Pattern of Organisms and Antibiotics Used in Treating Diabetes Foot Infection

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ABSTRACT

Introduction: The aim of this study is to determine the most common organisms isolated in diabetic foot infection and the most utilised antibiotic regimes as the first line of treatment. **Methods:** This is a retrospective record review of the National Orthopaedic Registry Malaysia among diabetes mellitus type 2 patients who had foot infections. All identified cases admitted to 18 government hospitals in Malaysia from the 1st January 2008 until the 31st December, 2009 were included in the study. **Results:** A total of 416 patients were included in the study. The most common organisms cultured were *Proteus species* (17.5%), *Klebsiella species* (17.1%) and *Staphylococcus aureus* (17.9%), while the most commonly used antibiotic was ampicillin/sulbactam (67.5%). None of the patients was appropriately treated with metronidazole, cefoperazone or fucidic acid. All patients were given appropriate antibiotics to treat *Serratia* infection. **Conclusion:** Significant number of patients with diabetic foot infections were not treated using appropriate antibiotics as the first line treatment.

KEYWORDS: Antibiotics, Diabetes Mellitus, Diabetes Complications, Foot Ulcer

INTRODUCTION

Foot infections are a common and serious problem in diabetic patients. Foot infection in patients with diabetes cause substantial morbidity with frequent visits to health care professionals. If inadequately managed, it may lead to amputation of lower extremities. They usually occur as a consequence of skin ulceration, which initially is colonized with normal flora, and later infected with pathogens. Infection is defined clinically by evidence of inflammation, and appropriate cultures can determine the microbial aetiology.[1]

Foot infection in diabetic patients can accelerate dramatically with devastating consequences if appropriate treatment is not given promptly. The role of professional healthcare providers managing these individuals is to identify and treat infection as early as possible, and preventing complications. However, diagnosing infection in an ulcerated diabetic foot is not always straightforward. In diabetics, the host inflammatory response to injury or infection may be reduced because of impaired leukocyte function, vascular disease, and neuropathy.[2] Diagnosing infection in diabetic foot ulcer is based on clinical signs and symptoms of inflammation. Properly culturing an infected lesion can disclose the pathogens and provide their antibiotic susceptibilities.[3]

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The first line of treatment is usually started prior to knowing what organism is involved. Organisms were usually determined within a week by the pathologists after antibiotics have been started. Thus, the match of between the organisms and the antibiotics can be investigated. This study aimed to determine the most common organisms isolated in diabetic foot infections in Malaysia. By understanding this pattern, recommendations of the most suitable regime of antibiotics to be used as the first line of treatment can be proposed.

MATERIALS AND METHODS

A retrospective record review was conducted from the National Orthopaedic Registry Malaysia (NORM) database. Patients with diabetes mellitus type 2 who had foot infections, admitted to 18 government hospitals in Malaysia from 1st January 2008 until 31st December 2009 were recruited into the study. The authors received permission from the NORM Committee and have received ethical clearance from the Ethical Committee of the Ministry of Health Malaysia. Patients with information regarding organisms and treated antibiotics were included in the study. The guideline for appropriateness of antibiotics towards the organisms were based on the National Antibiotic Guideline 2008[4] and Clinical Laboratory Standard Institute 2011 (40th Edition)[5].

The summary of the organism and antibiotic used is presented in Table I. Demographics data were obtained from patients' medical record, while the tissue specimens were obtained from biopsy, ulcer curettage, aspiration and wound swab. This study has been registered with the National Medical Research Register (NMRR-08-1349-2597).

Statistical analysis
Demographic data, types of antibiotics, types of organism and their appropriateness are tabulated for descriptive statistics such as in frequency (n) and percentage (%). A chi-square test was used to analyze the association of each organism that received appropriate antibiotics, the antibiotics that used for an appropriate organism and the appropriateness of treatment and the growth status. All analyses were performed using SPSS version 18.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp).

RESULTS

A total of 416 patients were included in the study. More than half (54.6%) of them were female. The majority of patients were Malay (83.7%) and in the age group of 50 years and above (71.9%) (Table II). Out of 416 patients, 79.8% (332/416) of patients had single growth, 17.8% (74/416) had mix growth (n=2) and 2.4% (10/416) of patients had multiple mix growth (n>2). The most common organisms cultured are *Proteus species (17.5%), Klebsiella species (17.1%), S. Aureus (17.9%), E.coli (9.2%), Haemolytic Streptococcus (8.0%), Enterobacter species (6.7%) and Pseudomonas Aeruginosa (8.6%).*

Table I: Summary of organism and suggested for antibiotic treatment for lower limb infection of diabetes patients

