STUDY ON ANTIMICROBIAL RESISTANCE AND ITS CORRELATION WITH ANTIMICROBIAL USE

REPORT SUBMITTED TO

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Abstract:

Since the advent of antimicrobial agents many deadly and crippling infectious disease were able to treat and cured the patients but due to the irrational use of antimicrobial agents the microbes were able to develop the antimicrobial resistance in the early stage then the expected time and frequency.

This study was done with the objectives to find out the pattern and extent of antimicrobial usage and the extent of antimicrobial resistance in hospital OPD.

This study was done in TUTH from January to December 2001. The antimicrobial usage pattern was studied by analyzing 100 prescriptions in every two months for one year duration and the drug consumption was calculated in DDD for each drugs. The antimicrobial resistance study was done by studying the antimicrobial resistance pattern of approximately 100 isolates in every 2 months for one year. The antimicrobial sensitivity test was done by using the disc diffusion method.

This study has reveled that for every prescription 0.8 antimicrobial agents was prescribed and of the total prescribed drugs 32% were antimicrobial agents. Amoxicillin was the most frequently prescribed antimicrobial agents among the antimicrobial agents followed by doxycycline, cipriofloxacin, cloxacillin.The antimicrobial sensitivity pattern revealed that among the most frequently isolated organisms, 59.3% of Staphylococcus were resistant to amoxicillin, 12.9% to ciprofloxacin and 12.9% of isolates were MRSA but only 7.9% of isolates were resistant to erythromycin.The study also demonstrated that 27.3% Streptococcus pneumoniae were resistant to amoxicillin, and TMP/SMX, and 9.1% to erythromycin but all the strain were sensitive to ciprofloxacin and cloxacillin. Among the Gram negative bacteria, 67.8% Escheriachia coli were resistant to amoxicillin, 24% to ciprofloxacin and 45.6% to norfloxacin. Similarly high resistance level was observed in Klebsiella, Citrobacter and Enterobacter spp. In contrast, only 6.6% isolates of Salmonella typhi were resistant to Amoxicillin, and all the isolates were sensitive to ciprofloxacin and ceftriaxxone. Similarly most of the strains of Salmonella paratyphi were sensitive to amoxicillin, ciprofloxacin and ceftriaxone.

In conclusion, there must be a hospital antimicrobial policy to treat the infections and physicians need to be educated on the local antimicrobial resistance pattern for rational prescribing. There should be defined a first line and reserved antimicrobial agents to treat the infections and to preserve some antimicrobial agents in life threatening conditions.

Acknowledgement

Acronyms and Abbreviations

ABST	Antimicrobial Sensitivity Test
DDD	Daily Define Dose
ENT	Ear Nose and Throat
G+O	Gynecology and Obstetrics
MDR	Multi Drug Resistance
MRSA	Methicillin Resistant Staphylococcus aureus
OPD	Out Patient Department
Ortho.	Orthopedics
TMP/SMX	Trimethroprim/ Sulphamethoxazole
TUTH	Tribhuvan University Teaching Hospital
VRE	Vencomycin Resistant Enterococci
WHO	World Health Organization

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1. Introduction

Antimicrobial agents are substances which are intended to use against the harmful microbes to reduce the morbidity, to prevent severe complications and to save life from the deadly infections. Antimicrobial agents have been used irrationally. The irrational use of antimicrobial agents is one of the major factors for the emergence of antimicrobial resistance. Antimicrobial resistance increases the morbidity, treatment cost and the mortality caused by infectious diseases.

This study was undertaken to find out the extent of antimicrobial use and degree of antimicrobial resistance in a teaching hospital setup.

2. Objectives of the study:

General:

The general objective of the study was to find out the pattern of antimicrobial use and degree of antimicrobial resistance and the relationship between antimicrobial usage and antimicrobial resistance.

Specific objectives.

To find out the prescribing pattern in OPD in TUTH

To find out the degree and pattern of antimicrobial usage in TUTH

To find out the antimicrobial resistance pattern in the hospital isolates

To find out the correlation between antimicrobial use and antimicrobial resistance.

3.   Literature review:

A study on prescribing in rural Sri Lanka (Indra 1989)reveled that analgesics were most commonly prescribed drugs and antimicrobial agents were the second common agent being prescribed. About 42% patients were prescribed antimicrobial agents. Similarly another study on drug prescribing pattern in Government and private institutions showed that the mean drug exposure ingovernment institutions varied between 3.6 to 3.7 where at the private institutions patients were exposed to an average of 7.2 drugs and antimicrobial agents were the most frequently prescribed class of drugs (Angunawela,1988). A base line survey on use of drug in the primary health care level in Bangladesh (Guyon, 1994) showed that the mean number of drugs prescribed per patient was 1..44, 78 % of the drugs were prescribed by their generic name, and 25% were treated with antibiotics. Another study in Seychells on prescribing pattern showed that on average less then two items per script were prescribed , generic name was used of the 40% of the items prescribed and 30% of the prescribed items were for an anti-infective preparations, 19% were for the minor analgesics and 14% were for drugs acting on the respiratory system (Chennabathni,1982).

