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Hypothetical Estimate of Drug-Burden on a Diabetic Foot Ulcer Patient and its Relevance to Microbiological Analysis

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A B S T R A C T

In a retrospective study, conducted in Chennai (India), during 2005, a total of 104 bacterial isolates, obtained from 75 diabetic foot ulcer patients, revealed the presence of 9-bacterial species, namely, *S. aureus*, CONS spp, *Streptococcus* spp, *Corynebacterium* spp, Enterococcus spp, *E. coli*, *Klebsiella* spp, *Proteus* spp, and *P. aeruginosa*, in different percentages. The in-vitro antibiotic sensitivity pattern of Pseudomonas aeruginosa, tested in the retrospective study, and the antibiotic sensitivity patterns of the 8-other pathogens as adopted from available literature relating to 2-South Indian locations (Kelambakkam and Bengaluru), and 2-North Indian locations (Chandigarh and New Delhi), were compared with the data of the multicentre trial studies related to diabetic foot infections, carried out by Citron, D.M., *et al.*, (2007), in the United States. There was a close agreement among the AMAs evaluated, in the case of all the 9-pathogens, in the antimicrobial susceptibility range of 100.0% to 66.7% (bacterial resistance range of 0.0% to 33.3%). A hypothetical estimate of drug-burden was made, by enlisting the number of AMAs needed to be administered on a patient, against the 9-pathogens, in order to obtain a cure. A discussion on the probable adverse reactions caused by AMAs is included. It is suggested that AMAs such as Ertapenem, Trimethoprim/sulfamethxazole, Tigecycline, Doxycycline, etc, tested in the United States, can be included in evaluating the antibiotic susceptibility patterns, in India. Such results, if generated, would be found useful when the currently-used AMAs happen to become ineffective due to bacterial resistance, in future. More number of AMAs, if tested, would make it easier to optimize on the choice of drugs.

Introduction

There is an increasing reason for optimism in offering treatment to diabetic foot ulcers, and other chronic wounds through enhanced understanding of pathogenic factors, at the advent of the latest improvements in identifying the causative agents versus suitable antibiotic agents (Cavanagh *et al.*, 2005; Lipsky *et al.*, in "2012- IDSA-Guidelines"). The Infectious Diseases Society of America (IDSA) classified diabetic foot infections into four classes, namely, i) Uninfected, ii) Mild, iii) Moderate to Severe, and iv) Severe, correlating with the corresponding clinical symptoms. Obviously,

the treatment approaches could be different in each class.

The diagnosis must be correctly carried out, in order to proceed with the treatment option.

Weng *et al.,* (2017) expressed a fear that any wrong diagnosis of a lower-extremity infection could lead to unnecessary medication and hospitalization charges, citing the estimated number of 50,000 to 130,000 misdiagnosed cases of Cellulitis, during the period of study, involving a wasteful expenditure of US$ 195 million to 515 million, in the United States alone. This would vouch for the importance of the correct diagnosis, for which the clinical symptoms and microbiological test results are the guiding factors.

Gadepalli *et al.,* (2006) suggested that amputation can be prevented, if the diabetic foot ulcer can be treated with adequate and timely care. This optimism gives a lot of hope for all the stake-holders, pointing towards a devoted-care needed in the task. However, the antibiotic resistance exerted by microbial pathogens against many antimicrobial agents administered on diabetic foot ulcer patients continues to pose a problem, often proving as a challenge to the therapeutic options preferred by clinicians.

Kruse and Edelman (2006) reported that the treatment to diabetic foot ulcer must address all three major concerns, namely, prompt debridement, offloading procedures, and infection control, and that antibiotic treatment must be started after initial culture tests, and that the treatment must be suitably modified, as revealed by subsequent culture tests. This sequence is important for initiating and enabling a quick-healing process.

Stevens *et al.,* (2005) reported that the response to initial antibiotic therapy must be judged by the outcome, namely, reduction in fever and toxicity, and reduction in the advancement of infection. Ho Kwong Li *et al.,* (2015) reported that oral therapy could not be considered as inferior to intravenous treatment, in terms of clinical outcomes, and that the cost of intravenous treatment system would involve ten times higher cost.

Lipsky *et al.,* (2008) compared the effectiveness of Pexiganan (a topical cream) versus Ofloxacin (Oral), in the case of mildly-infected Diabetic Foot Ulcer (DFU). Lauf *et al.,* (2014) reported the efficacy and effectiveness of Tigecycline versus Ertapenem, in patients, with and without Osteomyelitis.

