

Original Research Article

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Drug Resistance of *Pseudomonas aeruginosa* in Diabetic Foot Ulcers: A Comprehensive Analysis of Data in Indian Cities

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ABSTRACT

Drug resistance pattern of *Pseudomonas aeruginosa*, in the treatment of diabetic foot ulcer, against 9-standard antibiotic agents was tested, in a tertiary care hospital in Chennai during 2005. In this retrospective study, the bacterial prevalence was: *E.coli* (22.2%), *S.aureus* (17.3%), *P.aeruginosa* (17.3%), *Klebsiella* spp. (10.6%), *CONS* (10.6%), *Proteus* spp. (9.6%), *Streptococcus* spp. (5.8%), *Corynebacterium* spp. (3.8%), and *Enterococcus* spp. (2.9%). The resistance pattern of *Pseudomonas aeruginosa* was revealed as 5.5% to Imipenem, 11.0% to Piperacillin, 22.0% to Co-amoxiclav, 33.0% to Gentamicin, 33.0% to Ceftazidime, 44.0% to Ciprofloxacin, 44.0% to Ceftriaxone, and 55.5% to Cefotaxime. This result on the effectiveness of various antimicrobial agents (AMAs) in Chennai was compared with similar data reported by various other investigators, for 9-other cities in Southern India (Kelambakkam, Pondicherry, Karaikal, Salem, Coimbatore, Bengaluru, Thiruvananthapuram, Manipal and Hyderabad), and for 7-cities in Northern India (Mumbai, Karad, Ahmedabad, Chandigarh, Bathinda, New Delhi and Kolkata). The antimicrobial agents (AMAs) facing resistances in the workable range of 0.0% to 33.3% (susceptibility of 100.0% to 66.7%) were short-listed. Our studies in Chennai evaluated Imipenem, Piperacillin, Co-amoxiclav, Ceftazidime and Gentamicin as effective antimicrobial agents, against *Pseudomonas aeruginosa* isolated from diabetic foot ulcers, in the susceptibility range of 100.0% to 66.7%. On comparison of this result with the data reported by various other investigators from 16- other cities in India, a new set of details has been revealed, according to which the following highlights may deserve consideration in future studies: i) Imipenem, Piperacillin, Piperacillin/ tazobactam, Cefoperazone/ sulbactam, Meropenem and Amikacin, have been the most effective AMAs against *Pseudomonas aeruginosa* isolated from diabetic foot ulcers in a majority of the 17-cities, including Chennai. ii) Colistin, and Polymixin B were 100.0% effective against *Pseudomonas aeruginosa*, in one South Indian city (Kelambakkam, where the production of carbapenemase/ ESBL were recorded). iii) In Bathinda (North India) where ESBL and MBL production by *Pseudomonas aeruginosa* were produced, Piperacillin/ tazobactam was the only AMA which was effective against the pathogen, whereas many other AMAs failed, such as, Carbapenems, Aminoglycosides, Monobactam, Quinolones, and a few Cephalosporins. As a contrast to the resistance pattern of *Pseudomonas aeruginosa* isolated from diabetic foot ulcer, as reported above, the data reported by Gurung, *et al.*, 2015, describing the resistances exerted by *Pseudomonas aeruginosa* isolated from clinical (composite) samples in Shillong were compared. It is learnt that the bio-film forming *Pseudomonas aeruginosa* isolated from clinical (composite) samples proved to be pan-resistant, rejecting many AMAs tried, namely, Ofloxacin, Amikacin, Ciprofloxacin, Ceftriaxone, Cefoperazone and Ceftazidime. Therefore, it is recommended that biofilm-forming-strains of *Pseudomonas aeruginosa* must be separately identified, in order to select the suitable antimicrobial agents, even in the case of assessing the resistance pattern of *Pseudomonas aeruginosa* isolated from diabetic foot ulcers. (This set of data corresponds to 2430-diabetic foot infection patients reported by 17-investigators from various cities of India). Conclusions: 1. Routine microbiological analysis must include the testing for the presence of biofilm-forming-bacterial strains. 2. All combinations of antibiotic agents/beta-lactamase-inhibitors must be tried in carrying out the sensitivity tests, so that alternative antibiotic agents could be evaluated, in case of certain antimicrobial agents to which the patients may develop some allergic reactions. 3. In the Indian scenario of Healthcare administration, modernization of the existing Clinical & Microbiological Laboratories, with regard to instrumentation and staffing-pattern, in all the 683-District Hospitals in India, seems to be a viable solution for the generation of local data-bank on bacterial antibiotic sensitivity patterns, so that therapeutic strategy could be suitably evolved in each geographical zone, with the purpose of protecting the public health of rural India, as an exercise as good as protecting the borders of the country!

Keywords

Pseudomonas aeruginosa-bacterial biofilm-local data bank on drug resistance - geographical zone.

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Introduction

Selina Chen *et al.*, (2015) reported that medication for *Pseudomonas* infection was proving to be difficult, as any delay in giving proper treatment would lead to morbidity, to start with, and may even end up with a situation of mortality, in acute cases, if not attended to carefully. Marcus Friedrich *et al.*, (2015) have reported that *Pseudomonas aeruginosa* infections are complicated, and life-threatening in its effect. Some investigators have recommended that double-antibiotic therapy must be administered, in accordance with local susceptibility pattern, for skin and soft tissue infections (PastarI *et al.*, 2013; Giamarello *et al.*, 2001). We are given to understand that the local sustainability pattern in respect of each pathogen and each specific antimicrobial agent (AMA) is the deciding factor, for the success of a therapeutic option. The *Pseudomonas aeruginosa*, as a pathogen, is having many self-defense mechanisms to resist antibiotic treatment during the therapy, such as biofilm-formation, production of many beta-lactamases, cell-wall impermeability, Efflux Pumps, production of Penicillin Binding Proteins (PBPs), etc. as described subsequently.

