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Original Article

Antibiotic Resistance: Situation Analysis In a Tertiary Care Hospital of Bangladesh

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Emergence of multidrug resistant organism (MDR) is a global concern. Resistance pattern of organism varies from one country to another and within the country. Systematic data are lacking in many developing countries of the world. In view of the above, the present study was undertaken to investigate the current situation of antibiotic resistance and patterns of organism responsible for major infection in a seven hundred bed tertiary care hospital of Bangladesh. A total of 27,069 clinical samples collected over four years period (2011 to 2014) were included in the study. The samples were cultured in respective media as per standard procedure. Identification of organism and antibiotic sensitivity was performed according to CLSI guidelines. All data were analyzed by Whonet-5 software. Out of 27,069 clinical samples, urine was 59.7%, blood was 25.1%, pus/ wound swab was 7.9% and respiratory sample was 7.2%. Growth was obtained in 27.3% of the total sample. 28% urine, 8% blood, 66% pus and wound swab and 42% respiratory sample were found culture positive. Major Gram negative bacteria namely *Escherichia coli*, *Klebsiella* sp., *Salmonella sp., Pseudomonas sp.* and *Acinetobacter sp.* were 22,119 and major Gram positive bacteria namely *Staphylococcus aureus* and *Enterococcus* sp were 4353 in overall culture positive sample. The major Gram negative bacteria showed resistance to imipenem (3 -84%), third generation cephalosporin (61.6%-94.9%), aminoglycosides (10.8-88.6%), ciprofloxacin (56-90.1%), cotrimoxazole (58-80.3%), nitrofurantoin (14.3-91.7%), tazobactum+piperacillin (20.8-81.4%) and colistin (2.2-16.4%). The carbapenem resistant enterobacteriaceae (CRE) was 9.8%. ESBL positivity rate among *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp. and *Citrobacter* sp. were 44.8%, 31.1%, 29% and 15.4% respectively. Average ESBL producing enterobacteriaceae was 18 to 31% over four years. So there is considerable proportion of ESBL producing and imipenem resistant Gram negative bacteria. The isolation rate of MRSA was 33%. No vancomycin resistant *Staphylococcus aureus* (VRSA) and enterococci (VRE) was detected but 39% enterococci showed high level resistance to gentamicin (HLGRE). Of special interest, 92% *Salmonella* was nalidixic acid resistant (NARST).The high rate of NARST was consistant over four years. The result indicate high prevalence of resistant organisms to several antibiotics. Regular monitoring and surveillance is necessary for curbing the emergence of resistant organism and effective infection control in the hospital settings of Bangladesh.

Key words: Antibiotic resistance, Tertiary care hospital, ESBL, MRSA, NARST, CRE

Introduction

"Antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill" –reported by WHO in 2014 on global surveillance of antimicrobial resistance[1]. So in response to WHO it is our extreme need to fight against the drug resistant microbes and to save our future generations from these superbugs. So continuous surveillance is necessary to explore the current situation of antibiotic resistance globally. Resistance pattern of organism varies from one country to another and within the country. Systematic data are lacking in many developing countries of the world.

The development and spread of antibiotic resistance is multi-factorial. The resistant is best assessed when measurement is focused on pathogens that are recovered from patients after admission and monitoring resistance at the patient level (i.e. what percent of patients develop resistant)[2].

In view of the above, the present study was undertaken to address the current situation of antibiotic resistance and patterns of organism responsible for major infection over four years in a seven hundred bed tertiary care hospital of Bangladesh.

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Materials and Methods

The cross sectional study was conducted in Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM General Hospital), a seven hundred bed tertiary care hospital of Bangladesh. A total of 27,069 samples obtained for culture and sensitivity tests from inpatient and outpatient department during 2011 to 2014 were incorporated in this study. Samples included blood, urine, respiratory secretions, pus and wound swab. The samples were cultured in respective media for isolation of potential pathogens. Isolates were identified by standard methods[3]. Antibiotic sensitivity was performed according to CLSI guidelines by Kirby Bauer disk diffusion techniques[4]. All data were analyzed by WHONET-5 software.

