

Urinary Tract Infection Associated with Multidrug-Resistant Bacteria in a Second level Hospital During a Two Year Period

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Abstract

Objective: determine the frequency of urinary tract infections associated with MDR bacteria, characteristics patients with such infections and the mortality rate associated in Hospital ISSSTECALI during 2015-2016.

Design: Descriptive, observational, analytic, transversal

Methods: We collected data from clinical files of each patient that had been diagnosed with a urinary tract infection and had an uroculture of 10×10^5 CFU of bacteria with a multidrug-resistant profile. It included, gender, age, comorbidities, predisposing risk factors, obtained isolation, sensibility pattern, days of stay and proper technique of culture. We calculated frequencies and rates.

Results: During January 2015- November 2016 a total of 2401 urocultures were solicited, we isolated bacteria in 123 of them (5.12%). 94 urocultures were included, 71% of the cultures were from women with a median age of 68.14 years; comorbidities: Hypertension (50%), diabetes (41.5%), chronic renal disease (14.9%), history of stroke and bed-rest. An average of 14.15 days of stay was calculated. They all had a urinary catheter. Of the total of urocultures obtained, 54 urocultures demonstrated bacteria growth with a MDR phenotype (attack rate: 0.43 cases/1000 discharges) *Escherichia coli* was isolated in 26 (48.14%) cultures; *Pseudomona aeruginosa* 7.4%; and *Klebsiella pneumonia* 5.5%; its mechanism of resistance was calculated according to the reported phenotype on the antimicrobiogram, demonstrating resistance to more than two family of antibiotics. A mortality rate of 21.3% was calculated of which the direct cause was related to the infective process (rate: 0.23 deaths/1000 discharges).

Conclusion: the isolation of bacteria with a multidrug-resistant profile is not very common; however, they generate a high morbimortality index and a great weight in resources to our unit.

Recommendations: reinforcement of programs that encourage rational use of antibiotics as well as the control of nosocomial infections should be employed in the hospital.

Introduction

In the last decades, bacterial resistance to antibiotics have become a global public health problem. It has become apparent that the development of new antibiotics as well as their irrational use, and the evolutionary pressure caused by their therapeutic use are the main culprits. These factors have conditioned an increase of antibiotic resistance as time has passed. It would seem as if the answer to this problem would be to develop new antibiotics, however, as new antibiotics are released to the market, new resistance mechanisms are developed, making it harder to control the problem at hand. Because of this, the infections caused by multidrug resistant bacteria (MDR), cause an increase in morbidity and mortality in our patients, not to mention an increased economic burden in hospital costs, in the form of a prolonged hospital stay as well as many complications.

Urinary tract infections (UTI) are a frequent problem in both the hospital and ambulatory setting. Due to its common appearance, it often leads to the frequent use of antibiotics. The antibiotic pressure made over the most common uropathogenic microorganisms have caused these to become the pathogens which most commonly create antibiotic resistance, because of this it is common that first line antibiotics are often obsolete, and only help in developing even more resistances.

Material and Methods

Descriptive, observational, retrospective study. Performed in Hospital ISSSTECALI in Mexicali, Baja California, Mexico. For our sample size we looked through the electronic clinical file and took all urocultures with a bacterial isolate with 10^5 CFU/ml or more that were taken between January 2015- November 2016 of

patients who were over the age of 18 and had been diagnosed with an urinary tract infection and had presented at least one of the following symptoms: chills associated with fever or hypothermia, flank pain or pelvic pain, dysuria, urinary frequency or urgency or UTI related with an altered mental state and excluded all urocultures that did not report antibiogram results or had more than 1 bacterial isolate. General data including sex, age, comorbidities, place the uroculture, if the patient was hospitalized due to an UTI, service they were hospitalized in, what bacteria was isolated, and if the isolate had a nosocomial origin or an MDR profile, first treatment failure, length of hospital stay and if the patient was diseased during their stay was recorded on an Excel spreadsheet. SPSS-v21 was used to make a descriptive analysis of the data and an Excel sheet was used along with formulas to determine the global frequencies and susceptibility to the antibiotics used.

