Antimicrobial susceptibility testing and patterns of resistance at a tertiary care center

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ABSTRACT

Clinical microbiology laboratories are faced with the challenge of accurately detecting emerging antibiotic resistance in bacterial pathogens. In recent years, vancomycin resistant enterococci have emerged, as have penicillin resistant pneumococci and more recently, methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin. In order to detect these emerging resistant pathogens it is essential that antimicrobial susceptibility be carried out by laboratories as an integral part of therapeutic strategies. In this review, we discuss patterns of susceptibility of different antimicrobials as experienced at King Faisal Specialist Hospital and Research Centre, a tertiary care center in Riyadh.

Keywords: Susceptibility test, vancomycin resistance, enterococci, pneumococci.

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The modern era of chemotherapy began in 1936 with the discovery of the antibacterial effects of the sulfonamides. The first antibiotic penicillin was discovered in 1929 by Sir Alexander Fleming and was introduced in clinical practise during World War II. The subsequent discovery of streptomycin (1943), chloramphenicol (1947), chlortetracycline (1948), neomycin (1949), and erythromycin (1951) ushered in the era of the miracle drug. However, by 1953, during a *Shigella* outbreak in Japan, a strain of the dysentery bacillus was isolated which was multiple drug resistant. There was also evidence that bacteria could pass genes for multiple drug resistance between strains and even between species. It was also apparent that *Mycobacterium tuberculosis* was capable of rapid development of resistance to streptomycin which had become a mainstay in tuberculosis therapy. Resistance to penicillin in some strains of *staphylococci* was recognized almost immediately and today as many as 80% of all strains of *Staphylococcus aureus (S.aureus)* are resistant. Nonetheless the discovery and use of antibiotics and immunization procedures against infectious disease have greatly added to the average life span of humans in developed countries. Many people are still alive because an antibiotic conquered an infectious disease that would have otherwise killed an individual. Antibiotics are among the most prescribed drugs in the world today. They have transformed our ability to treat many infectious diseases that were previously killers. However, through massive and increasing use of antimicrobials in humans, agriculture, and fish farming, has given rise to antimicrobial resistance.[1] In the medical setting, a resistant microbe is one which is not killed by an antimicrobial agent after a standard course of treatment. Infections caused by resistant microbes fail to respond to treatment, resulting in prolonged illness and greater risk of death. This also increases the costs of treatment, both the direct costs of treatment and hospitalization in addition to indirect costs to loss of income.

Laboratory testing. Resistance in bacteria is most commonly detected during standard laboratory investigations to establish the cause of a patient's infection. Detection depends on the collection of specimens from the patient, and the availability of laboratory facilities for isolation, identification and susceptibility testing. This takes time and money and is often foregone. Thus resistance may not be detected until a course of treatment fails to cure an

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Table 1 - Comparative susceptibility of clinical isolates against meropenem and other antimicrobials percent susceptible.

Organism	**n**	**MER**	**IMP**	**PIP**	**FOX**	**CRO**	**CAZ**	**CIP**	**GM**	**SXT**	**TAZ**
Gram negative bacteria											
Escherichia coli	70	100	100	34	90	84	96	87	87	47	-
Klebsiella pneumoniae	45	100	100	38	91	65	78	91	76	78	-
Proteus mirabilis	22	100	100	77	91	95	100	95	91	46	-
Morganella morganii	3	100	100	67	33	100	67	100	100	67	-
Enterobacter cloacae	30	100	100	43	0	53	53	93	83	77	-
Citrobacter freundii	5	100	60	20	0	40	20	100	100	100	-
Serratia marcescens	6	100	83	67	0	0	83	100	83	0	-
Salmonella species	10	100	100	-	-	-	100	100	-	-	-
Pseudomonas aeruginosa	60	92	85	83	-	15	83	90	83	-	90
Stenotrophomonas maltophilia	5	20	0	20	-	0	20	60	60	-	20
Acinetobacter species	13	100	100	54	-	15	69	77	69	-	69
Haemophilus influenzae	5	100	-	-	-	100	-	-	-	-	-
Gram-positive bacteria	**n**	**MER**	**IMP**	**AMP**	**PEN**	**AUG**	**E**	**OX**	**GM**	**CIP**	**VA**
Staphylococcus aureus	62	81	81	-	3	81	60	81	69	85	100
C/N Staphylococci	20	50	50	-	8	32	38	38	40	80	100
Enterococci	25	9	100	92	-	-	-	-	-	24	96
Streptococcus pneumoniae	12	100	100	-	50	-	75	-	-	-	100

