Carbapenem-resistant enterobacteriaceae: a reality check

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Abstract

Resistance to antimicrobial agents in several bacteria is on the increase because of the irrational and rampant use of antimicrobial drugs. This is destroying the premise of modern medicine that whenever required, adequate antibiotic cover will be available to save the patient's life. Such premise is no longer true. Several multidrug-resistant bacteria are now detected with great frequency. Carbapenem-resistant enterobacteriaceae belong to this category of resistant bacteria that were recently labelled as superbugs too, simply because the commonly available antibiotics are ineffective against them.

It was destined to happen. Call it the breach of the last bastion or the burst of the antibiotic bubble, the emergence of antimicrobial resistance to carbapenems with little or no back-up drugs is hardly unsurprising. In fact it is the naïve response of the worldwide scientific community over the last fifty years that has been unexpected and perhaps disappointing. Bacterial resistance to antimicrobials has been increasing at a dizzying pace — a remarkable testimony to the ability of bacteria to collect and exchange resistant genes with unimaginable efficiency and complete lack of species specificity. The ultimate success in the practice of modern day medicine is based on the premise that whenever required, adequate antibiotic cover will always be available. However, if the efficacy of the top-of-the-line antibiotics is going to be reigned in by the ubiquitous bacteria as E. coli and K. pneumoniae, then in the near future, treatment options especially in critical care, oncology and transplant medicine are likely be in serious jeopardy.

Carbapenems (currently ertapenem, imipenem, meropenem and doripenem, etc.) are the most effective and potent β lactam antibiotics, with the broadest spectrum and the least resistance. They are reliably active against multidrug-resistant Gram-negative bacteria and form the mainstay in the treatment of serious infections in most hospitals across the world today. Resistance to these top-of-the-line antimicrobials in the traditional, established nosocomial pathogens namely Pseudomonas aeruginosa and Acinetobacter baumannii has been extensively described over the last eight years.1 But when bacteria residing in the gut as enterobacteriaceae find ingenious ways of survival, despite treatment with carbapenems, it is time to admit that the war against the microbes is taking an ominous turn.2 With the Gram-negative antibiotic pipeline having practically dried up for the next 10 -15 years, it is also time to dispel our misplaced optimism that some new drug is bound to arrive. The common mechanisms that are responsible for carbapenem resistance include changes in outer membrane proteins, overexpression of drug efflux pumps and carbapenem hydrolyzing enzymes. Carbapenemases potentially herald the end of treatment of Gram-negative infections because of all the major mechanisms conferring resistance the

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most menacing are these hydrolyzing enzymes, as they also compromise efficacy to other β-lactams. Additionally, there is the inevitable co-resistance to the other main classes of commonly used antibiotics, namely the fluoroquinolones and the aminoglycosides.

The high-level resistance to carbapenems by such carbapenemases is essentially of three types – Klebsiella pneumoniae carbapenemase (KPC); metallo beta lactamases (MBLs); and oxacillinases. Carbapenemases are beta lactamases and by tradition the nomenclature of beta lactamases is based on their substrates, biochemical properties, location of their discovery, location of the gene on the chromosome, strains of bacteria, patients providing the sample or even after the investigator who described them! Various MBLs in the recent past have been named after the cities associated with them, such as VIM (Verona Integron-encoded Metallo β-lactamase); GIM (German IMipenemase); SIM (Seoul IMipenemase). The infamous NDM-1 (New Delhi Metallo -1) was ostensibly named as it was first isolated from a Swedish patient who was admitted to a hospital in New Delhi. However, the fact that the gene encoding for this resistance actually originated in India cannot be proven. The NDM-1 gene shares little identity with the other MBLs and is apparently mobile on a plasmid that is readily transferable.

The Catch 22 situation in countries that have high rates of extended spectrum beta lactamases (ESBLs) in enterobacteriaceae compels them to place a higher reliance on carbapenems. The inevitable use of carbapenems is consequently bound to exert greater selective pressure. A recent pilot study from our tertiary care centre in central Mumbai that receives referral samples from the city and the State found a steady increase in carbapenem resistance in enterobacteriaceae from 0% in 2006 to 8% in 2009. In our cohort of cases where NDM-1 was detected, the main risk factor was the prior use of carbapenems, usually up to a month.

