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ANTIMICROBIAL RESISTANCE AMONG GRAM NEGATIVE UROPATHOGENIC BACTERIA

Pharmacology

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ABSTRACT

Infection of the urinary tract is amongst one of the most common infections in the hospital as well as in the community. Causative agents may vary in patients depending on their age, gender and geographical location. Clinical symptoms may include burning sensation during urination, pain above pubic bone, fever, urgency and frequency of urination etc. Antimicrobial resistance is the major problem in the treatment for UTI throughout the world. Resistance could be due to indiscriminate use of antimicrobials, inappropriate dosing and short course of therapy with antibiotics. Availability of over the counter drugs all over the country has played an important role for this widespread resistance in antibiotics. In this article an attempt has been made to review the antibiotic resistance pattern in the commonly involved organisms causing urinary tract infections.

KEYWORDS

Urinary Tract Infection, UTI, Antibiotic Resistance, Pyelonephritis

INTRODUCTION

Urinary tract infection (UTI) is defined as infection and microbial colonization of the structures of upper and lower urinary tract which includes pyelonephritis, cystitis and urethritis.. These constitute one of the most common infectious diseases in the community as well as in hospitals leading to substantial clinical and financial burden on individuals and on society[1].

Clinical symptoms of UTI may vary from burning sensation during urination, pain above pubic bone, cloudy urine, foul smell of urine, fever, urgency and increased frequency of urination, back pain etc. A growth of more than 10^5 colony forming units (CFU) of bacteria per ml of urine for asymptomatic individual and a much lower (~10^3 CFU/ml) for symptomatic individual indicates UTI[2]. However a urine sample obtained by suprapubic aspiration or in-and-out catheterization and in samples from a patient with an indwelling catheter, colony count of 10^2-10^4 /ml generally indicates infection[3]. Escherichia coli, Proteus mirabilis, Enterobacter agglomerans, Citrobacter frreundii and Klebsiella pneumonia account for over 70% of cases[4].

In most of the situations, Community acquired urinary tract infections (CA-UTIs) are treated empirically.

Often the selection of antibiotics against UTI is done by performing antibiotic sensitivity tests. Differences in microbial spectrum and susceptibility patterns may occur in different regions, and the knowledge of antimicrobial use serves as an important predictor of resistance[5]. Antimicrobial resistance remains the major problem in the therapy for UTI throughout the world. Fundamental mechanism of antibiotic resistance may be due to enzymatic degradation of antibiotics, alteration of bacterial proteins or changes in the membrane permeability to antibiotics. Antibiotic resistance can appear spontaneous because of random mutation or more commonly following gradual build up over time[6,7].

Some enterobacteriaceae are resistant to nearly all antibiotics, including carbapenems, which are often considered the antibiotics of last resort. More than 9,000 healthcare-associated infections are caused by CRE (Carbapenems resistant enterobacteriacaea) each year. Every year, approximately 600 deaths result from infections caused by the two most common types of CRE, carbapenem resistant *Klebsiella* spp. and carbapenem resistant *E. coli*[8]. Hence the choice of appropriate antimicrobial agents should be determined by the most likely pathogen isolated and their resistance pattern in a geographic area.

Keeping these issues in mind we have tried to analyse and compare previous studies to assess antimicrobial resistance among Gram negative uropathogenic bacterias.

Age and gender

The age group analysis of different studies indicate that young female patients in the range of 20-35 years had highest prevalence rate of CA-UTI[9].

Higher prevalence of UTI in females with a female : male ratio of nearly 2:1[10,11] may be attributed to the presence of a shorter urethra, urethral meatus being in close proximity to anus and increased frequency of sexual intercourse in middle age group women[12]. However studies have shown that the incidence of UTI increases among elderly males due to prostate enlargement and neurogenic bladder[9].

RISK FACTORS[13]

Factors resulting in compromise of normal host defenses to bacterial colonization like history of diabetes mellitus, recent history of genital instrumentation and immunosuppresion were found as common risks for UTI in different studies[13-15].

Causative Agents

Many bacterias are responsible for complicated and non-complicated UTI, commonest among which is E.coli, which is responsible for nearly 50% of the cases[14-16] followed by Klebsiella and Enterococcus. Some researcher also found Shigella, non-fermenters, Morganella in few cases of UTI[15-17]. Among the non-lactose fermenting organisms, UTI is mainly caused by acinetobacter spp. and pseudomonas spp. accounting for about 7.3% of total cases of UTI.