MER=meropenem, IMP=imipenem, PIP=piperacillin, CRO=ceftriaxone, CAZ=ceftazidime, CIP=ciprofloxacin, FOX=cefoxitin, GM-gentamicin, SXT=trimethoprim-sulfamethoxazole, TAZ=piperacillin/tazobactam, PEN=penicillin, E=erythromycin, OX=oxacillin, VA=Vancomycin, AMP - ampicillin, AUG - amovicillin/clavulanic acid, C/N=coagulase negative

infection. In vitro susceptibility testing of antimicrobial agents is important in instituting, modifying, and altering the administration of effective drugs. The most important indication for performing these tests is the presence of organisms whose susceptibilities cannot be predicted from knowledge of their identity or those that tend to develop resistance. Often, antimicrobial coverage or empiric therapy is initiated while laboratory studies are in progress. In such instances, knowledge of the general pattern of commonly isolated organisms in an institution is desirable.[2]

Resistant bacteria. Bacterial infections such as pneumonia, gonorrhoea, wound infections, urinary tract infections, dysentery, and tuberculosis are not being effectively treated because of growing resistance. In addition, penicillin-resistant *Streptococcus pneumoniae*, (*S.Pneumoniae*) fluoroquinolone-resistant *Enterobacteriaceae, S.aureus, Brucella melitensis (B.melitensis),* and vancomycin-resistant enterococci, and vancomycin intermediate *S.aureus* have appeared. Vancomycin-resistant enterococci (VRE) - were first reported in France in 1988. Since then, these organisms have been reported to have caused human infections in the USA, UK, Germany, the Netherlands, Spain and Saudi Arabia. The number of cases infected with VRE, as reported by the Centers for Disease Control and Prevention, increased from 0.3% to 8%, with a rapid increase in colonization, and a fecal carriage rate of 86%. A study at a tertiary care center in Saudi Arabia found a low number of VRE in 26 patients over a one year period (1995-1996) and fecal colonization in 6 of 4276 patient specimens examined. Since this study, only 24 cases of VRE have been reported at this center.[3] Multi-drug resistant Mycobacterium tuberculosis- Tuberculosis (TB) continues to be a health threat worldwide, with

Table 2 - In-vitro activity of cefepime and other cephalosporins against blood culture isolates.