Results

A total of 27,069 clinical samples were analyzed which included 6796 blood (25.1%), 16173 urine (59.7%), 1961 respiratory secretions (7.2%), 2139 pus and wound swab (7.9%). Growth was obtained in 27.3% of the total sample (Fig 1). 28% urine, 8% blood, 66% pus and wound swab and 42% respiratory sample were found culture positive. Major Gram negative bacteria namely *Escherichia coli*, *Klebsiella* sp., *Pseudomonas* sp. and *Acinetobacter* sp. were found in 22,119 and samples major Gram positive bacteria namely *Staphylococcus aureus* and *Enterococcus* sp. were found in 4353 samples. Among the four major Gram negative bacteria isolation rate of *Klebsiella* sp. (16.7% to 21.9%) and *Pseudomonas* sp. (12.9% to 15.9%) increased from 2011 to 2014 as shown in Table 1. Antibiotic resistance observed were 3-84% to imipenem, 61.6%-94.9% to third generation cephalosporin, 10.8-88.6% to aminoglycosides, 56-90.1% to ciprofloxacin, 58-80.3% to cotrimoxazole, 14.3-91.7% to nitrofurantoin, 20.8-81.4% to tazobactum+piperacillin and 2.2-16.4% to colistin in Gram negative bacteia. 70% *Escherichia coli and* 65% *Klebsiella* developed resistantce to 3rd generation cephalosporins, 77% *Escherichia coli* to fluoroquinolones, 16% *Klebsiella* and 58% *Pseudomonas* to carbapenem, 92% *Salmonella* to Nalidixic acid and 32% *Staphylococcus aureus* shown resistant to oxacillin (Table 4). ESBL positivity rate among *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp. and *Citrobacter* sp. were 44.8%, 31.1%, 29% and 15.4% respectively. Average ESBL producing enterobacteriaceae is 18 to 31% over four years (Fig 5). The carbapenem resistant enterobacteriaceae (CRE) was 9.8% (Fig 2). The average isolation rate of MRSA was 33% from 2011 to 2014 (Fig 5). No vancomycin resistant *Staphylococcus aureus* (VRSA) and *Enterococci* (VRE) was detected but 39% *Enterococci* showed high level resistance to gentamicin (HLGRE) (Table 2). Of special interest, 92% *Salmonella* sp. was nalidixic acid resistant (NARST) (Table 3).

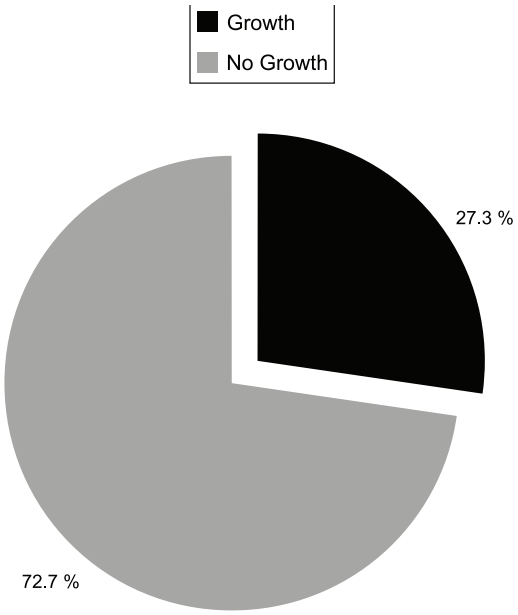

Figure 1. *Rate of culture positive samples (Total=27,069) over 4 years*

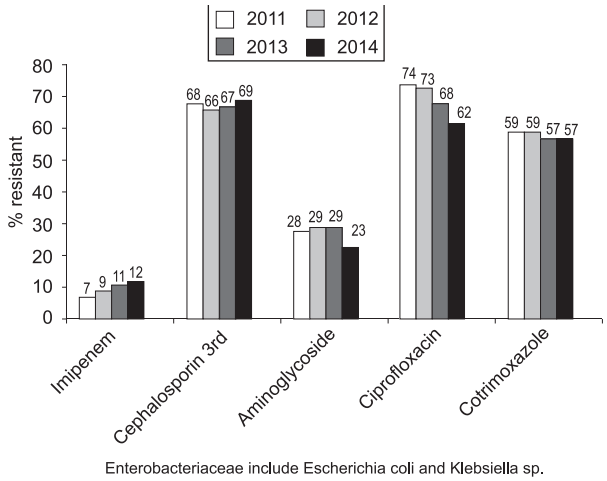

Figure 2. *Antibiotic resistance pattern of Enterobacteriaceae (N= 16089) from 2011 to 2014 isolated from clinical samples*

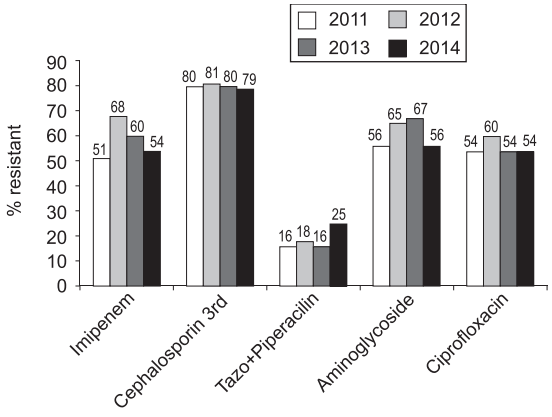

Figure 3. *Antibiotic resistance pattern of Pseudomonas sp. (N=2981) from 2011 to 2014 isolated from clinical samples*

