

Antibiotic Resistance Pattern of Community Acquired infections in Diabetic Subjects: A Clinico-microbiological Study from Eastern India

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Abstract

Background: Antibiotic resistance in bacteria is a major concern for clinicians all over the world. Healthcare associated infections are known to be multi-drug resistant. But recently, community acquired infections are also reported to be drug resistant in a significant number of cases. Diabetes is a metabolic disorder associated with increased propensity to infections. With the rising prevalence of diabetes in India, diabetes related infections are also becoming a significant burden on the healthcare system. Most infections in diabetic subjects are treated in the community. However, there is very little data on the microbiology of community acquired infections in Indian diabetic patients. Such data are essential in making comprehensive diabetes management protocols. This present study is aimed to generate data on the microbiology of community acquired infections in diabetics.

Material and methods: This was a cross-sectional observational study done in a tertiary care medical college of eastern India. Diabetic patients with community acquired infections were tested according to the clinical presentation. The type of organism and their antibiotic resistance patterns were noted. Only the clinical specimens yielding positive culture were included for the final analysis.

Results: There were a total of 77 subjects in this study with average age of 49.3 ± 16.6 years. There were 79 clinical samples (74% urine) from which a total of 83 bacteria were isolated. Of them, 18 (21.7%) were Gram-positive and the rest Gram-negative. *E. coli* was the commonest isolated organism ($n = 39, 47\%$; 95% CI: 36.6 - 57.6%) followed by *Klebsiella* ($n = 16$). In urine culture, Gram-negative organisms were predominant, while for blood culture, it was Gram-positive. Among the Gram-positive organisms, there was significant resistance to macrolides and clindamycin, while for Gram-negative subset, there was significant resistance to 3rd generation cephalosporins and fluoroquinolones. Nitrofurantoin resistance was found in 17 - 25% of isolates.

Conclusion: Community acquired infections in diabetics is mostly caused by Gram-negative bacteria. The organisms show significant resistance to most commonly used first-line antibiotics.

Key words: Diabetes mellitus; community acquired infection; Gram-negative bacteria; drug resistance; *E. coli*.

Introduction

Bacterial resistance to antibiotics is a catastrophic problem affecting patient care all over the world. A systematic review by Naylor *et al* (2018) found that antimicrobial resistance may cause up to three trillion dollars in GDP loss in the USA alone, over the next 30 years¹. This causes a significant burden on the healthcare system in terms of resource allocation, bed occupancy and patient morbidity¹. For low and middle income countries like India, antibiotic resistance and its financial effect is likely to put an even greater strain on an already overburdened and under-resourced health system.

Antibiotic resistance is known to be high in healthcare associated infections. A study by Heydarpour (2017) *et al* showed that hospital acquired infections are mostly caused by organisms resistant to all the common anti-microbial agents². Such infections increase the mortality almost twice

for hospitalised patients³. But even the bacteria responsible for community-acquired infections are showing an alarming trend of drug resistance. Studies have shown that community acquired bacteria like *E. coli* have significant resistance to commonly used antibiotics like fluoroquinolones⁴. This phenomenon will limit the available options for treatment of common infections in the daily practice.

Diabetes mellitus is a metabolic disorder where there is increased risk of opportunistic infections. Studies have shown that diabetic subjects had a much higher rate of infections like bone and joint infection or cellulitis, compared to non-diabetic controls⁵. Diabetes is also an important cause of infection-related hospitalisation and death⁵. Recent data have revealed that infections in diabetic subjects are often caused by organisms resistant to commonly prescribed antibiotics⁶. Organisms isolated from diabetic foot infection sites were found to be multi-

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drug resistant in a large number of cases⁶. Hence, in diabetic subjects, any infection can be multi-drug resistant, and a potential source of complications.

The incidence of infections in diabetic patients is much higher than the general population⁷. While there are more data on specific sites of infection like diabetic foot ulcer, any and every part of the human body may be affected by severe infections in diabetes. Besides bacterial infection, fungal and tubercular infection are also significantly higher in these subjects. A recent study has shown that only for diabetic foot infections, the estimated cost in a small country can be up to 0.4% of its GDP⁸. Thus, if all infections at different sites are considered, the financial burden, of only infections in diabetic subjects, is likely to be huge.

