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Original Article

Community Medicine Section

Pattern of Antibiotic Resistance Among Community Derived Isolates of *Enterobacteriaceae* Using Urine Sample: A Study From Northern India

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ABSTRACT

Background: Despite world-wide evidence of increased antibiotic resistance, there is scarce data on antibiotic resistance in community settings. One of the reason being difficulty in collection of biological specimen (traditionally stool) in community from apparently healthy individuals. Hence, finding an alternative specimen that is easier to obtain in a community setting or in large scale surveys for the purpose, is crucial. We conducted this study to explore the feasibility of using urine samples for deriving community based estimates of antibiotic resistance and to estimate the magnitude of resistance among urinary isolates of *Escherichia coli* and *Klebsiella pneumonia* against multiple antibiotics in apparently healthy individuals residing in a rural community of Haryana, North India.

Materials and Methods: Eligible individuals were apparently healthy, aged 18 years or older. Using the health management information system (HMIS) of Ballabgarh Health Demographic Surveillance System (HDSS), sampling frame was prepared. Potential individuals were identified using simple random sampling. Random urine sample was collected in a sterile container and transported to laboratory under ambient condition. Species identification and antibiotic susceptibility testing for *Enterobacteriaceae* was done using Clinical Laboratory and Standards Institute (CLSI) 2012 guidelines. Multi-drug resistant (MDR) *Enterobacteriaceae*, Extended Spectrum Beta Lactamase (ESBL) producing *Enterobacteriaceae*, and Carbapenem producing *Enterobacteriaceae* (CRE) were identified from the urine samples.

Results: A total of 433 individuals participated in the study (non-response rate – 13.4%), out of which 58 (13.4%) were positive for *Enterobacteriaceae*, 8.1% for *E. coli* and 5.3% for *K. pneumoniae*. Resistance against penicillin (amoxicillin/ampicillin) for *E. coli* and *K. pneumoniae* was 62.8% and 100.0% respectively. Isolates resistant to co-trimoxazole were 5.7% and 0.0% respectively. None of the isolates were resistant to imipenem, and meropenem.

Conclusion and recommendations: It is feasible to use urine sample to study magnitude of antibiotic resistance in population based surveys. At community level, resistance to amoxicillin was considerable, negligible for co-trimoxazole, and to higher antibiotics including carbapenems.

Keywords: Bacteria, Drug resistance, Epidemiology

INTRODUCTION

Antibiotics are commonly used drugs to treat various types of infections in humans [1]. According to an estimate, globally 30 to 60% of the patients at the level of primary health care receive antibiotics which probably is double to that of the clinical requirement [2]. Almost four-fifth of all antibiotics are used in the community settings [3]. As much as 20-50% of all antibiotics use is inappropriate which may lead to higher risk of side effects, increased cost of treatment, and increase in the antibiotic resistance among various pathogens [4]. Even with appropriate use, there is increase in the antibiotic resistance [5].

In community based studies, the proportion of resistant isolates among faecal *E.coli* was found to be almost two-fifth for ampicillin and cotrimoxazole [6]. In a community based study done on the commensals obtained from the urine samples, more than half of the isolates were resistant to ampicillin, ciprofloxacin, cotrimoxazole and nalidixic acid [6]. Globally, Carbapenem resistance is also one of the emerging threats in antibiotic treatment [7]. In 2010, presence of carbapenem resistant New Delhi Metallo Beta Lactamases-1 (NDM-1) positive bacteria in samples of seepage and drinking water were reported from Delhi. Its prevalence in seepage water was as high as 29%, and in drinking water it was 4% [8].

The increased levels of antibiotic resistance in community settings against some of the commonly used antibiotics along with recent evidence of presence of carbapenem resistant *Enterobacteriaceae* in environmental samples in New Delhi has highlighted the importance of antibiotic resistance surveillance [8]. Recently, studies in India have reported carbapenem resistant multi drug resistant (MDR) strains to be resistant to both tigecycline and colistin, a condition termed as Pan Drug Resistance (PDR), and an ominous harbinger of the so-called post antibiotic era [9,10].