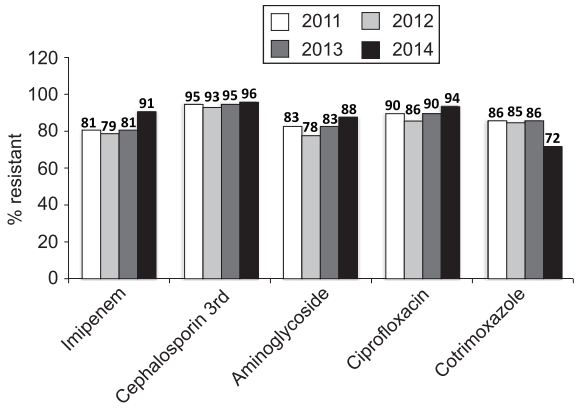

Figure 4. *Antibiotic resistance pattern of Acinetobacter sp. (N=2749) from 2011 to 2014 isolated from clinical samples*

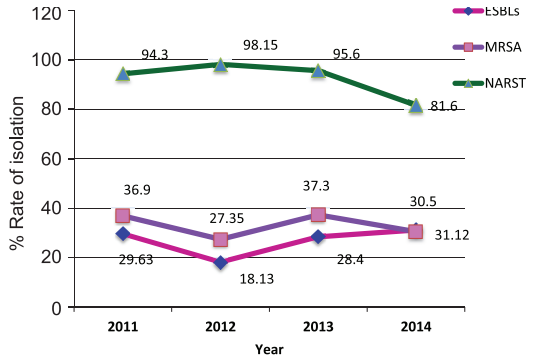

Figure 5. *Trends of ESBLs, MRSA, NARST from 2011 to 2014*

Table 1. *Isolation rate of four major Gram negative bacteria from 2011 to 2014*

Name of organisms	No of organism (%)			
	2011	2012	2013	2014
Escherichia coli	2537 (56.8%)	2860 (55.9%)	3196 (55.6%)	3319 (48.8%)
Klebsiella sp.	747(16.7%)	868 (16.9%)	1068 (18.6%)	1494 (21.9%)
Pseudomonas sp.	576(12.9%)	754 (14.7%)	875 (15.2%)	1075 (15.8%)
Acinetobacter sp.	607 (13.6%)	626 (12.2%)	608 (10.6%)	909 (13.4%)
Total no. (N)	4467	5108	5747	6797

Table 2. *Antibiotic resistance pattern of major Gram positive organisms from 2011 to 2014*

Name of antibiotic	% Antibiotic resistance				
Staphylococcus aureus	2011 (N=238)	2012 (N=696)	2013 (N=750)	2014 (N=957)	Average (N=2641)
Oxacillin	37.5	27.3	37.5	29.5	33
Cephalexin	57.5	28.9	40.6	30.7	39
Augmentin	62.9	66.4	47.0	42.0	55
Vancomycin	00	00	00	00	00
Enterococcus sp.	(N=480)	(N=343)	(N=406)	(N=483)	(N=1712)
Penicillin	32.7	38	34	30	34
Ampicillin	17.6	14.9	15.8	20	17
Gentamicin (High level resistance)	33.6	37.7	44.8	39.39	39
Vancomycin	00	00	00	00	00

Table 3. *Antibiotic resistance pattern of Salmonella sp. from 2011 to 2014*

Name of antibiotic	% Antibiotic resistance				
	2011(N=49)	2012(N=45)	2013(N=40)	2014(N=53)	Average(N=187)
Ampicillin	44.2	41.9	32.6	33.6	38
Cotrimoxazole	17	12.5	38.0	31.3	25
Choramphenicol	17.2	12.2	27.2	46.4	26
Nalidixic Acid	92.8	100	97.2	82.6	93
Ciprofolxacin	25.6	38.2	15.3	0	26
Azithromycin	16.4	37	49.5	41.6	36

Table 4. *Current situation of common antibiotic resistance in different bacteria from 2011 to 2014*