Lipsky *et al.*, 2012, reiterates on the necessity to wait for the culture results before initiating the empiric therapy, in mild to moderately severe cases of diabetic foot infections.

Any antibacterial agent interacting with an intracellular target must traverse the cell-wall and cytoplasmic membrane to reach the target. Once the drug is taken up, it was experienced with many antibiotics, that they were 'actively' effluxed. Fluoroquinolones, too, are affected by permeation barriers and efflux pumps, either in association with target modifications, or on their own (Delhoff, 2012).

Ramirez and Tolmasku (2010) reported that acetylation of aminoglycosides at 1-,3-,6-, and 2'-amino groups could occur and inactivate the normally popular aminoglycosides, such as Gentamicin, Tobramycin, and Amikacin, due to the production of aminoglycoside-modifying enzyme (acetyl-transferase) by *Pseudomonas aeruginosa*.

Keith Poole (2005) observed that aminoglycoside-phosphoryl-transferases found in *Pseudomonas aeruginosa* could be responsible for inactivating some aminoglycoside-antibiotics, such as, Kanamycin, Neomycin, and Streptomycin. They also reported that the acquired resistance in *Pseudomonas aeruginosa* include Beta-Lactamases, especially ESBL and the Carbapenemases which hydrolyse most Beta-lactam antibiotics. The organism's propensity to grow in-vivo, as an antimicrobial-tolerant biofilm and occurrence of hyper-mutator strains at higher frequency also compromise anti-pseudomonal chemotherapy. With limited therapeutic options, *Pseudomonas aeruginosa* would soon pose a threat. Keith Poole recommended Colistin as an effective ABA against *Pseudomonas aeruginosa*, if they are found to be ESBL/MBL-producers.

Giamerallou *et al.*, (1984) reported that all *Pseudomonas aeruginosa* produce chromosomally mediated beta-lactamases, whereas plasmids'code is known for the production of at least 15-different types of beta-lactamases. The former does not inactivate Carbenicillin or Ticarcillin. The latter would hydrolyze all anti-pseudomonal-penicillins. During the period of treatment with Piperacillin, an intrinsic resistance resulting from changes in Penicillin-Binding-Proteins (PBPs) would emerge. *Pseudomonas aeruginosa* cells, especially in patients with chronic infections, can develop

a biofilm, in which the bacteria is enmeshed into a mucous ex-polysaccharide, thus, becoming more resistant to beta-lactam antibiotics, and also to aminoglycosides.

Agarwal *et al.*, (2008) suggested that *Pseudomonas aeruginosa* resistant to Imipenem or Ceftazidime must be screened for suspected cases of MBL-production, by the Double-Disk Synergy Test, and Minimum Inhibitory Concentration (MIC) Test.

Keith Poole (2001, 2005) reported the limitations of Aminoglycosides against *Pseudomonas aeruginosa*, in great detail. According to Taneja *et al.*, (2003), and Troillet *et al.*, (1997), Imipenem proved to be having the advantage of being more stable against the hydrolyzing capacity of most of the beta-lactamases, compared to the third generation Cephalosporins.

Gladstone and Rajendran *et al.*, (2005), reported that carbapenems are usually used for offering treatment to patients with serious infections caused by multi-drug resistant Gram-negative bacilli, including *Pseudomonas aeruginosa*. They reported that the reasons for the resistance could be due reasons such as i) decreased outer-membrane permeability, ii) increased efflux systems in the bacterial cell, iii) alteration in the Penicillin-Binding-Proteins (PBPs), and iv) the bacterial production of carbapenemase-enzymes which are capable of hydrolyzing carbapenem antibiotics, and that the production of MBL (Metallo-beta-lactamases) would cause either chromosomally mediated resistance or plasmids-encoded resistance.

Livermore and Yang (1987) compared the interactions of chromosomal beta-lactamases of *Pseudomonas aeruginosa* with some selected antimicrobial agents, namely,

Imipenem, Carbenicillin, Cefotaxime, Ceftriaxone and Azlocillin, and reported the rates of counteracting against the hydrolyzing capacity of the beta-lactamases, and the corresponding reduction/increase in the susceptibility pattern, in each case, and concluded that the activity of Imipenem against the pathogen was more superior, followed by Carbenicillin.

Fujitani *et al.*, (2000) reported that many investigators agreed on the fact that certain ABAs were effective against *Pseudomonas aeruginosa*, namely, i) Aminoglycosides (Amikacin, Tobramycin, Gentamicin), Colimycin, ii) Carbapenems (Imipenem, Meropenem), iii) 3rd generation Cephalosporins (Cefoperazone, Cefsulodin, Ceftazidime, iii) 4th generation Cephalosporins (Cefepime, Cefpirome, Cefclidin, iv) Quinolones (Ciprofloxacin, Levofloxacin, Gatifloxacin, Moxifloxacin), v) Monobactam (Aztreonam), and vi) Extended Spectrum Penicillins (Ticarcillin, Piperacillin, Azlocillin). They also included Colistin in the list of effective AMAs.

