term for variceal bleeding) [3••, 38•, 39]. Moreover, since the extension of liver transplant programs, admission to the ICU has been generalized, with an increased use of invasive procedures and direct impacts on the microbiological profile (increased Gram-positive and TGC-resistant strains) [40, 41]. Long-term quinolone prophylaxis, current/recent contact with the healthcare system, ICU admission, exposure to systemic antibiotics within 3 months (≥ 5 days), and infection by an MDRO within the previous 6 months are recognized risk factors for MDRO infection [6, 42–46]. Since the end of the 1990s, a few studies have suggested that the prevalence of MDROs is increasing in cirrhosis [47–49]. In two consecutive prospective studies coming from Spain, the prevalence of MDROs increased from < 10% between 1998 and 2000 to 18 and 23% between 2005–2007 and 2010–2011, respectively [6, 40, 50]. Recently, a large multicenter European observational study reported significantly increasing trends of MDR bacterial infections in culture-positive episodes among decompensated cirrhotic patients for the last 8 years (29.2% in 2011 to 38% in 2017–2018) [46]. Nevertheless, MDR rates vary widely among European countries, being higher in northern and western countries in the CANONIC study (2011) and higher in eastern and southern countries in a more recent European cohort (2017–2018) [46]. A more worrisome situation is the spread of highly resistant strains, such as XDR and PDR. In a single-center prospective study from Italy, the number of XDR/PDR bacterial isolates increased twofold in the last 2 years of the report (16% in 2008–2009 and 36% in 2012–2013) [42]. In the previously mentioned large multicenter European study, the authors also described the emergence of CRE and VRE as XDR bacteria [46]. The most commonly isolated MDROs among cirrhotic patients are Gram-negative ESBL-*Enterobacteriaceae* and non-fermentable species (including *P. aeruginosa*/*Acinetobacter* spp.) and Gram-positive MRSA and resistant *Enterococci* [44, 46, 50–52]. Whereas the spread of MDR-GPC is relatively heterogeneous worldwide and mostly healthcare-associated (e.g., VRE/MRSA), the spreading of MDR-GNB, especially ESBL, is increasingly reported across the globe in healthcare settings as well as in the community [29, 31, 50]. GNBs pose a particular challenge in the healthcare setting, mainly in liver units, because they can express a wide variety of resistance mechanisms [29, 31].

For several reasons, resistance related to ESBL has been increasing in prevalence since the early 2000s among cirrhotic populations [6, 40]. First, these patients are more often admitted to the ICU, where ESBL is concentrated. Second, the broad use of prophylactic antibiotics (mainly quinolones and β-lactams) selects for ESBL strains [53]. Third, we have observed an increase in specific *E. coli* strains that produce ESBL, such as the emergent ST131 clonal group well-

known for its association with the CTX-M15 β-lactamase [50, 54]. ESBL-*Enterobacteriaceae* are predominant in Southern Europe and Asia, reaching 16 and 17% of all isolated strains in Italian and Korean series, respectively [43, 55]. Carbapenems are the treatment of choice for serious infections due to ESBL-producing bacteria. Similarly, there is intensive use of carbapenems in some areas, resulting in a spread of CRE. In a recent Greek study, the meropenem-resistance rate was 30.4% in SBP and spontaneous bacteremia [56]. Historically, GNB were the main cause of infection among patients with cirrhosis (more than 80%). Since the early 2000s, the prevalence of GPC has shifted higher, now accounting for almost half of the cases in hospitalized patients [6, 57]. Hospitalization, increased invasive procedures, and quinolone prophylaxis have changed the bacterial profile and have led to an increased rate of bacterial infection due to GPC (mainly MRSA and *Enterococci*) [6, 40, 41]. Several studies have reported a higher frequency of *Enterococcus* spp. among infections seen in patients with cirrhosis [41, 44, 52, 58]. Reuken et al., in a single-center retrospective trial over the past 12 years, identified nosocomial infection and recent antibiotic treatment as independent risk factors for enterococcal SBP. This was associated with poor survival outcomes, mainly due to first-line therapy failure [41]. Among XDR-GPC, the emergence of VRE (*Enterococcus* spp.), first in the USA during the 2000s and currently in EU countries, is particularly worrisome [30, 59]. In some liver units in the USA, VRE has become the main MDRO, accounting for 17% of all isolated bacteria [44].