Organism	Name of antibiotic	% Antibiotic Resistant			
		2011	2012	2013	2014
Escherichia coli	3rd generation cephalosporin	70.3	68.7	69.7	70.67
	Fluoroquinolone	83.1	80.9	74.7	71.1
Klebsiella sp.	3rd generation cephalosporin	66.3	63.5	63.6	67.1
	Carbapenem	11.6	16	19.2	20.0
Pseudomonas sp.	Carbapenem	51.1	68.4	60.0	53.7
Salmonella sp.	Nalidixic acid	94.3	98.2	95.6	81.6
Staphylococcus aureus	Methicillin	36.9	27.35	37.3	30.5

Discussion

In our study conducted over a period of four years from 2011 to 2014, high prevalence of multi drug resistant organisms were served. This scenario is also supported by several recent reports, which suggests high rate of resistant organisms among hospitalized patients of Bangladesh[5,6,7]. In this study the isolation rate of Gram negative bacteria (22,119) were five fold higher than Gram positive bacteria (4353). The cause of predominant isolation rate of the Gram negative organism among hospitalized patient might be due to selective pressure of broad spectrum antibiotics causing persistent of drug resistance genes/ plasmids, virulence factors like flagella, capsule, outer membrane in this class compared to Gram positive bacteria[8].

In this study it is alarming that 70% *Escherichia coli and* 65% *Klebsiella* developed resistant to 3rd generation cephalosporins, while resistence was observed among 77% *Escherichia coli* to fluoroquinolones, 16% *Klebsiella* and 58% *Pseudomonas* to carbapenem, 92% *Salmonella* to Nalidixic acid and 32% *Staphylococcus aureus* to methicillin. Wide spread use of cephalosporins, fluoroquinolones, carbapenems to limit the life threatening infection in the co morbid diabetic and non diabetic patient admitted in this hospital, may be the reason for this high rate of detection of these superbugs. More over misuse and overuse of the antibiotics, high consumption rate, easy accessibility of antibiotics[9], lack of hospital antimicrobial policy and concrete regulatory body for antibiotic stewardship program at national level are also important factors for this increasing rate of antibiotic resistance among Bangladeshi populations.

The emergence and rapid dissemination of carbapenem resistant enterobacteriaceae (CRE) is now global health threat[10,11]. Multi drug resistant bacteria are difficult to treat as the treatment options are limited. In our settings we found CRE was on an average 9.8% over four years. High prevalence of ESBLs limited the therapeutic options for drug resistant organisms resulting in increase the consumption of carbapenems. Other factors like long term hospitalization, frequent use of invasive medical devices have also fueled the rapid rise in carbapenem resistance[12].

Production of extended spectrum β lactamases (ESBLs) by enteric Gram negative bacteria in hospitals and community is now getting worsened. The enzyme effectively inactivates all group of β lactam drug except carbapenem. The present study showed high prevalence of ESBL producing enterobacteriaceae (18-31%). A study conducted in a referral hospital of Dhaka city had also noted 43.2% *Escherichia coli* and 39.5% *Klebsiella* were ESBL positive[13].

In a multicenter study involving four divisions of Bangladesh, the ratio of isolation of MRSA from hospital patients ranged between 32 to 63%[14]. In our observations MRSA was between 27 to 37% . This trend is alarming as there are not many inexpensive drugs to treat simple infection with MRSA.

Treatment failures with ciprofloxacin have slowly started to emerge in Bangladesh and other countries due to infection with nalidixic acid resistant *Salmonella typhi* or NARST[15]. NARST has decreased susceptibility to ciprofloxacin. In our study it was 92% which also correlate with the study done in same hospital over 6 years period where NARST was 80 to 90%[16].

However, antibiotic resistance is an increasingly serious threat to global public health that requires coordinated action across all government sectors and society. Antibiotics are losing effectiveness in every country in the world. Patients with infections caused by drug resistant bacteria are generally at increased risk of worse clinical outcomes and death, and consume more health-care resources than patients infected with the same bacteria that are not resistant. So coordinated actions of people, health workers, pharmacists, policy makers, scientists and industry can help to minimize emergence and spread of antibiotic resistance globally[17].

The study had some limitations. We did not calculate statistical value of the changing trends of all microbes and their sensitivity pattern. We did not attempt to investigate underlying disease condition of patients, risk factors or their source of infections to confirm the real pathogens or colonizer.

Conclusion

The results from this study indicate high prevalence of resistant organisms to several antibiotics. There is considerable proportion of ESBL producing and imipenem resistant Gram negative bacteria. The high rate of MRSA and NARST was consistant over four years. Gradual increase in number of organisms and their resistance to common antibiotics were also observed from 2011

to 2014. So the data collected from this report could provide an up-to-date overview of the present situation of antibiotic resistance in Bangladesh. Regular monitoring and surveillance is necessary for curbing the emergence of resistant organism and effective infection control in the hospital settings of Bangladesh.

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