ICU MANAGEMENT & PRACTICE

Volume 16 - Issue 3, 2016 - Cover Story

New Antibiotics for Abdominal Infections: What Can We Expect?

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Recently a number of new antibiotics or combinations for complicated intra-abdominal infections have been introduced. Here we review the currently available data of these new drugs and discuss how they can be used in critically ill patients with complicated intraabdominal infections.

Complicated intra-abdominal infections (cIAI) remain one of the most challenging infections in the intensive care unit (ICU). Compared to patients with other infections, patients with cIAI typically will develop multiple organ dysfunction syndrome (MODS) more often and have a higher risk of mortality; often they have a protracted stay in the ICU and in the hospital (De Waele et al. 2014). The management of these patients can be challenging. This includes evaluating the need for source control as well as effectively getting the source of infection controlled, but also selecting the appropriate antibiotic in times of changing susceptibility patterns and the rise of antimicrobial resistance (AMR).

The role of source control is more relevant in cIAI than in most other commonly encountered infections in the ICU. At times difficult choices have to be made (Leppäniemi et al. 2015). The role of surgery in this context is changing, new techniques are being introduced, and, increasingly, percutaneous drainage is being used as a primary strategy. Despite the prominent role of source control, administering appropriate antibiotics is equally important. Although there are fewer limitations in correctly diagnosing abdominal infections compared to e.g. respiratory tract infections, both timing and spectrum of empirical antibiotic therapy are critical. Antibiotics should be administered when the diagnosis is made and not postponed until intraoperative cultures are obtained.

Antibiotic resistance is also increasingly described in cIAI. In particular the spread of extended spectrum beta-lactamase (ESBL)- producing *Enterobacteriaceae* in community-acquired cIAI is striking, and may limit the use of many currently available antibiotics. This in turn may put an inappropriate strain on the carbapenem antibiotics with the risk of increasing resistance to this class of antibiotics. The need for new antibiotics in this context is urgent.

Options for appropriate empirical therapy are becoming limited in some situations, and every attempt should be made to choose the correct antibiotic for the patient with cIAI. It should also be remembered that cIAI are typically polymicrobial infections with both aerobic and anaerobic bacteria present in most situations, and will typically require antibiotics that cover both Gram-positive and Gram-negative pathogens.

See Also: Biomarker Guided Antibiotic Therapy: What's New?

Rise of Multidrug Resistance in cIAI

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As in other types of infections, AMR is a pressing issue in cIAI. Patients with cIAI may be at increased risk of AMR as they are often exposed to antibiotics for prolonged periods of time, and source control plays a crucial role. Particularly when source control is inadequate or even impossible, the inoculum persists. As bacteria are exposed to antibiotics during that time, AMR is bound to develop. This has been documented in severe abdominal infections including peritonitis and pancreatitis (De Waele 2016; Montravers et al. 2016).

As typically more than one pathogen is involved, the risk of encountering antibiotic resistance is also increased. For the same reason the extensive coverage needed to cover all pathogens (often with multiple antibiotics) may fuel AMR, as bacteria are exposed to more than one antibiotic at the same time. Whereas AMR was only relevant in nosocomial infections until recently, it is now also posing problems in community-acquired disease.

Overall, AMR is a concern mostly with Gramnegative pathogens. ESBL-producing bacteria are a primary worry worldwide (Sartelli et al. 2015), even more so in some areas, e.g. in Asia. Even then important regional differences are present.

The prevalence of ESBL in *E. Coli, K. pneumonia, K. oxytoca* and *P. Mirabilis* has increased dramatically from 2002 to 2011 in cIAI in Asia and the Middle East, where up to 40% of these pathogens isolated from cIAI produce ESBLs (Morrissey et al. 2013). It is unclear if this trend has changed in more recent years as epidemiological studies on AMR after 2013-2014 are lacking. Regional differences are important, and extrapolating data from other parts of the world to develop local empirical therapy guidelines should be avoided.

Carbapenemase-producing *Klebsiella pneumonia* (KPC) has been posing particular problems in nosocomial infections in some parts of the world. cIAI have not been exempt from KPC involvement, but this appears to be a regional problem mostly at this point.

Although the problem of AMR in cIAI is most relevant for Gram-negative pathogens, trends in Gram-positive infections should not be ignored. Enterococci are considered to be more pathogenic in nosocomial cIAI, and typically are involved in patients who have been exposed to antibiotics that do not cover enterococci, e.g. cephalosporins or fluoroquinolones. Apart from their different appreciation in nosocomial cIAI, resistance in enterococci is increasing as well; *E. faecium* is typically non-susceptible to penicillin antibiotics, but in *E. faecalis* ampicillin resistance is also rising. Infection with vancomycin-resistant enterococci is also increasingly described

New Antibiotics for cIAI

Recently a number of new antibiotics or antibiotic combinations have been studied in patients with cIAI. Antibiotics recently introduced or coming soon for the treatment of cIAI include ceftolozane/tazobactam, ceftazidime/avibactam and eravacycline. Although several other new antibiotics may have activity against pathogens typically associated with cIAI, none of them is currently under investigation for this indication, and will not be discussed.

