

Antibiotic Resistance Pattern and Stewardship Programme in Critical Care Settings

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Abstract

Sensitivity pattern of isolates from patients' specimens associated with infection, admitted to the critical care centres with empiric or prophylactic antibiotic use were assessed. Till identification of the organism and resultant sensitivity awaited; and compared with sensitive antibiotic to the isolates which could be used for management. This analytical cross sectional study carried out during the period of April 2016 to July 2016 in the Critical Care Centre (CCC) of Combined Military Hospital, Dhaka Cantonment. Urine and other specimens including wound swab, pus, sputum, tracheal aspirate, catheter tip, nasal swab, high vaginal swab, bronchoalveolar lavage, blood, urethral discharge were collected from the patients following aseptic precautions. Isolate identification was done using standard procedures at the Armed Forces Institute of Pathology (AFIP). Sensitivity was tested using antibiotic disc diffusion technique. A total of one thousand six hundred and seventy patients were dealt with in the study, and positive yield obtained in 190 (11.38%) cases. Of those, 116 were urine specimens which constituted 69 (57.76%) female and 47(42.24%) male patients. A total of 1088 discs of antibiotics were used on an average 9 discs per isolate. Six hundred and forty nine (59.65%) showed resistance to the antibiotic used against them, while four hundred and thirty nine (40.35%) showed sensitive response. The study population was of 2-80 years age group. Other specimens included 74 isolates, fifty (67.57%) were males and twenty four (32.43%) were females. A total of eight hundred and twenty seven (11.18 discs per isolate) antibiotic doses were used 479 (57.92%), showed resistant and 348 (42.08%) sensitive result. Enteric gram negative bacilli (GNB) were the majority of isolates in both types of specimens. The study indicated that, newer antimicrobials have a substantial impact in decreasing human morbidity and mortality rates. It encourages to expand surveillance of antibiotic resistance determinants and to exercise caution in dispensing antibiotics to maximize their continued efficacy. Excess or injudicious use is causing increase in cost as well as inducing drug resistance among the common bacterial isolates. A work on the clinical presentation with trends of antimicrobials used in the CCC setup right now in tertiary care hospital would be of supplemental value for the study.

Keywords: Isolate, Antibiotic resistance, Urine, Stewardship

Introduction

Familiarity with evolving patterns of antimicrobial resistance in enteric gram negative bacilli (GNB) is necessary in the selection of appropriate empiric therapy, particularly given the lag between published and real time resistance rates and the ever increasing prevalence of multidrug resistant (MDR) GNB. If broadspectrum treatment has been initiated and information on microbial susceptibility is become available, it is just as important to use the most appropriate narrow spectrum agent. This

type of antimicrobial stewardship will avoid unnecessary selection of and potential super-infection with resistant bacteria, may decrease costs, and maximize the useful longevity of available antimicrobial agent.¹ Likewise, it is important, not to treat patients who are colonized but not infected.² The antimicrobial resistance profiles of GNB vary with species, geographic location, regional antibiotic use, and hospital site e.g. intensive care units (ICUs) versus wards. Rodriguez B et al showed that a comprehensive "bundle" approach for control of hospital wise endemic MDR *Acinetobacter baumannii*, a GNB,

that could effectively control the spread and impact of MDRAb.³ Problems associated with excessive use of antibiotics were recognized shortly after their introduction into clinical use in 1940s.⁴ In his review on the subject in 1956, Jawetz was the first to recognize the problem caused by the attractiveness of new antibiotics to physicians, exaggerated claims by the pharmaceutical industry, and the enormous impact that promotion by the drug companies had on medical practice.⁵ Approximately, 60% of all hospitalized patients in the USA, receive at least one dose of an antimicrobial drug during hospitalization.^{6,7} It appears that as much as 50% of this use is unnecessary or otherwise inappropriate.^{8,9} Among the unwanted consequences of antimicrobial therapy are, increased length of hospital stay, increased cost, predisposition to secondary infections, and, most importantly the emergence of drug resistant organisms.¹⁰ Antimicrobial drug use is responsible for the rising incidence of serious health care-associated infection due to methicillin and glycopeptide resistant *Staphylococcus aureus*, vancomycin resistant *Enterococci* (VRE), extended-spectrum β -lactamase-producing Enterobacteriaceae, multidrug resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp, *Klebsiella* spp expressing *Klebsiella pneumoniae* carbapenemases, as well as proliferation of more virulent strains of *Clostridium difficile*.¹¹⁻¹³ The increase in rates of resistance is not matched by development of antimicrobial drugs, leading to the inevitable conclusion that we must be smarter in using the drugs we currently have, to preserve their usefulness.¹⁴ The antimicrobials are “special” because their use in one patient has the potential for adverse consequences in other who has not received the drug; the usefulness of these agents is declining with their increased use; this gave rise to the term “stewardship” in 1996 to draw attention to these unique characteristics.¹⁵ Previously referred to as