Results

A total of 1351 urocultures were taken in 684 patients in 2015 and 1050 urocultures in 714 patients in 2016. A total of 123 urocultures with bacterial growth of more than 105 CFU/ml were taken from

January 1 of 2015 to November 30 of 2016, of the which 29 were eliminated, (16 did not have a clinical file, 4 cultures were from the same patient during the same hospital stay and 9 were from minors or did not meet the criteria for inclusion). In total 94 cultures coming from 27 men (28.7%) and 67 woman (71.3%) were obtained, of which there was a median age of 68.14 (range: 18-93 years) (Table 1). The hospital services where the cultures were taken were men with 22 (23.4%) cultures, women with 45 cultures (47.9%), ICU with 7 cultures (7.4%), external consult with 8 (8.5) and the emergency room with 12 (12.8%). The comorbidities that were present with the most frequency were, hypertension with 47 cases (50%), diabetes mellitus with 39 cases (41.5%), chronic kidney disease with 14 (14.9%), followed by cardiomyopathy and stroke with 13 (13.8%) each. A total of 47 (50%) cultures were obtained in patients whose UTI diagnosis were amongst the main diagnosis during their ingress, 37 (39.4%) were identified as nosocomial UTI and in 38 (40.4%) a change of the first line antibiotic was required due to treatment failure. A mean of 14.15 (range: 0-256) of total days of hospital stay and a mortality of 20 (21.3%) was obtained of the patients who had an uroculture taken.

Table 1. Clinical Variables

Variables	Global		2015		2016		Global MDR	
	n (94)	%	n (45)	%	n (49)	%	n (54)	%
Age, mean (range)	68.14 (18-93)		68.62 (20-93)		67.69 (18-92)		65.8 (18-93)	
Sex								
Male	27	28.7	10	22.2	17	34.7	17	31.5
female	67	71.3	35	77.8	32	65.3	37	68.5
Comorbidities								
DM	39	41.5	22	48.9	17	34.7	20	37
HAS	47	50	24	53.3	23	46.9	25	46.3
CKD	14	14.9	9	20	5	10.2	9	16.7
BPH	4	4.3	3	6.7	1	2	2	3.7
CVE	13	13.8	10	22.2	3	6.1	8	14.8
Dementia	9	9.6	5	11.1	4	8.2	6	11.1
Cardiopathy	13	13.8	9	20	4	8.2	7	13
COPD	8	8.5	4	8.9	4	8.2	4	7.4
Hepatopathy	2	2.1	1	2.2	1	2	1	1.9
Cancer	9	9.6	5	11.1	4	8.2	3	5.6
Other*	23	24.5	16	35.6	7	14.3	15	27.8
Consult and ER	12	12.8	7	15.6	5	10.2	4	7.4
Entry due to UTI	47	50	24	53.3	23	46.9	26	48.1
Service								
Men	22	23.4	7	15.6	15	30.6	13	24.2
Female	45	47.9	26	57.8	19	38.8	28	51.9
ICU	7	7.4	2	4.4	5	10.2	5	9.3
Consult	8	8.5	4	8.9	4	8.2	4	7.4
ER	12	12.8	6	13.3	6	12.2	4	7.4
Nosomial Infection	37	39.4	18	40	19	38.8	24	44.4
MDR	54	57.4	22	48.9	32	65.3	54	100
First treatment failure	38	40.4	20	44.4	18	36.7	26	48.1

Hospital stay, mean (range)	14.15	(0-256)	14.36	(0-256)	13.69	(0-76)	14.59	(0.76)
Death	20	21.3	11	24.4	9	18.4	15	27.8

Legend: DM = Diabetes Mellitus, HAS = Hypertension, CKD = Chronic kidney disease, BPH = Benign prostate hyperplasia, CVE = Cerebral vascular event (stroke), COPD = Chronic obstructive pulmonary disease, UTI = Urinary tract Infection, UCI = Intensive care unit, MOR = Multidrug resistant. Others*: Epilepsy, Inflammatory Intestinal diseases, peptic disease, diverticulosis, hypothyroidism, hypothyroidism

The microorganism which appeared most frequently in isolates was *E. coli*, which corresponds to a 46.81% (44 isolates) in total, followed by *K. pneumoniae* with 9 (9.57%), *P. aeruginosa* with 6 (6.38%), *Citrobacter freundii* with 5 (5.31%), along with other bacteria (Table 2). Of the isolated MDR bacteria (n=54), 22 (48.9%) were isolated in 2015 and 32 (65.3%) in 2016, of these only 4 (7.4%) came from external consultation (Table 1). The most frequent bacteria with an MDR profile remained *E. coli* with 26 (48.14%), followed by *C. freundii* and *P. aeruginosa* each with 4 (7.4%) isolates (Table 3).

A number of mechanisms of resistance were identified among the MDR isolates, products of alterations in their DNA gyrase and topoisomerase were identified in 49 (90.74%) of the isolates, extended spectrum beta-lactamase in 46 (85.18%), and verona integron encoded metallo beta lactamase in 39 (72.2%) along with others (Table 4).