Organism	Suggested Treatment	
	Antibiotic (Preferred)	Antibiotic (Alternative)
1. Anaerobic – Bacteroides spp	Ampicillin PLUS Gentamicin PLUS Metronidazole	Ampicillin/sulbactam OR Amoxycillin/clavulanate OR Piperacillin-tazobactam OR Meropenem/ Imipenem
2.Coagulase positive Staphylococcus - Staphylococcus aureus	Cloxacillin	Erythromycin OR Cefuroxime OR Amoxycillin/ Clavulanate # Clindamycin (if allergy to Penicillin)
3. Enterobacteriaceae - Enterobacter spp - Klebsiella spp - Proteus spp - Serratia spp	Amoxycillin / clavulanate OR Cefuroxime	Ampicillin / sulbactam OR Piperacillin OR Piperacillin / tazobactam OR Meropenem/ Imipenem (severe / Multi re-sistant organism)
4. Pseudomonas spp - Pseudomonas aeruginosa	Ceftazidime OR Cefepime OR Piperacillin OR Piperacillin / tazobactam OR Ciprofloxacin	Meropenem/ Imipenem
5. Streptococcus spp - Enterococcus spp	Ampicillin	Erythromycin OR Cephalexin If resistant to Penicillin : Vancomycin OR Ampicillin / sulbactam
- Beta hemolytic Streptococcus (group A) - Streptococcus viridans	Benzylpenicillin PLUS Clindamycin	# Clindamycin (if allergy to Penicillin)
6. Acinetobacter spp	Ampicillin / sulbactam OR Cefoperazone / sulbactam	Meropenem/ Imipenem OR Ciprofloxacin PLUS Amikacin OR Ceftazidime

Table III shows the distribution of organisms and the appropriateness of antibiotics used. Many patients received appropriate antibiotics for organisms such as *Serratia* (100%: p=0.032), *Proteus* (78.7%: p<0.001) and *Klebsiella* (74.7%: p<0.001). Less were treated for *Staphylococcus Aureus* (22.0%: p<0.001), *E.coli* (14.9%: p<0.001), *Acinetobacter* (12.9%: p<0.001), *Pseudomonas Aeruginosa* (9.1%: p<0.001).

Table II: Distribution for demographic profile of respondent (N=416)

Profile		n (%)
Gender		
	Male	189(45.4)
	Female	227(54.6)
Race		
	Malay	348 (83.7)
	Chinese	32 (7.7)
	Indian	33 (7.9)
	Others	3 (0.5)
Age Group		
	18 - 29	8 (1.9)
	30 - 39	20 (4.8)
	40 - 49	89 (21.4)
	50 - 59	150 (36.1)
	>60	149 (35.8)

Table III: Distribution of organisms and the organisms that received appropriate antibiotics

Organism	N (%)	%	P-value
Proteus	89(17.5)	78.7(70/89)	<0.001
Klebsiella	87(17.1)	74.7(65/87)	<0.001
Staphylococcus aureus	91(17.9)	22.0(20/91)	<0.001
E.coli	47(9.2)	14.9(7/47)	<0.001
Pseudomonas aeruginosa	44(8.6)	9.1(4/44)	<0.001
Hemolyticstrep	41(8.0)	61.0(25/41)	0.247
Enterobacter	34(6.7)	64.7(22/34)	0.134
Acinetobacter	31 (6.1)	12.9(4/31)	<0.001
Enterococcus	19(3.7)	57.9(11/19)	0.624
Bacteroides spp	15(2.9)	60.0(9/15)	0.549
Serratia	5(1.0)	100.0(5/5)	0.032
Streptococcus viridian	4(0.8)	50.0(2/4)	0.923
Bacteroides	3(0.6)	66.7(2/3)	0.620

Percentages were calculated based on number of appropriate antibiotics used/n x 100

Table IV shows the association of the antibiotics that were used for appropriate organisms. The result was statistically significant (p<0001). The most commonly used antibiotic was ampicillin/ sulbactam (67.5%). All patients had been treated appropriately with ceftriaxone. More than half of patients received ampicillin (61.6%), ciprofloxacin (66.7%) and cefuroxime (69.4%) appropriately. None of these patients was appropriately treated with metronidazole, cefoperazone and or fucidic acid. There was a pattern of association between appropriateness of antibiotics and the status of organisms' growth as shown in Figure 1. Result showed that more inappropriate antibiotics were prescribed for mix growth organism.