In India, the incidence of diabetes is rising quickly. According to the International Diabetes Federation, more than 8% of the adult population in India currently has diabetes⁹. According to a 2017 report by the Indian Council of Medical Research, the number of DALYs due to diabetes rose by 174% over the last 25 years and prevalence increased by 64%¹⁰. This increased number of diabetic subjects will mean corresponding astronomical increase in healthcare costs. In addition to the chronic complications like nephropathy and retinopathy, recurrent infections are also responsible for the healthcare burden of diabetes.

However, in spite of the burden, there are very few studies on the epidemiology of infection in Indian diabetic patients. There are a few studies on diabetic foot. For example, a 2015 study from Bangalore recorded the organisms isolated from diabetic foot ulcers¹¹. However, data regarding the organisms and their drug resistance patterns in other types of infections like blood stream infection are largely absent in the Indian context. But as the prevalence of diabetes in India is increasing, such data will become crucial for the clinician. Treatment of infections is a very important part of comprehensive diabetic care and unless adequate data are available, effective guidelines cannot be created.

Our present study is aimed at addressing this literature gap in the Indian context, especially for the Eastern Indian population.

Material and methods

This was a cross-sectional, hospital based, observational study done in a tertiary care medical college of West Bengal. This college has patient pool from all over Eastern India, Bangladesh and Nepal. The study was approved by the Institutional ethics committee. The study was done for a period of 16 months from June 2017 to September 2018. The details of the study were explained to the subjects, and those who gave informed consent, were included. Patients

with history of any antimicrobial use or surgical procedure within the last two weeks, those with indwelling foreign bodies like catheter or feeding tube, those with prostheses, those having history of biological drug use and people with history of or active malignancy were excluded from the study. Patients were selected both from the outpatient department and indoors (admitted for less than 48 hours).

Since this was a pilot study, there was no prior data to determine the sample size. Based on the previous year's rate of patient turnover in the medicine department, we aimed to collect data from at least 70 patients fulfilling the inclusion and exclusion criteria over a period of one year. A consecutive sampling technique was used.

Adult (> 12 years) patients with diabetes (type 1 or type 2) were screened for clinical evidence of any infection. Based on the clinical examination findings, proper clinical samples were sent for microbiological examination. Samples were collected with proper aseptic technique and transported to the laboratory in a sterile manner within 30 minutes. The samples were inoculated simultaneously in blood agar and McConkey agar under aerobic conditions. After 24 hours, any growth in these media were tested by Gram stain. Drug sensitivity was tested in Muller-Hinton agar by Disc diffusion method. Resistance to a drug was interpreted according to CLSI guidelines.

The data, after analysis, were expressed as mean \pm SD for continuous data and percentage for categorical variables. Suitable statistical tests were done as needed. $P < 0.05$ was considered significant.

Results

There were a total of 77 subjects in this study. The male female ratio was 17: 60. Average age of the subjects was 49.3 ± 16.6 years, with age range of 18 - 82 years.

There were a total of 79 clinical samples, derived from 77 patients. Among the samples, 59 (74.7%) were urine, 12 (15.2%) were blood and the rest consisted of sputum (3), foot ulcer (2), CSF, pleural fluid and pus. Usually, one clinical sample, when cultured, yielded one bacterium. In only 3 cases (3.8%) the same sample grew more than one organism. In total, 83 bacterial organisms were isolated.

The isolated bacteria are shown in Fig. 1. It was seen that the most commonly isolated organism was *E. coli* ($n = 39$, 47%; 95% CI: 36.6 - 57.6%) followed by *Klebsiella* ($n = 16$, 19.3%; 95% CI: 12.2 - 29%). The next most common organisms were *Coagulase negative Staphylococcus* ($n = 8$) and *Enterococcus* ($n = 6$).