Table 2: Isolated Bacteria 2015-2016

	n	%
<i>E. coli</i>	44	46.81
<i>K. pneumoniae</i>	9	9.57
<i>P. aeruginosa</i>	6	6.38
<i>c. freundii</i>	5	5.31
<i>E. faeca lis</i>	4	4.25
<i>P. mirabilis</i>	3	3.19
Group 47 <i>Klebsiella</i>	2	2.12
<i>S. epidermidis</i>	2	2.12
<i>Enterobacter cloacae</i>	2	2.12
<i>Corynebacterium spp.</i>	1	1.06
<i>Citrobacter amalonaticus</i>	1	1.06
<i>Staphylococcus warneri</i>	1	1.06
<i>Salmonella spp.</i>	1	1.06
<i>Raoultella planticola</i>	1	1.06
<i>Raoultella terrigena</i>	1	1.06
<i>Pontoca agglomerans</i>	1	1.06
<i>E. faecium</i>	1	1.06
<i>Enterobacter aerogenes</i>	1	1.06
<i>Streptococcus spp.</i>	1	1.06
<i>Acinetobacter lwofi</i>	1	1.06
<i>P. putida</i>	1	1.06
<i>S. uberis</i>	1	1.06
<i>Klebsiella oxytoca</i>	1	1.06
<i>Kluyvera cryocrescens</i>	1	1.06
<i>S. aureus</i>	1	1.06
Total	94	

Table 3: Isolated MOR bacteria 2015-2016

n	%	
<i>E.coli</i>	26	48.14
<i>C. Freundii</i>	4	7.4
<i>P. aureginosa</i>	4	7.4
<i>K. pneumoniae</i>	3	5.55
<i>P. mirabilis</i>	3	5.55
Group 47 <i>Klebsiella</i>	2	3.7
<i>Corynebacterium spp.</i>	2	3.7
<i>Raoultella terrigena</i>	1	1.85
<i>Pontoca agglomerans</i>	1	1.85
<i>Enterobacter cloacae</i>	1	1.85
<i>E.faecium</i>	1	1.85
<i>Acinetobacter lwofi</i>		1.85
<i>P. putida</i>	1	1.85
<i>S. uberis</i>	1	1.85
<i>Klebsiella oxytoca</i>		1.85
<i>Kluyvera cryocrescens</i>	1	1.85
<i>S. aureus</i>	1	1.85
Total		54

Table 4: Resistance mechanisms present in isolated MOR bacteria 2015-2016

Mecanism	n	%
DNA gyrase and topoisomerase modification	49	90.74
ESBL	46	85.18
VIM	39	72.22
AAC6	34	62.96
AAC2	31	57.4
APH	9	16.66
AprD2	6	11.11
Betalactamase hyperproduction	6	11.11
Carbapenemase	4	7.4
Total cultures		54

Legend: ESBL = Extended spectrum betalactamase, VIM = verona integron encoded metallo beta lactamase, AAC6 = acetyltransferase '6 for tobramicin, Acetyltransferase '2 for aminoglycosides, APH = Phosfatidyltransferase'3 for AMK,

A percentage of the global resistance (2015-2016) was obtained which reported resistance to ampicillin in 93.24%, 72.88% for piperacillin/tazobactam, 40.58% for cefepime, 89.58% to ceftazidime, 74.63% for cefuroxime, 72.73% to ceftriaxone, 33.33% to meropenem, 33.84% to imipenem, 60% to ertapenem, 53.03% to gentamycin, 12.3% to amikacin, 22.95% to nitrofurantoin, 71.43% for trimethoprim/sulfamethoxazole, 66.2% to ciprofloxacin, 59.21% to levofloxacin, 67.14% to norfloxacin, 18.75% to vancomycin, 50% to tigecycline, and 40% for colistin (Table 5).