Enterobacteriaceae isolates have been most frequently used organism for the studies of antibiotic resistance [4,11,12]. Amongst *Enterobacteriaceae*, *E. coli* is the most commonly used organism [6]. *K. pneumoniae*, *Streptococcus pneumoniae*, and *Haemophilus influenza* had been used for the surveillance of antibiotic resistance in some of the previous studies [4,13].

In the surveillance studies of antibiotic resistance in community, stool samples have been commonly used sample for the isolation of *Enterobacteriaceae*. There is difficulty in the collection and transportation of faecal samples in community settings [14,15]. Urine has also been used as a source of *Enterobacteriaceae* in some studies [6]. There are evidences to prove that the bacteria that colonize in the gastro-intestinal tract get transferred to perineum or meatus or terminal part of urethra of an individual and then can be isolated from the urine [16-19].Thus, urine sample can be used as a proxy of stool sample as a source of normal gut flora.

Although there are many studies on the antibiotic resistance in hospital settings, there is limited literature available on the magnitude of resistance in a community setting. Most of the previous antibiotic

surveillance studies have been done on the faecal samples. Urine samples for such studies have not been explored in the past. Therefore, our objective was to explore the feasibility of using urine samples for community based assessment of antibiotic resistance and to assess the magnitude of resistance using urinary isolates of *E. coli* and *K. pneumoniae* amongst *Enterobacteriaceae* against various classes of antibiotics.

MATERIALS AND METHODS

This community-based cross-sectional survey was conducted in the Ballabgarh Health and Demographic Surveillance System (HDSS) [20] managed by Centre for Community Medicine (CCM), All India Institute of Medical Sciences (AIIMS), New Delhi. The study site was situated in Ballabgarh block of Faridabad district, Haryana, India. Study period was from November 2012 to December 2013. Residents of study area aged 18 years or older, willing to participate, and able to give valid consent were included in the study.

We could not find any study that could guide sample size calculation. Hence, prevalence of *Enterobacteriaceae* in urine was assumed to be 50% to calculate sample size since it would yield the maximum sample size. Taking absolute precision of 5%, level of significance 5%, power of 80%, and response rate of 80%, final required sample size was calculated to be 500.

Ballabgarh HDSS had Health Management and Information System (HMIS), which is a computerized database of information including, socio-demographics, antenatal care, birth, immunization, eligible couples, family planning, morbidity and mortality etc. of all the individuals residing in the area [20]. This computerized database was used to generate a random list of 500 eligible individuals. House to house visit was made to contact all 500 selected individuals. Minimum of two house visits were made to contact the individual. All the individuals were initially approached during from 8 AM to 7 PM. If an individual was not present, the likely time of his/her availability was ascertained and second house visit was made accordingly.

Study instruments included an interview schedule, sterile wide mouth container with screw cap, sterile platinum loop, Bunsen's burner, petri dishes, MacConkey agar, refrigerator, incubator, Mueller Hinton agar, antibiotic discs, stickers, and marker pens for labelling. Selected individuals were administered a semi-structured, pre-tested interview schedule having socio-demographic details.

A random urine sample was collected from all the selected individuals in sterile wide mouth container. Urine was collected up to half of the container capacity. Collected urine sample was kept at room temperature until it was transported to the laboratory at the sub-district hospital, Ballabgarh. In the laboratory, urine sample was plated on MacConkey agar plate using sterile platinum loop. Bunsen's burner, and gloves were used to maintain asepsis. After overnight incubation at 37 degree Celsius, agar plate that showed growth were transferred to the Microbiology department of All India Institute of Medical Sciences (AIIMS), New Delhi maintaining cold chain between 2°C and 8°C. In Bacteriology laboratory of Microbiology department, AIIMS, species identification was done first, using standard methods. If either *E. coli* or *K. pneumoniae* was present then antimicrobial susceptibility testing was done. Antimicrobial susceptibility testing and interpretation was performed using the disc diffusion method on Mueller Hinton agar following CLSI (Clinical and Laboratory Standards Institute) guidelines 2012 [21]. Resistance was tested against the following 8 classes of antibiotics namely: penicillin, cephalosporin, carbapenem, beta lactam and beta lactamase inhibitor combination, aminoglycosides, fluoroquinolones, cotrimoxazole, and nitrofurantoin.