Bacterial isolater (n)	Antibiotic	MIC 50	MIC 90	Range	% Susceptible
Acinetobacter Calcoaceticus (36)	Cefepime	2.0	>16	0.5->16	67
	Cephalothin	>16	>16	8->16	8
	Cefoxitin	>16	>16	8->166	8
	Cefotaxime	2.0	>16	1.0->16	51
	Ceftazidime	2.0	16.0	2.0->16	75
	Ceftriaxone	1.0	>16.0	0.5->16	14
	Ampicillin	>32	>32	4->32	6
Citerobacter freundii (12)	Cefepime	0.5	16.0	0.12->16	75
	Cephalothin	>16	>16.0	2.0->16	24
	Cefoxitin	>16	>16.0	2.0->16	35
	Cefotaxime	0.5	>16.0	0.25->16	55
	Ceftazidime	1.0	>16.0	0.5->16	85
	Ceftriaxone	0.5	>16.0	0.25->16	43
	Ampicillin	>32.0	>32.0	2.0->32	2
Enterobacter cloacae (31)	Cefepime	1.0	>16	<0.12->16	78
	Cephalothin	>16	>16	8->16	4
	Cefoxitin	>16	>16	8->16	4
	Cefotaxime	4.0	>16	4->16	4
	Ceftazidime	0.5	16.0	0.12-32	48
	Ceftriaxone	0.25	16.0	0.25->16.0	4
	Ampicillin	>32	>32	8->32	3
Escherichia coli (77)	Cefepime	<0.12	4.0	<0.12-16	98
	Cephalothin	4.0	16.0	4.0->16	52
	Cefoxitin	2.0	4.0	2.0>16	93
	Cefotaxime	<0.12	2.0	0.25->16	94
	Ceftazidime	0.25	0.25	0.12->16	94
	Ceftriaxone	0.12	0.12	0.03->16	93
	Ampicillin	>32	>32	8.0->32	28
Enterobacter species (16)	Cefepime	<0.12	0.5	<0.12-2.0	100
	Cephalothin	>16	>16	8->16	32
	Cefoxitin	16	>16	9->32	43
	Cefotaxime	0.25	16.0	0.12->16	71
	Ceftazidime	0.5	16.0	0.5->16	84
	Ceftriaxone	0.25	16	0.25->16	64
	Ampicillin	>32	>32	>32	0
Klebsiella oxytoca (15)	Cefepime	0.25	4.0	<0.12-8.0	100
	Cephalothin	4.0	>16	4.0->16	51
	Cefoxitin	8.0	>16	4->16	89
	Cefotaxime	0.12	4.0	0.06-4.0	100
	Ceftazidime	0.25	>16	0.25->16	73
	Ceftriaxone	0.5	>16	0.25->16	63
	Ampicillin	>32	>32	>32	0
Streptococcus pneumoniae (28)	Cefepime	<0.12	<0.12	<0.12-1.0	100
	Ceftazidime	0.5	0.5	0.25-8.0	100
	Cephalexin	0.25	8	0.24-8	100
	Penicillin	0.03	0.25	0.03-2.0	100
Streptococcus agalactiae (22)	Cefepime	0.12	0.12	≤0.12	100
	Ceftazidime	0.5	0.5	0.25-4.0	100
	Cephalexin	0.12	0.24	0.12-0.25	100
	Penicillin	0.12	0.25	0.06-0.5	100
Streptococcus pyogenes (31)	Cefepime	<0.12	<0.12	<0.12	100
	Ceftazidime	0.12	0.96	0.03-8	100
	Cephalexin	0.12	0.48	0.06-0.96	100
	Penicillin	0.06	0.12	<0.03-0.12	100
Staphylococcus aureus-methicillin sensitive (66)	Cefepime	2.0	4.0	0.5-8	100
	Ceftazidime	16	>16.0	4->16	38
	Cephalexin	0.5	>32	2.0->16	78
	Penicillin	>32	>32	2.0->32	3
Staphylococcus aureus-methicillin resistant (21)	Cefepime	>16	>16	2.0->16	7
	Ceftazidime	>16	>16	4.0->16	5
	Cephalexin	>16	>16	>16	0
	Amphicillin	>16	>16	>32	0

Table 2 continued - In-vitro activity of cefepime and other cephalosporins against blood culture isolates.