In any hospital setting, in India, the polymicrobial infection could be expected in the range of around 30.0% of the diabetic foot infection patients (Sajila *et al.,* 2015).

It was reported that as many as 7-strains of different bacterial species were present in a polymicrobial infection in a single diabetic foot ulcer patient, in India, namely, *Staphylococcus aureus*, *Enterococcus* spp, *Pseudomonas aeruginosa*, *Pseudomonas stuzeri*, *Escherichia coli*, *Proteus* spp, and *Alcaligenes* spp. (Shahi *et al.,* 2013).

The polymicrobial infections would often prove to be severe infections, or limb-threatening infections, requiring to be covered, in the antibiotic treatment, in the case of Gram-negative pathogens, as well as Gram-positive pathogens, among the aerobes and anaerobes (Grayson *et al.,* 1995; Lipsky and Berendt *et al.,* 2004; Rao and Lipsky *et al.,* 2007; Reiber and Lipsky *et al.,* 1998).

In the United States, Lipsky *et al.,* (2005) compared the effectiveness of two antimicrobial agents prevalent in diabetic foot infections, in a major multi centre trial studies, in two separate groups, namely,

administering Ertapenem @ 1.0 g daily, on the first-group of 295 diabetic foot infection patients, for 5-days, and giving Piperacillin/ tazobactam @ 3.375 g every 6-hours, on the second-group of 291 diabetic foot infection patients, for 5-days, and thereafter, giving Amoxicillin/clavulanic acid @ 825/125 mg every 12-hours, to both groups of patients. Investigators were given the freedom to decide on administering Vancomycin to patients of either group, for the purpose of giving coverage against the antimicrobial resistant *Enterococcus* species, and against the Methicillin resistant *Staphylococcus aureus* (MRSA). Based on clinical and microbiological outcomes, it was concluded that the effect of administering Ertapenem was equivalent to Piperacillin/tazobactam, and that the nature of adverse effects caused were similar, in both groups.

In China, Xu *et al.,* (2016) compared the antibiotic regimens against the pathogens prevalent in diabetic foot infection of 443 patients, by administering Ertapenem on one group of 219 patients, and administering Piperacillin/tazobactam on another group of 224 patients. It was concluded that the treatment by Ertapenem was non-inferior to the treatment by Piperacillin/tazobactam, in respect of clinical outcome, microbiological outcome, and adverse effects experienced by the Chinese patients. It was also hinted that Ertapenem had a lower rate of clinical resolution in severe diabetic foot infections.

A report by Clinical trials, gov (2010), compared Tigecycline versus Ertapenem to check their effectiveness in offering treatment to diabetic foot infections. Such comparisons of two antimicrobial agents (AMAs) took into consideration the various factors, like, the number of patients getting cured out of the total number of patients treated, the number of patients affected with adverse effects such as blood and lymphatic system disorders, cardiac disorders, liver-damage, general disorders such as abdominal pain, renal or urinary disorders, mental status changes, chest pain, fever, septic shock, allergic reactions, metabolism and nutritional disorders, etc. These factors are related to the choice of antimicrobial agents, for each pathogen prevalent in the diabetic foot infection. Decision to select a particular antimicrobial agent could be based on rating of Non-inferiority or Equivalence margin, such as 5.0% to 10.0%.

In the Indian scenario, fungal pathogens were reported to be prevalent in chronic wounds of diabetic patients, in addition to bacterial pathogens (aerobic and anaerobic), in many locations in India (Bansal *et al.,* 2008; Sanniyasi *et al.,* 2015, Chincholikar *et al.,* 2002). Anaerobic pathogens have been isolated and treated successfully by Anandi *et al.,* (2004), with a multi-disciplinary involvement, in a teaching hospital setting.

In addition to the antimicrobial agents used for fighting against the infection, in a diabetic patient, certain oral-hypoglycemic drugs, also, need to be administered, for maintaining the desired glycemic control. According to Armstrong and Lipsky (2004), a diabetic foot ulcer patient must first be medically stabilized, and secondly, metabolic aberrations, if any, must be carefully addressed. This factor does have relevance to the "drug-burden" on the diabetic foot ulcer patient, in the case of patients already experiencing system-factors such as hypertension, hyperlipidemia, atherosclerotic heart disease, obesity or renal insufficiency, etc. This aspect, therefore, deserves to be given a due consideration, at the time of planning the type of treatment to be given to a diabetic foot ulcer patient, on a case to case basis (Rowe and Khardori, 2017).