We used the following operational definitions: 1) Multi-drug resistant (MDR) *Enterobacteriaceae*: Bacteria was labelled as MDR if it was resistant to three or more classes of antibiotics; 2) Extended Spectrum Beta Lactamase (ESBL) producing *Enterobacteriaceae*: *Enterobacteriaceae* isolates resistant to either ceftazidime or ceftriaxone (third generation cephalosporin); 3) Carbapenem resistant *Enterobacteriaceae* (CRE): *Enterobacteriaceae* isolates resistant to either imipenem or meropenem. ATCC strain of *E. coli* 25922 was used as a control.

Quality assurance: The first author (AL) had received training on plating and checking for growth under the supervision of a senior microbiologists (AK). Species identification and antimicrobial susceptibility was done by a senior microbiologist (AK).

Ethical issues: All the individuals were explained about the purpose of the study, and were provided with a participant information sheet in local language. Individuals were informed regarding the consent process. Ethical approval was obtained from the Ethics Committee of the All India Institute of Medical Sciences, New Delhi. Informed written consent was obtained from all individuals.

STATISTICAL ANALYSIS

Data were entered in Epi-Info version 3.5.4 (Centre for Disease Control, United States of America), and cleaned using Microsoft Excel 2010 (Microsoft Corporation, United States of America). Analysis was done in Stata 11 (Stat Corp College Station Texas). Results of descriptive analysis are presented as proportions with 95% confidence intervals or as mean (SD) wherever applicable.

RESULTS

Of the 500 individuals selected for the study, information could be collected from 433 individuals (response rate 86.6%). Reasons for non-response included locked house/inability to contact after two visits (8.6%), refusal to participate in study (3.2%), and refusal to give consent (1.6%). Almost 52.0% of the study participants were males. Most of the individuals were in the age group 18-29 years (males 37.2%, females 38.4%). A small proportion (12.5% and 16.7% for males and females respectively) were aged 60 years and above. The demographic characteristics of male and female individuals were similar [Table/Fig-1,2].

Profile of *Enterobacteriaceae* isolates and their antibiotic susceptibility: Out of the 433 urine samples, 58 (13.4%) were positive for *Enterobacteriaceae*, 8.1% for *E. coli* and 5.3% for *K. pneumoniae*. All the *Enterobacteriaceae* isolates were subjected to antibiotic susceptibility testing [Table/Fig-3]. Proportion (95% CI) of ESBL producing isolates was 20.0% (10.0, 35.9) among *E. coli* and 8.7% (2.4, 26.8) among *K. pneumoniae*. Among *E. coli* and *K.*

Variable	Numbers (%)	
Sex		
Male	224 (51.7)	
Female	209 (48.3)	
Total	433 (100.0)	
Age		
Age group	Male Numbers (%)	Female Numbers (%)
18-29 years	83 (37.2)	80 (38.4)
30-39 years	49 (21.8)	39 (18.6)
40-49 years	35 (15.6)	32 (15.3)
50-59 years	29 (12.9)	23 (11.0)
>= 60 years	28 (12.5)	35 (16.7)
Total	224 (100.0)	209 (100.0)
Mean age		
Mean age (SD) (years)	38.08 (1.06)	39.08 (1.15)
Marital status		
Unmarried	45 (20.1)	18 (8.6)
Married	177 (79.0)	162 (77.6)
Widow (er)	2 (0.9)	29 (13.8)
Total	224 (100.0)	209 (100.0)