Bacterial isolated (n)	Antibiotic	MIC 50	MIC 90	Range	% Susceptible
Coagulase-negative staphylococci (62)	Cefepime	4.0	16	0.12->16	71
	Ceftazidime	>16	>16	4.0->16	29
	Cephalexin	>16	>16	4.0->16	28
	Ampicillin	>32	>32	4.0-32	9
Enterococci (43)	Cefepime	16	>16	8->16	24
	Ceftazidime	16	>16	8->16	8
	Cephalexin	>16	>16	>16	12
	Ampicillin	1.0	2.0	0.5->32	90
Klebsiella pneumoniae (61)	Cefepime	0.12	4.0	<0.12-16.0	93
	Cephalothin	8.0	>16	4.0->16	59
	Cefoxitin	8.0	8.0	4.0->16	91
	Cefotaxime	0.5	1.0	0.06->16	94
	Ceftazidine	0.25	16	0.25->16	79
	Ceftriaxone	0.25	2.0	0.06->16	92
	Ampicillin	>32	>32	16->32	1
Morganella morganii (20)	Cefepime	>0.12	2.0	<0.12-4.0	100
	Cephalothin	>16	>16	8->16	8
	Cefoxitin	>16	>16	4->16	21
	Cefotaxime	<0.12	2.0	<0.12-4.0	100
	Ceftazidime	0.12	2.0	0.12->16	94
	Ceftriaxone	<0.12	2.0	0.03-16	97
	Ampicillin	.32	>32	8->32	3
Proteus mirabilis (19)	Cefepime	<0.12	0.25	<0.12-0.25	100
	Cephalothin	2.0	>16	1.0->16	66
	Cefoxitin	2.0	8.0	1.0->16	96
	Ceftazidime	0.12	1.0	0.12-16	99
	Ceftriaxone	0.06	0.5	0.06-1.0	99
	Ampicillin	1.0	2.0	0.5>32	58
Pseudomonas aeruginosa (48)	Cefepime	2	>16	0.5->16	89
	Cefoitin	>16	>16	>16	0
	Cefotaxime	>16	>16	0.5->16	10
	Ceftazidime	2.0	>16	1.0->16	82
	Ceftriaxone	>16	>16.0	1.0->16	43
	pieracillin	8.0	128	8.0->128	86
Salmonella typhi (22)	Cefepime	<0.12	<0.12	<0.12	100
	Cephalothin	1.0	>16	1.0->16	89
	Cefotaxime	<0.12	0.5	<0.12->0.5	100
	Ceftriaxone	<0.12	0.25	<0.12-0.5	100
	Ceftazidime	<0.12	0.25	0.12-0.25	98
	Ampicillin	1.0	>32	1.0->32	82
Serratia marcescens (22)	Cefepime	2.0	>16	0.12->16	55
	Cephalothin	>16	>16	>16	0
	Cefoxitin	>16	>16	8->16	23
	Cefotaxime	2.0	>16	0.12->16	51
	Ceftazidime	2.0	>16	0.5->16	55
	Ceftriaxone	16.0	>16	2.0>16	49
	Ampicillin	>32	>32	2.0->32	6
Stenotrophomonas maltophilia (11)	Cefepime	8	>16	0.5->16	55
	Cefoxitin	>16	>16	>16	0
	Cefotaxime	>16	>16	4.0->16	10
	Ceftazidime	8	>16	4.0->16	28
	Ceftriaxone	>16	>16	>16	0
	Piperacillin	128	>128	8->128	2

MIC - mean inhibitory concentration

Table 3 - Etiology of the pathogens and their antimicrobial susceptibility from Intensive Care Unit patients.