Impact of Multidrug-Resistance on Prognosis in Patients with Cirrhosis

Early diagnosis and the rapid administration of effective empirical antibiotic therapy is the cornerstone of infection management in cirrhotic patients [1]. Moreover, the administration of ineffective antimicrobial therapy to a cirrhosis patient infected by an MDRO is associated with higher rates of sepsis, septic shock, and death [14, 60, 61]. Early identification of patients at high risk of MDRO infection is essential. Patients who receive inappropriate antibiotic therapy within the first 24 h after blood culture or who require a modification of antibiotic treatment experience a higher mortality rate at 3 months and 30 days, respectively [43, 51, 61]. Several studies have shown that failure of empirical antibiotic therapy is associated with higher rates of ACLF, sepsis, septic shock, longer hospital stay, and higher mortality [42, 46, 62, 63•]. This highlights the crucial importance of the empirical antibiotic choice. In the CANONIC study, the mortality rate after 28-day follow-up was 35.1% in patients with an MDRO-related infection and 18.1% in patients with infections caused by susceptible strains ($p < 0.001$) [46]. The success rate of empirical therapy is conditioned by the pattern of resistance, with a success rate of 40% for MDRO infections compared only a 10% rate of success for XDR infections [42]. In a prospective observational study, the 30-day mortality rate for patients with an XDR-related infection was 69.2% compared with 34.2% for the rest of the patients [56]. In a study by Bartoletti et al., a correlation between 30-day mortality rate and the resistance level of the infecting strain was observed. Mortality rates associated with infection by susceptible *E. coli*, ESBL-*E. coli*, and CREs were < 20, 23–30, and 60%, respectively [51]. Furthermore, Pouriki et al. reported a higher mortality rate in cirrhotic patients colonized with XDR compared with those without at 3-month follow-up [64].

Treatment in the Area of Multidrug-Resistant Organisms

During the last two decades, TGCs and amoxicillin-clavulanic acid (ACA) have been considered the gold standard for most infections among patients with cirrhosis because they are effective against *Enterobacteriaceae* and non-enterococcal *Streptococci* with a low incidence of side effects (low hepatic and renal toxicity). However, TGCs and ACA are currently ineffective in a significant percentage of healthcare-associated and nosocomial infections. TGCs, effective in the past, are frequently ineffective across the globe, with resistance observed in between 18 and 44% of cases [14, 41, 44, 45, 55, 56, 65]. Considering the emergence and spread of MDROs, empirical first-line antibiotics must be tailored according to the local prevalence of MDROs, risk factors for MDROs (long-term antibiotic prophylaxis, exposure to systemic antibiotics within 3 months, previous infection/colonization by MDRO, hospitalization ≥ 5 days in the last 3 months), the site of acquisition (community-acquired (CA), nosocomial, healthcare-associated (HCA)), and type and severity of infection [1, 50, 66]. Moreover, the spectrum of antibiotics should be narrowed according to bacteriological documentation and clinical improvement within 48–72 h [1, 66].

Antibiotic Strategies in Areas with Low Rates of MDROs

Considering the high rate of cephalosporin resistance that is present in healthcare-acquired infections, TGCs are generally restricted to infections acquired in the community. Piperacillin-tazobactam, with an extended-spectrum antibiotic for GPC (including non-*faecium-Enterococci*), anaerobic strains, and some ESBL-producing *P. aeruginosa*/*Acinetobacter* spp., is recommended in nosocomial episodes [1, 66]. The dosage of piperacillin-tazobactam is poorly defined in cirrhotic patients. In a pharmacokinetic study in cirrhotic patients admitted to the ICU who received the standard dosage of piperacillin-tazobactam, we observed excessive drug concentrations in the blood of

60% of the cases, mainly due to reduced clearance [67]. Excessive exposure to β-lactams may lead to some neurotoxicity, including hallucinations, confusion, and seizures [68]. Our observations have suggested that there is a potential association between excessive exposure and worsening of neurological status. In patients with healthcare-associated infections, empirical antibiotic regimens should be determined according to the severity (sepsis, septic shock) of infection and risk factors for MDRO. In cases of septic shock and risk factors for MDRO, we suggest choosing an antibiotic that covers MDROs according to local epidemiology [1, 50, 66, 69].

Antibiotic Strategies in Areas with High Rates of MDROs

The current therapeutic options for the most prevalent MDROs are summarized in Table 1. Some studies have demonstrated poor efficacy of TGC first-line therapy within centers with high rates of MDROs, with only 25–26% response rates [6, 63•]. In areas with high rates of ESBL-*Enterobacteriaceae*, carbapenems should be the empirical treatment. Glycopeptides should be added to empirical treatment in areas with high rates of VSE/MRSA [50, 66]. Recently, a randomized controlled trial confirmed that first-