In the case of poly-microbial infections, care must be taken to optimize the number of antibiotic classes, so that the adverse reactions

which are characteristically unique to each class of antimicrobial agents cannot become additive, in their effects on the same patient. This effort of optimization of antibiotic classes would help avoiding the occurrence of undesirable adverse effect on the diabetic foot ulcer patient, thereby, reducing the "drug-burden" on the patient.

In the selection of antimicrobial agents, the susceptibility patterns have to be considered, along with the probable adverse reactions/allergies/hyper sensitivity reactions, etc., which they could cause on the diabetic foot ulcer patient. Certain details need to be considered as listed below:

Allergy to Penicillin could vary from 5% to 10 % of hospitalized patients (Green *et al.*, 1971; Parker, 1972).

Borish *et al.*, (1987) highlighted on the necessity to look for allergy to penicillin in patients, before deciding about the medication.

Bronze *et al.*, (2017) reported that Amoxicillin/clavulanate is preferred as an alternative to patients who are feeling allergic, or intolerant to Macrolide class of antibiotics (Erythromycin, Azithromycin, and Clarithomycin) proving effective against Gram-positive cocci and some intracellular pathogens.

Bronze *et al.*, (2017) also claimed that Ertapenem (Invanz) was stable against hydrolysis by a variety of beta-lactamases, including Penicillinases, Cephalosporinases, and Extended beta-lactamases (ESBLs).

Edmonds (2009) reported that Amoxicillin/clavulanate would be able to kill the bacteria which would prove resistant to Amoxicillin (if applied alone), and that the probability for the occurrence of hepato-toxicity in the patient would be around six-times greater with this Amoxicillin/clavulanate treatment.

Joseph and Axler (1990) reported that combination therapy containing Clindamycin and Aztreonam or Ciprofloxacin could be found helpful for diabetic foot infection patients who are allergic to Beta-lactam antibiotics, and that less-severe infections can be treated with a single antimicrobial agent such as Ticarcillin/clavulanic acid, or Ampicillin/sulbactam. Cephalosporins with anaerobic activity (Cefoxitin, or Cefotaxime, or Ceftizoxime) can be used, in areas where *Enterococcus* is not a major problem.

Thus, it becomes necessary to select the therapy based on the personalized metabolic-system details of the patient, and also on the area-specific considerations. This is one reason as to why bacterial antibiotic sensitivity has to be assessed in each local centre, by testing appropriate AMAs against the pathogenic species.

Indian scenario

National Treatment Guidelines for Antimicrobial Use (2016) have been prescribed by the National Centre for Disease Control (NCDC) of the Ministry of Health and Family Welfare, Government of India, New Delhi, according to which the following hints are indicated, relevant to the selection of antimicrobial agents for treatment against Skin and Soft Tissue Infections:

For Vancomycin-resistant Enterococcal (VRE)-species, Linezolid has been indicated to be efficient, although it cannot be used for a long period of time, as intolerance may develop in some patients. Its use is not recommended for patients with impaired renal function. Daptomycin NOT approved for treatment of VRE-infection. Its use, as a Monotherapy, is not recommended.

For the ESBL (Extended Beta-lactamase)-producing Enterobacteriaceae, the Carbapenems (Imipenem, Meropenem, or Ertapenem) have been indicated as the drug of choice, for serious infections. For mild cases, Piperacillin/tazobactam or Cefoperazone/ sulbactam could be considered, when susceptibility *in-vitro* is favourably indicated.

Citing the CLSI-recommendations, it has been stated that ESBL-producing isolates must be considered resistant to all Penicillins, Cephalosporins (including Cefepime and Cefpirome) and Aztreonam, irrespective of the in-vitro test results. (It must be remembered that the emergence of ESBL-producing Enterobacteriaceae is related to indiscriminate use of Third Generation Cephalosporins).

For Carbapenem-resistant Enterobacteriaceae (CRE)-infections, involving ESBL, or AmpC and Porin-loss, or Acquired Carbapenemases, it has been indicated that either Polymixin, or Colistin, or Tigecycline and Fosfomycin can be recommended.

In the case of infections involving bones and joints, treatment must be based on culture of blood/synovial fluid/bone biopsy, and necessarily, with orthopaedic consultation.