Cornelis (2008) reported that phenotypic resistance associated to biofilm formation or to the emergence small-colony variants could be considered important in the response of *Pseudomonas aeruginosa* populations to antibiotic treatment.

Ryan *et al.*, (2004) reported that most of the *Pseudomonas* species were normally resistant to Penicillin, and majority of them were sensitive to some beta-lactam antibiotics, but some of them were sensitive to Piperacillin, Imipenem, Ticarcillin, or Ciprofloxacin, and that some Aminoglycosides, such as Tobramycin, Gentamicin, or Amikacin could be the other choices.

Harrison-Balestra *et al.*, (2003) reported that the biofilm can be formed by *Pseudomonas*

aeruginosa, within 10-hours after its taking position in the wound. Li *et al.*, (2015) have reported that the biofilm is directly related to the virulence of bacteria.

Sayanti Mukherjee *et al.*, (2012) reported that synergistic combination of Meropenem and sulbactam would open up a new prospective path, in the selection of antimicrobial therapeutic regimens towards continuing the fight against multi-drug resistant pathogenic organisms. (This would correspond to a combination therapy, similar to Piperacillin/tazobactam).

Pastar *et al.*, (2013) reported that the combination therapy of Imipenem-Levofloxacin or Imipenem-Ciprofloxacin could be useful in bringing down the drug-resistance of *Pseudomonas aeruginosa*. This would correspond to the 'double-antibiotic therapy'. There is a reasoning that double-antibiotic therapy could be tried only in cases of very severe symptoms.

Nasim *et al.*, 2015 reported the influence of AmpC Beta-Lactamase and ESBLs in inactivating the various groups of antimicrobial agents (AMAs). This point highlights the importance of microbiological tests to be carried out before commencing the empirical therapy.

Antibiotic resistant bacteria are transferred to cattle, swine, poultry and aquaculture where antibiotics are used, thereby, implying an impact on human health.

This includes the antibiotics contained in the animal-feed, poultry-feed, used for the purpose of expediting their growth, in addition to the antibiotics added in the medicinal products used to protect them from illness. The antibacterial resistance enters into the human-system through the eggs, milk and meat (consumed by the humans).

The waste materials from the animals, like their urine and faeces, discharge resistant-bacteria to the free-environment (Marshall and Levy, 2011; Dagherir and Drogui, 2013). Similarly, from the agricultural sector, antibiotics used for the growth and protection of crops and vegetables, reach the water resources and the soil-medium, thus affecting the overall environmental quality (Economou *et al.*, 2015). It was reported that the drugs used for food-producing animals, actively marketed in the United States, include Aminoglycosides, Cephalosporins, Penicillins, Sulfonamides, Tetracyclines, etc. Cabello (2005) reported that the heavy use of prophylactic antibiotics in aquaculture-practices could prove to be a hazard to animal health and human health.

These burdens of resistant bacteria vary from place to place, depending on the site-location, geographically. This factor adds a new dimension to the control of antimicrobial resistances in rural areas versus urban settlements.

Due to this factor also, it becomes essential to monitor the bacterial antibiotic resistance pattern for each pathogen, in each geographical setting, in various parts of India, to represent each geographical zone, as it would be difficult to assess the quantum of transfer of antimicrobial-resistant bacteria from the cattle, swine, poultry and aquaculture sectors in each geographical zone. Obviously, there are too many variables involved in the transfer-process of resistant-bacteria. The only measurable parameter, within our reach, is the bacterial sensitivity pattern to the antimicrobial agents.

The present study aim and objectives involves the analysis of a retrospective data gathered during a period of 5-months from May to September 2005, pertaining to drug resistance pattern of *Pseudomonas aeruginosa*. This finding was compared with

similar data reported by other investigators in various cities of India, as available in the current literature.

The objectives are: i) To enhance the knowledge on the dangerous pathogen, namely, *Pseudomonas aeruginosa* encountered in diabetic foot ulcers relating to the national scenario prevailing in India, ii) To assess whether it is time to start experimenting with double-antibiotic trials on *Pseudomonas aeruginosa*, in the light of the global literature back-up and iii) To impress upon the involvement of the Governments (both Central and State) in the fight against the drug-resistant pathogens, including *Pseudomonas aeruginosa*.

Materials and Methods

Pus swabs were collected from 75 patients attending Dr. V. Mohan's Diabetes Specialties Research Center, Gopalapuram, Chennai-600 028, Tamilnadu, India during a period of 5-months, from May to September 2005. The pus samples were transported to the Laboratory in Cary-Blair transport medium. All the isolates were identified, adopting the standard operative procedures. The antibiotic susceptibility tests were performed using commercially available antibiotic discs with *Pseudomonas aeruginosa* ATCC 25853 as control, in accordance with procedures indicated in Kirby-Bauer Disk Diffusion Method, vide NCCLS guidelines of 2002, for *Pseudomonas aeruginosa* isolates (Meenakshisundaram *et al.*, 2015 (a & b).

Antibiotics tested were, Penicillins: Ampicillin (10ug), Amoxicillin + clavulanic acid (20ug+10ug), Piperacillin (100ug); Carbapenem: Imipenem(10ug); Cephalosporins: Cefotaxime (30ug), Ceftazidime (30ug), Ceftriaxone (30ug); Aminoglycosides: Gentamicin(10ug); Quinolones: Ciprofloxacin (5 ug).

