Ceftazidime + avibactam

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.3. Reserve group antibiotics

EMLc | ATC codes: J01DD52

Indication	Carbapenem resistant Klebsiella pneumoniae ICD11 code: MG50.54
INN	Ceftazidime + avibactam
Medicine type	Chemical agent
Antibiotic groups	R RESERVE
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 2 g in vial + 0.5 g in vial powder for injection
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Ceftazidime + avibactam
DrugBank	Ceftazidime, Avibactam

Expert Committee recommendation

The Expert Committee recommended the inclusion of ceftazidime + avibactam on the complementary list of the EML and EMLc for the treatment of infections caused by carbapenem-resistant organisms which are pathogens classified as “critical priority” in the WHO Priority Pathogen List. The Committee agreed with the EML Antibiotic Working Group’s recommendation that this antibiotic should be classified in the AWaRe Reserve group. The Committee recommended further collaboration between relevant stakeholders to design and implement strategic public health orientated studies that will help to inform the choice of optimal single or combination treatment of both novel and older antibiotics for adults and children in different settings, with the goal of improving clinical outcomes, minimizing toxicity and reducing selection of resistance.

Background

This combination antibiotic had not previously been considered for inclusion on the EML. Ceftazidime is third generation cephalosporin listed on the EML complementary list and classified within the Watch group. Avibactam is a non-beta-lactam beta-lactamase inhibitor active against certain types of carbapenemases (e.g. KPC and OXA-48 but not active against metallo-beta-lactamases).

Public health relevance

Antibiotic-resistant bacteria are a significant threat to public health, both in high-income as well as low- and middle-income countries (LMIC) (1-3). A recent study estimated that infections with antibiotic-resistant bacteria were responsible for approximately 33 000 attributable deaths in Europe in 2015 (1). Fewer data are available for LMIC, but a retrospective study in ten hospitals in India found that resistant pathogens were associated with 2-3 times higher mortality than infections with susceptible strains after adjusting for several confounders (2). Over the last decade there has been increasing spread of multidrug-resistant Gram-negative pathogens such as carbapenemase producing Enterobacteriaceae (4). The Global

Antimicrobial Resistance Surveillance System (GLASS) Report published in 2018 found high levels of carbapenem resistance in Enterobacteriaceae and non-fermenters in many of the LMICs providing data for the report (2). The 2015 WHO Global Action Plan on Antimicrobial Resistance calls for the development of new antimicrobial medicines (3). To provide a framework for this endeavour, in 2017 WHO published a priority list of antibiotic-resistant bacteria – the WHO Priority Pathogens List (5). “Priority 1: critical” category includes four types of pathogens, all of which are Gram-negative: carbapenem resistant Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae; and third-generation cephalosporin resistant Enterobacteriaceae (6).

Benefits

Several RCTs have been conducted comparing ceftazidime + avibactam to carbapenems or best available therapy for cIAIs and cUTIs (7-10). Of note, all but one of the RCTs (7) included patients based on clinical syndromes and not based on the presence of infections confirmed to be caused by multidrug-resistant organisms. In that “descriptive” trial of patients with cUTI (plus some patients with cIAI) caused by ceftazidime-resistant Gram negatives, ceftazidime + avibactam treatment resulted in similar clinical response compared to best available therapy. So far, few data on the “real life” clinical use of ceftazidime + avibactam have been published. A retrospective single centre study at the University of Pittsburgh Medical Centre in Pittsburgh, USA examined outcomes of 109 patients with bacteraemia caused by carbapenem-resistant K. pneumoniae bacteraemia (97% of which were KPC producers) over the time period from 2009 to 2017. The 30-day survival rate was 92% (12/13) in patients treated with ceftazidime + avibactam vs. 69% (66/96) for patients treated with other regimens, but this obviously has to be interpreted with caution given the many potential confounding factors (11). Published data about use of ceftazidime + avibactam in children is very scarce and limited to a phase I study and case reports (12-14). However, two phase 2 RCTs have been conducted in children with cUTIs and cIAI and are awaiting publication (ClinicalTrials.gov Identifier: NCT02475733 and NCT02497781). Of note ceftazidime + avibactam may have a role in combination with aztreonam to treat infections caused by Enterobacteriaceae producing metallo-beta-lactamases at least until the combination of aztreonam with avibactam becomes available (15, 16).

Harms

In the RCTs the incidence of adverse events in the groups treated with ceftazidime + avibactam was similar to the control groups (7-10). However, in a meta-analysis of eight RCTs including 4093 patients, serious adverse events (SAEs) were more common with ceftazidime + avibactam (RR 1.24, 95%CI 1.00-1.54, I2 = 0%) but detailed data regarding the nature of these SAE were not available (17).

Additional evidence

N/A

Cost / cost effectiveness

United Kingdom: Basic NHS price: 10 vial pack £857.00 = £257.1 (about 340 USD) per day (standard dosing) Few data are available regarding the cost-effectiveness of ceftazidime-avibactam. A decision analytic model presented at ID week in October 2018 aimed to estimate the cost-effectiveness of treatment with ceftazidime + avibactam compared with colistin for a hypothetical cohort of patients with pneumonia and bacteraemia caused by carbapenemase-resistant Enterobacteriaceae over a 12 months period. The researchers assumed a 41% mortality with colistin treatment, a 23% (and hence very large) absolute reduction in mortality with ceftazidime-avibactam, daily costs of ceftazidime-avibactam of 1080 USD, a 42% incidence of nephrotoxicity with colistin treatment, a 56% probability of transfer to long-term care and a 1.8 fold improved odds of discharge home with ceftazidime-avibactam treatment (18). The authors estimated an incremental cost-effectiveness ratio for ceftazidime + avibactam compared with colistin of 110, 300 USD per quality adjusted life-year.

WHO guidelines

There are no available WHO guidelines for the treatment of infections due to multi-drug resistant organisms.

Availability

Ceftazidime-avibactam has FDA & EMA approval for cUTI & cIAI (for cIAI in combination with metronidazole) (11). EMA lists “HAP and other infections due to Gram-negative bacteria with limited treatment options” as further indication.

Other considerations

The Committee noted that there was very limited clinical trial evidence of the efficacy of recently approved antibiotics for infections caused by carbapenem-resistant bacteria, with activity against this type of infection based on studies with small sample sizes, methodological limitations and including heterogenous populations. The Committee was concerned that the current regulatory approval process for novel agents effective against “critical priority” pathogens (according to the WHO Priority Pathogens List (5)) does not adequately inform the urgent public health need for clear evidence-based guidance on the optimal management of these infections, which are associated with important morbidity and mortality.

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