Organism (n)	AMP	AN	AUG	CAZ	CF	CL	CRO	E	FOX	GM	IMP	OX	PEN	PIP	VA
Escherichia coli (152)	23	86	64	86	59	-	86	-	84	86	100	-	-	37	-
Klebsiella pneumoniae (99)	0	77	62	74	14	-	72	-	72	65	91	-	-	41	-
Enterbacter cloacae (47)	8	70	8	62	0	-	60	-	0	68	100	-	-	51	-
Serratia marcescens (48)	0	50	0	75	0	-	50	-	20	62	100	-	-	50	-
Pseudomonas aeruginosa (153)	-	74	-	64	-	-	24	-	-	63	86	-	-	71	-
Stenotrophomonas maltophilia (5)	0	40	0	40	-	-	0	-	-	40	0	-	-	9	-
Pseudomonas species (19)	-	0	-	74	-	-	37	-	-	0	47	-	-	94	-
Acinetobacter species (31)	6	65	16	83	-	-	16	-	-	65	93	-	-	32	-
Staphylococcus aureus (103)	3	-	84	-	84	86	-	53	-	58	100	85	3	-	100
C/N staphylococci (27)	5	-	32	-	26	51	-	28	-	0	87	51	5	-	100
Enterococci group D (26)	60	-	91	-	-	-	-	-	-	0	100	-	-	-	100
Pneumococci (11)	-	-	-	-	100	100	-	-	-	33	100	-	100	-	100

AMP=ampicillin, AN=amikacin, AUG=amoxicillin/clavulanic acid, CAZ=ceftazidime, CF=cephazolin, CL=clindamycin, CRO=ceftriaxone, E=erythromycin, FOX=cefoxitin, GM=gentamicin, IMP=imipenem, OX=oxacillin, PEN=penicillin, PIP=piperacillin, VA=vancomycin, C/N=coagulase negative, - = not tested

8-10 million new cases and 3 million deaths annually. Approximately 14% of all cases in the USA have bacilli resistant to at least 1 major anti-tuberculous drug. Resistance is not uniform in the USA and tends to be more prevalent in areas that have large numbers of persons infected with HIV. The figure varies between 3% in Guinea Bissau to 36% in Turkey and in the Philippines almost 80% of patients in one community based study had resistance to one drug.[4] Multi-drug resistant tuberculosis particularly presents challenges for therapeutic options and successful outcome. A literature review of patients from Saudi Arabia including King Faisal Specialist Hospital (KFSH) showed an overall resistance of 15%. Resistance to streptomycin (9%), isoniazid (7%), and rifampicin (6%) were the most common reported. There were as many patients with multiple drug resistance as there were single drug resistance. The high rate of anti-tuberculous resistance in Saudi Arabia as other countries may be due to poor supervision of anti-TB treatment, an infant healthcare system, over the counter antibiotic availability and treatment of endemic diseases such as brucella with rifampicin.[4]

Methicillin resistant Staphylococcus aureus (MRSA). The introduction in the early 1960's of penicillinase-resistant penicillins, like methicillin, oxacillin, nafcillin and the cloxacillins, led to the emergence of methicillin-resistant *S.aureus* (MRSA), especially in hospital settings, accounting for 50% of total isolates. In tertiary care settings its incidence varies between 8-45%.[5] We tested 102 isolates of MRSA from tertiary care patients and found none to be resistant to minocycline, with minimum inhibitory

Table 4 - Drug susceptibility of bacterial pathogens isolated from pediatric bacteriuria specimens (n=1081).

	Percentage of isolates susceptible to drug												
Organism (n)	**AMP**	**SMX**	**TMP**	**NI**	**CRD**	**GEN**	**AMC**	**CXM**	**CAZ**	**PEN**	**ERY**	**VA**	**OX**
Escherichia coli (596)	23	14	32	85	90	89	69	95	83	-	-	-	-
Pseudomonas aeruginosa (129)	0	0	0	-	-	81	-	-	94	-	-	-	-
Klebsiella pneumoniae (108)	29	35	67	31	85	87	92	85	56	-	-	-	-
Proteus mirabilis (45)	31	16	24	88	71	60	91	93	83	-	-	-	-
Enterobacter species (14)	3	18	60	28	8	62	23	22	10	-	-	-	-
Citrobacter species (21)	14	24	71	71	52	86	33	33	83	-	-	-	-
Morganella morganii (16)	100	20	33	0	0	100	93	23	33	-	-	-	-
Proteus vulgaris (5)	0	50	100	0	0	100	75	0	100	-	-	-	-
Acinetobacter species (4)	33	33	0	0	33	33	67	100	-	-	-	-	-
Enterococcus species (66)	90	2	80	90	0	20	-	100	-	0	0	100	-
Coagulase-negative staphylococci (28)	11	-	-	-	-	71	-	-	-	7	39	100	-
Staphylococcus aureus (11)	18	100	-	-	-	100	-	100	-	-	50	100	57
Streptococcus group B (5)	100	-	-	-	-	-	-	-	-	100	100	-	-