[Table/Fig-1]: Socio-demographic characteristics of study participants-1

Variable	Male Numbers (%)	Female Numbers (%)
Occupation		
Professional	1 (0.4)	0 (0.0)
Semi-professional	6 (2.7)	0 (0.0)
Clerical, shop owner, farmer	59 (26.3)	0 (0.0)
Skilled worker	57 (25.4)	2 (1.0)
Semi-skilled worker	8 (3.6)	1 (0.5)
Unskilled worker	30 (13.4)	5 (2.4)
Unemployed/ Homemaker	63 (28.2)	201 (96.1)
Total	224 (100.0)	209 (100.0)
Literacy status		
Professional	1 (0.4)	0 (0.0)
Graduate/ Post-graduate	29 (12.9)	5 (2.3)
Intermediate/ Diploma	57 (25.4)	27 (12.9)
High school	42 (18.8)	22 (10.5)
Middle	29 (12.9)	30 (14.4)
Primary	33 (14.8)	23 (11.0)
Illiterate	33 (14.8)	102 (48.9)
Total	224 (100.0)	209 (100.0)

[Table/Fig-2]: Socio-demographic characteristics of study participants-2

pneumoniae, proportion (95% CI) resistant to at least one antibiotic was 77.1% (60.9, 87.9) and 100% (85.0, 100.0) respectively [Table/Fig-4]. The prevalence (95% CI) of MDR isolates among *E. coli* and *K. pneumoniae*, was found to be 28.6% (16.3, 45.1) and 8.7% (2.4, 26.8) respectively [Table/Fig-5].

DISCUSSION

We assessed the feasibility of using urine samples for community based study of antibiotic resistance and also, the magnitude of antibiotic resistance in this apparently healthy population in community setting. There were many studies available in the literature giving information regarding antibiotic resistance profile among pathogens isolated from various bodily samples in hospital based settings. But very few studies have been done so far showing magnitude of antibiotic resistance in apparently healthy individuals from community settings in rural areas. These organisms have the potential to cause various infections in human body. Magnitude of antibiotic resistance identified from the hospital settings represents only the tip of the iceberg. Knowledge regarding resistance in community settings can help us better frame the policies and guidelines regarding treatment of various infections. It can also help frame strategies to combat the antibiotic resistance at community and national level.

Type of antibiotic	*E. coli* (n=35) Number (%age)	*K. pneumoniae* (n=23) Number (%age)
Penicillin (amoxycillin /ampicillin)	22 (62.8)	23 (100)
2nd gen. cephalosporin (cefuroxime)	12 (34.2)	3 (13.0)
Ceftazidime	7 (20.0)	1 (4.3)
Cefotaxime	2 (5.7)	2 (8.7)
Imipenem (Carbapenem)	0 (0.0)	0 (0.0)
Meropenem (Carbapenem)	0 (0.0)	0 (0.0)
Amoxicillin + clavulanate	13 (37.1)	2 (8.7)
Cefoperazone + sulbactam	0 (0.0)	0 (0.0)
Piperacillin + tazobactam	0 (0.0)	0 (0.0)
Amikacin	2 (5.7)	0 (0.0)
Aminoglycoside	3 (8.5)	1 (4.3)
Norfloxacin	8 (22.8)	0 (0.0)
Ciprofloxacin	3 (8.5)	0 (0.0)
Co-trimoxazole	2 (5.7)	0 (0.0)
Nitrofurantoin	0 (0.0)	0 (0.0)

[Table/Fig-3]: Distribution of resistance pattern among isolated *E. coli* and *K. pneumoniae* by type of antibiotics

