به نام حضرت دوست

Carbapenem use in critically ill patients

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INTRODUCTION

- Carbapenems are one of the latest b-lactam with one of the broadest spectrum.

- Their stability against hydrolysis by most b-lactamases makes them major weapons in the treatment of severe nosocomial infections including the ones caused by ESBL-producing Enterobacteriaceae (ESBL-PE).

- The prevalence of ESBL-PE has significantly increased in the last decade,
- this ongoing pandemic is responsible for a global rise in carbapenems consumption that may hasten the dissemination of carbapenem-resistant Gram-negative bacteria including carbapenem- resistant P. aeruginosa (CRP) and carbapenemase- producing Enterobacteriaceae (CPE)

CARBAPENEM INDICATIONS, USUAL ROLE, AND CONSUMPTIONS

- Carbapenems inhibit synthesis of the bacterial cell wall by complexing penicillin-binding proteins (PBPs) such as high molecular weight enzymes PBP1a, 1b, 2, and 3.

- Doripenem and Meropenem have higher affinities for PBP2 and PBP3 in Pseudomonas aeruginosa than Imipenem, which may explain why the former are more active against this species than the latter.

- Except Ertapenem (inactive on P. aeruginosa and Acinetobacter baumannii), carbapenems are active against both Gram-positive bacteria (except methicillin-resistant Staphylococcus aureus MRSA, Enterococcus faecium, and Enterococcus faecalis apart from Imipenem) and Gram-negative bacteria (except Stenotrophomonas maltophilia) and anaerobic species.

- Plasma protein binding of available carbapenems is low except Ertapenem.
- Carbapenems are distributed primarily extracellularly and tissue concentrations are in the same range than in plasma

- Bactericidal activity of carbapenems can be compromised by resistance mechanisms.
- The mechanisms of resistance are:
- a low affinity for certain PBPs (no carbapenem has a high affinity to PBP2a
- in MRSA or PBP5 in E. faecium which explains why these species are naturally resistant),
- a modification of PBPs (rarely leading on its own to high-level resistance),

- an enzyme-mediated hydrolysis (carbapenemase such as class B metaloenzymes IMP,
- NDM, VIM, SPM, GIM, and SIM, or class A carbapenemase Klebsiella pneumoniae carbapenemase KPC),
- A membrane impermeability (reduction or abolition
- of the OprD porin),
- efflux mechanisms (the MexA-MexB-OprM pump system in P. aeruginosa conferring only low-level resistance).

- All b-lactams in high concentrations can cause seizures, and this seizure propensity is related to their binding to g-aminobutyric acid (GABA) receptors.
- A meta-analysis demonstrated that carbapenem increases the risk of seizure [Odds ratio (OR) ¼ 1.87; 95% CI, 1.35–2.59].
- Nevertheless, the risk remains low (2 per 1000 persons).

- Imipenem/cilastatin is the most epileptogenic carbapenem with a marked incidence of 23% and an OR of 3.50 (95%
- CI, 2.23–5.49),
- whereas the ORs for risk of seizures from Meropenem, Ertapenem, and Doripenem are 1.04 (95% CI, 0.61–1.77), 1.32 (95% CI, 0.22–7.74), and 0.44 (95% CI, 0.13–1.53), respectively

- Postmarketing reports indicate a seizure incidence with imipenem of 1.5–2% with predisposing factors of advanced age, history of seizures or stroke, central nervous system disease or infection, and impaired renal
- Therefore, especially when Imipenem is used at high dose, dose adaptation using therapeutic drug monitoring may be helpful

- The risk of delirium associated with carbapenems and non-carbapenem b-lactam antibiotics remains similar in a recent prospective cohort study performed in critically ill patients

- The use of carbapenems is increasing, partly as the result of a suspected rising prevalence of multiresistant Gram-negative pathogens.
- Between 2000 and 2010, the global consumption of antibiotic drug increased by 35%.