Table 5: Resistance Percentage in 2015-2016

	AMP	PIP	PIP/TAZ	CEFE	CEFT	CEFU	CFTX	MPM	IMI	ERT	GEN	AMK	NT	TMP/SMX	CPR	LEV	NOR	VAN	TIG	COL
Global Resistance: (n*)	69	43	6	28	43	50	8	6	7	3	35	9	14	50	47	45	47	3	3	2
Intermediate Resistance	0	0	1	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	0
Total*:	74	59	41	69	48	67	11	18	19	5	66	73	61	70	71	76	70	16	6	5
% resistance	93.243	72.881	14.634	40.58	89.583	74.627	72.727	33.333	36.842	60	53.03	12.329	22.951	71.429	66.197	59.211	67.143	18.75	50	40
	AMP	PIP	PIP/TAZ	CEFE	CEFT	CEFU	CFTX	MPM	IMI	ERT	GEN	AMK	NT	TMP/SMX	CPR	LEV	NOR	VAN	TIG	COL
Urocultures 2015 Resistance: (n*)	20	19	0	10	14	18	0	0	1	0	12	1	5	18	17	16	18	0	0	0
Intermediate Resistance	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total*:	20	19	10	17	16	19	0	6	7	0	17	20	13	21	18	17	19	1	0	0
% resistance	100	100	0	58.824	87.5	94.737	-	0	14.286	-	70.588	5	38.462	85.714	94.444	94.118	94.737	0	0	-
	AMP	PIP	PIP/TAZ	CEFE	CEFT	CEFU	CFTX	MPM	IMI	ERT	GEN	AMK	NT	TMP/SMX	CPR	LEV	NOR	VAN	TIG	COL
Urocultures 2016 Resistance: (n*)	37	23	6	16	24	25	6	4	6	3	20	8	8	28	27	23	24	3	3	2
Intermediate Resistance	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
Total*:	38	29	21	36	24	34	7	7	9	5	37	39	31	37	38	37	35	8	5	4
% resistance	97.368	79.31	28.571	44.444	100	73.529	85.714	57.143	66.667	60	54.054	20.513	25.806	75.676	71.053	62.162	68.571	37.5	60	50
	AMP	PIP	PIP/TAZ	CEFE	CEFT	CEFU	CFTX	MPM	IMI	ERT	GEN	AMK	NT	TMP/SMX	CPR	LEV	NOR	VAN	TIG	COL
	45	39	6	25	35	41	6	4	7	2	31	9	11	40	41	36	39	3	2	2
Intermediate Resistance	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
Total*:	45	39	24	38	37	42	6	12	14	3	42	44	36	48	43	39	41	8	3	3
% resistance	100	100	25	65.789	94.595	97.619	100	33.333	50	66.667	73.81	20.455	31.429	83.333	95.349	92.308	5.122	37.5	66.66	66.667

Legend: *n = Number of sensidisks placed in urocultures, AMP = Ampicillin, PIP = Piperacillin, PIP/TAZ = Piperacillin/tazobactam, CEFE = Cefepim, CEFT = Ceftazidime, CEFU = Cefuroxime, CFTX = Ceftriaxone, MPM = Meropenem, IMI = Imipenem, ERT = Ertapenem, GEN = Gentamicyn, AMK = Amikacin, NT = Nitrofurantoin, TMP/SMX = Trimethoprim/sulfamethoxazole, CPR = Ciprofloxacin, LEV = Levofloxacin, NOR = Norfloxacin, VAN = Vancomycin, TIG = Tigecycline, COL = Colistin

The three most frequent agents (*E. coli*, *K. pneumoniae* and *P. aeruginosa*) reported a resistance percentage to ampicillin of 90.48%, 100% and 100% respectively, to nitrofurantoin 15.63%, 20% and 100%, to cefuroxime 73.68%, 57.14% and 100%, to cefepime 40.54%, 14.29% and 66.67%, to imipenem 0%, 0% and 80%, to trimethoprim/sulfamethoxazole 71.05%, 57.14% and 100%, to ciprofloxacin 69.23%, 40% and 66.67%, to levofloxacin 65%, 16.67% and 0% (tables 6-8).

Table 6: E coil Resistance Percentage 2015-2016

	Cephalosporin							Carbapenemics				Aminoglycosides		Fluoroquinolones					
	AMP	PIP	PIP/TAZ	CEFE	CEFT	CEFU	CFTX	MPM	IMI	ERT	GEN	AMK	NT	TMP/SMX	CPR	LEV	NOR	TIG	COL
Resistance: (n*)	38	25	3	15	20	28	1	0	0	1	17	2	5	27	27	26	25	1	0
Intermediate Resistance	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Total*:	42	32	31	37	23	38	2	8	9	3	36	43	32	38	39	40	34	4	3
% resistance	90.476	78.125	9.6774	40.541	86.957	73.684	50	0	0	33.333	47.222	4.6512	15.625	71.053	69.231	65	73.529	25	0

Table 7: pneumonia resistance percentage 2015- 2016

	Cephalosporin			Carbapenemics				Aminoglicosides		Fluoroquinolones									
	AMP	PIP	PIP/TAZ	CEFE	CEFT	CEFU	CFTX	MPM	IMI	ERT	GEN	AMK	NT	TMP/SMX	CPR	LEV	NOR	TIG	COL
Resistance: (n*)	38	25	3	15	20	28	1	0	0	1	17	2	5	27	27	26	25	1	0
Intermediate Resistance	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Total*:	42	32	31	37	23	38	2	8	9	3	36	43	32	38	39	40	34	4	3
% resistance	90.476	78.125	9.6774	40.541	86.957	73.684	50	0	0	33.333	47.222	4.6512	15.625	71.053	69.231	65	73.529	25	0