AMP=ampicillin, SMX=sulfamethoxazole, TMP=trimethoprim, NI=nitrofurantoin, CRD=cephradine; GEN=gentamicin sulfate, AMC=amoxicillin/clavulanate potassium, CXM=cefuroxime, CAZ=ceftazidime, PEN=penicillin, ERY=erythromycin, VA=vancomycin, OX=oxacillin sodium, -=not tested.

concentrations of less than 1-2 ug/ml. The only other drug that inhibited all strains was vancomycin, followed by ciprofloxacin (87%), clindamycin (55%) and chloramphenicol (52%). Gentamicin, beta-lactams, tetracycline and trimethoprim-sulfamethoxazole had little or no activity against our isolates of MRSA. Methiciliin resistant *S.aureus* with reduced vancomycin susceptibility (mean inhibitory concentration (MIC) = 8mg/l) was first reported in 1997. The strain was isolated from the surgical room of a 4-month old infant who underwent heart surgery for pulmonary atresia. Since the wound infection was refractory to vancomycin therapy, the patient was successfully treated with arbekacin (an aminoglycoside approved for MRSA infection in Japan) and ampicillin/sulbactam. Since then isolation of *S.aureus* with reduced susceptibility of vancomycin have been reported from Michigan and New Jersey. We are not aware of any report from the Middle East about the incidence of infection by such *S.aureus*. We have screened over 5,000 isolates of both MSSA and MRSA at our institution and have not detected *S.aureus* with reduced vancomycin susceptibility.

Penicillin resistant S.pneumoniae. Like most other members of the genus *Streptococcus, pneumococci* were for a long time considered universally sensitive to penicillin. Although as early as 1945 Eriksen showed in vitro development of increased resistance in bacteria grown in the presence of sub inhibitory concentrations of penicillin, the first clinical isolate with penicillin resistance was not reported until 1965. Since then a number of investigators from several parts of the world have isolated relatively penicillin-resistant (RPR) pneumococci MIC of 0.1-1.0 mg/l and resistant pneumococci (with MIC of >1.0 mg/l) from clinical specimens. The majority of the isolates have been found to be RPR, their prevalence varying from a low level of 1.3-4% in Canada and England to 51% in Spain. During 1991-1992, the incidence of RPR in a tertiary care hospital in Riyadh was 31% and in a medical school affiliated tertiary hospital was 40%. The incidence now has increased to 60%. However, totally penicillin resistant pneumococci (MIC>1.0mg/l) are rare.[6]

Drugs evaluated at KFSH. Imipenem is the first semisynthetic thienamycin with a spectrum of bactericidal activity which includes gram-positive and gram negative, organisms, aerobes as well as anaerobes. It is unaffected by bacterial beta-lactamases and has the broadest spectrum of of any known antibiotic, making it effective in the treatment of patients with serious and life threatening infections.[7] Imipenem was tested at KFSH against different nosocomial pathogens isolated from patients. All isolates of *Enterobacteriaceae* (246), *Acinteobacter calcoaceticus (A.calcoaceticus)* (27), *Haemophilus influenzae (H.influenzae)* (7) were susceptible to imipenem.

Meropenem. Meropenem is a newer carbapenem was tested against 393 clinical isolates. Of the 191 strains of Enterobacteriaceae, all 100% were susceptible. Of 60 strains of *Pseudomonas aeruginosa* (*P.aeruginosa)* 92% were susceptible compared to 85% for imipenem, and 83% each for gentamicin, ceftazidime and piperacillin. All MRSA, pneumococci and 96% of enterococci were susceptible to meropenem (Table 1).