Table IV: Distribution of antibiotics and the antibiotics that were used for appropriate organism

Antibiotics	n (%)	%
Ampicillin/ Sulbactam	281(67.5)	61.6(173/281)
Cloxacillin	41(9.9)	31.7(13/41)
Cefuroxime	36(8.7)	69.4(25/36)
Metronidazole	21(5.0)	0.0(0/21)
Ceftazidime	7(1.7)	14.3(1/7)
Cefoperazone	6(1.4)	0.0(0/6)
Ampicillin	5(1.2)	20.0(1/5)
Ceftriaxone	3(0.7)	100.0(3/3)
Ciprofloxacin	3(0.7)	66.7(2/3)
Amoxicillin/ Clavulanate	2(0.5)	50.0(1/2)
Fucidic acid	2(0.5)	0.0(0/2)
Piperacillin/ Tazobactom	2(0.5)	50.0(1/2)
Others	7(1.4)	14.3(1/7)

The association was statistically significant with p - value < 0.001. Percentages were calculated based on number of appropriate antibiotics used/n x 100.

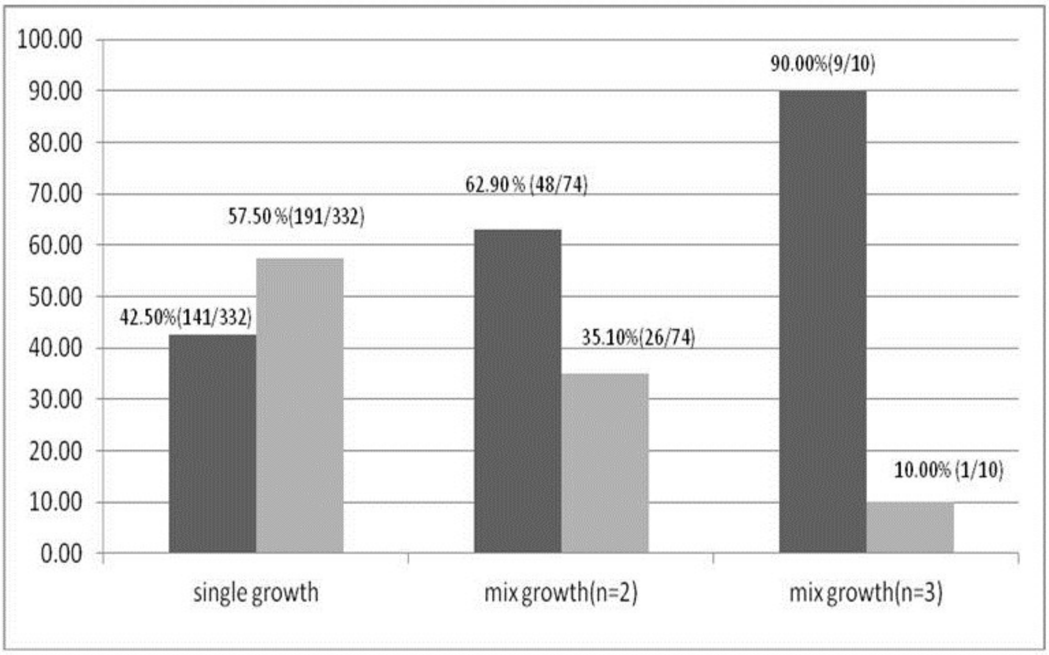

Figure 1. Result showed that more inappropriate antibiotics were prescribed for mix growth organism.

DISCUSSION

The aim of this study is to determine the most common organisms isolated in diabetic foot infection and to recommend the most suitable regime of antibiotics to be used as the first line of treatment. The most common organisms cultured in our study are *Proteus sp* (17.5%), *Klebsiella species* (17.1%) and *Staphylococcus aureus* (17.9%). Anaerobic species (includes bacteroides) were only cultured in 3.5%. This is because many specimens were not sent for anaerobic culture. *Pseudomonas species* was cultured in 8.6% of patients. *Pseudomonas* is the main cause of hospital-acquired infections especially in the long hospital stay patients.

Data on Methicillin Resistant Staphylococcus Aureus (MRSA) infection was not known, as we only take the specimen on the day of admission before antibiotics were started. More than 60% of anaerobic organisms were treated with appropriate antibiotics. The most common antibiotics given in our study were ampicillin / sulbactam (67.5%), cloxacillin (9.9%), cefuroxime(8.7%) and metronidazole(5.0%). From our study, we showed that the appropriate treatment for diabetic foot infection caused by *S. aureus* occurs in only 22.0% of patients. In order to improve the antibiotic appropriateness as our current antibiotic regimes, clinicians are recommended not to tackle the *Staphyloccus* infection. Therefore, our recommendation is to include cloxacillin in all diabetic foot infection to cover for the staphylococcus infection before the definitive culture received.