Table 8: P.aureginosa resistance percentage 2015-2016

	Cephalosporin			Carbapenemics				Aminoglicosides		Fluoroquinolones									
	AMP	PIP	PIP/TAZ	CEFE	CEFT	CEFU	CFTX	MPM	IMI	ERT	GEN	AMK	NT	TMP/SMX	CPR	LEV	NOR	TIG	COL
Resistance: (n*)	38	25	3	15	20	28	1	0	0	1	17	2	5	27	27	26	25	1	0
Intermediate Resistance	0	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Total*:	42	32	31	37	23	38	2	8	9	3	36	43	32	38	39	40	34	4	3
% resistance	90.476	78.125	9.6774	40.541	86.957	73.684	50	0	0	33.333	47.222	4.6512	15.625	71.053	69.231	65	73.529	25	0

Legend: *n = Number of sensidisks placed in urocultures, AMP = Ampicillin, PIP = Piperacillin, PIP/TAZ = Piperacillin/tazobactam, CEFE = Cefepim, CEFT = Cefazidime, CEFU = Cefuroxime, CFTX = Ceftriaxone, MPM = Meropenem, IMI = Imipenem, ERT = Ertapenem, GEN = Gentamicyn, AMK = Amikacin, NT = Nitrofurantoin, TMP/SMX = Trimethoprim/sulfamethoxazole, CPR = Ciprofloxacin, LEV = Levofloxacin, NOR = Norfloxacin, TIG = Tigecycline, COL = Colistin

Discussion

The infections associated with health care are an issue with a tendency to increase. According to the World Health Organization, between 2.5 to 15% of the total global load of infections correspond to MDR pathogens.

A urinary tract infection is one of the three most common diseases reported in the world, this is associated to an invasion of the urinary tract, comorbidities, gender and age. The patients who are most affected are those that by the nature of their comorbidities are in the need of prolonged hospital stays, seeing themselves subjected to antibiotic pressure at times, which in turn generates resistant bacteria and infections by opportunistic pathogens. It is because of this that a strict vigilance of said patients must be made, so as to detect these patients in an early manner and reduce the times of stay and, more importantly, the morbidity and mortality of these patients.

Within the proposed methodology for the vigilance and prevention, we count with urocultures, along with clinical presentation, a resource that allows us to make an etiological diagnosis over 90% of the time. In our study a low recovery rate was obtained, though it is perhaps associated with the unnecessary request of urocultures, which is why we consider that patients must be better evaluated with the finality of making better use of hospital resources.

Of the isolates obtained, with relation with antibiotic resistance, in comparison with data obtained by the INCAN where nosocomial hospital resistance to fluoroquinolones was of levofloxacin 49.05%, ciprofloxacin 43.49% and norfloxacin 26.41%, our study showed a global resistance which oscillated between 60% for all three of the mentioned antibiotics. In the MDR isolates we identified resistances to quinolones in more than 90% of the agents, which makes them a poor choice for treatment for UTIs. A poor sensibility was reported for cephalosporin as well as for carbapenemics, which further reduces the possibilities for treatment of these patients. Because of the aforementioned reasons, we must seek to reinforce the protocol for the rational use of antibiotics, with the objective of reversing the current resistances, as well as infections with an MDR

profile since, though they are not all that frequent in the hospital, they do considerably increase the lethality rate.

Conclusion

Urocultures are overemployed in our unit, as such, patients must be better selected when requesting this resource so as to not waste hospital resources. Though the isolates that we obtained, we have determined that fluoroquinolones and cephalosporin are not a viable treatment option, as well as trimethoprim/sulfamethoxazole despite them being amongst the first line and second line treatment options for this disease, nor are carbapenemics as there seems to be pathogens that are developing resistances to them, however we have found that amikacin is a viable treatment option for UTIs in our unit since it has a high sensitivity. Another alarming finding is that out of the 54 MDR isolates, only 24 of them were compatible with a nosocomial infection, which means that 30 of those isolates developed bacterial resistances in the ambulatory setting, which further exemplifies both the fact that the irrational use of antibiotics both in the ambulatory and hospital setting is what is increasing bacterial resistance, and that we need to closely adhere and enforce the rational use of antibiotic protocol established in our unit so as to lower the mortality associated with MDR urinary tract infections.

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