The 104 numbers of pus samples collected from 75 patients admitted for treatment of Diabetic Foot ulcers, on bacteriological processing and identification carried out as per standard procedures, revealed the presence of 22.1% of *Escherichia coli* (23/104), 17.3% of *Staphylococcus aureus* (18/104), 17.3% of *Pseudomonas aeruginosa* (18/104), 10.6% of *Klebsiella* spp.(11/104), 10.6% of Coagulase Negative *Staphylococcus*(CONS) spp.(11/104), 9.6% of *Proteus* spp.(10/104), 5.8% of *Streptococcus* spp.(6/104), 3.8% of *Corynebacterium* spp.(4/104), and 2.9% of *Enterococcus* spp.(3/104).

The resistance pattern shown by *Pseudomonas aeruginosa* in Chennai studies were compared with the findings of other investigators from various locations in India, namely, the data reported for Pondicherry (presently known as Puducherry), Karaikkal (in Puducherry Union Territory), Kelambakkam (near Chennai), Salem, Coimbatore, Bengaluru, Thiruvananthapuram, Manipal (near Mangalore), and Hyderabad (thus, representing 9-Cities in Southern India); and Ahmedabad, Mumbai, Karad (in Maharashtra), New Delhi, Chandigarh, Bathinda(in Punjab), and Kolkatta (thus representing 7-Cities situated in Western, Northern, Northwestern, and Eastern India).

In the Chennai studies, among the 18 numbers of *Pseudomonas aeruginosa* strains, 3-numbers (2.9%) corresponded to Wagner Grade 2; 9-numbers(8.6%) pertained to Wagner's Grade-3; 4-numbers(3.8%) pertained to Wagner's Grade-4; and 2-numbers(1.9%) in Wagner's Grade-5.

Table-1 presents the resistance pattern exhibited by the clinical isolates of *Pseudomonas aeruginosa* to the various antimicrobial agents used in the retrospective Study in Chennai during 2005.

It can be seen from Table-1 that the resistances exerted by *P.aeruginosa* were 38.9% to Ampicillin, 22.0% to Co-amoxiclav, 11.0% to Piperacillin, 55.5% to Cefotaxime, 44.0% to Ceftriaxone, 33.0% to Ceftazidime, 44.0% to Ciprofloxacin, 33.0% to Gentamicin and 5.5% to Imipenem.

Antimicrobial agents in the workable susceptibility range of 100.0% to 66.7% (resistance range of 0.0% to 33.3%), were evaluated in our retrospective study, as Imipenem, Piperacillin, Co-amoxiclav, Ceftazidime and Gentamicin. This means that a maximum of 33.3% of the drug would be wasted, as a trade-off.

This result was compared with the resistance patterns exerted by *P.aeruginosa* in diabetic foot ulcers in 9-South Indian cities, and 7-North Indian cities (shown in Figure-1), as reported by various other investigators, as found in the published literature. Summarised details are presented in Table-2 and Table-3, for the purpose of comparison.

The effectiveness of performances of various antimicrobial agents (AMAs) against *Pseudomonas aeruginosa* has been tabulated according to the different slabs of resistance-ranges, namely. i) 0.0% to 20.0%, ii) 20.1% to 33.3%, and iii) 33.4% to 100.0%. This analysis has been helpful to understand the trend of reliability of the various antimicrobial agents (AMAs), in various parts of India, in comparison to Chennai, as listed in Tables-2. Referring to Table-3, the following trends are indicated.

i) Imipenem, proving as an effective AMA in Chennai, has proved effective in 6-other cities in South India, and in 5-cities in North India, out of 14 cities tried in India (successful in 78.6% of cities where it was tried).

ii) Piperacillin, proving as an effective AMA in Chennai, has proved effective in 3-cities in South India and 3-cities in North India, out of 9-cities tried in India (successful in 66.7% of cities where it was tried).

iii) Co-amoxiclav and Ceftazidime proved moderately effective in a few cities in India.

iv) Gentamicin did not prove effective in majority of the cities according to the findings of the 17-investigators.

(These details make it clear that Imipenem and Piperacillin, individually, can be considered mostly effective in all the 17-cities, including Chennai, against the *Pseudomonas aeruginosa* strains isolated from diabetic foot ulcer).

v) Apart from the above two AMAs evaluated in the retrospective study in Chennai city, some more AMAs were identified by the 16-other investigators in India, namely, Piperacillin/tazobactam (effective in 11-cities out of 12 cities tried in India, leaving out Kolkata); Cefoperazone/sulbactam (proving effective in 5-cities out of 7-cities tried in India); Meropenem (proving effective in 7-cities, out of 10-cities tried in India); and Amikacin (proving effective in 10-cities out of 16-cities tried in India).

vi) It can be seen in Table-2, that there are various other AMAs proving effective against *Pseudomonas aeruginosa*, based on the area-specific reports of the 16-investigators in India, in the susceptibility range of 100.0% to 66.7%, against *Pseudomonas aeruginosa* isolated from diabetic foot ulcers, namely, Colistin, Polymixin B, Carbenicillin, Cefoperazone, Cefotaxime, Ceftazidime, Cefixime/

tazobactam, Tobramycin and Ticarcillin/clavulanic acid, Amoxicillin/ clavulanic acid (Co-amoxiclav), Cefepime, Cefixime, Ceftriaxone, Ceftazidime/clavulanic acid, Netilmycin, Erithromycin, Ofloxacin, Aztreonam, etc. However, more data needs to be generated in various parts of India to document the National Data Bank on Bacterial Antibiotic Resistance.

