Carolina Antimicrobial Stewardship Program | UNC Hospitals

Guidance for the empiric use of restricted β-lactams with activity against carbapenem-resistant *Enterobacterales* (CRE)

(e.g., ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol)

Although specific data is lacking for the benefit of empiric anti-CRE active β-lactam agents (ceftazidime-avibactam, meropenem-vaborbactam, imipenem-relebactam, cefiderocol), available efficacy data in randomized control trials and empirical reports of effective use of these agents as CRE-infection treatment regimens, makes empiric anti-CRE therapy administration in defined situations and at the discretion of a consulting Infectious Diseases specialist reasonable. The range of expanded anti-CRE activity for each agent depends upon the specific bacterial resistance mechanism (see page 2). Anti-CRE active beta-lactam agents are not broader than carbapenems against Gram-positives, and depending upon the agent, may be less active against gut anaerobes. Given the complexities of decision-making related to the use of the agents active against carbapenem-resistant organisms, especially in patients with underlying immune compromise, the use of these agents requires consultation with Infectious Diseases.*

This document pertains to the empiric use of β-lactams with activity against CRE. For the full list of restricted anti-infectives at UNC Medical Center see Restricted Anti-infective Drugs.

Empiric use of anti-CRE beta-lactam agents is restricted, and assessments must be performed in consultation with an Infectious Diseases specialist. The empiric use of these agents requires that *both* patient *and* microbiological criteria are met.

1. **Patient factors**:

There is little evidence that antibacterial antibiotic administration is an emergency in patients with stable hemodynamics and preserved end-organ function (including mental status). Therefore, the decision to start *any* empiric antibiotic requires the assessment of the current severity of illness, the likelihood of deterioration prior to a microbiological diagnosis, the likelihood that the chosen antibiotic will avert a poor patient outcome, the drug-toxicity risk to an individual patient, and the potential for promoting multidrug resistance.

a. Patient with any 1 of the following clinical indicators of severe infection.
    i. Hemodynamic instability likely related to infection
    ii. Multi-organ dysfunction likely related to infection
    iii. Altered mental status likely related to infection

and

b. Patient with proven or probable infection in a specified site (e.g. lungs, abdomen, urinary tract, blood stream).

AND

2. **Microbiological factors**:

Carbapenem exposure is known to increase risk of CRE colonization and infection. Therefore, it may be reasonable to initiate an anti-CRE β-lactam agent empirically in the following situations:

a. A patient with ongoing or recent (last 90 days) carbapenem exposure if either
    i. Patient factors (1a) are clearly established, and infection is the most likely explanation for clinical decompensation; or
    ii. A Gram-negative organism has been isolated from a sterile site, identification/susceptibility testing is forthcoming (the Infectious Diseases team should contact the microbiology laboratory

to obtain information about the isolate phenotype (i.e. lactose-fermenter or non-lactose fermenter) and if possible, genus-species to inform choice of anti-CRE agent.

b. Patients with documented history of CRE infection or colonization at any time point
c. Patient is housed in a hospital unit with a known ongoing outbreak of CRE as determined by Infection Prevention
d. Patients who have received medical care within the previous 12 months in countries with a relatively high prevalence of metallo-beta-lactamase producing CRE - ***NOTE****: empiric treatment regimens for metallo-beta-lactamase producing CRE differ; cefiderocol or ceftazidime/avibactam plus aztreonam preferred.*

*Empiric use of ceftazidime-avibactam, meropenem-vaborbactam, ceftolozane-tazobactam, imipenem-relabactam or cefiderocol requires approval by the Antimicrobial Stewardship Program or the Infectious Diseases sub-specialist physician (fellow or attending). Microbiological specimens must be collected, and results are forthcoming prior to the first dose. Bedside evaluation prior to first-dose will be performed at the discretion of the Infectious Diseases sub-specialist.

- Bedside evaluation and documentation of indication for approval is expected within 24 hours of approval.
- After formally evaluating the patient, the consulting Infectious Diseases team can elect to either continue or discontinue empiric use.
- The default duration of the initial approval will not extend beyond 72 hours.
- As guided by the clinical situation, the treating teams should tailor a final antibiotic regimen targeted to resulting microbiological data.
- Ongoing use of anti-CRE agents in the absence of confirmed or very high suspicion for CRE is prohibited. Extended use of the agent after 72 hours will be permissible only by the Infectious Disease Consultant pending a decision by the weekly clinical ICHD conference (review of adult patients with burns, solid organ transplants and hematology malignancies) or Antibiotic Stewardship (all other patients).
- Absence of Infectious Diseases sub-specialist or Antimicrobial Stewardship Program approval will result in automatic discontinuation of the agent.

Background Material

According to current CDC guidelines, carbapenem-resistant *Enterobacterales* (CRE) are “those *Enterobacteriales* that test resistant to any of the carbapenems (i.e., minimum inhibitory concentrations [MIC] of ≥4 µg/ml for doripenem, meropenem, or imipenem OR ≥2 µg/ml for ertapenem) or are documented to harbor a gene encoding a carbapenemase or are positive for carbapenemase production. For *Enterobacterales* that exhibit intrinsic imipenem non-susceptibility (i.e., *Morganella morganii*, *Proteus* spp., *Providencia* spp.), resistance to carbapenems other than imipenem is required”. Of note, CDC-defined CRE include both carbapenemase-producing *Enterobacterales* (CPE) and non-carbapenemase-producing *Enterobacterales*. Some CDC-defined CRE, especially non-carbapenemase producing CRE, may display susceptibility to non-carbapenem antibiotics and/or other carbapenems (e.g. resistance to ertapenem and susceptibility to meropenem).

Novel non-β-lactam β-lactamase inhibitors: avibactam (inhibition of *K. pneumoniae* carbapenemases [KPC] and OXA-48-like carbapenemases), vaborbactam (KPC inhibition), and relebactam (KPC inhibition) were specifically designed in response to the threat of CPE. These agents do NOT inhibit metallo-β-lactamases such as New Delhi metallo-β-lactamases [MB] (ie. NDM, VIM, IMP). Cefiderocol has activity against MBLs. Other drugs with activity against MBL-producing CRE infections include: plazomicin, eravacycline, and omadacycline.

Of note, ceftolozane-tazobactam does not have acceptable anti-CRE activity to be used on an empiric basis for CRE. Ceftolozane-tazobactam is active against some MDR *Pseudomonas aeruginosa*, and it may be the only drug that has activity against some *Pseudomonas aeruginosa* isolates. Ceftazidime-avibactam, imipenem-relebactam, and cefiderocol also have a role in difficult to treat gram-negative infections other than CRE (ie. *Pseudomonas, Stenotrophomonas, Acinetobacter, Achromobacter)*. Ceftazidime-avibactam may also be used in difficult to treat infections due to nontuberculous *Mycobacteria spp.*

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