Drug resistant infectious agents - those that are not killed or inhibited by antimicrobial comounds are an increasingly important public health concern. Hospitals, worldwide are facing unprecedented cries form the rapid emergence and dissemination of other microbes resistant to one or more antimicrobial agents.

Staphylococcus aureus resistant to methicillin(MRSA) Vencomycin resistant Enterococci (VRE), Penicillin resistant Streptococci, Penicillin or Tetracycline resistsnt Gonococci, Chloroquine resistant malaria, Multi-drug resistant tuberculosis and , resistant strains of highly pathogenic bacteria causing the diaarrhoeal diseasses such as Shigella dysenteriae, Compylobacter, Vibrio cholerae, Escherichia coli and salmonella are(causing major public health problem.(NIAID fact sheet,2002). Of

that level of resistance to MRSA, Escherichia coli, Salmonella typhi, Streptococcus pneumoniae has been mainly addressed in this study.

The variety of mechanisms by which bacteria acquire resistance to antimicrobial drug is astonishing. More research is urgently needed to define the mechanism of resistance, to look for new target for antimicrobial drugs, to discover more effective ways of using existing drugs, to minimize the development of resistance, to ascertain the most useful therapy for infections due to multidrug resistant organisms, and to learn how to prevent these infections (Wood,1996). International co-operation on surveillance of drug resistance is desirable to determine the extent to which different national prescribing practices translate in to different resistance rates. To this end , WHO is establishing network of surveillance. At other exreeme a good local surveillance is needed to empirical treatment and to help individual hospital to manage their resistance problems(Livermore,1998)..

4.   Materials and Methods:

Anttimicrobial usage

This study was done in Tribhuvan university teaching Hospital (TUTH), Kathmandu , Nepal from January to December, 2001 for one year. Antimicrobial usage pattern was studied by analyzing approximately 100 prescriptions in every two months for six occasions. For this purpose the prescriptions were collected from ENT, Orthopedics, Gynecology and Obstetrics, General surgery and General medicine OPD. The data collection from the prescription were based on WHO guidelines - selected drug indicators based in WHO /DAP/93.1′.The antimicrobials quantity were converted to daily define Dose (DDD)when tabulating the data.

Antimicrobial resistance:

Antimicrobial resistance pattern was studied by studying 100 isolates obtained in each 2 months for 6 occasions from the different samples in TUTH

5. Results

Analysis of prescribing indicators of TUTH OPD

Of the 804 prescriptions analyzed a1917 drugs were prescribed which demonstrated that 2.4 drugs were prescribed per prescription. Out of 804 prescrptions analyzed 204(25.4%) were prescribed in generic name and   for every prescription there was o.76 antimicrobial agents prescribed(612/804).

Table 5.1   Analysis of prescribing indicators of TUTH OPD

Ward	N0.of prescription analyzed	N0 of drug prescribed	No of drug prescribed in generic name	No of antimicrobials prescribed
ENT	220	492	77	146
Ortho	116	261	18	79
G+O	109	289	18	107
Surgery	160	352	48	136
Medicine	199	523	43	144
Total	804	1917	204	612

Number of drugs prescribed per prescription:

The prescriptions analysis reveled that 1-6 number of drugs per prescription were prescribed and 48.9% of prescriptions were containing only two drugs, followed by 31.4% prescription containing 3 drugs and 10% prescriptions containing 4 drugs and 7.9 % of prescriptions containing only one drug per prescription.

Table 4.2   Number of drugs prescribed in TUTH OPD

Name of OPD	No of drug Prescribed						
	1	2	3	4	5	6	Total
ENT	24	94	58	24	3	3	206
Orthopedics	1	42	60	9	0	0	112
G+O	4	52	34	16	1	2	109
Surgery	17	93	24	14	0	0	148
Medicine	16	98	69	15	6	1	205
Total	62	379	245	78	10	6	780
%	7.9	48.9	31.4	10.0	1.3	0.8	100.

Pattern of Antimicrobials use in TUTH OPD

The prescription analysis reveled that the Amoxicillin (1755DDD).was the most commonly prescribed antimicrobial agents followed by Doxycycline (1464DDD),Ciprofloxacin (720DDD), and cloxacillin (720DDD)

