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Emergence of Metallo-β-Lactamases and Carbapenem Resistance

We read with interest the recent article by Murki, *et al.* on impact of cephalosporins restriction on incidence of extended spectrum β-lactamases (ESBLs) producing gram negative bacteria [1]. Antibiotics restriction and their cycling are no doubt proven strategies to limit emergence of resistant microbial flora, provided they are employed judiciously. However, while attempting this policy in intensive care units (ICUs), one needs to be careful regarding the inadvertent overuse of carbapenem groups of antibiotics, the most potent weapon in our armamentarium to fight ESBL producing gram-negative organisms. Although ESBLs producing bugs have now become a major threat to the utility of cephalosporins, particularly to the broad spectrum third and fourth generation members of this group, the recent resurgence of another group of beta-lactamases, the metallo-β-lactamases (MBLs) in enterobacteriacae [2] have far more serious threat to the antimicrobial world. They hydrolyze virtually all beta-lactam antibiotics including extended-spectrum cephalosporins and carbapenems, not inhibited by serine beta-lactamase inhibitors like clavulinic acid, sulbactum, and tazobactum, and more seriously, they are often plasmid-borne making them readily transferable among various species of bacteria [2]. The most worrying part of carbapenem-resistance is that there is hardly any effective antibiotic to treat these infections. With the detection of a new type of MBL, New Delhi metallo-beta-lactamase-1 (NDM-1) from few Indian hospitals has further compounded the problem [3].

Another worrisome aspect is the fact that these MBLs producing carbapenem-resistant organisms are not only confined to the ICUs of big hospitals in metropoliton cities alone but they have also made deep inroads in to the smaller cities of India too. We share our recent experience of treating similar MBL-producing multi-drug resistant (MDR) gram negative infections emanating from a level-3 neonatal intensive care unit (NICU) at Bijnor, a small city of western Uttar Pradesh. Since April 2009, we have treated 14 such neonates admitted in our NICU where nosocomial sepsis was responsible for emergence of MDR gram negative bacteria. The organisms isolated on automated blood culture (BACTEC 9050) included *Klebsiella pneumoniae* (8, 60%), *Acinetobacter baumini* (2, 10%), and *Pseudomonas aeruginosa* (4, 30%). Modified Hodge test was used to screen for MBLs production. All 14 cases showed distorted carbepenem inhibition zones, indicating production of MBLs. These organisms were resistant to all cephalosporins, aminoglycosides, monobactams, quinolones, piperacillin-tazobactum combination, and even to carbapenems. However,

they were 100% sensitive to colistin and polymyxin-B. All these cases were treated with polymyxin-B along with other antibiotics. Six cases out of these 14 died and 8 survived. Out of these 8 neonates, 50% developed multiple complications like meningitis and arthritis, hydrocephalus, etc. None of the isolates from community acquired infections had similar sensitivity pattern.

The above brief description highlights not only the occurrence of MBL-producing gram-negative organisms from some smaller places, but also underscores the hazard of MBL-producing carbapenem-resistant organisms that ultimately cause high morbidity and mortality. The need of the hour is to preserve this group of antibiotics and trials should be encouraged to study the impact of carbapenem restriction for treatment of ESBLs on the incidence of MBL-producing gram-negative pathogens.

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