E. coli was mostly isolated from urine samples (36 out of 39 *E. coli* samples; 92.3%). For *Klebsiella*, the commonest

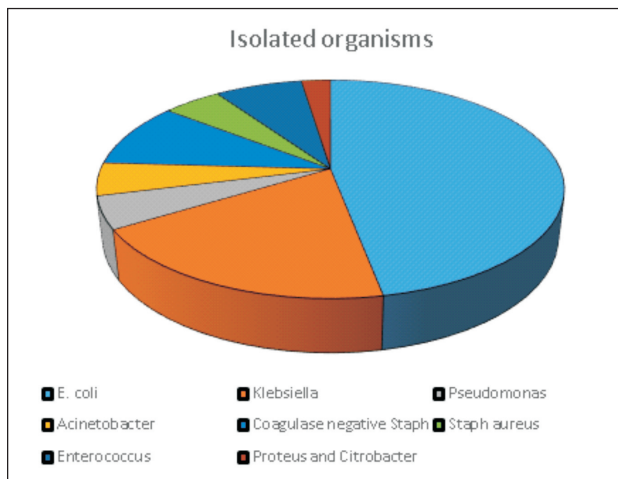


Fig. 1: Pie diagram showing the bacteria isolated from diabetic patients in this study.

associated clinical sample was also urine (11 out of 16; 68.8%). The various clinical samples and organisms isolated are shown in Table I. As seen in this table, among the blood samples, 50% (n = 6) grew coagulase negative *Staphylococcus* and among the sputum samples, 67% grew *Klebsiella*.

Table I: Table showing the organisms isolated from various clinical specimens.

Organism (N = 83)	Clinical sample				
	Urine	Blood	Sputum	Footulcer swab	Others
<i>E. coli</i>	36	0	0	1	2
<i>Klebsiella</i>	11	2	2	1	0
<i>Coagulase negative Staph.</i>	2	6	0	0	0
<i>Enterococcus</i>	5	1	0	0	0
<i>Pseudomonas</i>	3	0	0	1	0
<i>Acinetobacter</i>	2	1	1	0	0
<i>Staph. Aureus</i>	0	3	0	1	0

Antibiotic resistance pattern of the organisms are shown in Tables II and III. In Table II, it is seen that, among the Gram-positive organisms, 75% of *Staphylococcus aureus* and 87% of *Coagulase negative Staphylococcus* showed resistance to macrolides. 50% of *Staphylococcus aureus* also showed resistance to clindamycin. 83% of the *Enterococci* were resistant to fluoroquinolones.

In Table III, it is seen that among the Gram-negative organisms, 46% of *E. coli* and 75% of *Acinetobacter* showed resistance to ceftriaxone. Among the *Pseudomonas*, 50% showed resistance to meropenem and 25% showed resistance to amikacin. Nitrofurantoin resistance was found

in 18% of the *E. coli* and 25% of *Klebsiella*.

Table II: Antibiotic resistance pattern of Gram-positive organisms (in %) n = 18.

Organism	Drugs						
	Coamoxy-clav	Erythro-mycin	Cipro-floxacin	Vanco-mycin	Line-zolid	Doxycyc-line	Clinda-mycin
<i>Staph. Aureus</i>	25	75	25	0	0	0	50
<i>Coagulase negative Staph.</i>	37.5	87.5	62.5	0	0	37.5	75
<i>Enterococcus</i>	33	50	83.3	0	0	NA	33

Table III: Antibiotic resistance pattern of Gram-negative organisms (in %) (n = 65).

Organism	Drugs								
	Amo-xydclav	Pipera-cillin	Ceftri-axone	Mero-penem	Poly-myxin	Cipro-floxacin	Amik-acin	Cotrimo-xazole	Nitro-furantoin
<i>E. coli</i>	69.2	30.8	46.2	23.1	2.6	46.2	12.8	69.2	17.9
<i>Klebsiella</i>	62.5	31.3	18.8	12.5	0	50	31.3	37.5	25
<i>Pseudomonas</i>	50	75	50	50	0	25	25	50	25
<i>Acinetobacter</i>	50	50	75	25	0	75	25	50	50

Discussion

In this pilot study, it was found that *E. coli* was the most common organism in diabetic infections, especially urinary infection. In blood stream infections, *Coagulase negative Staphylococcus* was most common. There was significant resistance to commonly used antibiotics like macrolides and fluoroquinolones, in both Gram-positive and Gram-negative bacteria.