Table 4.3 Pattern of Antimicrobials use in TUTH OPD

Antimicrobials	Unit dose	ENT ward	Ortho ward	G+O ward	Surgery ward	Med. ward	Total	Total DDD(%)
Amoxicillin	500 mg	1929	1163	14	676	1485	5267	1756 (31.1)
cloxacillin	500mg	653	585	0	1091	441	2770	693(12.2)
Ciprofloxacin	500mg	193	88	124	370	665	1440	720(12.7)
Norfloxacin	400mg	20	0	0	20	0	40	20(0.3)
Erythromycin	500mg	140	0	0	28	440	608	152(2.0)
Doxycycline	100mg	360	90	664	88	262	1464	1464(25.9)
Tetracycline	500mg	0	0	56	0	0	56	14(0.2)
Metronidazole	400mg	36	147	564	141	153	1041	355(6.3)
Tinidazole	500mg	0	0	82	74	0	156	68(1.0
Cephazolin	500mg	10	0	84	40	0	134	33.5(0.5)
Cephalorodine	500mg	0	144	20	51	30	245	61.(1.0)
Cephalexine	500mg	282	0	0	62	0	344	115(2.0)
Cephaclor	500mg	40	0	0	40	0	80	27(0.5)
Cephadroxil	500mg	20	100	0	40	0	160	80(1.4)
Cefotaxime	1gm	57	0	0	31	0	88	29(0.4)
Gentamycin	80mg	25	40	0	0	0	65	22(0.3)
Augmentin		90	30	0	0	0	120	40(0.7)
Total								

Organisms isolated and studied:

Staphylococcus aureus was the most frequently isolated organism (315%) and Escherchia coli (26.6%) . Klebsiella pnumoniae(12.7%), Pseudomonas spp (7.8%,and Salmonella typhi (5.2%) were other frequently isolated organisms.

Of the 62 isolates from the respiratory tract infections Pseudomonas spp 16(25.8%), Haemophilus influenzae14 (22.6%), Klebsiella pneumoniae 13 (21%) and Streptococcus pneumoniae 9(14.5%) were the most common isolates from the sputum.

Of the 81 isolates from the blood culture Salmonella typhi 30(37.0%). Staphylococcus aureus 24(29.6%), Coagulase negative Staph 9(11.1%)) and Salmonella paratyphi 6(7.4%) were most frequently isolated organism in blood culture.

 Out of 247 organism isolated from the swab Staphylococcus aureus145(58.7%), was the most commonly isolated organism followed by Escherichia   coli 30 (12.1%), Klebsiella pneumoniae 27 isolates (10.9%), Pseudomonas 25 (10.1%) were the frequently isolated organisms.

Of the 185 isotes obtained from the urine culture 120(64.9%) of isolate were Escherichia coli, 30(16.2%) were Klebsiella pneumoniae, Coagulae negative Staphylococcus 9(4.9%) and Staphylococcus aureus 7 isolates(3.7%) were the frequently isolated organisms.

Table 5.4 Distribution of Isolates from different clinical specimen:

Isolates	Sputum	Blood	Swab	Urine	Total	%
Streptococcus pneumoniae	9	4	0	0	13	2.2
Streptococcus pyogenes	2	0	3	0	5	0.86
Steptococcus faecalis	0	0	0	2	2	0.34
Staphyloccus aureus	5	24	145	7	181	31.47
Staphylococcus coagulase negative	0	9	2	9	20	3.47
Haemophilus influenzae	14	0	0	0	14	2.43
Pseudomonas aeruginosa	16	0	25	4	45	7.82
Citrobacter freundii	1	2	6	3	12	2.08
Proteus spp	2	0	3	2	7	1.22
Escherichia coli	0	3	30	120	153	26.6
Klebsiella pneumoniae	13	3	27	30	73	12.70
Acinetobacter	0	0	2	2	4	0.68
Enterobacter	0	0	3	1	4	0.68
Providencia	0	0	1	3	4	0.68
Morganella	0	0	0	2	2	0.34
Salmonella typhi	0	30	0	0	30	5.21
Salmonella paratyphi	0	6	0	0	6	1.06
Total(%)	62(10.8)	81(14.1)	247(43.0)	185(32.1)	575(100)	99.84

Antimicrobial sensitivity pattern of the isolated organisms

Staphylococcus aureus:

Of the 182 strains of Stayphylococcus aureus tested against different antimicrobial agents 108(59.3%) were resistant to amoxicillin, 67(36.8%) to cotrimoxazle and 43/178(24.2%) to cephalexin , 23(12.9%) to ciprofloxacin, 22 (12.4%) to cloxacillin.and 14(7.9%) to Erythromycin. (Table 4.5)

Table 4.5 ABST pattern of Staphylococcus aureus:

Antimicrobial	Tested	Sensitive	%	Resistant	%
Amoxicillin	182	74	40.7	108	59.3
Co-trimoxazole	182	115	63.2	67	36.8
Cephlexin	178	135	75.8	43	24.2
Ciprofloxacin	178	155	87.1	23	12.9
Cloxacillin	178	156	87.6	22	12.4
Erythromycin	178	164	92.1	14	7.9
Norfloxacin	4	3	75	1	25
Nitrofurantoin	4	3	75.0	1	25.0
Chloramphenicol	9	7	77.8	2	22.2
Cefuroxime	15	3	20.0	12	80.0
Tetracycline	6	6	100.0	0	0.0
Ceftriaxone	28	24	85.7	4	14.3
Cefotaxime	11	9	81.8	2	18.2
Augmentin	11	11	100	0	0