- India wasthe largest consumer with 12.9 109 units a year, which represented 10.7 units per person.
- The rise of the consumption rate of carbapenems was 45% worldwide
- Carbapenems are the third antibiotic used worldwide for community-acquired infections in ICU (10.7%) and the first for hospital-acquired infections (21.5%)
- Faropenem, the new oral penem used as a new alternative to carbapenem in India, has seen its consumption worryingly increasing of 154% from 2010 to 2014

- A recent French survey in healthcare facilities evaluated prospectively the characteristics of carbapenem use.
- Imipenem was mostly frequently used.
- In ICU, 66% of the patients were prescribed carbapenems on empirical basis for a medium duration of 8.
- De-escalation was a reason of carbapenem cessation in only 15.1%, more frequently with the contribution of the antibiotic stewardship team

- The increase in ESBLE carriage reaching more than 20% in most of the ICUs increases the likelihood of receiving carbapenems in sepsis.
- In a cohort of 594 ESBLE carriers, carbapenem exposure increased in both infected and uninfected carriers when compared with noncarriers (627, 241, and 69 carbapenem days per 1000 patient days, respectively, P ¼ 0.001
- In case of sepsis in ESBL-PE carriers, empirical therapy included carbapenem in 27.6% of the episodes but infection was finally related to ESBL-PE in only 7% of the cases

- However, the intensity of the effect is very difficult to evaluate because of the numerous uncontrolled factors and methodological issues
- The respective impact of carbapenems as compared to noncarbapenem antibiotics on the emergence of carbapenem-resistant organisms is still unknown
- In patients under carbapenem therapy, the previous colonization with carbapenem resistant organisms (such as S.maltophilia, A. baumannii, and P. aeruginosa) was the main determinant of breakthrough infections

- It was also recently shown that carbapenemuse exposes to an increase risk of cross colonization with carbapenem-resistant K. pneumoniae in ICU
- In patients with sepsis, acquisition of carbapenem resistance correlates with the duration of carbapenem exposure.
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OPTIMIZATION OF CARBAPENEM USE IN CRITICALLY ILL PATIENTS

- Because Carbapenem have the broadest spectrum of activity of any of the b-lactam antibiotics, they are the drugs of choice for infections caused by multiresistant bacteria such as ESBL-PE and P. aeruginosa.

- The legal approval of United States and European agencies for carbapenems are different between components:
- (1) Imipenem: Lower respiratory tract infections (LRTI), complicated urinary tract infections (UTI), intra-abdominal infections (IAI), gynecologic infections, bacterial septicemia, bone and joint infections, skin and skin structure infections (SSTIs) and endocarditis

- (2)Meropenem: Complicated SSTIs, complicated IAIs, and bacterial meningitis

- (3) Ertapenem: Moderate to severe infections caused by susceptible bacteria: complicated IAIs, complicated SSTIs including diabetic foot infections without osteomyelitis, community acquired pneumonia, complicated UTIs, acute pelvic infections including postpartum endomyometritis, septic abortion, and postsurgical gynecologic infections

- Carbapenem is commonly used in severe infections because of synergistic infections involving Gram-positive, Gram-negative bacteria, and anaerobes and to multidrug resistant Gram-negative bacteria (ESBL, AmpC Enterobacteriaceae, and carbapenem-susceptible A. baumannii and P. aeruginosa).
- As mentioned earlier, it may explain the dramatic increase in the carbapenem consumption in the ICUs.

- In critically ill patients, the modified volume distribution, augmented renal clearance, renal replacement therapy, and hypoalbuminemia are a common cause of pharmacokinetic variability.

- The optimization of dosage and choice of infusion, and the monitoring of plasmatic drug concentrations maintained above the MIC of at least 40% of time is crucial.

- In a meta-analysis, Vardakas et al. showed a survival benefit of prolonged infusions of antipseudomonal b-lactams in patients with sepsis even if the benefit seems to be lower for Meropenem than for Piperacillin/tazobactam
- Prolonged or continuous infusion of Meropenem should be considered (with a loading dose to start the regimen) especially when the MIC is high and the bacterial inoculum important

- In patients with septic shock and possible augmented renal clearance, doses should be increased and/or administration should be performed by prolonged or continuous infusion.
- In case of sustained low efficiency dialysis, there is a relevant PK variability significantly influenced by the degree of residual diuresis
- For patients with ECMO, Meropenem intermittent infusion of 1 g intravenously every 8h will be sufficient to reach an objective of 40% of time above a concentration of 8 mg/l (breakpoint MIC of P. aeruginosa) in the plasma and in the subcutaneous adipose tissue

