

## Drug resistant pathogens, their resistance genes, and cost implications

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The nosocomial pathogen, their drug resistance genes and cost implications are underestimated and under-reported in Nepal despite the nosocomial outbreaks of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Methicillin Resistant *Staphylococcus aureus* (MRSA), and *Enterobacteriaceae* are prevalent. They are multi-drug (MDR), pan-drug (PDR), and extensively-drug resistant (XDR) either by acquiring antibiotic resistant genes through horizontal gene transfer or emerged in several ways (mutations/recombination, drug efflux pumps etc.). Hence, they are resistant to myriad of older and newer antibiotics causing therapeutic dead locks.

Extended spectrum  $\beta$  lactamase genes (wild type and mutants of *bla*<sub>TEM</sub> and *bla*<sub>SHV</sub>, *bla*<sub>CTX-M</sub>, *bla*<sub>VEB</sub>, *bla*<sub>PER</sub>, *bla*<sub>IMP</sub>, *bla*<sub>VIM</sub>, *bla*<sub>SIM</sub>, *bla*<sub>OXA</sub>, and *ampC*), loss of outer membrane porins (CarO, OmpW, HMP-AB), aminoglycoside resistance genes (*aac3*, *aadD1*, *aadA1*, *aphA1*, *aacA4* etc.), tigeicycline resistance gene (*text*), and rifampicin resistance gene (*arr-2*) or mutation in RNA polymerase subunit  $\beta$  (*rpoB*) are the few important genetic basis of resistance to antibiotics in Gram negative non-fermenters. Largest genomic resistance island (GRI) AbaR1 (86 Kb) has been identified in *A. baumannii* strain AYE and carries 45 drug resistance genes. Similar GRIs, AbaR2, -R3, -R4, and R5 have been described in international clones of *A. baumannii*. Some of these resistance genes including metallo  $\beta$  lactamases in nosocomial *Enterobacteriaceae* have already caused nuisance in health care settings. Similarly, genetic resistance in MRSA is mediated by large segment of DNA (60 kb), SCC*mec* element which carries *mecA* gene that confers resistance to methicillin. MRSA is simultaneously resistant to several antibiotics like; oxacillin, gentamicin, erythromycin, clindamycin, trimethoprim-sulphamethoxazole, rifampicin, chloramphenicol, tetracycline, and ciprofloxacin. Vancomycin is a drug of choice for treatment of MRSA but *vanA* mediated vancomycin resistant *S. aureus* has already been noticed.

Presence of these resistance genes in nosocomial pathogens directly correlates with the cost to the patient. Third and 4<sup>th</sup> generation cephalosporins either alone or in combination with  $\beta$  lactamase inhibitor are used to treat MDR Gram negative nosocomial pathogens and treatment usually is costly (US\$ 40 to US\$ 190/course). Treatment of

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patients with ampicillin, cefoxitin, and carbapenems will induce expression of molecular class C extended spectrum  $\beta$  lactamase gene (*ampC*) which can hydrolyze all cephalosporins and  $\beta$  lactamase inhibitors. The choice of treatment of *ampC* ESBL producer is always carbapenem (Imipenem, Meropenem, Itrapenem, or Doripenem) and a single dose of this antibiotic cost around US\$100 (US\$ 1,000/course). Despite the high cost, some strains develop in-vivo resistance or others already possess carbapenemases (IMP, VIM, SIM, KPC, or OXAs) which can easily hydrolyze this antibiotic. The treatment then relies on colistin alone or in combination with rifampicin. Colistin-effective in 1970s and considered as a magic bullet for MDR and PDR strains-now costs US\$ 238 to 439/course. But, colistin resistant strains of *E. coli*, *Proteus* spp., *P. aeruginosa*, and *A. baumannii* have been isolated. Similarly, the treatment of MRSA relies on vancomycin and linezolid and the cost is US\$ 14 to 68/dose and US\$ 156/dose, respectively. Tigecycline is a newer antibiotic which has a good coverage for multidrug resistant nosocomial pathogen and the cost is US\$ 98/dose but pathogens are equipped with *tetX* gene and efflux pump which pumps this antibiotic effectively. Despite of all these expenses and the availability of resources, these pathogens cannot be contained if they emerge as XDR.

For a country where the IV antibiotics are not manufactured in house, it has to bear a maximum cost on importing expensive antibiotics if irrational antibiotic use persists. A patient being treated for nosocomial infection for 10 days will spend around US\$ 280 to 2,000 and 30 patients admitted at a time for 10 days in a hospital with 30 ICU beds will spend US\$ 8,400 to US\$ 60,000. ICU beds in a tertiary hospital located at the Kathmandu city will be occupied with patients under broad spectrum antibiotics round the year and the cost is beyond our imagination. National antibiotic use policy, monitoring and surveillance of MDR, PDR, and XDR pathogens, formulation of infectious disease treatment guidelines, and molecular epidemiological studies to monitor the epidemic and resistant strains will help to contain antibiotic resistance and preserves the existing drugs.

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