Synercid. Synercid (quinupristin/dalfopristin, RP 59500) is a water soluble streptogramin which offers some advantages over the commercially available antimicrobials against drug resistant gram-positive bacteria. In a study of 837 gram-positive bacteria tested 834 (99.6%) were inhibited by <0.6-4.0 mg/l of Synercid. It had excellent activity against both staphylococci and streptococci, including MRSA and VRE.[9]

Cephalosporins have attracted much attention because of their spectrum, safety profile and pharmacokinetics. They comprise 35-50% of all antimicrobials prescribed for hospitalized patients in the USA. Newer parenteral cephalosporins have been found to be more active against *Enterobacteriaceae* than orally active agents. Cefepime is an aminothiazolylacetamido cephalosporin with a wider spectrum and greater potency than many currently available cephalosporins. Since the blood culture isolates from patients of the study centre in Saudi Arabia are significantly more resistant to antimicrobial agents in clinical practice, we evaluated the in-vitro activity of cefepime and 6 other beta-lactam antibodies against 390 and 273 isolates of gram-negative and gram-positive bacteria. Cefepime had a broad spectrum of activity against the *Enterobacteriaceae* (MIC50 < 0.12 mg/L), *P.aeruginosa,* Acinetobacter spp. and methicillin susceptible *S.aureus* (MIC50 2.0 mg/L). The activity of cefepime was generally 2 to 4-fold greater than that of ceftazidime. Resistance to cefepime was most often encountered with Serratia *spp* (45%), *Citrobacter spp*. (25%), *Enterobacter cloacea* (22%), and *Stenotrophomonas maltophilia* (45%). It had little or no activity against MRSA and *enterococci*. Cefepime was highly active, with a spectrum better than ceftazidime against gram-negative, and better than cephalothin against gram-positive blood culture isolates.[10] (Table 2).

Fluoroquinolones are a major advance in antimicrobial therapy and have evolved from chemical modifications of nalidixic acid. They can be administered orally as well as parenterally and are rapidly distributed in the body attaining therapeutic concentrations in most soft tissues. They have proved effective in the treatment of urinary tract, respiratory tract, soft tissue and bacterial gastroenteritis. Some of the 3rd generation fluoroquinolones such as sparfloxacillin and lomefloxacin, exhibit increased serum levels and half-life, allowing the possibility of single daily dosing. In a study carried out at KFSH a

total of 1,034 clinical isolates were tested against 6 fluoroquinolones. These were norfloxacin, ciprofloxacin, lomefloxacin, sparfloxacin, temafloxacin and CI-960. All 6 fluoroquinolones showed excellent in vitro activity inhibiting >90% of *E.coli* at an MIC of <0.03-0.5 mg/L, *K.pneumoniae* at 0.12-2.0 mg/L, Enterobacter at 0.12-2.0 mg/L, *S.marcescens* at 0.12-2.0 mg/L, *P.aeruginosa* at 0.5-2.0 mg/L, *S.aureus* at <0.03-1.0mg/L., and coagulase negative *staphylococci* (CNS) at an MIC of 0.12-2.0 mg/L. Some resistance was exhibited by *S.maltophilia* to norfloxacin, ciprofloxacin, lomefloxacin and temafloxacin, but was inhibited by sparfloxacin and CI-960. A majority of isolates of enterococci were resistant to norfloxacin, ciprofloxacin, lomefloxacin, ciprofloxacin, lomefloxacin and CI-960, but sparfloxacin and temafloxacin inhibited 92% and 82% of these strains.[11]

Rufloxacin (MF934) another fluoroquinolone was evaluated against 1095 isolates clinical isolates. It was highly effective against the *Enterobacteriaceae*, inhibiting 98% of isolates at 1 mg/l. However, 98% of methicillin-susceptible, 87% of MRSA and 76% of CNS required 4 mg/l for growth inhibition. The MIC values of rufloxacin for most bacteria were 4-16 times higher than those of ciprofloxacin and norfloxacin. Some of the most common nosocomial infections are found in urinary tract infections and intensive care units. The comparative susceptibilities of antimicrobials used in these patient populations at KFSH are shown in Tables 3 and 4.