antimicrobial “management or “control” programmes^{16,17}. The focus of these programs tended to be financial, because antibiotic expenditures accounted for as much as 30-50% of a hospitals total drug budget.¹⁸ Support of antimicrobial stewardship programmes (ASPs) in hospital received a major boost in 2007 with the publication of stewardship guidelines from the Infectious Diseases Society of America (IDSA).¹⁹

Antimicrobial stewardship: The programmes for improvement in the quality of patient care, with the goals of improving clinical outcomes and stabilizing or reducing rate of resistance is called Antimicrobial Stewardship Programme (ASP).²⁰ Firstly, one must understand constrains under which physicians work and the pressure that are exerted on them to prescribe drugs. It has become more of a psychological or philosophical endeavor than a scientific exercise.²¹

Factors identified leading to inappropriate use of antimicrobial agents:^{22,23}

- i) Good intentions;
- ii) Inappropriate dosing;
- iii) Inappropriate prophylaxis-Hospitalized patients receives antimicrobial agents for a variety of other prophylactic purposes that are not evidence-based and that may contribute to the resistance emergence;
- iv) Use of multiple antimicrobial agents or broad spectrum combinations to cover the possibility of infection caused by uncommon organisms. The approach generalized from management of neutropenic, febrile patient, is often used as a substitute for appropriate diagnostic evaluation;
- v) Pressure from the patient to be treated with an antimicrobial agent;
- vi) Time constrains;
- vii) Cost and availability of radiographic studies and diagnostic tests in relation to the ready solution offered by prescribing;
- viii) Inadequacy of some physicians’ knowledge of diagnostic procedures and management of infectious diseases;
- ix) Malpractice considerations and fear of litigation;

- x) “Spiraling empiricism” refers to concerns about increasing prevalence of antimicrobial resistance and the perceived need to prescribe ever more broad spectrum antimicrobials to “cover” these pathogens; and
- xi) Easy solutions provided by the manufacturers.

Some clinicians believe that ASPs impose unnecessary or even deleterious constraints on the practice of medicine.^{24,25} Their skepticism arises from the perception that there is a lack of documented efficacy of ASPs across varied health care settings, a paucity of direct evidence demonstrating an improvement in clinical outcomes, limited time or incentive to pursue such efforts and, a weak causal link between the emergence of resistance and antibiotic use patterns.

Stewardship strategies are as follows:

- i) Antibiotic order forms;
- ii) Antibiotic rotation;
- iii) Antimicrobial formulary restriction;
- iv) Automatic stop orders;
- v) Clinical practice guidelines;
- vi) Computer –assisted management programmes;
- vii) Costing of items in clinical microbiology laboratory;
- viii) Direct interaction;
- ix) Educational programmes;
- x) Formal seminars;
- xi) Multidisciplinary approaches;
- xii) Newsletters;
- xiii) Performance evaluation;
- xiv) Prior approval programmes;
- xv) Purchase plans;
- xvi) Simple chart entry;
- xvii) Telephone approval; and
- xviii) Therapeutic substitution and streamlining programs.

Materials and Methods

This analytical cross sectional study was carried out in the Critical Care Center of Combined Military Hospital, Dhaka Cantonment, Bangladesh from April 2016 to July 2016. Admitted patients in Critical Care Centres (CCC) with clinically diagnosed conditions including

fever, diabetes mellitus with or without complications (DM), coma, single or multi-organ organectomy and more were included in the study. Following strict aseptic precautions and standard procedures, midstream clean catch urine and other specimens were collected as done. Approval of appropriate authority was taken for conduction of the study. Data were analysed for patients showing positive culture, in AFIP, Dhaka Cantonment from these, the pattern of isolate and sensitivity pattern were evaluated after employing standard microbiological method of bacterial identification and sensitivity by Kirby-Bauer disc diffusion method. Finally, Microsoft excel data analysis tool were used for analysis for result generation.

Sample collection: Urine and other samples were collected for the bacteriological examination from the critical care set up of CMH Dhaka. Collection of midstream clean catch urine was adopted and other specimen collections were done following strict aseptic precautions. Transportation of specimens was carried out carefully to the laboratory.

Isolation and identification: The collected samples were cultured into blood agar and MacConkey agar media. Appropriate and specific procedure were followed for morphological and biochemical identification of the isolated organisms.

