In the Quest of Drugs for Bad Bugs: Are Newer Fluoroquinolones Any Better?

Sir,

The consumption of antimicrobials and the development of bacterial resistance go hand in hand. This is evident from the fact that soon after the discovery of the first antimicrobial compound, penicillin, reports of bacteria developing resistance to it started appearing.[1] Fluoroquinolones are definitely the most widely used and misused antimicrobial agents in most of the developing and developed nations. Since the serendipitous discovery of the first member of the quinolone class of drugs (nalidixic acid, which truly is a naphthyridine derivative) as a by-product during synthesis of antimalarial compound, chloroquine, in 1962,[2] a whole spectrum of newer quinolone compounds have been discovered which are in clinical use now-a-days; some of those having been claimed to be effective against multi drug resistant (MDR) organisms. The definition of various classes of drug resistance also varies among scientific community. One group proposes the carrying out surveillance of organisms on the basis of degree of MDR, and define pan drug resistance (PDR) and extreme drug resistance (XDR) in gram-negative bacilli (GNB) in the following manner.[3]

PDR gram-negative bacilli are not susceptible to all of the following antibiotics:

- Antipseudomonal cephalosporins (e.g., ceftazidime and cefepime);
- Antipseudomonal carbapenems (e.g., imipenem and meropenem);
- Piperacillin/tazobactam; and
- Ciprofloxacin and levofloxacin.

XDR gram-negative bacilli are not susceptible to all of the following antibiotics:

- Antipseudomonal cephalosporins (e.g., ceftazidime and cefepime);
- Antipseudomonal carbapenems (e.g., imipenem and meropenem);
- Piperacillin/tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam;
- Ciprofloxacin and levofloxacin;
- Aminoglycosides (i.e., gentamicin, tobramycin, and amikacin);
- Tigecycline; and
- Polymyxins (e.g., polymyxin B and colistin).

The other group proposes that the terms, "pan drug resistance," "extensive drug resistance," and "multi drug resistance" should designate, respectively, resistance of a pathogen to all, resistance to all, but 1 or 2, and resistance to ≥ 3 classes of antimicrobial agents, among those that are available at the time of use of the definition and in most parts of the world and that are regarded as potentially effective against the respective pathogen.[4]

In this context, we evaluated the efficacy of two newer entrants in the Indian market; one third generation fluoroquinolone, i.e., pazufloxacin (other members of the group being levofloxacin, sparfloxacin, tosufloxacin, and balofloxacin), and the second, a fourth generation fluoroquinolone, i.e., prulifloxacin (other members of the group being clinafloxacin, gemifloxacin, moxifloxacin, and trovafloxacin),[2] for both of which there is paucity of data regarding their antimicrobial susceptibility profile in the Indian scenario, but have been claimed to be effective in case of MDR - GNB and methicillin resistant *Staphylococcus aureus* (MRSA) infections with respect to higher antimicrobial agents like carbapenem (meropenem) and combination of beta lactam/beta lactamase inhibitor (BL-BLI, piperacillin/tazobactam). The motive of selection of these antimicrobials was to evaluate whether these two higher generation fluoroquinolones conferred any significant additional benefit over the conventional second generation fluoroquinolones and establish any justification (if any) for their inclusion as a part of empirical treatment regimen in clinical conditions where MDR isolates are anticipated, as their inclusion would significantly raise the treatment costs vis-a-vis conventional second generation fluoroquinolones. Three MDR gram-negative pathogens, namely *Klebsiella pneumoniae, Escherichia coli, and Pseudomonas aeruginosa*, in which MDR is common, were included in the study.

The susceptibility to various antimicrobial agents was carried out using the Kirby Bauer disk diffusion technique employing commercially available antimicrobial disks (HI-MEDIA Laboratories Pvt. Ltd., Mumbai, India) following standard protocols. A total of 110 XDR - GNB isolates (i.e., resistant to ciprofloxacin, amikacin, cetazidime, and cefepime) were included in the study. Their susceptibility to ofloxacin, gatifloxacin, pazufloxacin, prulifloxacin,

Table 1: Antibiogram of multi drug resistant-gram-negative bacilli

Isolate	Antimicrobial agents (Percentage susceptibility)					
	Ofl-oxacin	Gatifl-oxacin	Pazufl-oxacin	Prulifl-oxacin	Mero-penem	Piperacillin/ tazobactam
Klebsiella pneumoniae (n = 40)	01	13	01	00	15	25
Escherichia coli (n = 40)	00	15	01	00	15	43
Pseudomonas aeruginosa (n = 30)	00	00	00	00	13	27

meropenem, and piperacillin/tazobactam was determined. The observations recorded are given as under in Table 1.

In case of *Klebsiella pneumoniae,* out of 40 isolates of the study, 18 (45%) turned out to be PDR. In case of *Escherichia coli,* out of 40 isolates of the study, 18 (45%) turned out to be PDR. In case of *Pseudomonas aeruginosa,* out of 30 isolates of the study, 18 (60%) turned out to be PDR.

The data in the table from our study makes it amply clear that the two newer fluoroquinolones, i.e., pazufloxacin and prulifloxacin did not confer any significant additional benefit over the conventional second generation fluoroquinolones, i.e., ciprofloxacin, ofloxacin, and gatifloxacin. However, additional studies on a higher sample size of the isolates across India will be required to formulate institution based guidelines to incorporate representative fluoroquinolone compound in the empirical treatment regimen, which is both rational and cost effective. It may be pointed out that a still more recent fluoroquinolone to enter Indian market is balofloxacin, which also needs to be evaluated.

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