

Reviewer's Comments

Current trend of Resistant for the Commonly Prescribed New Fluoroquinolones among Hospitalised Patients in Sana'a, Yemen.

Abstract

Background: The new fluoroquinolones have demonstrated enhanced activity against the most common bacteria involved in lower respiratory tract infection (LRTI). Moxifloxacin is the most commonly prescribed respiratory fluoroquinolone drug in Yemen. Pneumonia is a major and an on-going public health problem globally. With the widely use of fluoroquinolones in the clinical practice, the potential for developing resistance has become a concern.

The objectives: The aim of present study was to determine the trend of moxifloxacin resistant and the distribution of resistant for different sample types among hospitalised patients in Sana'a, Yemen.

Methods: The study was performed at a private hospital in Sana'a, Yemen. The records were taken from the microbiology department for hospitalised patients. Moxifloxacin susceptibility samples were collected from January, 2017 to December, 2017. The moxifloxacin susceptibility was studied against several isolates. Full ethical clearance was obtained from the qualified authorities who approved the study design. All data were analyzed using SPSS Statistics version 21.

Results: Out of 927 sample isolates, 580 (62.6%) were moxifloxacin resistant isolates and only 30.1% were sensitive. The *Escherichia coli* was observed in 24.4% of total sample isolates, followed by *Pseudomonas aeruginosa* (12.1%). From the study findings, 44.8% of total sample was isolated from sputum cultures. There was a statistically significant difference between bacteria type and culture results ($P\text{-value} < 0.001$). Moreover, 96.2% of *Acinetobacter species* and all *Acinetobacter baumannii* isolates were moxifloxacin resistant. The study findings reported that 70.4% of *Escherichia coli* isolates were resistant for moxifloxacin, followed by methicillin resistant staphylococcus aureus (64.7%), *Klebsiella pneumoniae* (60.6%), and *Pseudomonas aeruginosa* (46.4%). However, 86.1% of staphylococcus aureus isolates were moxifloxacin resistant. Results in this study showed that there was high significantly relationship between culture results and sample type ($P\text{-value} < 0.001$). Also 44.8% of sample isolates were from sputum cultures. Moreover, 74.2% of sputum cultures isolates were moxifloxacin resistant. There was a statistically significant difference between culture results with age groups ($P\text{-value} = 0.02$). Also 64.1% of males had moxifloxacin resistant and 36.9% of isolate resistant were aged > 60 years

Conclusion: This study reveals that varieties of pathogens are responsible for LRTI and moxifloxacin resistance has become a great public health issue. The possibility of reducing resistance by controlling the use of antibiotics is a reasonable approach. Inappropriate and irrational drug usage should be avoided. This study may help the government's regulatory authority to develop a policy about rational prescription of antibiotics to minimize resistance of new antibiotics and also to ensure the maximum safety to the health of patients.

Keywords: Moxifloxacin, Prevalence, Resistance

Introduction:

The classic fluoroquinolones such as ciprofloxacin, norfloxacin, fleroxacin and ofloxacin have had strong activity against Gram-negative bacteria, but the effectiveness of these compounds against Gram-positive bacteria has been debated. The new fluoroquinolones developed during the 1990s, such as levofloxacin and moxifloxacin, have demonstrated enhanced activity against the most common bacteria involved in lower respiratory tract infection (LRTI). The mechanism of newer fluoroquinolone activity is the inhibition of essential bacterial type II topoisomerases (DNA gyrase) and topoisomerase IV^[1]. All new fluoroquinolones have a bactericidal

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activity and a post-antibiotic effect. Compared with ciprofloxacin, all new fluoroquinolones have a longer elimination half-life that allows once daily dosing. In addition, these antibiotics have excellent penetration into respiratory tissues, with the highest concentrations found in the epithelial lining fluid and alveolar macrophages^[2]. The newer fluoroquinolones such as levofloxacin and moxifloxacin are currently available in both IV and oral formulations. With regard to the pharmacodynamic characteristics, the new fluoroquinolones cause concentration-dependent killing^[3].