A few highlights are presented below to help the brain-storming inferences:

- a) It must be noted that in Karad (Maharashtra), Chavan *et al.*, (2015) reported that the *Pseudomonas aeruginosa* isolated from diabetic foot ulcer patients were producing both ESBL(Extended Spectrum Beta Lactamases) and MBL (Metallo-beta- lactamases), where many standard AMAs faced 100.0% resistance, namely, Ciprofloxacin, Ofloxacin, Cefoxitin, etc. However, Piperacillin/tazobactam was available as the only effective AMA, coming to the rescue.
- b) In Chandigarh (Haryana), Bansal *et al.*, (2008) reported that samples taken from diabetic foot ulcer patients contained fungi, in addition to the usual bacterial pathogens, including *Pseudomonas aeruginosa*, where many standard AMAs faced 100.0% resistance from *Pseudomonas aeruginosa*, namely, Ampicillin, and Amoxicillin. Also, Amoxicillin/clavulanic acid faced resistance higher than 96.0%, from *P.aeruginosa*. However, there were other AMAs, quite effective against the *Pseudomonas aeruginosa*, namely, Imipenem, Ceftazidime, Cefoperazone/sulbactam, Piperacillin, Tobramycin, Ceftriaxone, Cefotaxime and Amikacin.
- c) In Kolkata, Chakraborty and Sukumar, (2015) reported that 70.0% of the patients were positive for Multi Drug Resistant Organisms (MDROs), and that they had poor glycemic control (HbA1C=11+(-)2). They reported that infections with MDROs was 'common in diabetic ulcers', and that it would be associated with risk-factors like inadequate glycemic control, the presence of neuropathy, Osteomyelitis, increase in ulcer-size, and increased requirement for surgical treatment. They recommended that continuous monitoring of bacterial resistance to drugs would provide the basis for empirical treatment, and would help in avoiding further-complications. Clinical conditions of the patient was highlighted as a parameter for consideration in the overall analysis of the bacterial response.
- d) Murali *et al.*, (2014) have reported that about 9.3% of *Pseudomonas aeruginosa*-isolates collected from diabetic foot ulcer patients were pan-resistant (against all the AMAs tried, namely, Aztreonam, Cefepime, Ceftazidime, Ciprofloxacin, Gentamicin, Co-ticarclav and Netillin). They reported *Pseudomonas aeruginosa* as one of the high-biofilm-forming multidrug resistant organisms.
- e) The data on the most effective antibiotic agents against the *Pseudomonas aeruginosa* found in diabetic foot infections, all over India, has revealed the unpleasant fact that the effectiveness in bacterial killing by the older (erstwhile) first-line antibiotics have started diminishing; and that only the carbapenems have to come to the rescue, in most of the Indian cities.
- f) We believe and recommend that carbapenems are to be reserved for emergencies only. Therefore, there is a

need for generating local data-bank, in each city, for studying the drug-resistance pattern of all pathogens, including *Pseudomonas aeruginosa*, and for devising a modified approach to therapeutic options and wound management procedures, preferably with the ideal involvement of multi-disciplinary experts. Combinations of beta-lactam antibiotics/ beta-lactamase-inhibitors, double-antibiotics, etc., in several pairs must be tried in the bacterial sensitivity tests, in local centres, in order to enhance the selection of empirical treatment.

- g) By way of surveillance, the various State Governments, in India, may consider upgrading the existing Clinical & Microbiology Laboratory in each District Hospital, with specialized manpower of qualified microbiologists, so that it can function as a Referral Laboratory, with the co-ordination and co-operation of the Government of India, in response to the appeal made by the World Health Organization++, in the interest of protecting Public Health.

All the above data pertaining to the resistance patterns of *Pseudomonas aeruginosa* isolated from diabetic foot ulcers were compared with data pertaining the resistance patterns of *Pseudomonas aeruginosa* isolated from clinical (composite) samples in Nagpur (Maharashtra), reported by Choudhary *et al.*, (2013), and in Shillong (Meghalaya), reported by Gurung *et al.*, (2015).

In Shillong, a few AMAs were susceptible against non-biofilm-forming *Pseudomonas aeruginosa* isolated from clinical (composite samples), namely, Ofloxacin, Amikacin, Ciprofloxacin, Ceftriaxone, Cefoperazone, and Ceftazidime, in the resistance range of 0.0% to 33.3%. All these AMAs proved

ineffective against the biofilm-forming *Pseudomonas aeruginosa* isolated from clinical (composite) samples, thus closing all options for antibiotic therapy (as shown in Table-2),

In Nagpur, however, Meropenem and Amikacin were found effective against the *Pseudomonas aeruginosa* isolated from Clinical (composite) samples.

There are indications in global literature that Polymixin B, or Colistin could be effective against Metallo-Beta-Lactamase-producing *Pseudomonas aeruginosa* (Alexandre *et al.*, 2006). However, Varaiya *et al.*, (2008) reported that the patients in Mumbai were treated with Gatifloxacin, Amikacin, or Piperacillin/tazobactam, considering the high cost of Colistin. Such data on clinical trials are urgently needed to be documented, more and more, in this perspective. Our future research efforts must deserve attention in these lines.