Table 1 Current antibiotic options for the most prevalent MDROs

	Type of MDROs	Current antibiotic options
GNB	ESBL-*Enterobacteriaceae*	• Carbapenems are the treatment of choice for severe infections (meropenem or imipenem, reserve ertapenem for non-severe infection)
		• Uncomplicated urinary tract infections: Oral fosfomycin or nitrofurantoin[a]
		• Alternative options: ceftolozane-tazobactam/ceftazidime-avibactam
	Carbapenem-resistant *Enterobacteriaceae*	• Combination therapy with two or more drugs including at least one carbapenem and tigecycline and/or colistin and/or aminoglycoside
		• Combination of meropenem and colistin or tigecycline in low-level resistant strain
		• Combination of tigecyclin and colistin in high-level-resistant strain (MIC > 8 mg/L)
		• Fosfomycin may be used in combination therapy against urinary tract infections
	MDR *Pseudomonas aeruginosa*	Ceftolozane-tazobactam/ceftazidime-avibactam
		Colistin
		Highly resistant strain: combination cefepime/amikacin or ticarcillin/tobramycin/rifampin or ceftazidime/colistin
GPC	Methicillin-resistant *Staphylococcus aureus*	• Vancomycin is considered to be the gold standard
		• Daptomycin and teicoplanin (daptomycin should not be used for treatment of pneumonia)
		• Alternative options: ceftaroline (alone or in combination), linezolid, telavancin, trimethoprim-sulfamethoxazole (in combination)
	Vancomycin-resistant *Enterococcus*	• First-line therapy for severe infections included linezolid and daptomycin[b]
		• Alternative options: tigecycline[c] and telavancin
		• Ampicillin monotherapy should be used preferentially for non-severe ampicillin-susceptible VRE infection. Combination with an aminoglycoside is recommended for the treatment of an endovascular infection.

[a] Should be administered cautiously in patients with liver disease

[b] High-dose daptomycin use should be considered (8–12 mg/kg), synergy with a β-lactam can be attempted for refractory cases

[c] Should not be used for VRE bacteremias

ESBL, extended-spectrum β-lactamase; *GNB*, Gram-negative bacilli; *GPC*, Gram-positive cocci; *MDR*, multi-drug-resistant; *MIC*, minimum antibiotic concentration; *VRE*, vancomycin-resistant *Enterococcus*

line therapy with a broad-spectrum antibiotic (e.g., carbapenem + glycopeptide) in cirrhotic patients with HCA infections significantly reduced in-hospital mortality compared with TCG (25% vs 6% $p \leq 0.01$) in areas with high rates of MDROs [70•]. Linezolid/high-dose daptomycin should replace glycopeptides in areas with a high prevalence of VRE [63•]. Linezolid use is limited among cirrhotic patients because of thrombocytopenia, and daptomycin cannot be used for the treatment of pneumonia (inhibited by pulmonary surfactant).

The Worrisome Spread of XDR

Carbapenems are the treatment of choice for serious infections due to ESBL-producing bacteria. Consequently, there is intensive use of carbapenems, resulting in the emergence of carbapenem-resistant strains [31, 56]. CREs are resistant to all or almost all β-lactams and are commonly cross-resistant to fluoroquinolones and/or aminoglycosides. The most effective antibiotherapy choice for CREs in the general population is combination therapy with two or more drugs, including at least one carbapenem [71]. CREs can be susceptible to tigecycline, a drug also active against MRSA, VSE, VRE, and ESBL-producing *Enterobacteriaceae*. The combination of high-dose tigecycline with carbapenem in a continuous infusion is suggested as a treatment option for these XDR strains [50]. Some types of CRE are susceptible to a new cephalosporin-β-lactamase inhibitor combination, ceftazidime-avibactam.

A combination of IV amikacin/tobramycin or colistin plus a carbapenem/ceftazidime (needed as synergistic antibiotics in spite of antibiotic resistance) is required against MDR *P. aeruginosa* (resistant to carbapenems, ceftazidime, and quinolones). A new therapeutic option for this XDR strain could be the combination of ceftolozane and tazobactam.

Conclusions

We have observed a dramatic increase in MDRO-related infections in the cirrhotic population, mainly due to aggressive management and over-use of broad-spectrum antibiotics. The therapeutic options are limited, particularly for XDR bacteria. Very few advances have recently been made in the research and development of new antibiotics or alternative treatment strategies. This situation was summarized by the World Health Day 2011 slogan "Combat antibiotic resistance: no action today, no cure tomorrow." In our clinical practice, we must constantly promote infection control measures (hand washing, suitable use of gloves, seclusion of patients, close monitoring via swabs and aspirates, and a strict environmental cleaning plan for wards) to avoid the spread of MDROs. Moreover, we must provide an evidence-based rationale to justify the prescription of antibiotics in our institutions to limit the occurrence of resistance. In our opinion, we cannot propose general algorithm to manage MDROs-related infections in cirrhotic patients. Indeed, strategies must be largely defined by local microbiological epidemiology, availability of drugs, and clinical conditions of patients.

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Compliance with Ethical Standards

Conflicts of Interest Thierry Gustot reports grants from Promethera Biosciences and grants from Martin Pharmaceuticals, outside the submitted work. Lukas Otero Sanchez has nothing to disclose.

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- • Of importance
- •• Of major importance

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