Antimicrobial sensitivity pattern of coaguase Negative Staphylococcus

Of the 21 strains of Coagulase Negative Staphylococcus 7(33.7) strains were resistant to
Amoxicillin, 6(28.6%) to cotrimoxazole, 9(42.9%) cephalexin, 1(4.8%) ciprofloxacin. where as all
the tested strains of coagulase negative Staph was sensitive to cloxacillin and erythromycin

Table 5.6   Antimicrobial sensitivity pattern of coaluase Negative Staph

Antimicrobial	Tested	Sensitive	%	Resistant	%
Amoxicillin	21	14	66.7	7	33.3
Co-trimoxazole	21	15	71.4	6	28.6
Cephlexin	21	12	57.1	9	42.9
Ciprofloxacin	21	20	95.2	1	4.8
Cloxacillin	21	21	100	0	0
Erythromycin	21	19	21	0	0
Norfloxacin	4	3	75	1	25
Nitrofurantoin	6	6	100	0	0
Chloramphenicol					
Cefuroxime					
Tetracycline					
Ceftriaxone	6	6	100	0	0
Cefotaxime					
Augmentin					

Antimicrobial sensitivity pattern of Streptococcus pneumoniae:

Of the 11 strains of Streptococcus pneumoniae 3(27.3%) strains were resistant to amoxicillin and cotrimoxazole, 2(18.2%) were resistant toCephalexin, 1(9.1%) was resistant to erythromycin. Where as all the strains was sensitive to ciprofloxacin and cloxacillin.

Table 5.7   Antimicrobial sensitivity pattern of Streptococcus pneumoniae:

Antimicrobial	Tested	Sensitive	%	Resistant	%
Amoxicillin	11	8	72.7	3	27.3
Co-trimoxazole	11	8	72.7	3	27.3
Cephlexin	11	9	81.8	2	18.2
Ciprofloxacin	11	11	100	0	0
Cloxacillin	11	11	100	0	0
Erythromycin	11	10	90.9	1	9.1

Antimicrobial sensitivity pattern of Streptococcus pyogens:

Of the 5 isolates of Streptococcus pyogens all were sensitive to amoxicillin, Cephalexin, ciprofloxacin, cloxacillin. In contrast 4(80%) isolates were resistant to cotrimoxazole, and 1(20%) was resistant to erythromycin.

Table 5.8   Antimicrobial sensitivity pattern of Streptococcus pyogens:

Antimicrobial	Tested	Sensitive	%	Resistant	%
Amoxicillin	5	5	100	0	0
Co-trimoxazole	5	1	20	4	80
Cephlexin	5	5	100	5	0
Ciprofloxacin	5	5	100	0	0
Cloxacillin	5	5	100	0	0
Erythromycin	5	4	80	1	20

Table 5.9   ABST pattern of Streptococcus faecalis:

Antimicrobial	Tested	Sensitive	%	Resistant	%
Amoxicillin	2	0	0	2	100
Cotrimoxazole	2	0	0	2	100
Cephlexin	2	0	0	2	100
Ciprofloxacin	2	1	50	1	50
Cloxacillin	2	1	50	1	50
Erythromycin	2	1	50	1	50
Norfloxacin	2	1	50	1	50
Nitrofurantoin	2	1	50	1	50

ABST pattern of Escherichia coli:

Of 155 strains tested against the amoxicillin 105(67.8%) were resistant to amoxicillin, 77(49.7%) to cotrimoxazole. Similarly 37.9% of isolates were resistant to cephalexin, 24% to ciprofloxacin,30.3% to nitrofurantoin, 45.6% to norfloxacin,.(table 4.10)

Table 5.10   ABST pattern of Escherichia coli:

Antimicrobial	No tested	sensitive	%	resistance	%
Amoxicillin	155	50	32.2	105	67.8
Co-trimoxazole	155	78	50.3	77	49.7
Cephalexin	116	72	62.1	44	37.9
Ciprofloxacin	104	79	76	25	24
Nitrofurantoin	119	83	69.7	36	30.3
Norfloxacin	102	65	63.7	37	36.3
Nalidixic acid	119	65	54.6	54	45.6
Gentamycin	114	88	77.2	26	22.8
Amikacin	114	104	91.2	10	8.8
Cefuroxime	7	4	57.1	3	42.9
Augmentin	22	18	81.8	4	18.2
Cefotaxime	12	12	100	0	0
Ceftazidime	28	23	82.1	5	17.9
Ceftriaxone	27	23	85.2	4	14.8
Netilmicin	5	4	80	1	20

ABST pattern of Klebsiella pneumoniae:

Antimcrobial sensitivity pattern of Klebsiella pneumoniae reveled that 91.2 % tested strains were resistant to Amoxicillin, 72.1% to cotrimoxazole, 72.9% cephalexin, 50.8% to ciprofloxacin, 50% nitrofurantoin, 47.4% to norfloxacin, 62.5% to nalidixic acid.(Table 4.11)

Table 4.11 ABST pattern of Klebsiella pneumoniae:

Antimicrobial	No tested	sensitive	%	resistance	%
Amoxicillin	68	6	8.8	62	91.2
Co-trimoxazole	68	19	27.9	49	72.1
Cephalexin	59	16	27.1	43	72.9
Ciprofloxacin	63	31	49.2	32	50.8
Nitrofurantoin	24	12	50	12	50
Norfloxacin	19	10	52.6	9	47.4
Nalidixic acid	24	9	37.5	15	62.5
Gentamycin	59	34	57.6	25	42.4
Amikacin	59	52	88.1	7	11.9
Cefuroxime	4	0	0	4	100
Augmentin	11	9	81.8	2	18.2
Cefotaxime	7	2	28.5	5	71.5
Ceftazidime	18	7	38.9	11	61.1
Ceftriaxone	18	12	66.7	6	33.3
Netilmicin	12	9	75	3	25
Chloramphenicol	12	6	50	6	50

Table 4.12   ABST pattern of Klebsiella oxytoca.

Antimicrobial	No tested	sensitive	%	resistance	%
Amoxicillin	3	1	33.3	2	66.7
Co-trimoxazole	3	1	33.3	2	66.7
Cephalexin	3	0	0	3	100
Ciprofloxacin	3	2	66.7	1	33.3
Gentamycin	3	3	100	0	0
Amikacin	3	3	100	0	0

Table 4.12   ABST pattern of Enterobacter spp

Antimicrobial	No tested	sensitive	%	resistance	%
Amoxicillin	4	2	50	2	50
Co-trimoxazole	4	3	75	1	25
Cephalexin	4	3	75	1	25
Ciprofloxacin	4	3	75	1	25
Nitrofurantoin	2	1	50	1	50
Norfloxacin					
Nalidixic acid	2	1	50	1	50
Gentamycin	4	3	75	1	25
Amikacin	4	3	75	1	25

Table 4.13   Antimicrobial sensitivity pattern of Citrobacter spp:

Antimicrobial	No tested	sensitive	%	resistance	%
Amoxicillin	12	0	0	12	100
Co-trimoxazole	12	3	25	9	75
Cephalexin	9	4	44.4	5	55.6
Ciprofloxacin	9	7		1	77.8
Nitrofurantoin	3	0	0	3	100
Nalidixic acid	3	0	0	3	100
Gentamycin	12	12	100	0	0
Amikacin	12	12	100	0	0

Table 4.12   ABST pattern of Pseudomonas spp

Antimicrobial	Tested	Sensitive	%	Resistant	%
Ciprofloxacin	45	23	51.1	22	48.9
Gentamicin	45	24	53.3	21	46.7
Amikacin	45	34	75.6	11	24.4
Ceftazidime	22	14	63.6	8	36.4
Carbenicillin	10	5	50	5	50
Netilmicin	6	3	50	3	50

4.13   ABST pattern of Haemophilus influenzae

Antimicrobial	Tested	Sensitive	%	Resistant	%
Amoxicillin	14	14	100	0	0
Co-trimoxazole	14	6	42.8	8	57.2
Cephlexin	14	13	92.9	1	7.1
Ciprofloxacin	14	14	100	0	0
Gentamycin	8	8		0	0
Amikacin	8	8	100	0	0
Chloramphenicol	8	8	100	0	0

ABST of Salmonella typhi

Ot the 30 strains of Salmonella typhi Tested 2 strains (6.6%) were resistant to amoxicillin,2(6.6%) to cotrimoxazole, 1(3.3%) t0 cephalexin,.All the straiwere sensitive to Ciprofloxacin and ceftriaxone.(Table 4.14)

Table 4.14   ABST of Salmonella typhi

Antimicrobial	No tested	sensitive	%	resistance	%
Amoxicillin	30	28	93.3	2	6.6
Co-trimoxazole	30	28	93.3	2	6.6
Cephalexin	30	29	96.6	1	3.3
Ciprofloxacin	30	30	100	0	0
Ceftriaxone	30	30	100	0	0

Table 4.15   ABST of Salmonella paratyphi

Antimicrobial	No tested	Sensitive	%	Resistance	%
Amoxicillin	6	6	100	0	0
Co-trimoxazole	6	5	83.3	1	16.7
Cephalexin	6	6	100	0	0
Ciprofloxacin	6	6	100	0	0
Ceftriaxone	6	6	100	0	0

Table 4.16   ABST pattern of Other GNB

Antimicrobial	No tested	sensitive	%	resistance	%
Amoxicillin	17	3	13.7	14	86.3
Co-trimoxazole	17	6	35.2	11	64.8
Cephalexin	17	10	58.8	7	41.2
Ciprofloxacin	17	12	70.6	5	29.4
Nitrofurantoin	8	4	50	4	50
Nalidixic acid	8	4	50	4	50
Gentamycin	17	14	82.4	3	17.6
Amikacin	17	14	82.6	3	17.6

6.Discussions:

Prescribing pattern

The main objectives of the study were to find out the extent of antimicrobial use in a Teaching hospital OPD and to find out the pattern of antimicrobial resistance. The prescribing indicators were also measured while assessing the antimicrobial usage in OPD.WHO prescribing indicators were applied to observe the prescribing pattern. Which are average number of drug prescribed per encounter, percentage of drugs prescribed in generic name, percentage of encounters with an antibiotic prescribed, percentage of encounters with an injection prescribed and percentage of drugs prescribed from essential drugs list or formulary (Hogerzeli,1993).   Analysis of the prescribing indicators showed that in average 2.38 drugs were prescribed per prescription or encounter and 25.37% of the drugs were prescribed in generic name. For every prescription there was 0.76 antimicrobial agent being prescribed.. Similar types of study on drug use pattern and antimicrobial resistance pattern in Sri Lanka reveled that on average 2.5 drugs were prescribed per prescription, 27.5% of drugs were prescribed in generic name, 39.8% of drugs were prescribed from the essential drug list and 29.8% of prescription had antimicrobial agentas prscrbed.(Rijal, 1997). Similarly a study on prescribing pattern in rural Sri Lanka reaveled that   42.% were being prescribed with antimicrobial agents(Angunala,1989) In the Urban area (Kandy) of Sri Lanka the mean drug use in the Government institutions varied between 3.6-3.7 and in the private nursing home patient were exposed to 7.2 drugs. There were no difference in drug exposure in relation to sex but a tendency towards increased drug exposure was noted with increasing age and longer duration of stay in the hospital. The study also showed that antimicrobials was the most frequently used class of drugs(Angunawela,et al,1998) .

Antimicrobial agents usage pattern:.

Of the 804 prescription analyzed during the study1917 drugs were prescribed which indicated 2.38 drugs per prescription and of the 1917 items prescribed 612(31.9%) of the drugs were antimicrobial agents. Study on antibiotic use in rural Bangladesh showed that 26% of the total drug perched were antibiotic.(HOSSAIN,1982)and another study also in Bangladesh reveled that 25% of the patient were treated with antibiotics(GUYON,1992) Which also revealed that there is no

significant change in antibiotic use in 10 years interval. Study of prescribing pattern in rural Sri Lanka demonstrated that 20% of the total drugs prescribed were antimicrobial agents and 42.4% of patients were treated with antimicrobial agents(Angunawela,1989) and another study in Urban area in Sri Lanka raveled that antimicrobiaal agents were most frequently prescribed class of drugs (Angunawewela et al,1988) and another study done in General Hospital. Peradeniya revealed that 19.6% of the of the out patient department drug consumption were antimicrobial agents and it occupied 24.% of the indoor patient drug consumption(Jayawardana,1989)

Commonly prescribed antimicrobial agents:

As this study reaveled that of the total drug prescribed 31.9% were antimicrobial agents and study done in other South Asian countries reveled that antimicrobial consumption is approximately 1/4 to 1/3 of the total drug consumption. Th is study has demonsstrated that Amoxicillin was the most commonly used antimicrobial agents of 17 antimicrobial agents being used in the OPD practice followed by doxycycline, ciprofloxacin, cloxacillin, Metronidazole and cephalosporin.(Table 4.3). Study done in Seychelles(Chennabathi1982) reveled that 30.4% of the all prescriptions were for infection. Out of the antimicrobial agenta ampicillin was the most commonly pcrescribsd antimicrobial agents and followed by Co-trimoxazole 14.8%, tetracycline 6.55.percent. Similar to this the children,s hospital in winningipeg (Schollenbergand Albritton,) also showed that Amoxicillin /ampicillin was the most commonly prescribed antimicrobial agents followed by Gentamycin and cloxacillin.. Another study in a medical wards of University Hospital, Bangkok (Aswapokee, Vaithayapichet,1990) raveled that Penicillin was most frequently used antimicrobial agents followed by Gentamycin, cephalosporins and ampicillin.

Organism isolated and their antimicrobial resistance pattern:

In this study 575 isolates of bacteria were isolated from the different clinical samples. Of the 575 isolates 62(10.8%) were from sputum, 81(14.1%) from the blood, 247(43%) fromthe swab and 185(32.1%) were from the urine. Pseudomonas aeruginosa , Haemophilus influenzae, Klebsiella pneumoniae and Streptococcus pneumoniae were the common isolates fromt he respiratory system. Salmonella typhi, staphylococcus aureus, coagulase negative Staph and Salmonella paratyphi were the frequently issssolated organism from the blood. Escherchia coli, Klebsiella pneumoniae , Caagulase negative Staphylococcus and Staphylococcus aureus were the common isolates from the

urine. Staphylcoccus aureus, Escherichia coli,,Ppseudomonas aeruginosa and Klebsiella pneumoniae were freqquently isolated organisms from the swab.

Of the 182 strains of Staphylococcus aureus isolate tested againsst amoxicillin and cotrimoxazole 108(59.3%) were resistaant to anmoxicillin and 67(36.8%) isolates were resistant to Cotrimoxazole. Of the 178 Staphhylococcus aureus subjected againsst Methicillin only 22(12.4%) were resistant to methicillin. Simililarly, 14(7.9%) isolates were resistant to Erythromycin(Table 4.5).