The differences among the cities of India, covered under this study, are that they are located in different geographical settings, with the obvious factors related to differences in contrasting aspects, such as i) the climate-dominated weather patterns, ii) ecology-dependent biodiversity variations, iii) differences in food habits, iv) differences in poverty-levels, etc. These differences do not seem to weigh heavily in reflecting the bacterial antibiotic resistance patterns exerted by *Pseudomonas aeruginosa* strains isolated from diabetic foot ulcers, in the various cities of India, covered under this analysis, relating to 2430-diabetic foot ulcer patients of India, investigated over a period of 10-years. As the results relate to retrospective studies, in some places, the findings could provide only guidance, and there is a need to generate local data on bacterial sensitivity to antibiotic treatment to be of use for the current-practice, so as to build-up a National Data

Bank. Why not? The laboratory analysis is required in the local centres in each geographical region wherever the hospital is situated, in order to generate a meaningful data-bank on resistance patterns of all pathogens, inclusive of *Pseudomonas aeruginosa*, so that it would be possible for local experts to decide on the much-needed clues for empirical treatment, and to avoid making the first error in empirical treatment which would decide subsequently on the prospects of healing of the wound or on the prospects of developing further complications.

Although antibiotic resistance may sound as a medical problem, it has got the potential of exerting its own impact on the society, as the replacement of older antibiotics with newer antibiotics would involve a higher financial burden, in addition to other problems (Ganguly NK, et al., 2011). The choice of the newer antibiotics must be done after ensuring about the personal response of the patients on allergy-related symptoms, and after ensuring that no adverse effects would occur to the functioning of the heart, liver, kidney, gastro-intestinal system, etc.

Table.1 Resistance Pattern of *Pseudomonas aeruginosa* Strains
(Total number of *Pseudomonas aeruginosa* isolates = n=18)

S.no	Antimicrobial agent	No of resistant strains	% Resistance
1.	Ampicillin	7	38.9
2.	Co-amoxyclav	4	22.0
3.	Piperacillin	2	11.0
4.	Cefotaxime	10	55.5
5.	Ceftriaxone	8	44.0
6.	Ceftazidime	6	33.0
7.	Ciprofloxacin	8	44.0
8.	Gentamicin	6	33.0
9.	Imipenem	1	5.5

Table.2 Effectiveness of Antimicrobial Agents (AMAs) in the various ranges of resistance exerted by *Pseudomonas aeruginosa*, in diabetic foot infections, in various cities of India

City (State)	Investigator, City, Year	R=0.0% to 20.0%	R=20.1% to 33.3%	Remarks	R=33.4% to 100.0%
Chennai (Tamil Nadu)	Meenakshi-sundaram C, et al., 2005,	I Pi	AMC CAZ, G	T5-dfu patients (2005-data)	Cip, CTR, Amp CTX
Kelambakkam	Priyadharhini S, et al., 2014	I*, Ci*, PMB*, CFS*	Pi/t MER	75-dfu patients) Carbapenemase/ESBL-noted.	Cip, AT, Ofi CAZ, G, CPM. Tob

City (State)	Investigator, City, Year	R=0.0% to 20.0%	R=20.1% to 33.3%	Remarks	R=33.4% to 100.0%
(near Chennai) (Tamil Nadu)		Crb, AK		(2012-data)	
Salem (Tamil Nadu)	Suganthi P, <i>et al</i> 2014	AK, MER CFS, CPZ AT,Pi/t TCC.	CFXM, CPM, CTR, Pi, CAZ/c	64-dfu- Patients. ESBL-noted (2014-data).	CX,RIF,AMC Cefpodoxime (Cfpdx)
Coimbatore (Tamil Nadu)	Sivamaliappan TS, <i>et al.</i> , 2011	CTX (Cefo- taxime)	-----	270-dfu- Patients. (some, limb- threatening samples) (2007-data)	I,Cip,CAZ,G AK,Pi,Tob,Tet, CPZ,Ti,COT, Amp#, Nor#, E#
Bengaluru (Karnataka)	Sajila NM, <i>et al.</i> , 2014	Pi/t, I Lev	AK,MER G, Tob	290-dfu- Patients. (2013-data)	CPM, NTM, Cefuroxime, AMC
Thiruv- anantha- Puram (Kerala)	Nair SR, <i>et al.</i> , 2015	I	Pi/t AT,CFS	250-dfu- Patients. (WG 1&2 excluded) (2014-data)	CAZ,AK,Cip, G
Manipal (Karnataka)	Murali TS, <i>et al.</i> , 2014	Pi	AK	357-dfu- Patients; bio- film studied). (2012-data)	G,CAZ,Cip CPM,AT,TCC, Tob,NET
Hyderabad (Andhra- Pradesh, now in Telangana)	Krishna Mohan N, <i>et al.</i> ,2015		AK	100-dfu- Patients. (WG 3,4,5- Prominent) (2015-data)	I, CFS, MER