Antimicrobial susceptibility test: Susceptibility pattern were performed using disc diffusion method in Mueller-Hinton agar plate. Cultures were tested against antibiotics in common use in management of patients. The proportion of ineffective antimicrobials was calculated as the sum of the resistant isolates relative to the total number of drug tested. The organisms were more such agents, considered multi drug resistant (MDR) when showing resistance to the effect of three or more.

Results

Out of 1670 specimens, 190 showed positive culture yield. *E. coli* was the most frequent organisms isolated from the 116 urine specimens. (table I)

Table I: Number of isolates yielded in urine

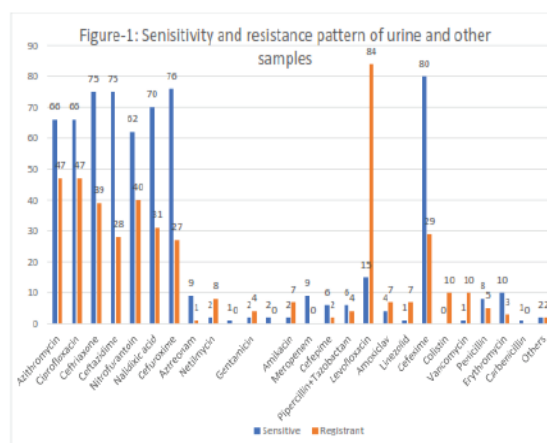
Organism	Total number	Percent
<i>E coli</i>	82	70.69
<i>Enterococci</i>	11	9.48
<i>Pseudomonas</i>	3	2.59
<i>Klebsiella</i>	8	6.90
<i>Acinetobacter</i>	6	5.17
<i>Proteus</i>	0	0
<i>Staph aureus</i>	3	2.59
<i>Enterobacter</i>	2	1.72
<i>Candida</i>	1	0.86

Antibiotic sensitivity of the isolates to used doses of the various antibiotics studied in urine specimen isolates, showing 58.41% sensitive to Azithromycin (table II).

Table II: Antibiotic resistance statistics of antibiotics used in urine

Antibiotic	Resistant	Percent	Antibiotic	Resistant	Percent
Azithromycin		58.41	Aztreonam		90.00
Ciprofloxacin	66	58.41	Netilmycin	2	20.00
Ceftriaxone	75	65.79	Gentamicin	2	33.33
Ceftazidime	75	72.82	Amikacin	2	22.22
Nitrofurantoin	62	60.78	Meropenem	9	100.00
Nalidixic acid	70	69.31	Cefepime	6	75.00
Cefuroxime	76	73.79	Piperacillin+Tazo	9	
Livofloxacin	15	15.15	Erythromycin	10	76.92
Linezolid	15	11.11	Carbenicillin	1	100.00
Amoxyclav	80	73.40	Others	2	50.00
Colistin	0	0			
Vancomycin	1	9.10			
Penicillin	8	61.54			

Resistance trends of all the antibiotics used in urinary isolates, indicated more antibiotics were resistant in the isolates than sensitive. Sensitivity pattern of first eight isolates from urine specimens, clearly shown that about 60% resistant and only about 40% sensitive (figure 1).



The percent of sensitivity/resistance were delineated along with percent of disc used in first seven urinary specimens. Isolate number in other specimens showed highest number of acinetobacter (table III).

Table III: Isolate number in other specimen (n=74)

Organism	Total number	Percent
<i>E coli</i>	16	21.62
<i>Staph aureus</i>	11	14.86
<i>Acinetobacter</i>	18	24.32
<i>Enterococcus</i>	6	8.11
<i>Klebsiella</i>	7	9.46
<i>Streptpneu</i>	6	8.11
<i>Proteus</i>	4	5.41
<i>Pseudomonas</i>	4	5.41
<i>Salmonella</i>	2	2.70

Sensitivity and resistance pattern of the isolates in other specimens indicated 18 (24.32%) *Acinetobacter*, the most frequent yield followed by *E coli* 16 (21.62%) and *Staphylococcus aureus* 11 (14.86%) (table IV).

