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A.17 Imipenem/cilastatin/relebactam

MSF supports the inclusion of imipenem/cilastatin/relebactam (IMR) in Section 6.2.3 "Reserve group antibiotics" in the WHO Model List of Essential Medicines (EML).

Currently, imipenem/cilastatin is included in the Complementary List of Section 6.2.2 "Watch group", in the EML, as a therapeutic alternative to meropenem.

Imipenem is a carbapenem antibacterial, cilastatin is a renal dehydropeptidase inhibitor, and relebactam is a beta-lactamase inhibitor that protects imipenem from degradation by certain serine beta-lactamases such as SHV (sulfhydryl variable), TEM (temoneira), CTX-M (cefotaximase-Munich), P99 (*Enterobacter cloacae* P99), and PDC (*Pseudomonas*-derived cephalosporinase). IMR has activity against many class A and class C beta-lactamases including *Klebsiella pneumoniae* carbapenemases (KPCs).

IMR is particularly useful for the treatment of difficult-to-treat resistant (DTR) *Pseudomonas aeruginosa (P.aeruginosa)* (carbapenem-resistant/MDR/XDR), while it is also active against carbapenem-resistant Enterobacterales (CRE) KPC-producers.

IMR is less active against class D carbapenemases (OXA-type) and does not have activity against class B carbapenemases (MBLs) (1) MRSA, E. faecium, *Stenotrophomonas maltophilia*, some *Burkholderia spp*, MBLs (NDM, VIM, IMP) and some oxacillinases (2).

Imipenem/cilastatin/relebactam is FDA approved for:

(1) Hospital acquired and ventilator associated bacterial pneumonia in adults with limited/no alternative treatment options caused by susceptible gram-negative bacteria: *Acinetobacter calcoacetius-baumanii, Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella spp., Pseudomonas aeruginosa, Serratia marcescens.*

(2) Complicated urinary tract infections in adults with limited/no alternative treatment options caused by susceptible gram-negative bacteria: *Enterobacter cloacae, Escherichia coli, Klebsiella spp., Pseudomonas aeruginosa.*

(3) Complicated intra-abdominal infections in adults who have limited/no alternative treatment options caused by susceptible gram-negative bacteria*: Bacteroides spp., Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Fusobacterium nucleatum, Klebsiella spp., Parabacteroides distasonis, Pseudomonas aeruginosa.*

IMR has some non-FDA approved uses, for MDR infections including bacteremia, pneumonia, and osteomyelitis, with limited clinical and efficacy data.

The Infectious Diseases Society of America (IDSA) 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections (3) recommends IMR be preferentially reserved for treating carbapenem-resistant organisms or polymicrobial infections including organisms exhibiting carbapenem resistance.

IDSA states that IMR is the preferred option for pyelonephritis or complicated urinary tract infections caused by CRE; infections caused by Enterobacterales that are not carbapenemase producing and that do not exhibit susceptibility to carbapenem; for infections outside of the urinary tract caused by CRE if KPC production is present; for uncomplicated cystitis, pyelonephritis and infections outside the urinary tract caused by DTR *Pseudomonas aeruginosa*.

IMR is an alternative option for uncomplicated cystitis caused by CRE; treatment of MDR *Pseudomonas aeruginosa* infections in critically ill patients or those with poor source control with *Pseudomonas aeruginosa* isolates resistant to carbapemens but susceptible to traditional β-lactams. IMR can be considered for treatment of infections outside urinary tract caused by CRE if NDM (or other MBL) present, and no OXA-type present, and resistant to cefidericol or if combination therapy with ceftazidime-avibactam and aztreonam is not possible.

IDSA states that limited data on emergence of resistance to CRE to IMR are available and that if susceptibility to IMR is confirmed, combination antibiotic therapy for treatment of infections caused by DTR *Pseudomonas aeruginosa* are not suggested.

The last European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines (4) for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by the European Society of Intensive Care Medicine) (ESICM) were published in 2022 and state that there is insufficient evidence for imipenem/relebactam. There is no evidence to recommend for or against the use of imipenem/relebactam and fosfomycin monotherapies for CRE and in patients with severe infections due to difficult to treat CRPA, therapy with ceftolozane-tazobactam if active *in vitro* is suggested, at the time of writing (2022).

MSF would like to draw the attention of the Expert Committee to the following points:

- Discrepancies emerge between the recent USA guidelines (IDSA 2024) which recommend IMR as an alternative agent for CRE (KPC-producers) and DTR-*Pseudomonas.aeruginosa* and the European guidelines (ESCMID 2022) which refrain from making recommendations given lack of clinical data. However, since the publication of both guidelines, one published randomized controlled trial and one non-inferiority study have demonstrated clinical efficacy:
  - Li J et al (5): IMR vs Piperacillin/Tazobactam phase III, double-blind, multinational, randomized, controlled non-inferiority trial to study the efficacy and safety of IMR vs piperacillin/tazobactam in 270 patients with hospital-acquired bacterial pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP). IMR met non-inferiority criteria in terms of 28-day mortality versus Piperacillin/Tazobactam with comparable safety profile to Piperacillin/Tazobactam in adult patients with Hospital-HABP and VABP.
  - Chaftari AM et al (6): randomized non-inferiority study comparing IMR with standard-of-care Gram-negative (cefepime/piperacillin-tazobactam or meropenem) coverage in 100 cancer patients with febrile neutropenia: 49 participants to the IMR arm and 50 to the standard-of-care antibiotic arm, assessed at end-of-IV therapy, test of cure and late follow-up. Patients on IMR had a higher favourable clinical response than those on standard-of-care antibiotic; responses were similar at test-of-cure and late follow-up, microbiological eradication was comparable at all 3 timepoints, adverse events were similar in both groups, with no study drug-related mortality.

- Currently, access is severely lacking in most resource limited settings due to prohibitive prices and lack of registration: barriers which should be addressed in order to guarantee that all patients in need can benefit (together with microbiology laboratory support for diagnosis). MSF emphasizes that actions to foster access are sorely needed given very high prices and limited number of countries where IMR is registered.

- The inclusion of imipemem/cilastatin/relebactam in the EML will serve as a basis for National Essential Medicines lists and therefore will help motivate additional manufacturers, particularly in low- and middle-income countries.

Considering all these elements, MSF urges the 25th Expert Committee on the Selection and Use of Essential Medicines to consider the inclusion of imipenem/cilastatin/relebactam in the WHO Model List of Essential Medicines as a Reserve antibiotic (Section 6.2.3 Reserve group antibiotics). Imipenem/cilastatin/relebactam should be used solely for the treatment of DTR-*Pseudomonas aeruginosa* and carbapenem-resistant Enterobacterales (KPC-producers) when there are no other antibiotic alternatives, and where diagnostic and antimicrobial stewardship support is available. MSF **does not support** imipenem/cilastatin/relebactam indication for less extensive forms of resistance for which there are safe and effective alternatives, e.g. for treatment of Enterobacterales ESBL producers still susceptible to carbapenems.

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