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Review

New drugs for the treatment of complicated intra-abdominal infections in the era of increasing antimicrobial resistance

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ABSTRACT

The continuing increase in multidrug-resistant organisms (MDROs) worldwide has created new challenges in treating complicated intra-abdominal infections (cIAIs). A number of novel antimicrobial agents have been developed against resistant pathogens. To target extended-spectrum β-lactamase (ESBL)-producing pathogens, novel β-lactam antibiotics, such as ceftolozane/tazobactam, ceftazidime/avibactam, aztreonam/avibactam, imipenem/relebactam and S-649266, are antimicrobial alternatives for cIAIs. Two new drugs, eravacycline and plazomicin, have activity against *Klebsiella pneumoniae* carbapenemase (KPC)-producing *K. pneumoniae*, carbapenem-resistant *Acinetobacter baumannii* and ESBL-producers. New lipoglycopeptides and oxazolidinones provide feasible options against resistant Gram-positive pathogens. These novel antimicrobials may play a role in improving the clinical outcomes of cIAIs caused by MDROs.

1. Introduction

Complicated intra-abdominal infections (cIAIs), defined as when the infectious process proceeds beyond a single organ and causes either localised or diffuse peritonitis, are a substantial cause of morbidity and mortality in hospitalised patients worldwide [1,2]. Adequate management of cIAIs has included surgical intervention for source control and appropriate antibiotic administration. Current guidelines suggest that empirical antibiotics for IAIs should be active against enteric Gram-negative bacilli and enteric Gram-positive streptococci and should be driven by disease severity and local microbiology reports. Previous guidelines recommended empirical monotherapy (including cefoxitin, ertapenem, moxifloxacin or tigecycline) or combination of a cephalosporin with metronidazole for patients with mild-to-moderate community-acquired IAI, and meropenem, imipenem, doripenem, piperacillin/tazobactam, or cefepime plus metronidazole for severe or healthcare-associated IAIs [3,4]. However, the optimal choice of empirical antibiotics for cIAIs may be very complicated due to the diverse pathogens and the ever-increasing possibility of infection caused by resistant pathogens in different regions around the world. Inappropriate or delayed therapy for cIAIs will increase the risk of treatment failure, mortality and costs as well as the healthcare burden [5].

cIAIs are usually polymicrobial in nature and are derived from the indigenous flora of the gastrointestinal tract, mainly Enterobacteriaceae. The increasing rate of drug-resistant Enterobacteriaceae observed in community-acquired infections as well as the complex pathogens of post-operative IAIs during hospitalisation, especially drug-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterococcus* spp. and *Candida* spp., poses greater challenges in IAI treatment than before. Resistant pathogens can cause severe

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infections and require intensive care, which increases treatment difficulties, hospital stay and medical costs [6,7]. To combat these highly resistant pathogens, the traditional regimens suggested in IAI guidelines are insufficient and novel antibiotics are urgently required.

2. Emerging resistance problems in complicated intra-abdominal infections

Because Enterobacteriaceae are major pathogens in IAIs, one of the primary global concerns regarding antibiotic resistance in cIAIs is extended-spectrum β-lactamase (ESBL)-producing organisms. An ongoing surveillance study, the Study for Monitoring Antimicrobial Resistance Trends (SMART), which has been conducted since 2002 in most regions of the world, reported increasing proportions of ESBL-producers among *Escherichia coli* (from 9% in 2003 to 18% in 2005–2007) and *Klebsiella pneumoniae* (from 14% to 26.2%); there was decreasing susceptibility to fluoroquinolones (from 79–81% in 2003 to 71–73% in 2005–2007) and third-generation cephalosporins (from 85–90% to 77–82%) [8,9]. The cefepime susceptibility rate among ESBL-producing isolates was 56.7% for *E. coli* and 61.3% for *K. pneumoniae* according to 2013 Clinical and Laboratory Standards Institute (CLSI) criteria [10]. The resistance problem is especially severe in the Asia-Pacific region, where the proportion of ESBL-producing *E. coli* causing cIAIs increased dramatically from 14.5% in 2002 to 40.4% in 2012 [11]. However, the figures varied greatly across countries and species, ranging from 65.8% in China to 2.3% in Malaysia for *E. coli*, and from 45.7% in Thailand to 9.4% in Taiwan for *K. pneumoniae* isolates [12]. CTX-M was found to be the most common ESBL, followed by SHV and TEM [13]. Although the carbapenems (ertapenem, imipenem and meropenem) remain the first choice for treating infections due to ESBL-producing organisms, decreased susceptibility to ertapenem in ESBL-producing *K. pneumoniae* was observed [11]. Furthermore, in Latin America the ertapenem susceptibility rate in ESBL-producing *K. pneumoniae* was <70%, which might predispose to treatment failure [14]. Even without ESBL, some Enterobacteriaceae isolates with AmpC β-lactamase or carbapenemase had higher ertapenem minimum inhibitory concentrations (MICs) (≥0.5 μg/mL) and potentially led to treatment failure in cIAIs [13]. In addition, the widespread use of carbapenems promotes the emergence of carbapenemase-producing organisms, which has already been recognised, and is also correlated with the increasing incidence of healthcare-associated infections caused by carbapenem-resistant *A. baumannii* [15,16]. In addition to the Enterobacteriaceae, *P. aeruginosa* is the third most frequent pathogen in IAIs and it has shown a marked decrease in susceptibility to amikacin, ceftazidime, cefepime and imipenem (to <70%) in nosocomial IAI isolates. Of note, a decline in carbapenem susceptibility (<30% for imipenem) was noted among *A. baumannii* isolates causing cIAIs [17,18]. Global resistance data from SMART are summarised in Fig. 1 [11,12,14,17,19–23]. Emerging resistance in Gram-negative bacilli can be expected to cause treatment failure with current antibiotic regimens for IAIs, and inappropriate antibiotics might select more resistant pathogens during therapy.

