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Editorial

Multidrug Resistance and Higher Drug Derivatives

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Infectious diseases caused million of deaths each year. Bacterial diseases like fever (*Escherichia coli* 0157, *Pseudomonas aeruginosa*, *Salmonella enterica*), diphtheria (*Corynebacterium diphtheriae*), TB (*Mycobacterium tuberculosis*), cholera (*Vibrio cholerae*), tetanus (*Clostridium tetani*), plague (*Yersinia pestis*), gonorrhea (*Neisseria gonorrhoeae*), syphilis (*Treponema pallidum*), leprosy (*Mycobacterium leprae)* and cough (*Klebsiella pneumoniae*) have been controlled by vaccination and antibiotic therapy. However, recently some infections were not cured by old but potent antibiotics like ampicillin (block cell wall peptidoglycan synthesis), tetracycline (removes drug from cytoplasm), chloramphenicol and erythromycin (inhibit protein synthesis) as well as rifampicin (inhibits RNA polymerase) and novobiocin (inhibits gyrase; DNA topoisomerase II). Scientists discovered that some plasmids (3-15kb) carried drug resistant genes which coded proteins for drug inactivation by drug cleavage (beta-lactamase cleaves penicillin), drug efflux (tet protein removes tetracycline), drug acetylation (cat protein acetylates chloramphenicol), drug phosphorylation (strA/B phosphorylates streptomycin) and drug adenylation (aad protein adenylates spectinomycin and streptomycin). Important facts such genes were discovered between 1950-1960 and important new drugs were developed to overcome such failure of antibiotic therapy. As for example, penicillin resistance was overcome by development of cephalosporins (cefotaxime, ceftriaxone) and further development was made by synthesizing carbapenem drugs like imipenem and meropenem, targeting cell wall peptidoglycan synthesis similar to ampicillin. Interestingly, carbapenem drugs are toxic and needs hospitalization. However, some time it was absolutely necessary where the bacteria got blaCTX-M gene that could inactivate the cefotaxime drug. Sad fact, blaNDM-1 gene inactivates imipenem and doripenem drugs. It seems, there are many mdr genes to inactivate antibiotics! How so many genes (average 2000nt each) could be accommodated in small plasmids? Bacteria also improved its plasmids (70-500 kb) by rearrangement with F' conjugative plasmid (62.5 kb) and created many transposable IS elements (IS-10, IS-5, IS-21, IS-110) including recombinases and integrases to make new genes against new antibiotics available today. Not only new mdr protein, sometime mutation of the target protein cause drug resistance. As for example, beta subunit of RNA polymerase mutated to give rifampicin resistance and gyrA as well as gyrB subunits of Gyrase gave resistance to ciprofloxacin and enoxacin. Thus, even you found many big plasmids in *E. coli, P. aeruginosa, K. pneumoniae* and *S. enterica*, the plasmid level in *M. tuberculosis* and *N. gonorrhoeae* found very low. Surely tight host specificity and organ specificity may be important. But drug resistance in TB for tuberculosis specific drugs like ethambutol, ethionamide, azithromycin, isoniazid, and dapsone were also reported due to mutation of chromosomal genes (katG, embB, erm, rpsA, ethA, inhA).

Intestinal microflora has significant load of diverse species bacteria ($4x10^{12}$) that synthesize nutrients and vitamins for human and animal cells and must not be removed by antibiotics. Today, we know probiotic bacteria capsule must be taken after each antibiotic dose. Sometime, some antibiotic preparation come with probiotic bacteria like *Lactobacillus lactis*, *Bacillus coagulans* and *Bifidobacterium bifidum*. Thus, antibiotic therapy should be advised by doctor and non-prescription antibiotic therapy must be avoided. Recently, I was infected in my chest and doctor prescribed cephalosporin (1^{st} phase; penicillin derivative), doxacycline (2^{nd}

phase; tetracycline group drug) and mitomycin (3rd phase; amino quinone group drug) including Fusidic acid cream (protein synthesis inhibitor; active against MRSA *Staphylococcus aureus*) and Clindamycin lotion (higher derivative of erythromycin and azithromycin). So instead one antibiotic therapy as was between 1940-1970, now multiple antibiotics were needed to remove systemic MDR bacterial infection. I had no idea if I was infected during my work with MDR bacteria.

The story with protozoal diseases reported similar drug resistance. In Kala-Azar (*Leishmania donovani*) Sodium stibogluconate resistant species were reported. In malaria (*Plasmodium falciparum*), chloroquine as well as to lesser extent mefloquine and artemisinin resistant species were reported. Sleeping sickness (*Trypanosoma brucei*) drug resistance against suramine, nifurtimox, melarsoprol and pentamidine were reported. In cancer, drug resistance reported due to mdr-1 drug efflux gene expression and amplification. Drugs against viral diseases were also discovered. As for example, Corona virus replication was inhibited by RNA-dependent RNA polymerase nucleoside-analogue inhibitors and also reverse transcriptase inhibitor to stop HIV replication in AIDS.

In summary, MDR infections are alarming as 35000 deaths in the USA per year and an estimate described that in 2050 such death in Asian countries could reach as high as 10 million. Due to rapid drug resistance, drug companies were reluctant to invest in new drug discovery which needed 10-50 million dollars per drug. Drug Database pointed only few new drugs marketed in recent years for infectious diseases where as so many drugs for cancer, diabetes and hypertension. In that situation, Indian Government has stressed for the discovery of Ayurvedic drugs. We reported that roots and bark organic extracts from *Suregada multiflora*, *Cassia fistula* and *Jatropha gossypifolia* killed MDR bacteria isolated from Ganga River, milk, chicken meat and human hair. Such small trees cultivated in roof of flat in the Kolkata city giving enough roots or bark to treat individual MDR infection. However, genetic drugs like antisense to mdr genes cocktail may be effective to control MDR infection epidemic. We hope researchers, doctors and engineers act together to save human race as new drug discovery needs costly instruments like MASS, NMR, FTIR, MRI spectroscopes as well as HPLC and TLC separation techniques [1-7].

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