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Moxifloxacin (Avelox; Bayer), a “fourth-generation” fluoroquinolone, is often used in the empirical treatment of severe community-acquired pneumonia (CAP), which is one of the most common infectious diseases and among the primary causes of death worldwide^[4]. *Streptococcus pneumoniae* is the primary pathogen responsible for CAP, but many other microorganisms, including Gram-negative and atypical bacteria (e.g., *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*), may also be etiological agents^[5]. The recommended dose of moxifloxacin is 400 mg/day (q.d.). No dosage adjustment is required in elderly patients, obese patients^[6], or patients with renal or mild hepatic impairment^[7]. Furthermore, due to the risk of a prolonged QT interval (a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle), it is recommended that the daily dose of moxifloxacin should not exceed 400 mg^[8].

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The clinical efficacy of the newer fluoroquinolones in the treatment of LRTI has been demonstrated in several randomized, double-blind, prospective studies. In comparative community-acquired pneumonia (CAP) studies, newer fluoroquinolones almost have more activity than the cephalosporins (e.g. ceftriaxone, cefaclor or cefuroxime axetil) and the macrolides (e.g. erythromycin or roxithromycin)^[1]. Niederman *et al.*^[9] compared hospitalization and mortality in patients with CAP being treated with moxifloxacin, amoxicillin or clarithromycin. The mortality rate for moxifloxacin-treated patients was significantly better ($P = 0.045$) than for comparator-treated patients. Current treatment guidelines for the management of LRTI in adults recommend fluoroquinolones for empirical treatment in several patient groups. The new fluoroquinolones currently available offer major therapeutic advances compared with previous agents, and the incidence of adverse events is clearly outweighed by their clinical use^[1]. As with other antimicrobials, the development of resistance is a potential problem associated with their increased use in RTIs. Rational prescribing and continuous control of antibiotic resistance levels are needed to keep their future antibacterial efficacy. The new fluoroquinolones have demonstrated enhanced activity against the most common bacteria involved in LRTI. Moxifloxacin is the commonly prescribed respiratory fluoroquinolone drug in Yemen. Pneumonia is a major and an on-going public health problem globally. Thus, the aim of present study was to determine the trends of moxifloxacin and the distribution of resistant for different sample types among hospitalised patients in Sana'a, Yemen.

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Methods:

This retrospective study was performed at a private hospital in Sana'a, Yemen. Moxifloxacin susceptibility samples were collected from January, 2017 to December, 2017 from the records of hospitalised patients. The moxifloxacin susceptibility was studied against several isolates. Full ethical clearance was obtained from the qualified authorities who approved the study design. All data were analyzed using SPSS Statistics version 21.

Results:

According to the present study, the mean age of study sample (n=927) was 49year (with SD \pm 21.3 year) and ranged between 1 and 120 years. Out of 927 samples, 580 (62.6%) were **moxifloxacinresistant** isolates and only 30.1% were sensitive. Also (69.0%) of total patients were females and (31.0%) were males. Among 927 of patients, (28.2%) was aged between 41- 60 years and 35.5% more than 60 years. The *Escherichia coli* was observed in 24.4% of total sample isolates, followed by *Pseudomonas aeruginosa*(12.1%). From the study findings, 44.8% of total sample was isolated from sputum cultures (table 1).

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Table 1. Distribution of Study variables