City (State)	Investigator, City, Year	R=0.0% to 20.0%	R=20.1% to 33.3%	Remarks	R=33.4% to 100.0%
Mumbai (Maharashtra)	Chopdekar KA, <i>et al.</i> , 2012	I,Pi/t,Pi CPM	CPZ CAZ	113-dfu-Patients (WG 1-5 Included) (2010-data)	G,Cip Tob,AK
Karad (Maharashtra)	Chavan SK, <i>et al.</i> , 2015		Pi/t	78-dfu-Patients (ESBL+MBL Noted). (2012-data)	I, Tob, MER CAZ,CTX,CTR, AT,AK,AMC Levo,G,Nor,Ti Cip#,OfI#,CX#, Cflrd#,Cfpdx#, Cfxtn#
Ahmedabad (Gujarat)	ManishaJ, <i>et al.</i> , 2012	MER CPM/t Pi/t	AK, CAZ Pi,NTM Cefpirome(Cfpr)	125-dfu-Patients. WG&bio-burden Correlated. (2010-data)	CTX,CFXM,G AT,Cip,Kan, Lom, Lev, Clarithromycin (Clrm)
New Delhi	GadepalliR, <i>et al.</i> , 2006	I*,MER*, TCC CFS	Pi/t AK	80-dfu-patients. (ESBL-noted). (2006-data)	AMC,Pi, CTX, CAZ,Cip
Chandigarh (Hariyana)	BansalE, <i>et al.</i> , 2008	I*, CAZ CFS Pi, Tob	CTR AK	103-dfu-Patients. (Fungi present). (2006-data)	G,AMC, Cip Amp#,Amx# Cfrx#,COT# **
Bathinda (Punjab)	Kaur N, <i>et al.</i> , 2014	MER* PMB*, I	AK Pi/t	106-dfu-Patients. (2013-data).	NTM,CPZ, CAZ G, Cip, CTX
Kolkata	ChakrabortyP, <i>et al.</i> ,	I*		90-dfu patients	MER,G,

City (State)	Investigator, City, Year	R=0.0% to 20.0%	R=20.1% to 33.3%	Remarks	R=33.4% to 100.0%
(West-Bengal)	2015			(ESBL-noted). (2013-data) studied.	AK,Pi/t CPM
Shillong (Meghalaya)	GurungJ, <i>et al.</i> , 2014 (non-biofilm-forming aeruginosa)	Ofl.	AK Cip CTR CPZ CAZ	Clinical (composite) Samples from hospital Wards. (2010-data).	Nil
	GurungJ, <i>et al</i> 2012 (BIO-FILM-forming P.ae)	Nil	Nil	-do-	Ofl,AK, Cip,CTR CPZ,CAZ (Resistances Greater than 63.0%).
Nagpur (Maharashtra)	Chaudhary V, <i>et al.</i> , 2012	MER	AK	Clinical (composite) Samples. (2010-data).	Pi,G,Cip

Note: I*, MER*, CFS*, Ci*.PMB*, indicate Imipenem, Meropenem, Colistin, and Polymixin B, which are having 100.0% activity against *Pseudomonas aeruginosa*, respectively (experiencing 0.0% resistance from *Pseudomonas aeruginosa*).

Note:

** In Chandigarh, 3-AMAs faced 100.0% resistance: Amp, Amx, and COT. Also, AMC-faced resistance greater than 96.0%..

*** In Coimbatore, 3-AMAs faced 100.0% percent resistance: Amp, E, and Nor.

LEGEND:

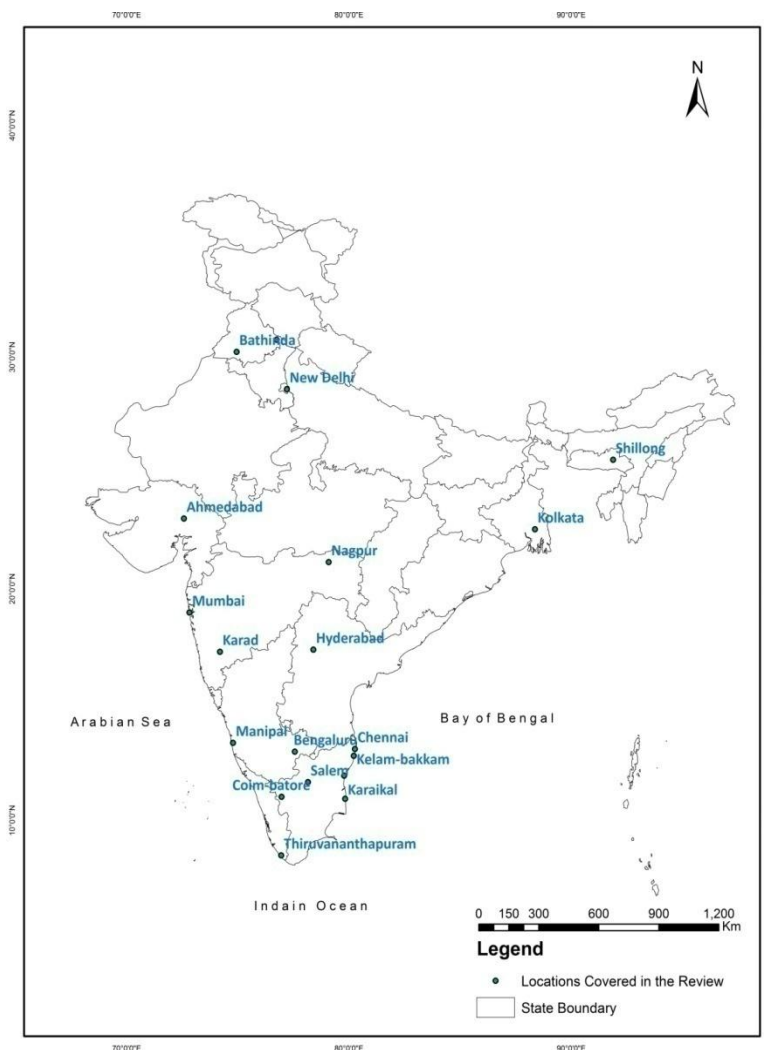
Amp=Ampicillin; Amx=Amoxicillin; AMC=Co-amoxyclav=Amoxicillin/clavulanic acid; As=Ampicillin/sulbactam
 AK=Amikacin; AT=Aztreonam; Cip=Ciprofloxacin; CFXM=Cefixime(3rd); CPM=Cefepime(4th); Cfxtn=CX=Cefoxitin(2nd); CPZ=Cefoperazone(3rd); CPM/t=Cfepime/tazobactam
 CFZ/c=Cefoperazone/clavulanic acid; CFS=Cefoperazone/sulbactam; Cfrx=Cefuroxime(2nd); Cfpr=Cefpirome(4th); Cflrd=Cefalorid(1st); Cfxtn=Cefoxitin (2nd); Cfpdx=Cefpodoxime(3rd); CAZ=Ceftazidime(3rd); CAC=CAZ/c= Ceftazidime/clavulanic acid; CAZ/s=Ceftazidime/sulbactam; CTX=Cefotaxime(3rd); CTR=Ceftriaxone(3rd); Cef=Cefalexin(1st); Ci=Colistin; Crb=Carbenicillin; COT=Co-trimoxazole(a sulfonamide antibiotic combination); Clrm=Clarithromycin(made from Erythromycin:6-O-methylerythromycin); Cd=Cld=Clindamycin (lincomycin antibiotic); E=Erythromycin; G=Gentamicin; I=Imipenem; Kan=Kanamycin; Levo=Levofloxacin; Lome=Lomefloxacin; MER=Meropenem; NET=Netl=Netilil; NTM=Netilmycin; Nor=Norfloxacin; Oxa=Oxacillin; OfI=Ofloxacin; Pc=Ureidopenicillin; PI=Pi=Piperacillin; PI/t=Pi/t= PIT=Piperacillin/tazobactam; PMB=PmB=PolymixinB; RIF=Rif=Rifampicin; TCC=Ticarcillin/clavulanic acid; TI=Ti=Tacarcillin; TOB=Tob=Tobramycin; Tet=Tetracycline