Control of antimicrobial resistance. Control of antimicrobial resistance in order to contain the threat of antimicrobial resistance, it is important to determine the magnitude and trends of resistance and define contributing factors such as therapeutic, behavioural, economic, social and veterinary and agricultural misuse. In particular, overuse must be reduced. The majority of patients are prescribed antimicrobials even in the absence of appropriate indications. In many countries, antimicrobials can be purchased without a prescription and in some countries low quality antibiotics are sold and used for self medication. Patients often poorly comply creating an ideal environment for microbes to adapt, rather than be killed.[12]

Due to the ease and rapidity with which organisms can travel from one geographic location to another, it is desirable to widen knowledge of susceptibility of common bacterial isolates from different parts of the world for optimal patient care. For example, the resistance of *E.coli* to trimethoprim-sulfamethoxazole has remained at 3-8% at many medical centers within the USA. However, at two medical centers in Saudi Arabia 44% and 72% were resistant to this drug. A resistance rate of 44% in Santiago, Chile, and 40% in Bangkok, Thailand has been reported. Similarly, 85% to 88% of Chilean and Thai isolates of *E.coli* were resistant to ampicillin as compared to 49% in the USA and 62% at this hospital.[13] In general, the resistance pattern of bacterial isolates in developing countries to parenteral drugs has remained similar or lower than those in the USA and Europe. On the other hand, over the counter availability and indiscriminate use of oral drugs in developing countries has led to a higher degree of resistance to antimicrobials like ampicillin, trimethoprim sulfamethoxazole, tetracycline, and chloramphenicol.[14]

In conclusion, medical care has changed substantially in the last few decades and involves aggressive surgical interventions, new instrumentations, catheterizations, organ transplants, and immunosuppressive irradiation and chemotherapeutic treatments. These advances have not come without a price, particularly with the increase in nosocomial infections and bacterial resistance. Hospital acquired infections caused by drug resistant bacteria and other pathogens cost an estimated $30 billion each year. Among non hospitalized patients more than 133 million courses of antibiotics are prescribed each year, of these 50% are considered unnecessary.[15] During 1980-1989 the rate of bacteremic infections caused by CNS increased from 161 to 754%, *S.aureus* from 122 to 283% and *enterococci* from 120 to 197%. The crude mortality rate for nosocomial bacteremias caused by CNS, *S.aureus* and *Enterococcus* was reported to be around 45-55%, compared to 28-34% by gram-negative bacteria and 15-20% by Candida spp. Thus effective eradication of these pathogens, especially MRSA, VRE and other resistant gram-positive bacteria, is of prime importance. In Saudi Arabia the problem has been exacerbated by the easy availability of broad spectrum antibiotics and the lack of guidelines for their use. In a multicenter survey in 7 Middle Eastern countries, beta-lactamase was produced by 65% of all isolates, representing 61% and 75% of gram-negative and gram-positive organisms. Using standardized disk susceptibility testing, high rates of resistance were observed among gram-negative and gram-positive organisms, respectively, for penicillin (86% and 75%), ampicillin (67% and 66%) and amoxicillin (58% and 52%).[16] In order to keep pace with changing patterns of resistance, laboratories may not be able to rely on single susceptibility testing methods. In future it will be necessary to employ conventional, quantitative, or single concentration agar screening tests for screening some resistant species. This will enable laboratories to apply different approaches to detect resistance in common and infrequently encountered pathogens.

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