variable	Level of variable	Frequency	Percent
Culture Result	I	68	7.3
	R	580	62.6
	S	279	30.1
	Total	927	100.0
Sex	M	287	31.0
	F	640	69.0
	Total	927	100.0
Age order	1-20 years	124	13.4
	21-40 years	213	23.0
	41-60 years	261	28.2
	> 60	329	35.5
	Total	927	100.0
Type of bacteria	<i>Acinetobacterbaumannii</i>	24	2.6
	<i>Acinetobacter species</i>	185	20.0
	<i>Alpha Hemolytic Streptococcus</i>	2	0.2
	<i>B-Hemolytic Streptococcus-Group-A</i>	1	0.1
	<i>B-Hemolytic Streptococcus-Group-D</i>	1	0.1
	<i>CitrobacterSpp</i>	5	0.5
	<i>Coagulase negative Staphylococci</i>	57	6.1
	<i>EnterobacterSpp</i>	3	0.3
	<i>Enterococcus Spp</i>	19	2.0
	<i>Escherichia coli</i>	226	24.4
	<i>Klebsiellapneumoniae</i>	99	10.7
	<i>KlebsiellaSpp</i>	50	5.4
	<i>Moraxella Spp</i>	4	.4
	<i>Methicillin Resistant Staphylococcus aureus(MRSA)</i>	17	1.8
	<i>Neisseria Spp</i>	1	0.1
	<i>Nocardia SPP</i>	1	0.1
	<i>Proteus mirabilis</i>	3	0.3
	<i>Proteus Spp</i>	10	1.1
	<i>Proteus vulgaris</i>	1	0.1
	<i>Pseudomonas aeruginosa</i>	112	12.1
	<i>SerratiaSpp</i>	4	0.4
	<i>Staphylococcus aureus</i>	72	7.8
	<i>Streptococcus pneumoniae</i>	3	.3
<i>Streptococcus spp.</i>	27	2.9	
Total	927	100.0	

Type of sample	Aspirated Fluid Culture	1	0.1
	Blood Culture	22	2.4
	Cerebro Spinal Fluid (CSF) C/S	144	15.5
	General swab for Culture	17	1.8
	Pleural Fluid For Culture & Sensitivity	27	2.9
	Ascitic fluid c/s and sensitivity	6	0.6
	Pus For Culture & Sensitivity	91	9.8
	Sputum Culture	415	44.8
	Throat swab Culture	1	0.1
	Urine Culture	120	12.9
	Wound Swab For Culture	83	9.0
	Total	927	100.0

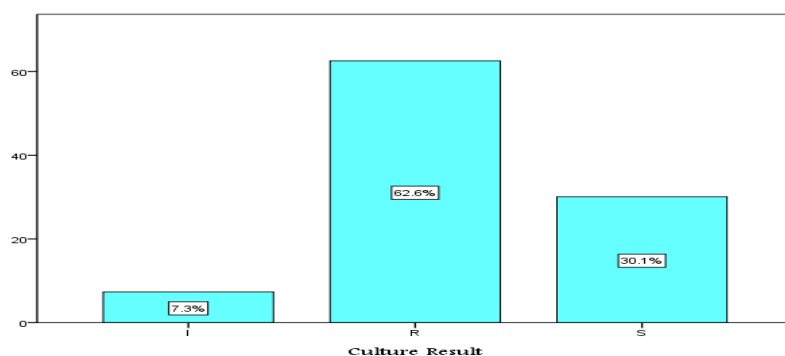


Figure 1. Distribution of Moxifloxacin Susceptibility among Study Sample

Results in table 3 indicated that the relationship between bacteria type and culture results was statistically significant (P -value < 0.001). In the present study, 96.2% of *Acinetobacter* species were moxifloxacin resistant and all *Acinetobacterbaumannii* isolates were moxifloxacin resistant. Also the study findings reported that 70.4% of *Escherichia coli* isolates were resistant for moxifloxacin, followed by *Klebsiella pneumoniae* (60.6%), methicillin resistant *Staphylococcus aureus* (64.7%), *Pseudomonas aeruginosa* (46.4%). However, 86.1% of *Staphylococcus aureus* isolates were moxifloxacin resistant.

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Table 2. Distribution of bacteria type according to culture results

Type of Bacteria	Culture Result			Total	P-value
	I	R	S		
<i>Acinetobacterbaumannii</i>	0	24	0	24	
<i>Acinetobacter species</i>	2	177	6	185	
<i>Alpha Hemolytic Streptococcus</i>	0	1	1	2	
<i>B-Hemolytic Streptococcus-Group-A</i>	0	1	0	1	
<i>B-Hemolytic Streptococcus-Group-D</i>	0	1	0	1	
<i>CitrobacterSpp</i>	2	1	2	5	
<i>Coagulase negative Staphylococci</i>	19	14	24	57	
<i>EnterobacterSpp</i>	2	0	1	3	
<i>Enterococcus Spp</i>	0	18	1	19	