- The addition of Amikacin to Meropenem can increase the microbiological success rate in case of suspected infection because of P. aeruginosa.
- This combination can also decrease the risk of Enterobacteriaceae and Pseudomonas aeruginosa being resistant to both drugs
- Despite the fact that some studies showed that low concentrations of Colistin seem to restore the sensitivity to Carbapenem, the addiction of Meropenem to Colistin was not superior to Colistin alone and did not improve clinical feature in case of severe A. baumannii infections resistant to carbapenems

FUTURE PROSPECTS: AVOID OVERUSE OF CARBAPENEMS AND STEWARDSHIP PROGRAMS

- Because Carbapenem consumption is increasing and concurrently carbapenem-resistance in Gram-negative bacteria rising, it is crucial to slow its emergence by sparring Carbapenem when possible.

- But there are no directly equivalent antibiotics and the alternatives are less well supported by clinical trials.

- A hospital wide program showed that carbapenem prescription is inappropriate in about 50% of the cases and that compliance to antibiotic stewardship team advice resulted in a three-fold reduction in the DDD of carbapenem therapy without adverse effects on the patients' outcome

- A total of 158 antimicrobial stewardship programs (ASP) interventions were made.
- These included carbapenem discontinuation (35%), change to narrower-spectrum antibiotic (32%), dose optimization (17%), further investigations (including imaging and procalcitonin) (11%), infectious diseases referral (3%), antibiotic discontinuation (other than carbapenem) (1%), and source control (1%).
- Of 220 unique patients, carbapenem use was inappropriate in 101 (45.9%) patients

- Antibiotic stewardship team has been shown to reduce antimicrobial resistance in the hospital [40] and can also have a positive impact on the duration of carbapenems treatment in promoting de-escalation

- The positive impact of a carbapenem sparing antibiotic stewardship intervention in ICU has never been studied.

- Antimicrobial de-escalation is a strategy to reduce the spectrum of antimicrobials and change the first broad-spectrum antibiotic for another, based on the results of the bacterial samples.
- The second antibiotic should be as efficient as the first one but with a narrowed spectrum to prevent the emergence of bacterial resistance.
- There is no consensus definition of when and how to de-escalate
- As systematic review concluded that de-escalation is well tolerated in ICU but did not demonstrate an effect on the rate of antimicrobial resistance at the individual level

- Another important challenge for carbapenem sparing policies is the treatment of ESBL-PE severe infections with alternative to carbapenems.

- A considerable literature abstracted in a recent review concluded that carbapenem should be the first choice therapy for severe infections but that alternative should be used in less severe infections.
- In a cohort of 108 ICU patients with severe infections, de-escalation from carbapenem to another pivotal antimicrobial was well tolerated

- Despite their clinical efficiency and simpler use, oral use of carbapenems is a subject of serious concern because of their worryingly increasing consumption in countries with high rates of ESBL-PE and CPE organisms (Faropenem in India) and the undeniable ecological impact.
- The development of new oral carbapenem such as Tomopenem active against MRSA and P. aeruginosa should be considered cautiously

CONCLUSION

- Carbapenems are the first b-lactam used in treatment of severe nosocomial infections because of its large spectrum covering anaerobes and both Grampositive and Gram-negative aerobes.

- It is also active in most part of the multiresistant Gram-negative bacteria such as ESBL-producing and AmpC hyper producer Enterobacteriaceae and multiresistant P. aeruginosa in ICU.

- The major consumption increase is linked with the emergence and dissemination of resistance such as carbapenemase-producing Enterobacteriaceae.

- It is thus crucial to know the specificities of prescription to optimize clinical efficiency and to de-escalade if possible.

KEY POINTS

- Carbapenem is the first-line antibiotic in case of suspected or confirmed sepsis in known or presumably known ESBLE carriers in ICU patients.
- Because of specific pharmacokinetic modifications in severe critically ill patients, high off-label dose is often necessary and the monitoring of plasmatic concentration is crucial.
- The increase in the overall consumption in the past years with lack of systematic de-escalation observed is responsible of and carbapenem-selection pressure that contribute to the increase of carbapenem-resistant enterobacteriaceae, A. baumannii and P. aeruginosa in ICUs.

Thank You
For Your Attention