(These guidelines provide the most authoritative information applicable to skin & soft tissue infections. However, there is a need to generate more data at local and regional levels, in order to streamline efforts in the direction of augmenting endeavours to fight against the ever-increasing menace of antibiotic resistance. Such data can be made available to the National Data Bank on Bacterial antibiotic resistances, in the case of all diseases, in order to serve the purpose of justifying policy-formulations, related to therapeutic strategy enhancement (Meenakshisundaram *et al.,* 2016).

Factors related to glycaemic control

Bansal *et al.,* (2008) reported that about 67% of the diabetic foot ulcer patients had random blood sugar (RBS)-levels greater than 200 mg/dL, and a majority of them had HbA1c-levels above 7.0%, and that, among the total of 103-diabetic foot ulcer patients, the HbA1c (%) varied around 8.15+/-1.75.

In case of Hypoglycemia (blood sugar level dropping below 70 mg/dL), treatment is given in the form of 15 to 20 gram of fast-acting carbohydrates, like a fruit juice, glucose-tablet, sugar-cube, etc. But, fats or proteins, if consumed, can slow down the body's absorption of sugar, and may cause an increase in the blood sugar level (Mayo Clinic Diseases and Conditions: diabetic hypoglycemia, 2015).

In maintaining the glycemic control, Fernando *et al.,* (2016) reported that glycemic interventions include subcutaneous insulin administration, continuous insulin infusion, oral-hypoglycemic drugs (anti-diabetes agents), life-style intervention or a combination of these interventions. Oral anti-diabetes therapy include four classes of hypoglycemic drugs, namely, Sulfonylureas, Metformin, Thiazolidinedione's and Alpha-glucosidase inhibitors. The main side-effects caused by alpha-glucosidase inhibitors are flatulence (intestinal gas-related problem) and diarrhea which are usually mild, and not necessitating the cessation of therapy. (Thomas Higgins, 2017).

Sawin *et al.,* (2010) reported that Metformin did not cause hypoglycemia in hospitalized diabetic patients, and yet the theoretical risk of Metformin inducing lactic acidosis must be monitored.

The risk factors relating to the occurrence of increased lactic acidosis or increased lactate levels, in case of anti-diabetes drugs, such as Metformin versus other anti-hypoglycemic

treatments, became a debate, and hence, the situation must be monitored (Salpter *et al.*, 2006). Kendall *et al.*, (2006) reported that persons with diabetes might avoid taking the antimicrobial agent Gatifloxacin, a third-generation broad spectrum Fluoroquinolone which has activity against Gram-negative / Gram-positive (aerobic/anaerobic) and atypical pathogens, as it undergoes minimal bio-transformation, and is excreted renally Uckay *et al.*, (2009), and Richard *et al.*, (2008) reported that skin commensals, such as Coagulase negative *Staphylococcus* (CONS) spp, *Corynebacterium* spp, or *Bacillus* spp, would require treatment, only when associated with an infection involving osteosynthetic material or hardware.

Factors related to cross-resistivity

With regard to cross-resistivity between two antimicrobial agents or alternatives in the selection of antibiotics, the following points need to be considered:

Cephalosporins become acceptable to a majority of patients who were found to be allergic to Penicillin (Romano *et al.*, 2004). However, in some cases, fatal ends have been reported (Pumphrey *et al.*, 1999). Cross-resistivity between Penicillins and Carbapenems were reported to be low (Romano *et al.*, 2007).

There was no Cross-resistivity between Penicillins and Monobactam.

In the case of Quinolones, increases of IgE-mediated anaphylactic reactions were reported, perhaps, due to the large scale use of the Quinolones (Manfredi *et al.*, 2004; Hein, 1997; Sachs *et al.*, 2006; Venturini Diaz *et al.*, 2007). Aminoglycosides rarely cause hyper-sensitivity reactions, although some reports indicated the occurrence of IgE-mediated systemic reactions (Solensky *et al.*, 2010).

Chloramphenicol (on prolonged use, perhaps) was associated with anemia (resulting from decreased production or increased reduction of red blood cells), according to Smith Marsch (of the University of Illinois at Chicago) 2017).