After the discovery of the antimicrobial agents there has been substantially reduced the threat posed by infectious diseases. The use of these drugs and improvements in sanitation, housing and nutrition and the advent of the wide spread immunization programme , has lead to a dramatic drop in death from diseases that were previously wide spread, untreatable and frequently fatal. Over the years antimicrobials have saved the lives and eased the suffering of the million people. These gains are now seriously jeopardized by another recent development,' the emergence and spread of microbes that are resistant to cheap and effective first line drugs. The bacterial infections which contribute most human diseases are also those in which emerging microbial resistance are most evident. Diarrhoeal diseases, respiratory tract infection meningitis, sexually transmitted infections and hospital acquired infections are some example.Penicillin resistant Streptococcus pneumoniae, Vencomycin resistant enterococci, Methicillin resistant Staphylococcus, multi-resistant Salmonella and multi resistant Mycobacterium.tuberculosis are most important threat(WHO. Fact Sheets,2002). In this study of 178 isolates of Staphylococcus aureus tested against methicillin only 22(12.4%) isolates were resistant to Methicillin. Similar study in 2years ago raveled that 12.9% of the strains were resistant to Methicillin.(Rijal, et al 2000). Similar study in Estonia in 1998 showed that the MRSA varied from 2%-8.4% in two different part of the same country(Joks,2000). The hospital study in Tran also reveled that Staph. aureus isolated in hospital were relatively resistant to commonly used antibotics(Shakibaie,et al2003).

In the 1970s and 1980 a number of outbreak of methicillin resistant Staphylococcus aureus occured in various part of the world including the United States. MRSA have spread from the large tertiary care teaching hospital to smaller community hospitals and residential facilities (Cohen,1992). The review study demonstrated that after the introduction and use of penicillin in Boston city hospital there was sharp drop in the number of cases and particularly of death due to

bacteriemic staphylococcus infections, bur they then rose steadily through most of the 1950s with some reversal of these trend during the 1960(Finland,1972)

Twenty one strains of coagulase negatibve Staphylococcus were tested against Amoxicillin, Cotrimoxazole,cephalexin,ciprofloxacin , methicillin and eythromycin. The study reveled that all the isolates were sensitive to methicillin,only one isolates(4.8%)   were resistant to to ciprofloxacin, 7(33.3%) were resistant to amoxicillin, 6(28.6) to cotrimoxazole, 9(42.9%).

Of the 11 isolates of Streptococcus pneumoniae subjected against 6 antimicrobial agents, all the Streptococcus pneumoniae were sensitive to coprofloxacin and cloxacillin but 3 (27.3.%) were resistant to amoxicillin, and cotrimoxazole, 2(18.2%) to cephalexin and 1(9.1%) to erythromycin.. In other study in USA, a*mong multidrug resistant Strepto pneumoniae four resistance pattern were most commonly observed: Penicillin and TMP/SMX; penicillin, macrolide,chloramphenicol; penicillin , mecrolide tetracycline; ad TMP/SMX; and penicillin,macrolide, tetracycline,TMP/SMX and chloramphenicol (Doern,2002) . Although penicillin was not directly tested in this study the high percentage of strains resistant amoxicillin also indicates high level of Steptococcus . pneumoniae resistant to penicillin. The study in Bangladesh on Streptococcus strains causing childhood infections in Bangledesh reveled that 11.6% of isolates were intermediately resistant and 1.1% complete resistance and a remarkely high, 64.% of strains were resistant to cotrimoxazole(Shah,et al,1999) In present study also demonstrated hihgh level of Strepto.pneumoniae resistant to cotrimoxazole.*

Five strains of Strepto pyogenes were subjected aagainst 6different antimicrobial agents which demonstrated that all the isolates were sensitive to amoxicillin,, cephalexin, ciprofloxacin cloxacillin and 4(80%) of were resistant to cotrimoxazole and 1(20%) were resistant to cloxacillin.

Of the 155 isolates of Escherichia coli tested against the Amoxicillin and cotrimoxazole, 105 (67.8%) were resistant to amoxicillin and 77 (49.7%) of isolateswere resistant to cotrimoxazole. Similarly 37.9% of isolates of Escherichia coli were resistant to Cephalexin, , 42.9% to cefuroxime,, 17.9% to ceftazidime,14.8% to ceftriaxone but all the isolated tested were sensitive to cefotaxime. 24% of isolates were resistant to ciprofloxacin, 36.2% of isolates were resistant to norfloxacin, 30.3% of isolates to nitrofurantoin, 45.6% to nalidixic acid, 8.8% to amikacin, 22.8% to gentamycin. Of the these types entero pathogen isolated in this study high percentage of Escherichia coli were

resistant to different antimicrobial agents. Similar to present study earlier study reveled that 75% community isolated Escherichia in India are resistant to ampicillin and TMP/SMX. Of the greater concern is that fact that some of these Escherichia coli are resistant to ampicillin and clavulanate and ampicillin and solbactum. Escherichia coli is an important cause of community and hospital acquired infections such as uncomplicated urinary tract infections, pyelonephritis and hospital bacteremia(Neu,1992). The study of antibiotic resistance in Estonia reveled that high rate of Escherichia coli resistance to ampicillin, sulfonamides, cephalosporin and piperacin. A higher degree of resistance was found among the hospital strain than the community strains   In contrast the above studies the study done in USA has shown relatively low level of resistance which showed that 10 % of the isolates were multi drug resistant, , and non of the isolates were resistant to ceftrixone and ciprofloxacin.(CDC,2003).