No. of antibiotics for which the resistance was noted	*E. coli* (n=35) Number (%age)	*K. pneumoniae* (n=23) Number (%age)
0	8 (22.9)	0 (0.0)
1	10 (28.6)	20 (86.8)
2	7 (20.0)	1 (4.4)
3	3 (8.6)	0 (0.0)
4	2 (5.6)	1 (4.4)
5	1 (2.9)	0 (0.0)
6	1 (2.9)	1 (4.4)
7	2 (5.6)	0 (0.0)
8	1 (2.9)	0 (0.0)
Resistance against at least 1 antibiotic (%) [95% CI]	27 (77.1) [60.9, 87.9]	23 (100) [85.0, 100.0]

[Table/Fig-4]: Distribution of resistance pattern among isolated *Enterobacteriaceae* by number of antibiotics* for which the resistance was noted
*- Total no. of antibiotics tested was 15

No. of antibiotics for which the resistance was noted	*E. coli* (N=35) Number (%age)	*K. pneumoniae* (N=23) Number (%age)
0	8 (22.8)	0 (0.0)
1	11 (31.4)	20 (87.1)
2	6 (17.1)	1 (4.3)
3	5 (14.3)	1 (4.3)
4	2 (5.7)	1 (4.3)
5	3 (8.7)	0 (0.0)
Resistance to ≥3 classes of antibiotics (%) [95% CI]	10 (28.6) [16.3, 45.1]	2 (8.7) [2.4, 26.8]

[Table/Fig-5]: Distribution of resistance pattern among isolated *Enterobacteriaceae* by number of classes of antibiotics† for which resistance was noted
†- Total no. of classes of antibiotics tested was 8

The proportion of male individuals was 51.7% in the study which is same as the proportion of males in the study area (51.7%). Amongst males, most of the individuals were from age group 18-29 years (37.2%), which is almost same as the total population (38.1%). Similarly for females, most of the individuals were from the age group 18-29 years (38.4%) which is almost same as that of total population (38.2%). Thus, the study population was truly representative of the source population.

Feasibility of using urine samples for community based study on antibiotic resistance

Urine samples have been used previously for community based studies of antibiotic resistance. The rate of bacterial isolation from urine samples is lower as compared to the faeces sample which is a more commonly used sample for such studies. But using urine sample has many advantages which includes good compliance rate, and ease of collection of sample [6]. In this study, *Enterobacteriaceae* carriage rate (13.6%) in urine was significantly lower than the reported carriage rate of gram negative bacteria in gastro-intestinal tract of adult asymptomatic individuals which was usually more than 90% [12,13,22]. Whether antibiotic resistance pattern among *Enterobacteriaceae* isolated from urine and faecal samples of the same individual is same or not is not clear. And, this would require a separate study. Assuming that the resistance pattern is same irrespective of type of specimen, the only remaining question is the low bacterial yield from urine sample which appears to be almost one-seventh of faecal sample. Thus, an option exists between a much smaller sample that is reassured but difficult to obtain stool sample, and a larger sample but easy to obtain urine sample. The choice would depend upon study setting. In health care facility setting, faecal sample may be appropriate. However,

in community setting, urine sample may be a more attractive and feasible option.

Isolates extracted from urine samples

Out of all the *Enterobacteriaceae* isolated, 60.3% were *E. coli* and rest were *K. pneumoniae*. This finding is similar to other studies done abroad as well as in India wherein *E. coli* had been found to be the most common organism causing community acquired urinary tract infection (UTI) [23-29] and asymptomatic bacteriuria [29-31].

Antibiotic resistance profile in community settings

We found that 20.0% of *E. coli* and 8.7% of *K. pneumoniae* isolates were producing ESBL. This was similar to the findings reported by different Indian [32-34] as well as foreign investigators [35,36]. A multicentre study involving three centres i.e. Delhi, Vellore, and Mumbai had also ascertained drug resistance among commensals. In our study, the overall resistance against penicillin class of drugs (amoxicillin/ ampicillin) was similar to that of Delhi centre which was 71.0% among commensals. Proportion of isolates resistant to ciprofloxacin was similar to their Vellore centre (3.5%), and against cefotaxime and gentamicin was similar to their Mumbai centre, which was 5.9% and 6.2% respectively [6]. Resistance to other antibiotics was different from this multicentre study, which could be due to differences in antibiotic usage among the communities studied.