Side effects due to common antimicobial agents in use

Anderson (2017) reviewed and updated an exhaustive list of antimicrobial agents, considering the various side-effects produced by each class of antibiotics, although it was concluded that the antimicrobial agents are generally safe, when used in "appropriate" doses. The highlights of side-effects are given below:

Penicillins (Ampicillin, Amc, Pi, Pi/t, Nafcillin, Oxacillin) causing hyper-sensitivity, including Anaphylaxis; (in addition to nausea, vomiting, diarrhea, skin-rash, drug-fever, abdominal pain);

Cabapenems (Imipenem/cilastatin identified with probable hypersensitivity; Meropenem causing hypersensitivity in penicillin-allergy patients); in addition to diarrhea, nausea, vomiting, liver-toxicity, eosinophilic leukocytosis, Aminoglycosides (G, Tob, Ak), causing oto-toxicity or renal toxicity on long-term use; in addition to dizziness, nausea, vomiting, nystagmus (rhythmical oscillation of the eye-balls, either horizontal, rotary or vertical).

Cephalosporins (Cefolexin, Cefaclor, Cefuroxime, Ceftibuten, Cefdirnir, Cefixime, Ceftriaxone) causing cross-hyper sensitivity in penicillin-allergic patients; in addition to skin-rash, diarrhea, nausea, vomiting (although rare); serum-sickness (involving reaction by the immune system)

Glycopeptides (Vancomycin causing Red man syndrome; Televancin causing Taste-

alteration), nausea/vomiting, headache, dizziness); Macrolides (Erythromycin, Azithromycin, Clarithromycin) causing sometimes high rate of intestinal side effects; in addition to diarrhea, nausea, vomiting, taste-alteration, anorexia (aversion for food)

Sulfonamides (T/S, Erythromycin/ sulfisoxazole, Sulfasalazine, etc) causing Stevens Johnson syndrome, Toxic epidermo-necrolysis involving necrosis and loosening of tissues), photosensitivity; in addition to anorexia, dizziness, diarrhea, nausea, vomiting, headache, rash, abdominal pain

Tetracyclines (Tet, Doxi, Mino) causing Liver toxicity, Photosensitivity; in addition to diarrhea, nausea, vomiting, abdominal pain, anorexia (diminished appetite)

Quinolones (Cip, Lev, Mxf, Ofl) causing severe photosensitivity, Insomnia, abdominal pain, lethargy; in addition to diarrhea, nausea, vomiting

Metronidazole will cause metallic taste, in addition to nausea/vomiting, dizziness, headache; (Alcohol consumption while being treated with Metronidazole would aggravate symptoms). Lipsky *et al.,* (2012b), also, described the relative merits and de-merits of many antimicrobial agents, to be used in oral route versus parenteral route.

The above sets of informations derived from literature, are to be treated as reference material (or hints) only. It must be inferred that the local data on bacterial sensitivity pattern, in the antimicrobial treatment, does play a major role in deciding the prospects of healing of the diabetic foot ulcer wound.

Aim and objectives

The present study was conducted with the following aim and objective:

To estimate the probable drug-burden which would result on the diabetic foot ulcer patient, in the treatment process, using the data on the bacterial pathogens isolated from the wound, and the data on antibiotic sensitivity, and

To assess whether any other antimicrobial agents are to be newly tested in India for their in-vitro susceptibility against each pathogen found in diabetic foot ulcers, based on hints acquired from international literature.

Materials and Methods

Pus swabs were collected from 75-diabetic foot ulcer patients being treated in Dr.V.Mohan's Diabetes Specialties Center, Gopalapuram, Chennai-600 028 (South India), during a period of 5-months, from May to September, 2005. The 104-pus samples collected from the patients were transported to the Laboratory in Carey-Blair transport medium of Hi-media (India). All the isolates were identified, adopting the standard procedures indicated in the NCCLS, 2002 (Meenakshisundaram *et al.,* 2015). Drug resistance pattern of *Pseudomonas aeruginosa* only was evaluated using antimicrobial agents representing various classes of standard antimicrobial agents, namely, Ampicillin (10ug), Amoxicillin/clavulanic acid (20ug + 10ug), Piperacillin (100ug), Imipenem(10ug), Cefotaxime (30ug), Ceftazidime (30ug), Ceftriaxone (30ug), Gentamicin(10ug) and Ciprofloxacin (5ug).

Antimicrobial agents (AMAs), with a susceptibility range of 100.0% to 66.7% (facing bacterial resistance of 0.0% to 33.3% from *Pseudomonas aeruginosa*) were evaluated.