Table 1: - Percentage Of Organisms Responsible For UTI

Organisms	Study 1[14]	Study 2[18]	Study 3[19]	Study 4[16]	Study 5[17]	Overall (%)
E.coli	55.1	48.9	36.11	70	36	49.22
Enterococcus	15.8	14	4.4	15	6	11
Pseudomonas	4.5	6.3	14.65	10	1.06	7.3
S.aureus	6.2	7	0.78	-	7.4	5.35
Klebsiella	13.7	14	18.06	5	4.23	11
Proteus	4.1	1.3	1.78	-	1.06	2
Nonfermenter	-	4.6	5.06	-	6	5.2
Citrobacter	-	1.3	-	-	3.3	2.3
Morganella	-	-	0.43	-		0.43
Shigella	-	-	-	-	0.53	0.53

UTIs may be classified as uncomplicated or complicated. Identification of patients with complicated urinary tract infections is important for proper treatment of the patient and to prevent recurrence of the disease20.

Risk factors for complicated UTI comprises of the following :

- Known lesion on prior diagnosis
- Functional and structural urinary tract anomaly
- Obstruction (Stone, ureteropelvic junction obstruction)
- Pregnancy
- Diabetes
- Spinal cord injury
- Neurological disorders that affect bladder function eg. multiple sclerosis
- Indwelling catheter
- Comorbidity that predispose to papillary necrosis (sickle cell disease, severe diabetes, analgesic abuse, pseudomonas infection)
- Infection with unusual infection (Tuberculosis)

Suspected lesion based o n history

- Unresolved urinary tract infections – failed response to antimicrobial therapy
- Bacterial persistence (recurrent UTI with same microorganism)
- Infection with urea splitting organism
- Recurrent febrile UTI in children

Suspected lesion based on symptoms

- Febrile UTI (especially > 3 days)
- Renal colic
- Gross haematuria

Percentage of resistance pattern of the uropathogens to various antibiotics

The uropathogens may show the resistance to all of the available antibiotics and resistance can be vary from 3.2% to 74%. Among the Carbapenems class of Beta lactam drugs, least resistance was observed with Meropenem (nearly 3.2%) followed by Imipenem where in resistance were observed in 0.65 to 4% of isolates, average having 2.3% of resistance.

High percentage of the Gram's negative bacteria also shows resistance with aminoglycosides i.e amikacin (5%-28%) and gentamicin (10% - 49%) having average resistance in 14% and 25.5% of isolates. A good number of isolates were also resistance to ciprofloxacin and nitrofurantoin having average resistance observed was 40% and 36% respectively.

Table 2: Percentage Of Resistance Pattern Of The Uropathogens To Various Antibiotics

Antibiotics	Study 1[15]	Study 2[17]	Study 3[21]	Overall (%)
Amikacin	28	5	9	14
Ciprofloxacin	74	17	30	40.3
Cotrimoxazole	33.5	17	52.5	34.3
Gentamicin	49	10	17.5	25.5
Imipenem	4	-	0.65	2.33
Meropenem	4	2.4	-	3.2
Nitrofurantion	29	-	43	36
Norfloxacin	74	4.4	31	37
Ofloxacin	74	-	-	74

Antibiotic resistance (%) pattern in E.coli

E. coli isolated from urine of different patients showed the following antibiotic resistance pattern. The percentage of isolates resistant to various classes of antibiotics varied from 4% (imipenem) to maximum 81% (ampicillin). Imipenem resistance was also observed from different studies, however all isolates were sensitive to imipenem in a study conducted by Jubina et al from Thrissur (Kerala)[22].

A high percentage of E.coli isolates were also resistance to piperacillin (38%) and piperacillin-tazobactam (38%) that varied from 2%-73.5% and 25% -48% respectively. It indicates that, E.coli causing UTI were extended spectrum beta-lactamase (ESBL) producer.

Table 3:- Antibiotic resistance (%) pattern in E.coli

Antibiotics	Study[18]	Study[19]	Study[23]	Study[21]	Study[22]	Overall (%)
Ampicillin	91	73	94.7	-	90	81
Cefuroxime	72.7	82	66.7	-	-	77
Cefotaxime	70.3	74	58	68	60	66
Ciprofloxacin	66.4	81	-	68	60	69
Gentamicin	35	47	16	26.5	20	29
Amikacin	7.8	38	6	19	5	15
Co-trimoxazole	58.8	38	52	49	58	51
Norfloxacin	67	-	-	72	70	70
Nitrofurantoin	17.8	28	9.8	18	10	17
Piperacillin	37.4	-	-	73.5	2	38
Piperacillin-tazobactum	25.5	48	-	25	-	33
Imipenem	7.9	8	-	2	00	4.5

Anti-biotic resistance (%) pattern in Klebsiella

High percentage of resistance to antibiotics was observed in Klebsiella by different observer than the E.coli. Resistances to different antibiotics were observed from minimum 28% with imipenem and amikacin and maximum with ampicillin (97%) and a high percentage of isolates were also resistant to piperacillin and piperacillin-tazobactam.