Table.3 Resistance pattern of *P.aeruginosa* in diabetic foot ulcer to antibiotic agents

AMA	Cities tried		R=0.0%	To 33.3%	R=33.4%	To 100.0%
	S.I	N.I.	S.I.	N.I.	S.I.	N.I.
Imipenem	8	6	6 Chen Pondy, Karai Kelam Benglr, Thiruv	5 ND Chand Kolkt Mumb Bathin	2 Coim Hyd	1 Karad
Pi	5	4	3 Chen Salem Manip	3 Mumb Chand Ahmd	2 Pondy Coim	1 ND
Pi/tazo	6	6	6 Pondy Karai Kelam Salem Bengalr Thiruv	5 Mumb Ahmd ND Bathin Karad		1 Kolkt
CFS	5	2	3 Kelam Salem Thiruv	2 ND Chand	2 Pondy Hyd	
MER	5	5	4 Pondy Salem Kelam Bengalr	3 ND Bathin Ahmd	1 Hyd	2 Karad Kolkt
AK	9	7	6 Kelam Salem Pondy Manip Bengalr Hyd	4 Ahmd ND Chand Bathin	3 Karai Coimb Thiruv	3 Karad Kolkt Mumb

Note: Ahmd=Ahmedabad; Bengalr=Bengaluru; Bathin=Bathinda; Chand=Chandigarh; Chen=Chennai; Coim= Coimbatore; Hyd=Hyderabad; Karad=Karad; Karai=Karaikal; Kelam=Kelambakkam; Kolkt=Kolkata; Manip=Manipal; Manip=Manipal; ND=New Delhi; Pondy=Pondicherry (Puducheri); Salem=Salem; Thiruv=Thiruvananthapuram;

Fig.1 Cities in India, covered under this review



Accordingly, more numbers of appropriate drugs must be included in assessing the antibacterial susceptibility tests, so that options would be available for selecting the empirical therapy, in consideration of allergies or adverse reactions.

Careful management of available antimicrobial agents (AMAs), and 'robust' monitoring of bacterial resistance pattern in local areas, and enforcement of infection control measures are the three important aspects of the vigil required for fighting against the menace of antibiotic resistance.

To conclude,

- i) The carbapenems seem to be successful against the *Pseudomonas aeruginosa*, in general, followed by Piperacillin/tazobactam or some of the third generation-cephalosporins/beta-lactamase-inhibitors, especially, - Cefoperazone/sulactam.
- ii) Also, Piperacillin/tazobactam is found to be very effective when compared to Piperacillin being administered alone. This trend must be studied, in depth, in future.

- iii) The generation of zonal data-bank, with regard to sensitivity of each pathogen to each antibiotic drug, if made available, will greatly help optimizing the use of important drugs which are meant for use as a last-resort, thus reducing the probable increase in the bacterial resistance to these precious drugs (such as Colistin, the last weapon against the pathogen) in each local zone, thereby controlling the abusive/mistaken use of certain life-saving antibiotics.
- iv) With respect to microbiological studies related to pathogens in diabetic foot infections, the conventional culture studies may be performed, supplemented by molecular typing methods, using advanced instrumentation techniques, including the use of a scanning electron microscope (SEM).
- v) The decision relating to double-antibiotic therapy must be entrusted to the joint-consultation of multi-disciplinary experts. Also, the debate can be started whether the merits of combination therapy versus double-antibiotic therapy could be assessed, at the national level, for future guidance.
- vi) Generation of baseline data on bacterial sensitivity in each zonal centre, aiming at the creation of a national data-bank, becomes a need of the hour.

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