Ceftolozane Plus Tazobactam

Ceftolozane is a new fifth-generation cephalosporin antibiotic that has been marketed in combination with a well-known beta-lactamase inhibitor (BLI), tazobactam, in a fixed 2:1 ratio. It is active against a wide range of Gramnegative bacteria, including *Pseudomonas aeruginosa* and many ESBL-producing *Enterobacteriaceae*. It has been approved by the United States Food and Drug Administration for the treatment of complicated urinary tract infections and cIAI (combined with metronidazole for the latter). Dosing for patients with normal renal function is 1000mg ceftolozane plus 500mg tazobactam TID.

Three clinical trials have been performed in patients with cIAI. In a phase 2 study, 121 patients with cIAI requiring surgery were randomised to receive either meropenem or ceftolozane/ tazobactam with metronidazole (Lucasti et al. 2014). Clinical cure rates were 83.6% and 96% for ceftolozane and meropenem respectively, on the basis of which the noninferiority of the drug was concluded. The *Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-abdominal Infections (ASPECT-cIAI)* programme, reporting on two identical phase 3 studies with a similar setup to the phase 2 study, and using the same comparator, included 993 patients, 806 of which were analysed in the modified intention to treat (MITT) group (Solomkin et al. 2015). For the primary endpoint clinical cure rates were 83% with ceftolozane/ tazobactam plus metronidazole vs. 87.3% with meropenem in the MITT population. In both studies the incidence of adverse effects reported was similar in both groups. Based on these studies, ceftolozane/tazobactam was approved for the indication of cIAI at the end of 2014.

In a recent substudy investigating the outcomes of patients with *Pseudomonas aeruginosa*, the strong in vitro activity of ceftolozane against these pathogens was confirmed, with high clinical cure rates in the subgroup of patients with *Pseudomonas* infections (Miller et al. 2016).

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Ceftazidime Plus Avibactam

Avibactam is a novel BLI that restores the activity of beta-lactam antibiotics such as ceftazidime against ESBL-producing pathogens.

In a phase 2 study the combination of ceftazidime/ avibactam (2000mg/500mg TID) with metronidazole 500mg TID was compared with meropenem in 204 patients with cIAI (Lucasti et al. 2013). Clinical cure was 91.2% and 93.4% for ceftazidime/avibactam co-administered with metronidazole and meropenem respectively. Adverse events were comparable in both groups.

In two large phase 3 studies with an identical setup 1066 patients with cIAI requiring surgery of percutaneous drainage were randomised to receive ceftazidime/tazobactam plus metronidazole and the combination was found to be noninferior to meropenem (Mazuski et al. 2016). In the microbiologically MITT group, clinical cure at test of cure was statistically not different in the ceftazidime/tazobactam plus metronidazole group (81.6% vs. 85.1% respectively), and at other time points outcome was comparable. Safety evaluation did not demonstrate any differences between the groups.

Eravacycline

Eravacycline is a novel antibiotic in the tetracycline class, structurally comparable with tigecycline. It inhibits bacterial protein synthesis through binding to the 30S ribosomal subunit and has broad-spectrum antimicrobial activity against Gram-positive, Gram-negative and anaerobic bacteria with the exception of *Pseudomonas aeruginosa*, but including MDR pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and some carbapenem-resistant Gram-negative bacteria. In a phase 2 study the efficacy and safety of two dose regimens of eravacycline was compared with ertapenem in adult hospitalised patients with cIAI requiring surgical or percutaneous intervention: 1.5 mg/kg of body weight every 24 hours (q24h), or 1.0 mg/ kg every 12 h (q12h) (Mazuski et al. 2016). In the microbiologically evaluable population the clinical cure was 92.9% and 100% in the groups receiving eravacycline at 1.5 and 1.0 mg/kg respectively, and 92.3% in the ertapenem group. Another large phase 3 study comparing eravacycline with ertapenem has been finalised but not yet published (IGNITE 1)—the manufacturer has reported that noninferiority was demonstrated but full analysis is not yet available (Tetraphase Pharmaceuticals 2014).

Caveats for Critical Care

Shortcomings of Recent cIAI Studies From a Critical Care Perspective

Although these antibiotics represent new therapeutic options in the management of cIAI, there are some things to consider from a critical care perspective. This is primarily related to the type of patients in the studies with these new antibiotics, and with the type of patients not included due to an often long list with exclusion criteria. Overall the patients in these studies are mild to moderately ill only, with a high prevalence of infections that are typically not encountered in the ICU, such as appendicitis.