Multicentric studies across major cities are required to validate whether the NDM -1 gene is the predominant resistance mechanism responsible in carbapenem-resistant enterobacteriaceae (CRE), and whether transmission can occur in the community; more importantly, whether asymptomatic carriage can occur and if so for how long. The dissemination of transposons and integrons have given rise to gene epidemics and new genetic and biochemical mechanisms continue to be described such as plasmid addiction and the phenomenon of hypermutability (especially with fluoroquinolones). It is simplistically assumed that resistance comes at a fitness cost and reduction in prescribing will directly translate to a reduction in the prevalence of resistance. Unfortunately, this is not necessarily entirely true. Evolution ultimately selects bacteria with the least fitness burden.

Gastrointestinal carriage of resistant commensals in the absence of direct selective pressure with carbapenems is what we now need to worry about. A disturbing example is that of the ESBLs produced by enteric pathogens that have spread worldwide since their first description in 1983. As a result of mutations, more than 300 types of ESBLs are described today in various species of the Enterobacteriaceae family and even in other non-enteric organisms. The TEM and SHV type β-lactamases, mainly produced by Klebsiella pneumoniae, have spread throughout hospital settings, and CTX-M enzymes, mainly produced by Escherichia coli, have become predominant in the community. The alarming precedence set by the spread of these ESBL-producing organisms in the community is now proving a force to contend with, especially in community-acquired infections of the urinary tract. Also, in some regions, fecal carriage of ESBLs has become a fairly frequent feature (up to 20% patients). As a corollary to this, the possibility of a similar phenomenon occurring with gut microorganisms acquiring resistance to carbapenems at no apparent fitness cost and
in the absence of any selective pressure is very real.

How does this happen? We must not forget at the same time that essentially, it is the antibiotic usage that is the main driver of resistance, and that resistance is clearly a function of the volume consumed. If resistance to antibiotics is unavoidable, then the simple truth about antibiotics is — the more you use them, the more you will lose them. Increased prescription of antibiotics, paradoxically whether appropriate or indiscriminate, is responsible. Prescribing an antibiotic to a single patient also amounts to prescribing it at the same time to billions of bacteria who have certainly not been taking it “lying down” for the last five decades. It is not the appropriate use but the inappropriate use of antibiotics not only in medical practice but also as growth promoters in veterinary practice and their use in agriculture, etc. that we need to address and curb.

From the perspective of medical health, there is an urgent call to take stock of the situation and salvage what we can. National antibiotic policies should form the framework on which we can tailor local guidelines. These guidelines will help in maximizing the outcome for an individual patient while minimizing the collateral damage to our microbial ecology. But writing and formulating guidelines for the rational use of antimicrobials is easy — the caveat lies in their strict audit and implementation. Mandatory institutional mechanisms to regulate antibiotic prescription must be in place. Evidence-based medicine dictates that in seriously ill patients, inappropriate treatment is the most important predictor of mortality, and this is probably the basis for hitting hard and early with carbapenems. Commitment to rapid de-escalation to narrower spectrum drugs is where we now need to focus. To enable such a streamlining of therapy to actually take place, “cultures” have to be sent before any antimicrobial is initiated, so that the etiologic pathogens are isolated and their susceptibility is available. Additionally, development and evaluation of advanced, improved and rapid diagnostic methods is a vital need.

Needless to add, good infection prevention policies in hospitals that prevent cross-transmission of resistant bacteria from patient to patient is certainly warranted. However, good infection control is less likely to be effective when resistance arises readily by mutation or when the ultimate pathogen has long been a colonizer in the bowel.

The sad truth is that no single strategy to combat this burgeoning problem of antibiotic resistance seems to be working effectively worldwide. The “10 x 20” initiative promises a global commitment to develop ten new antibacterials by 2020. Whether this will come to pass is a matter of conjecture. If we, as responsible doctors, have to hand over our antibiotic legacy to the next generation, there is an urgent need for introspection. After all, resistance in bacteria is not a matter of “if” but of “when”.

References and bibliography