In a 2017 study from Andhra Pradesh, Sharma *et al* found that in elderly (> 60 years) type 2 diabetics, *E. coli* was the commonest cause of UTI (70%), followed by *Klebsiella* (16%)¹². In our present study also (vide Table I), *E. coli* was the commonest cause of UTI (61%) followed by *Klebsiella* (18.6%). However, in contrast to the aforementioned study (which included above - 60 years patients), our study included patients of all age groups. In the Andhra Pradesh study, among the *E. coli*, 52% showed resistance to nitrofurantoin, 40% to Amikacin and 30% to Levofloxacin¹². In our study, among the *E. coli*, 46% showed resistance to fluoroquinolones (FQ), 13% to amikacin and 18% to Nitrofurantoin. Thus, in the Eastern Indian context, nitrofurantoin is still likely to be effective for *E. coli* infection. In our study, in the *Klebsiella*, 31% showed resistance to Piperacillin, 50% to fluoroquinolones and 12% to carbapenems. In contrast, in the study by Sharma *et al*, piperacillin resistance was found in 89% and FQ resistance in 15%¹². Such difference in sensitivity patterns in different regions of the country

will necessitate different local guidelines.

Aswini *et al* (2014) compared the antibiotic resistance patterns among diabetic and non-diabetic subjects with UTI¹³. It was seen that there was no significant difference between the two groups¹³. There was around 50% resistance to commonly used cephalosporins like ceftriaxone and cefotaxime. For norfloxacin, in *E. coli*, there was 75% resistance while in *Pseudomonas*, there was more than 80% resistance¹³. In a study from Kuwait (2016), it was seen that in UTI, both *E. coli* and *Klebsiella* showed significant resistance to cotrimoxazole, FQ and 3rd generation cephalosporins¹⁴. In our study, cotrimoxazole resistance varied from 50 - 70% (vide Table III). In the Kuwait study, a subgroup analysis was done between subjects with controlled and those with uncontrolled glycaemia. There was no difference in the microbiology of infections in the two groups. Thus, although patients with uncontrolled diabetes are more susceptible to infections, the organisms responsible for those infections are no different from those with well controlled diabetes.

In some studies, it has been found that a large proportion of UTI in diabetes is caused by gram positive organisms like *Staphylococcus* and *Enterococcus*¹⁵. In many cases, bacterial culture of specimens from diabetic patients yield *Candida Spp*. But whether it is a coloniser or a pathogen is often undetermined¹⁵. Compared to urinary infection and diabetic foot, there is very little data on infection of other sites in diabetic patients. In a study from Saudi Arabia, it was seen that *E. coli* was the commonest organism isolated from blood in diabetic subjects, followed by *Staph. Aureus*¹⁶. Diabetic foot and intravenous access sites were common causes of bloodstream infection¹⁶. In our study, among blood culture positive cases, *coagulase negative Staphylococcus* was the commonest followed by *Staph. aureus* (vide Table I). Thus, Gram-positive organisms were predominant while no cases of *E. coli* was found.

In our study, all the sputum culture positive cases were due to Gram-negative bacteria. In other studies also, it has been shown that respiratory infections in diabetic subjects are often caused by Gram-negative pathogens, which is in contrast to non-diabetic subjects where Gram-positive bacteria predominate¹⁷. Ahmed *et al* (2017) showed that in cases of community acquired pneumonia in diabetics, the main organisms were Gram-negative ones like *Klebsiella* and *Pseudomonas*¹⁷. Thus, in cases of community acquired respiratory tract infections in diabetic subjects, Gram-negative antibiotic coverage must be given.

In the present study, among the Gram-positive organisms, macrolide resistance was found in 50 - 87% of cases and clindamycin resistance was found in 33 - 75% of cases (vide Table II). Such high degree of antibiotic resistance in

community acquired Gram-positive organisms has also been shown in other Indian studies¹⁸.

The main strength of the present study is the depiction of data on microbiology of community acquired infections in diabetics in an Eastern Indian population. Such data are vital in formulating local guidelines. However, this study is also limited by the small number of patients and lack of genetic study for drug resistance in bacteria. Such studies are planned in the future.

Conclusion

In a sample Eastern Indian population, *E. coli* was the commonest organism isolated in cases of community acquired infections in diabetic subjects. There was a high predominance of Gram-negative infections in diabetic subjects. Both Gram-positive and Gram-negative organisms showed significant resistance to macrolides, cotrimoxazole, fluoroquinolones and 3rd generation cephalosporins.

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