Study by Tentolouris et, al,.(1999) stated that Gram-positive aerobic bacteria were the commonest micro-organism isolated (56.7%) followed by Gram-negative aerobic bacteria and anaerobes (29.8% and 13.5%, respectively). Of the Gram-positive aerobes, *S. aureus* was found most frequently and 40% were MRSA. MRSA was isolated more commonly in patients treated with antibiotics prior to the swab compared to those who had not received antibiotics.[6]

Aerobic gram-positive cocci are the major pathogens in diabetic foot infections. These may be the sole isolate(s) in acute uncomplicated infections, but they are usually accompanied by aerobic gram-negative bacilli or anaerobes in chronic or previously treated infections. Patients with mild infections can be treated as outpatients with oral antibiotics, but others require hospitalization and broad-spectrum parenteral antibiotics.[7] *S. aureus* was the most common isolate; being isolated in 38.4% of cases. Other organisms includes *Pseudomonas aeruginosa* (17.5%), *Proteus mirabilis* (18%), and anaerobic gram-negative organisms (10.5%), mainly *Bacteroides fragilis*. Imipenem, meropenem, and cefepime are the most effective agents against gram-negative organisms. Vancomycin is the most effective against gram-positive organisms.[8]

Aerobic gram-positive cocci are the most important pathogens. In chronic, complex or previously treated wounds, concurrent infection with gram-negative bacilli and anaerobes may occur, resulting in polymicrobial infection.[1] Aerobic gram-positive cocci (especially *S. aureus*) are the predominant pathogens in diabetic foot infections. Patients who have chronic wounds or who have recently received antibiotic therapy may also be infected with gram-negative rods, and those with foot ischemia or gangrene may have obligate anaerobic pathogens.[9]

Among aerobic pathogens, *Enterobacteriaceae* family (48%), *Staphylococcus species* (18.2%), *Streptococcus spp* (16.8%) and *Pseudomonas spp* (17%) were seen frequently. Among anaerobes *Peptostreptococcus spp.* and *Clostridium spp.* comprise of 69.4% of infection. Gram-negative anaerobes like *Bacteroides spp.* and *Fusobacterium spp.* were present in 30.6%.[10] Therapy aimed solely at aerobic gram-positive cocci may be sufficient for mild-to-moderate infections in patients who have not recently received antibiotic therapy. Broad-spectrum empirical therapy is not routinely required but is indicated in severe infections, pending culture results and antibiotic susceptibility data.

Taken into consideration any recent antibiotic therapy and local antibiotic susceptibility data, especially the prevalence of MRSA or other resistant organisms. Definitive therapy should be based on both the culture results and susceptibility data and the clinical response to the empirical regimen.[9] Antibiotic regimens are usually selected empirically initially, then modified if needed based on results of culture and sensitivity tests and the patient's clinical response. Initial therapy, especially in serious infections, may need to be broad-spectrum, but definitive therapy can often be more targeted. Severe infections usually require intravenous therapy initially, but milder cases can be treated with oral agents.[1]

Therapy should nearly always be active against staphylococci and streptococci, with broader-spectrum agents indicated if Gram-negative or anaerobic organisms are likely.[11] *S aureus* is the most common isolate in these infections. Increasing incidence of MRSA over the past two decades has further complicated antibiotic treatment. While chronic infections are often polymicrobial, many acute infections in patients not previously treated with antibiotics are caused by a single pathogen, usually a gram-positive coccus.[9]

Antibiotic therapy is necessary for virtually all infected wounds, but it is often insufficient without appropriate wound care.[9] When culture and sensitivity results are available, specific or definitive therapy should be addressed. Changing to narrower spectrum agents is preferred but it is important to assess how the infection has been responding. If the lesion is healing and the patient is tolerating the empiric regimen there may be no reason to change, even if some or all of the isolated organisms are resistant to the agents is being used. On the other hand, if the infection is not responding, treatment should be changed to cover all the isolated organisms. If the infection is worsening despite the isolated organisms being susceptible to the chosen regimen, consider the need for surgery or the possibility that fastidious organisms were missed.[11]

Study limitation

This study has few limitations. The recruited subject might not cover all diabetes patients in Malaysia. However, these findings were derived from a multi-centre study and relatively has large sample (n=419). Previous studies showed that results derived from studies with sample size closed to 500 subjects or more are likely to have the same parameters as a particular population.[12] In addition, not all sample culture was taken from tissue or aspirate. Some were taken using wound swab. Majority of the samples were obtained intraoperative as deep tissue specimen, however due to the nature as patient registry data, this study could not estimate the minority samples that were obtained from wound swab. Therefore, future research is suggested to emphasize on sample obtained from tissue.

CONCLUSION

The most common organisms cultured in this study are *Proteus sp, Klebsiella sp.* and *S. aureus*. The most common antibiotic usage is ampicillin/ sulbactam. *Staphylococcus* infection in diabetic foot is not properly treated in our study. This information may help the healthcare provider to understand the prescription pattern and serves as a guide on the most appropriate treatment for diabetes foot infections.

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CONFLICT OF INTEREST

We declare that we do not have any conflict of interest of this manuscript.

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