Table 4 : Antibiotic resistance (%) pattern in Klebsiella

Antibiotics	Study1[18]	Study[19]	Study[21]	Study[22]	Overall(%)
Ampicillin	99.4	97.6	-	95	97
Cefuroxime	70.5	85	-	-	78
Cefotaxime	67	80	38	70	64
Ciprofloxacin	59.5	78	21	55	53
Gentamicin	49	62	22	60	48
Amikacin	26	55	24	8	28
Co-trimoxazole	64.2	73	61.5	55	63
Norfloxacin	59.5	-	26	00	28.5
Nitrofurantoin	75	48	47	30	50
Piperacillin	82	-	76.5	20	59.5
Piperacillin-tazobactum	45	65	22	-	44
Imipenem	17.3	24	0.4	70	28

Antibiotic resistance pattern of *Pseudomonas*

Pseudomonas is a Gram negative bacteria causing urinary tract infection. A high percentage of isolates were resistant to both piperacillin and piperacillin – tazobactem combinations that are 32% and 25.5% respectively. But upto 40% of isolates were resistant to piperacillin which was observed by Sukumaran *et al*. Now a days, many observers also found imipenem resistance in proteus, maximal imipenem resistance was 33% which was observed by Patel *et al*[19] and least resistance (0.2%) was observed by Thattil *et al* [21]. It indicates that imipenem resistance in pseudomonas is increasing day by day.

Table 5: Antibiotic resistance pattern of Pseudomonas

Antibiotics	Study 1[18]	Study[19]	Study[21]	Study[22]	Overall (%)
Ampicillin	80	-	-	-	80
Cefuroxime	79	-	-	-	79
Cefotaxime	52.5	59.5	43	90	61
Ciprofloxacin	52.5	74	30	90	62
Gentamicin	47.5	53	11	30	35
Amikacin	40	45	12	20	29
Co-trimoxazole	100	-	45	-	72.5
Norfloxacin	54	-	18	-	36
Nitrofurantoin	77.5	-	55	-	66
Piperacillin	40	-	26	30	32
Piperacillin-tazobactum	33.5	46	12.4	10	25.5
Imipenem	25	33	0.2	-	19

Antibiotic resistance pattern of *Proteus*

Average 80% of Proteus strains were resistant to ampicillin but few observers found 100% resistance with ampicillin and cefuroxime[14]. Only 5% of proteus strains were resistant to imipenem. A high percentage of resistant strains of Proteus were also found by different observer with ciprofloxacin and gentamicin[14,19,24]

Table 6: Antibiotic resistance pattern of Proteus

Antibiotics	Study1[18]	Study[19]	Study[21]	Study[14]	Overall(%)
Ampicillin	56	84	-	100	80
Cefuroxime	50	88	-	100	79
Cefotaxime	12.5	64	61	-	46
Ciprofloxacin	12.5	76	2	58.3	37

Gentamicin	0	68	.4	92	40
Amikacin	0	56	1.7	8	16.4
Co-trimoxazole	25	76	31.5	-	44
Norfloxacin	18.8	-	9	-	14
Nitrofurantoin	-	84	52	-	68
Piperacillin	18.8	-	17	-	18
Piperacillin-tazobactum	0	32	15	-	16
Imipenem	6.3	8	.2	-	5

CONCLUSIONS

After analysis of different studies, we found that most common organism causing urinary tract infection (UTI) was E.coli causing nearly 50% of total UTI. After E.coli, second most common cause of UTI was due to Enterococcus and Klebsiella that were 11% of total UTI found and least common cause was Morganella.

In this review, a good percentage of Gram negative strains were found resistant to newer antibiotics as well. Least percentage of resistant Gram negative strain observed with meropenem and imipenem and highest resistant observed with ofloxacin (70%) and ciprofloxacin (40%) and the trend of resistance was increasing day by day. The possible explanation is the the high resistant rates among the uropathogens which could be due to indiscriminate use of antimicrobials by private practitioners, pharmacists and nurses. Inappropriate dosing and short course of therapy with antibiotics also contributes to this problem of resistance.

Availability of over the counter drugs all over the country has played an important role for this widespread resistance in antibiotics. The widespread use of antimicrobials in farming animals may be another factor for the emergence of resistant strains. Another reason for high rate of resistance in the present review is that the isolates which were tested in a laboratory based study may be mostly from patients with previous antibiotic treatment failure or from patients with other underlying risk factors.

The uropathogens showed highest sensitivity to carbapenems. The next best alternatives were aminoglycosides. But again, nearly 14 and 26% of the uropathogens showed resistance against amikacin and gentamicin, respectively. Also, the carbapenem-resistant organisms, although only a few in the present review, raise a concern over the available options to treat complicated and drug-resistant cases. Until recently, carbapenems were almost uniformly active against resistant Gram-negative organisms, but some strains have now developed very effective ways to deal with the carbapenems. There are various mechanisms by which these organisms achieve such resistance, by producing beta lactamases which destroy the antibiotics, by blocking the entry of these antibiotics, or by efflux pumps which actively pump out these antibiotics[25]. Furthermore, some of these mechanisms are not antibiotic or class specific, and can also be easily transferred from one organism to another. The situation is worsening everyday as no new antibiotics against these multidrug-resistant organisms are in advanced stages of clinical development.

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