Bacterial resistance of other 8-bacterial species isolated in the diabetic foot ulcer specimens were not evaluated in the bacterial sensitivity test, in the retrospective study, due

to limited scope of the study. In order to fill up this gap, antimicrobial susceptibility patterns reported in the literature in India, relating to diabetic foot infections, were used, choosing 2-other locations in South India, namely, Kelambakkam (near Chennai, Tamilnadu State, as reported by Priyadarshini *et al.,* 2013), and Bengaluru (in Karnataka State, as reported by Sajila *et al.*, 2015), and choosing 2-locations in North India, namely, Chandigarh (in Hariyana State, as reported by Bansal *et al.,* 2008), and New Delhi (as reported by Gadepalli *et al.,* 2006).

In all cases, antimicrobial agents (AMAs) effective against the pathogens in the susceptibility range of 100.0% to 66.7%, as evaluated in the 5-cities in India, were compared with the data relating to similar data collected in the multicenter trial studies on diabetic foot ulcers, in the United States, as reported by Citron *et al.,* (2007).

The overall drug-burden on the individual diabetic patient will correspond to the antibiotic agents needed to be administered on the patient, in order to eradicate all pathogens, inclusive of aerobic organisms, anaerobic organisms and fungal species prevalent in the patient. The drugs have to be optimally selected, so as to earn a healing of the wound, with minimum number of drug-types, so that the side-effects can be minimized. Allergies and cross-resistances become additional factors for consideration, in the selection of the drugs.

Results and Discussion

The prevalence of different bacterial species isolated from the 104-samples in Chennai, in the retrospective study is presented in table 1.
Table 2 presents the details of the most effective antimicrobial agents (AMAs) whose susceptibility patterns were in the range of 100.0% to 66.7% against the particular pathogen, namely, *Pseudomonas aeruginosa* (the bacterial resistances varying from 0.0% to 33.3%).

According to the data shown in table 2, it becomes clear that any one of the five antimicrobial agents (AMAs) can be administered against *Pseudomonas aeruginosa* found in a diabetic foot ulcer patient, choosing either Imipenem or Pipeacillin or Amoxicillin/clavulanic acid, or Ceftazidime, or Gentamicin.

This result is presented in table 3, in comparison to the multicentre- trial studies carried out in the United States by Citron *et al.,* (2007) who evaluated 7-antimicrobial agents to be effective against *Pseudomonas aeruginosa*, namely, Imipenem, Gentamicin, Ceftazidime, Piperacillin/ tazobactam, Amikacin, Ciprofloxacin, Levofloxacin, and Moxifloxacin. This implies that there is a closer agreement between our Chennai-data of the retrospective study, in comparison to the multicentre-study data of the United States.

Being encouraged by this trend, it was attempted to compare the antimicrobial sensitivity patterns of the other 8-pathogens, namely, *Staphylococcus aureus* (MSSA, MRSA), CONS spp, *Streptococcus* spp, *Enterococcus* spp, *Corynebacterium* spp, *Escherichia coli*, *Klebsiella* spp, and *Proteus* spp., choosing informations available in the published literature, as reported for 2-South Indian locations (Kelambakkam and Bengaluru), and 2-North Indian locations (Chandigarh and New Delhi), in contrast to similar data pertaining to the multicentre trial study in the United States, as shown in table 3. Several similarities are found among the antimicrobial agents evaluated in India and the United States, considering separately, the Gram-positive and Gram-negative aerobic bacterial categories. It is found that more number of antimicrobial agents are used in the antimicrobial susceptibility tests in India, than

in the United States, perhaps due to the predominance of Gram-negative bacteria prevalent in diabetic foot ulcers in India or factors related to the commercial availability of the various classes of drugs, in different geographical locations of India.

In the case of the present study, it was assumed, hypothetically, that all the 9-bacterial pathogens to be present in a single patient, namely, 5-Gram-positive pathogens (aerobic) and 4-Gram-negative pathogens (aerobic). A hypothetical estimate was made to identify the antimicrobial agents needed to be used against all the 9-pathogens, in order to obtain a cure for the patient.