<i>Escherichia coli</i>	7	159	60	226	0.001
<i>Klebsiellapneumoniae</i>	10	60	29	99	
<i>KlebsiellaSpp</i>	2	42	6	50	
<i>Moraxella Spp</i>	0	0	4	4	
<i>Methicillin Resistant Staphylococcus aureus(MRSA)</i>	6	11	0	17	
<i>Neisseria Spp</i>	0	0	1	1	
<i>Nocardia SPP</i>	0	0	1	1	
<i>Proteus mirabilis</i>	0	3	0	3	
<i>Proteus Spp</i>	2	6	2	10	
<i>Proteus vulgaris</i>	0	0	1	1	
<i>Pseudomonas aeruginosa</i>	11	52	49	112	
<i>SerratiaSpp</i>	0	0	4	4	
<i>Staphylococcus aureus</i>	3	7	62	72	
<i>Streptococcus pneumoniae</i>	0	0	3	3	
<i>Streptococcus spp.</i>	2	3	22	27	
Total	68	580	279	927	

There was not a statistically significant difference between culture results with sex (P -value = 0.25). However, there was a statistically significant difference between culture results with age groups (P -value = 0.02). Also, 64.1% of males had moxifloxacin resistance and 36.9% of isolates resistant were aged >60 years (table 3).

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Table 3. Distribution of age group and sex according to Culture results

Variable	Culture results			Total	<i>P</i> -value
	I	R	S		
Sex	F	26	170	91	0.25
	M	42	410	188	
	Total	68	580	279	
Age group	Less 20	14	62	48	0.02
	21-40	12	134	67	
	41-60	13	170	78	
	> 60	29	214	86	
	Total	68	580	279	

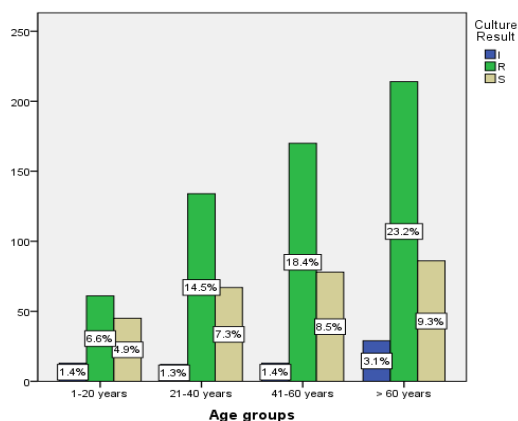


Figure 2. Distribution of age group and sex according to Culture results

The relationship between culture results and sample type was analyzed in the table 4. Results in this table showed that there was high significantly relationship (P -value<0.001). Also 44.8% of sample isolates were from sputum cultures. Moreover, 74.2% of sputum cultures isolates were moxifloxacin resistant.

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Table 4. Distribution of culture results according to sample type

Sample Type	Culture Result			Total	P-value
	I	R	S		
Ascitic fluid c/s and sensitivity	0	0	1	1	0.001
Aspirated Fluid Culture	0	8	14	22	
Blood Culture	18	62	64	144	
Cerebro Spinal Fluid (CSF) C/S	0	14	3	17	
General swab for Culture	2	18	7	27	
Pleural Fluid For Culture & Sensitivity	0	1	5	6	
Pus For Culture & Sensitivity	6	31	54	91	
Sputum Culture	28	308	79	415	
Throat swab Culture	0	0	1	1	
Urine Culture	7	83	30	120	
Wound Swab For Culture	7	55	21	83	
Total	68	580	279	927	

Discussion:

The primary objective in the development of moxifloxacin was to produce an appropriate spectrum antibiotic for the treatment of community-acquired RTIs with a good tolerability profile, good efficacy against the relevant pathogens, and low propensity for the development of bacterial resistance, thus benefiting patients and helping clinicians to treat these diseases^[10].