Table IV: Resistance pattern of antibiotics in isolates of other specimen

Antibiotic	Resistant	(%)	Antibiotic	Resistant	(%)
Azithromycin	38	52.05	Aztreonam	20	100
Ciprofloxacin	28	37.84	Netilmycin	11	52.38
Ceftriaxone	36	49.32	Cefepime	19	90.48
Ceftazidime	30	61.22	Piperacillin+Taz	19	95.00
Nitrofurantoin	1	100	Livofloxacin	7	30.44
Nalidixic acid	1	50	Amoxyclav	46	63.89
Cefuroxime	36	78.26	Linezolid	1	12.50
Cefixime	41	56.94	Cephalexin	41	75.93
Colistin	2	9.52	Flu, Clo, Pef	00	0
Vancomycin	0	00.00	Other	35	72.92
Penicillin	15	65.22			
Erythromycin	5	21.74			
Gentamicin	0	Nu*			
Meropenem	0	Nu*			

*Not used

Discussion

Periodical surveillance of the prevalent isolate pattern and their antimicrobial susceptibility are valuable information for determination of appropriate therapy for infections in critically sick patients.²⁶ The study, recorded two *Enterobacter* spp isolates in urine specimen, one is only Colistin sensitive, another is sensitive to Netilmycin and Amikacin in addition to Colistin. This study did not include any VRE. It is evident from the record that irrespective of the complain(s), patients were given more than one antibiotic management in CCC. Isolate yield in specimen of urine with *E coli* as the most frequent organism 82 (70.69%) followed by *Enterococci*, and least is *Enterobacter* only 2 (1.72%). Most sensitive were Colistin (100%), Linezolid 15(11.11%), Netilmycin 2(20.00%), Amikacin 2 (22.22%)and Gentamicin 2 (33.33%). Most resistant were Meropenem and Carbenicillin 9, 1 (100.00%) used respectively; then Aztreonam, Erythromycin, Cefepime and Cefuroxime. The sensitivity pattern of the used antibiotics highest activity were delineated by Flucloxacillin, Cloxacillin, Pefloxacin, Ofloxacin and Vancomycin, all appeared sensitive in the study. Colistin and Linezolid come next in efficacy. Most resistant were Nitrofurantoin, Cefuroxime, Cephalexin, Cephradine. Prevalence of resistance rates expressed in earlier works are fewer than it is now, 25% as a whole in 2013, an indication of gravity of the antibiotic resistance problem. The result indicated that these organisms were in possession of drug resistance acquired due to empiric or prophylactic antibiotics applied prior to obtaining sensitivity pattern of the growth. About 60% of the used antibiotics were resistant in isolates, and they were nosocomially gained infection in CCC setup. The study did not include finding out the exact cost in the purchase of antibiotic drug in the CCC set up in CMH, reliable source indicate it to be above 60% of drugs budget. A survey in 47 hospitals in phase 3 Project ICARE (Intensive Care Antimicrobial Resistance Epidemiology) revealed that all hospitals had an antimicrobial formulary and 91% of them used at least one of the following three mechanisms to improve use: stop orders, antibiotic restriction, or clinical practice guidelines. Antibiotic resistant bacterial

nosocomial infections are a leading problem in intensive care units (ICU). To study the pattern of microorganism and bacterial resistant to antibiotic in ICU of Bangabandhu Sheikh Mujib Medical University (BSMMU) of Bangladesh a similar study, as the one in question was carried out.²⁷ The causal link between the use of antibiotics for animal growth promotion and augmentation of resistance in human pathogens has been disputed²⁸, but more recent evidence is convincing that transfer of resistance gene occurs through the food human consume.^{28, 29} It was reported that, aquatic environments are particularly rich in bacterial population replete with antibiotic resistance genes³⁰. A Vancomycin resistant *E coli* was isolated in urine specimen in the study. Reports of VRSA in Japan and the United States showed that common, invasive microbial pathogens may become refractory to any chemotherapeutic agent in future.³¹

Analysis of bacterial resistance to antibiotics in south east Asian region revealed that multi drug resistant (MDR) Tuberculosis, extended drug resistant TB (XDR) reported from Bangladesh, India, Indonesia and Thailand.³²

A report recommends total volume of antibiotic prescribing quinolones, cephalosporins, coamoxyclov and other broad spectrum agents as well as 3 days course for trimethoprim, nitrofurantoin and pivmecillinum.³³ Poor public health indicators, rising incomes, and the availability of inexpensive antibiotics over the counter without a prescription are converging to create the ideal conditions for a large scale selection and dissemination of resistance genes in India. India is not alone in this battle, and the experiences of other countries in dealing with antimicrobial resistance are described in the most recent State of the World's Antibiotics Report.³⁴

Conclusion

It may be concluded that the appropriate surveillance, a hospital laboratory may efficiently and rapidly detect the emergence of new resistance, or the presence of a new microbial strain, within a specific unit or patients. Work on the clinical presentation, with the trends of antimicrobials used in the CCC setup in tertiary

care hospital would be of complemented value to the study for further steps towards implementation of antibiotic stewardship programme.

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