In the studies investigating ceftolozane, it was not reported how many patients were diagnosed with severe sepsis or septic shock, or were admitted to an ICU. In the first study more than half of the patients were treated because of appendicitis, and median Acute Physiology and Chronic Health Evaluation (APACHE)-II score was 6 and 7 respectively (Lucasti et al. 2014). Similarly, in the ASPECT-cIAI programme, APACHE-II scores were 6 and 6.2 in the study groups and degree of organ dysfunction was not reported (Solomkin et al. 2015). Both studies excluded patients with thrombocytopenia or abnormal renal function.

The studies investigating avibactam in combination with metronidazole excluded severely ill patients; exclusion criteria in the phase 2 study included APACHE-II score of 26 or higher, abnormal renal function and fluid-unresponsive septic shock (Lucasti et al. 2013). Only 1 out of 6 patients had an APACHE-II score between 10 and 25, and the appendix and stomach were the most frequent sites of the primary infection. The phase 3 study included mainly patients with low to moderate disease severity as exemplified by the APACHE-II score that was 10 or lower in about 85% of the patients (Mazuski et al. 2016). That study also excluded patients with septic shock or who were receiving haemodialysis. The fact that patients could not be treated with an antifungal agent may have precluded including patients with more severe disease in the study.

One particular finding in the phase 3 study was the worse outcome in patients with moderate renal impairment, defined as a creatinine clearance of 30-50ml/min. This may have been caused by the rapid changes in renal function in the subsequent days when patients still received renal function adjusted doses of the drug, although the effect should be present in both the interventional and comparator group (Mazuski et al. 2016).

The study investigating eravacycline excluded more critically ill patients such as patients with septic shock or an APACHE-II score of 25 or higher. Effectively, APACHE-II score was 6 and 8.2 in the study groups, and appendicitis was the source of infection in more than 50% of the patients. The use of ertapenem as a comparator can also limit the number of critically ill patients included, as this drug is not recommended for the treatment of severe cIAIs (Solomkin et al. 2010).

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Implications for Critically Ill Patients With cIAI

So how does this translate to the use of these new agents in the critically ill? Although it is clear that the in vitro activity of these drugs against a wide range of pathogens is similar or better than many of the antibiotics that we are using now, the changes in physiology of the critically ill may be profound and lead to lower concentrations than expected. This phenomenon has been demonstrated for many antibiotics (Roberts et al. 2014) and is now an integral part of most drug development programmes.

In this context it is remarkable that an ongoing study comparing ceftolozane/tazobactam to meropenem for hospital-acquired pneumonia (*Safety and efficacy study of ceftolozane/tazobactam to treat ventilated nosocomial pneumonia (MK-7625A-008*) (ASPECT-NP), NCT02070757) uses a dose that is double what was used in the cIAI study (***clinicaltrials.gov/ct2/show/NCT02070757***). It is unclear if this is solely because of the different infection focus. Future pharmacokinetic studies of these new antibiotics in more severely ill patients should answer these concerns.

The exact place of these new agents in our current armamentarium will need to be discussed primarily considering the local ecology. This is where antibiotic stewardship teams should jointly define the indications as well as consider restriction in the use of these powerful agents. Apart from treating the infections adequately, new agents should be cherished and used only where they have a clearly added value – whether this is in empirical therapy in one country or directed therapy for highly resistant pathogens in another.

Conclusions

Antibiotic therapy of cIAI is becoming increasingly challenging due to the changes in susceptibility of pathogens involved. Although our current armamentarium may be effective in the treatment of many patients, new therapeutic options are highly desirable. The development of ceftolozane/tazobactam, ceftazidime/avibactam and eravacycline offers an opportunity to effectively treat MDR pathogens and avoid more toxic regimens. The exact place of these agents in the treatment of cIAI should be defined by local antibiotic stewardship teams, considering local ecology and other available options.

Conflict of Interest

Jan De Waele declares Consultancy for AtoxBio, Bayer Healthcare, Cubist, Fresenius, Merck. He is Infection section Chair at the European Society of Intensive Care Medicine, President of the Belgian Society of Intensive Care Medicine, Past President of WSACS - the Abdominal Compartment Society and Senior Clinical Investigator at the Flanders Research Foundation.

Abbreviations

AMR antimicrobial resistance

APACHE Acute Physiology and Chronic Health Evaluation

ASPECT-cIAI Assessment of the Safety Profile and

Efficacy of Ceftolozane/Tazobactam in Complicated

Intra-abdominal Infections

BLI Beta-lactamase inhibitor

cIAI complicated intra-abdominal infections

ESBL extended spectrum beta-lactamase

ICU intensive care unit

KPC *Klebsiella pneumonia*

MDR multi-drug resistance

MITT modified intention to treat

MODS multiple organ dysfunction syndrome

Published on : Tue, 27 Sep 2016

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