Thirty strains of salmonella typhi were isolated and tested against the 6 antimirobial agents which revealed that 6.6% of strains were resistant to amoxicillin,6.6% to cotrimoxazole, 3.5% to cephalexin   and all the strains were sensitive to ciprofloxacin and Ceftriaxone. Similalarly, 6 strains of Salmonella paratyphi were tested and it was shown that all the strains were sensitive to Amoxicillin, cephaalexin, and ciprofloxacin but only 16.7% of strains were resistant cotrimoxazole. In contrast to present study high percentage of Salmonella typhi were resistant in Dhaka Banglladesh. A significant number of the Salmonella typhi strains were demonstrated to be multiple drug resistant(MDR) the vast majority of MDR strains were resistant to chloramphenicol, ampicillin, trimithroprim, sulphamethoxazole and and tetracycline(Hermans et al,1996) .

In this study 14 strains of Hemophilus influenzae were isolated and tested against the 7 antimicrobial agents which revealed that all the strains were sensitive to amoxicillin, ciprofloxacin, Gentamycin, amikacin and chloramphenicil but 57.2% of strains were resistant to cotrimoxazole and 7.1% of strains were resistant to cephalexin.

Antimicrobial usage pattern and antimicrobial resistance pattern:

This study demonstrated that amoxicillin(31.1%) was the most commonly prescribed antimicrobial agents in the TUTH OPD followed by Doxycycline(25.9%), ciprofloxacin(12.7%), cloxacillin (12.2%)(Table 4.3)., The study also reveled that 69.% of the Staphylococcus aureus were resistant to amoxicillin, Similarly 33.3%of the coagulase negative Staph,, 27.7% of the Streptococcus pneumoniae were resistant to Amoxicillin. The higher proportion of Gram negative

bacteria was resistant to amoxicillin. The study showed that 67.8% of the Escherichia coli, 91.2% of Klebsiella pneumoniae, were also resistant to Amoxicillin.

In contrast to amoxicillin, isolates resistant to cloxacillin were very low. Only 12.4% of the Staphylococcus aureus were resistant to cloxacillin. All the tested coagulase negative Staphylococcus, Streptococcus pneumoniae and Streptococcus faecalis were sensitive to cloxacillin.

Ciprofloxacin is another commonly prescribed antimicrobial agent in the OPD. Antimicrobial sensitivity pattern showed that 12.9% of the Staphylococcus aureus were resistant to ciprofloxacin, and only 4.8% of coagulase negative Staphylococcus were resistant to ciprofloxacin and all the Streptococcus pneumoniae were sensitive to ciprofloxacin. But In compare to Gram positive organism high percentage Gram negative bacilli were resistant to ciprofloxacin. 24% of Escheriachia coli, 50% of the Klebsiella pneumoniae were resistant to ciprofloxacin.

Conclusions:

This study has shown that the 2 drugs per prescription (Median value), was the most frequently prescribed ,25% of prescribed drugs were in generic name and of the prescribed drugs 31.9% were antimicrobial agents. This study also reveled that of the 17 antimicrobial agents being used in OPD Amoxicillin was most commonly prescribed antimicrobial agents followed by Doxycycline, ciprofloxacin and cloxacillin.

Of the 575 isolated organism from the different clinical sample tested against different antimicrobial agents, 12.4 of the Staphylococcus aureus were MRSA, 59.3% of Staphylococcus aureus resistant to amoxicillin, 24% to cephalexin and more than 90 of the isolates were sensitive to erythromycin. The study also reveled that nearly 1/3 isolates of Streptococcus pneumoniae were resistant to amoxicillin and trimethroprim / sulphamethoxazole. All the isolates of staphylococcus aureus were sensitive to cloxacillin and more than 90% of the isolates were sensitive to Erythromycin. It has also demonstrated that high percentage of Escherichia coli were resistant to commonly used amoxicillin, cephaalexin, Gentamycin. In contrast to Other Gram negative pathogens most of the tested Salmonella typhi and para typhi were sensitive to commonly used antimicrobials.

The drug prescription pattern of teaching hospital OPD was exemplary or model which should be followed by other public and private institutions. The study also revealed that most commonly prescribed antimicrobial agents is amoxicillin and many of the pathogenic organism are resistant to most commonly used agents. This information needs to be widely disseminated among the physicians. Similarly ciprofloxacin is another frequently prescribed antimicrobial agents and many pathogenic organisms has emerged resistance to this drug therefore more prudent use is demanding for this drug. Antimicrobial usage in the hospital should be based upon local antimicrobial resistance pattern.

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