Referring to table 3, the antimicrobial agents evaluated in the 5-Indian cities, were compared, for optimally choosing the suitable antimicrobial agents, as detailed below:

Table.1 Isolation rate of other bacteria

(Number of isolates=104)

S.no	Organism	No. of organisms (%)
A.	Gram-positive (aerobic): (40.4%)	
1.	*Staphylococcus aureus*	18 (17.3%)
2.	Coagulase Negative Staphylococcus (CONS)	11 (10.6%)
3.	*Streptococcus* spp.	6 (5.8)
4.	*Corynebacterium* spp.	4 (3.8)
5.	*Enterococcus* spp.	3 (2.9
B.	Gram-negative (aerobic): (59.6 %)	
6.	*Escherichia coli*	23 (22.2)
7.	*Pseudomonas aeruginosa*	18 (17.3)
8.	*Klebsiella* spp.	11 (10.6)
9.	*Proteus* spp.	10 (9.6)

Table.2 List of AMAs effective against *Pseudomonas aeruginosa*

(Total number of P. aeruginosa isolates=n=18)

S.no	Antimicrobial agent	No of resistant strains	% Resistence
1.	Imipenem	1	5.5
2.	Piperacillin	2	11.0
3.	Co-amoxyclav	4	22.0
4.	Ceftazidime	6	33.0
5.	Gentamicin	6	33.0

Table.3 Comparison of antibiotic agents effective against pathogens found in diabetic foot ulcers, in the workable susceptibility range of 100.0% to 66.7%

S. No	Micro-Organism	(1) Multi-Centre Trials (U.S.A).	(2) Chennai (S.India)	(3) Kelam-Bakkam,(S.India)	(5) Bengaluru (S.India)	(7) Chandigarh (N.India)	(8) New Delhi (N.India)
1.	*P. aeruginosa*	Ak,G,Cip,I,Pi/t,Lev Mxf,Caz	Amc,Pi,G.I Caz	Ak,Crb,Ci,I Mer,Pi/t,PmB,Cfs	Ak,G,I,Pi/t,Lev Mer,Tob	Ak,Pi,Tob,I Ctr,Caz,Cfs	Ak,I,Mer,Pi/t Tcc,Cfs
2.	*S, aureus*				Cldm,Ofl,Oxa,E,G Lom,Tet,Lin,Van Cpz	Amp,Amc,Cip G, E,I,Ctr, Cfrxm,Cfs	Rif
2.11	MSSA	Amc,Etp,Pi/t,Lev Mxf,Cip,Cldm T/S,Dox, Cfl	……	G,Ntlmc,E,Cldm, Clrmp,Van,Lin,Rif Teic,Clxcln,Cfzln Cot	…	….	…..
2.2.2	MRSA	Dox T/S	……	Ntlmc,Cldm,Van Clrmp,Teic,Lin	…..	….	….
3.	CONS Spp.	Amc,Etp,Pi/t,LevMxf, Cldm,T/S,Cip,Dox,Cfl	….	Ntlmc,Lin Van, Teic	Amc,Cldm,Ofl.Oxa G,Tet,Lin,Van,Cpz,Cpm	….	Ak, Tet,Cldm Clrmp,Rif,Cot
4.	*Streptococcus* spp.	Amc,Etp,Lev,Mxf Cip,Cldm,Pi/t T/S,Cfl	….	Ofl,Van,Teic Tet,Cldm,,Lin	(S.pyo):Amc,Cdm,E Ofl,Oxa,Lom,G,Lin Tet,Van,Cpz,Cpm	…	….
5.	*Enterococcus* Spp.	Amc,Pi/t,Cip,Lev Mxf,T/S	…	.	Amc,Tet,Lin,Van	(E.faec)Amc, Caz,Cfs,G	….
6. 7.1	*Corynebacterium* Spp. Entero-Bacteriaceae	Amc,Etp,Pi/t Dox, Cfl Ak, Etp,I,Pi/t,G,Cip Lev,Mxf,Dox,T/S, Caz	…. ….	…. Ak,Tet,Tob,G,Cip Mer,Ofl,Ci,Pi/t Clrmp,I,PmB,Cot Cpm, Cfs,Cfrxm Cftxm	…….. Ak, Cip,G,Lev,Pi/t Mer,Tob,Ntlmc	…… ….	…… …
7.21	*E. coli*	…….	…..	Ak, I, G Pi/t,Clrmp Ci, PmB,Cfs	Ak, G,I, Lev,Pi/t	Ak,I,Cfs Caz	I, Mer,Tcc Cfs
8.	*Klebsiella* Spp.	…….	….	Ak, I,Mer,Pi/t, Ci PmB,Cfs	Ak,G,I,Lev,Pi/t	(K.oxy)Ak,I,Cfs, Caz (K.pne) I,Ctr,Cfs	(K.pne) Amc,Cip Mer,Pi/t,Tcc,Cfs Ak,I,Caz,Cftxm
9.	*Proteus* Spp.	Etp,I, Pi/t,Ak,Cip,Lev Mxf,G,T/S,Dox,Caz	……	Cfs, I,Clrmp Tet, Pi/t	Ak, I,G.Cip,Lev,Pi/t Cfrxm,Cpm,Cpz	(P.vul)Ak,G,I, Caz,Cfs,Cfrxm Ctr	I,Cip,Tcc Mer,Cfs