When considering healthcare-associated IAIs, one retrospective report showed that two groups of species, namely *Enterococcus* (29% in healthcare-associated IAIs) and *Candida* (33%), were more common than in the clinical setting of community-acquired infections. Of note, 9% of *Enterococcus* isolates were resistant to vancomycin [24]. Therefore, combination regimens to cover resistant Gram-positive pathogens must be considered for cases of severe nosocomial IAIs, and novel antibiotics are, of course, welcomed and anticipated.

3. Novel β-lactam antibiotics under development

To overcome these treatment difficulties, especially β-lactamase-producing Enterobacteriaceae, β-lactam antibiotics in combination with β-lactamase inhibitors might be a feasible approach for maintaining their antibacterial activity against resistant pathogens. Two new β-lactam antibiotics (ceftolozane and S-649266) and new β-lactamase inhibitors (avibactam and relebactam) are now available for the treatment of IAIs.

3.1. Ceftolozane/tazobactam

Tazobactam, a well established β-lactamase inhibitor, inhibits most class A β-lactamases, including common ESBL enzymes such as CTX, SHV and TEM, as well as some class C β-lactamases. It has been used in combination with piperacillin for decades. Piperacillin/tazobactam, initially thought to be active in vitro against ESBL-producing strains, shows reduced antibacterial activity and poses a significant risk of treatment failure in treating infectious diseases due to ESBL-producing Enterobacteriaceae [25]. Tazobactam in combination with a novel cephalosporin, ceftolozane, extends the antibacterial coverage for many ESBL-producing Enterobacteriaceae and multidrug-resistant (MDR) *P. aeruginosa.* Ceftolozane, structurally similar to ceftazidime, has a heavier, substituted pyrazole ring that can prevent hydrolysis of the β-lactamase active site among AmpC β-lactamase-overproducing *P. aeruginosa*. In addition, ceftolozane possesses an aminothiazole ring and an oxime group, which confer stability against β-lactamases and therefore enhance the inhibitory activity against resistant Gram-negative pathogens [26]. As with cephalosporins, ceftolozane inhibits penicillin-binding proteins and bacterial cell wall synthesis, resulting in cell death. Its efficacy is best correlated with the time that the plasma drug concentration exceeds the MIC ($T_{>MIC}$) of a given pathogen and requires dose adjustment in patients with renal function impairment. In vitro studies reported that ceftolozane/tazobactam has activity against common Gram-negative bacteria, streptococci and some anaerobic pathogens such as *Bacteroides fragilis*, *Prevotella* spp. and *Fusobacterium* spp., but it has limited activity against *Staphylococcus*, *Acinetobacter* and *Clostridium* spp. [27,28]. Livermore et al. reported that ceftolozane/tazobactam had good in vitro activity for CTX-M-, SHV-, TEM- and PER-1-producing *E. coli* and *K. pneumoniae*, AmpC-derepressed isolates and MDR *P. aeruginosa*, with MIC_{90} values of 8/8 μg/mL [29]. However, its antibacterial activity was poor for pathogens that harboured *K. pneumoniae* carbapenemase (KPC) or metallo-β-lactamase (MBL) with MICs of ≥128 μg/mL [29].

With therapeutic potential against resistant pathogens, a number of clinical trials have been conducted on the treatment efficacy of ceftolozane/tazobactam in patients with cIAIs. A first double-blind, randomised, phase 2 trial compared the efficacy of ceftolozane/tazobactam plus metronidazole with that of meropenem in patients with cIAIs during 2010 and 2011 [30]. The clinical cure rate at the test of cure (TOC) visit was higher in the meropenem group both of the microbiological modified intention-to-treat (mMITT) population [ceftolozane/tazobactam vs. meropenem: 83.6% vs. 96.0%; treatment difference, −12.4%, 95% confidence interval (CI), −34.9% to 11.1%] and the microbiologically evaluable (ME) population (88.7% vs. 95.8%; treatment difference, −7.1%; 95% CI −30.7% to 16.9%). For microbiological success rates, ceftolozane/tazobactam presented a high eradication rate in the cases of *E. coli* (89.5%; 34/38), *K. pneumoniae* (100%; 8/8) and *P. aeruginosa* (100%; 4/4) infections. Only three patients had ESBL-producing Enterobacteriaceae infections, which demonstrated a clinical cure rate of 66% when treated with ceftolozane/tazobactam. In the subgroups based on risk factors of poor prognosis, ceftolozane/tazobactam therapy