More than half of the *E. coli* and all of the *K. pneumoniae* were found to be resistant to penicillin class of drugs (amoxicillin or ampicillin). Similarly, the resistance of *E. coli* isolates against amoxicillin and clavulanate combination was found to be 37.1%. This finding suggests that the use of this antibiotics for common ailments should be avoided and the drug should be reserved as a second line drug. Nitrofurantoin, which is excreted primarily in urine and used commonly to treat UTI in pregnancy, had also been found to have 100% susceptibility against *E. coli* and *K. pneumoniae* isolates. This finding supports the use of nitrofurantoin for the treatment of UTI in pregnancy. Among other antibiotics, resistant isolates against norfloxacin and ciprofloxacin were found to be lesser than the other commonly used antibiotics. Therefore these antibiotics can be used to treat the urinary infections on the empirical basis, and especially for norfloxacin which is known to have a primary renal excretion.

Carbapenem class of drugs constitute the last step towards a therapeutic dead end. The isolates resistant to carbapenem are sensitive only to two antibiotics i.e. tigecycline, and colistin [7]. So, the resistance against carbapenem class of drugs has clinical as well as public health implications. In this study, none of the isolated *Enterobacteriaceae* were found to be resistant to imipenem and meropenem (carbapenem class of drugs). This finding contradicts the finding by Walsh et al., which had reported the presence of carbapenem resistance bacteria (New Delhi Metallo-beta lactamases-1) in the environmental samples of New Delhi [8]. They had concluded that NDM-1 beta lactamase was widely disseminated in New Delhi and has spread into key enteric pathogens on the basis of the presence of isolates in drinking and seepage samples. The authors also stated that resistant bacteria seems to be circulating in the community and may pose a high level of risk for the travelers and residents. Our study provides direct evidence of the absence of carbapenem resistant bacteria among adults residing in rural Haryana which was approximately 40 kilometres from Delhi. In addition, some potential conflict of interest was identified by Kant et al., with Walsh's study [37]. The findings of our study suggests that conclusions regarding the presence of NDM-1 in Delhi and surrounding areas, as reported by Walsh, should be interpreted with caution.

Other antibiotics like cefotaxime, ceftazidime, aminoglycoside, cefoperazone & sulbactam combination, and piperacillin & tazobactam combination should be reserved for the infections which do not respond to the first-line antibiotics or on the basis of results of culture and sensitivity.

This study had following limitations: pathogens and commensals were not differentiated in the study which restricted clinical implications of the findings. Only two species i.e. *E. coli* and *K. pneumoniae* were studied among the *Enterobacteriaceae*. Hence we were unable to comment on other species of *Enterobacteriaceae*. However, since this was a community based study, the direct extrapolation of results to the source community can be done; unlike other studies where some proxy indicators were used to extrapolate the results to the community level. Simple random sampling was done so the results are generalizable to the source population. Also, this is likely to be one of the initial studies that estimated antibiotic resistance in community settings in rural India. All samples were tested in one laboratory by a qualified microbiologist. The laboratory had internal quality checks in place. Hence, the results are likely to be valid and reliable.

CONCLUSIONS AND RECOMMENDATION

In community settings, it is feasible to use urine samples to isolate bacteria for estimating the magnitude of antibiotic resistance.

Study suggested that the use of penicillin class of drugs for the empirical treatment should be avoided. Instead co-trimoxazole can be used effectively for these infections and higher antibiotics should be reserved for resistant and complicated infections only. Such community based surveillance should be continued in future and these results could serve as baseline data for comparison with future surveillance studies.

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