Amp=Ampicillin;Amc=Amoxicillin/clavulaninicacid;Ak=Amikacin; Caz=Ceftazidime;Ctr=Ceftriaxone;Cip=Ciprofloxacin;Cftxm=Cefotaxime; Cfrxm=Cefuroxime; Cfl=Cefalexin; Cfzln=Cefazolin; Cpm=Cefepime; Cpz=Cefoperazone; Cfs=Cefoperazone/sulbactam; Crb=Carbenicillin; Cot=Cotrimoxazole; Cldm=Clindamycin; Ci=Colistin; Clxcln=Cloxacillin; Clrmp=Chloramphenicol; Dox=Doxycycline; E=Erythromycin; Etp=Ertapenem; G=Gentamicin; I=Imipenem; Lev=Levofloxacin; Lin=Linezolid; Lom=Lomefloxacin; Mer=Meropenem; Mxf=Moxifloxcin; Ntlmc=Netimycin; Oxa=Oxacillin; Ofl=Ofloxacin; Pi=Piperacillin; Pi/t=Piperacillin/tazobactam; PmB=PolymixinB; Rif=Rifampicin; Tcc=Ticarcillin/clavulanicacid; Tet=Tetracycline; Teic=Teicoplanin; Tob=Tobramycin; T/S=Trimethoprim/sulfamethoxazole; Van=Vancomycin

Case-1: For the 4-species of Gram-positive bacteria present in the diabetic ulcer wound, namely, *Staphylococcus aureus*, Coagulase negative staphylococcus (CONS) species, *Streptococcus* species, and *Enterococcus* species, the recommended AMAs, would be Linezolid or Vancomycin, as evaluated in India. For the *Corynebacterium* species, Amoxicillin/clavulanate may be tried as reported in the multi centre-trial data of the United States, in the absence of Indian data for this particular pathogen.

Case-2: For the 4-numbers of Gram-negative bacterial species present in the same diabetic foot ulcer wound, namely, *Escherichia coli*, *Klebsiella* species, *Proteus* species and *Pseudomonas aeruginosa*, the recommended AMAs would be either Piperacillin/ tazobactam, or Cefoperazone/ sulbactam, or Imipenem (chosen from data reported for the 5-Indian cities).

In addition to the estimates made in Case-1 and Case-2, it is to be said that appropriate medication must be included for covering the anaerobic pathogens and fungal pathogens, if present in any other situation.

Metronidazole has been reported to be effective against majority of anaerobic pathogens (Anandi *et al.*, 2004; Chincholikar, 2002). An antifungal cream (such as Fluconazole) must be included in the list, as a topical medicine, if fungal pathogens are present (Sanniyasi *et al.*, 2015). Also, Citron *et al.*, (2007) reported that Ertapenem, Piperacillin / tazobactam, Amoxicillin / clavulanic acid, or Clindamycin could be effective against the anaerobic pathogens found in diabetic foot infections.

Thus, all these medicines administered on a hypothetical patient would represent the "drug-burden", on the patient, in addition to the anti-diabetes (oral-hypoglycemic) drugs to be consumed by the patient, for the purpose of maintaining a normal glycemic control.

There is, therefore, a necessity to optimize on the number of drugs to be administered on the patient, by choosing the AMAs, in such a way that the chosen drug would be effective against more than one pathogen, without causing any adverse effect.

The choice of drugs to be administered is to be left to the prerogative decision of the team of experts who attend on the diabetic foot ulcer patient. The input from a microbiologist is needed during the various stages of the treatment process.

Certain antimicrobial agents such as Ertapenem, Tigecycline, Doxycycline, Trimethoprim/ sulfamethoxazole, etc., found useful in the multicentre studies in the United States, can be included in the in-vitro susceptibility tests in India, to assess their effectiveness in offering treatment to diabetic foot infections.

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