An effective new antimicrobial agent is necessary in light of the therapeutic problems posed by the increasing prevalence of antibiotic resistance of the common respiratory tract pathogens, which have become increasingly resistant to traditional first-line antibiotics such as penicillins and macrolides^[11].

According to study results, 62.6% of study sample were moxifloxacin resistant isolates and only 30.1% were sensitive.

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Moxifloxacin treatment failure is being increasingly reported, particularly in the Asia-Pacific region along with increasing detection rates of resistance mutations^[12].

Fluoroquinolone resistance is rare in North America. Surveillance studies in the United States from 1987 to 2009 demonstrated low rates of resistance to moxifloxacin (0.1%)^[13]. Similarly, the prevalence of fluoroquinolone resistance in Canada remained low from 1998 to 2009. Although total per capita outpatient use of fluoroquinolones increased during this 10-year period, levofloxacin and moxifloxacin resistance remained unchanged at <2% in the >26,000 isolates collected^[14].

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In contrast to study findings in Pakistan, the prevalence of Moxifloxacin resistant was 42.4%^[15]. From the present study findings, 44.8% of total sample was isolated from sputum cultures. Moreover, 74.2% of sputum cultures isolates were moxifloxacin resistant. The increasing resistance to antibiotics by respiratory pathogens has complicated the use of empirical treatment with traditional agents and a definitive bacteriological diagnosis and susceptibility testing would be required for effective management of LRTI^[16]. The study findings reported that 70.4% of *Escherichia coli* isolates were resistant for moxifloxacin, followed by MRSA (64.7%), *Klebsiella pneumoniae* (60.6%), and *Pseudomonas aeruginosa* (46.4%). Also results in this study showed that there was a statistically significant difference between culture results with age groups and 36.9% of patients with moxifloxacin resistant isolates were aged > 60 years.

During the last several years, resistance to fluoroquinolones has remained very high among MRSA, *P. aeruginosa* and other pathogens isolated from intensive care unit patients. In addition, the recent reports of an overall increase in resistance to fluoroquinolones among bacteria causing community-acquired infections, such as *E. coli* have a major concern in clinical practice. These surveillance data demonstrate that fluoroquinolone resistance has to be associated with both particular bacterial species and patient populations^[13].

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Conclusion and Recommendation:

LRTIs comprise a wide range of diseases from acute bronchitis to severe pneumonia leading to death. This study reveals that varieties of pathogens are responsible for LRTI and moxifloxacin resistance has become a great public health issue. The possibility of reducing resistance by controlling the use of antibiotics is a reasonable approach. Inappropriate and irrational drug usage should be avoided. This study may help the government's regulatory authority to develop a policy about rational prescription of antibiotics to minimize resistance of new antibiotics and also to ensure the maximum safety to the health of patients.

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Conflict of Interest:

The authors declare that they have no competing interests.

References:

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1. Lode H. & Allewelt M. Role of newer fluoroquinolones in lower respiratory tract infections. *Journal of Antimicrobial Chemotherapy*. 2002; 49: 709–712
2. Wise, R. & Honeybourne, D. Pharmacokinetics and pharmacodynamics of fluoroquinolones in the respiratory tract. *European Respiratory Journal*. 1999; 221–9.
3. Blondeau, J. M. Clinical utility of the new fluoroquinolones for treating respiratory and urinary tract infections. *Expert Opinion on Investigational Drugs*. 2002; 10, 213–36

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4. Wiemken TL, Peyrani P, Ramirez JA. Global changes in the epidemiology of community-acquired pneumonia. *SeminRespirCrit Care Med.*2012; 33:213–219.
5. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax.*2012; 67:71– 79.
6. Kees MG, Weber S, Kees F, Horbach T. Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients. *J AntimicrobChemother.*2011; 66:2330 –2335
7. Balfour JA, Lamb HM. Moxifloxacin: a review of its clinical potential in the management of community-acquired respiratory tract infections. *Drugs.* 2000; 59:115–139
8. O' brink-Hansen K, Hardlei TF, Brock B, Jensen-Fangel S, Kragh Thomsen M, Petersen E, Kreilgaard M. Moxifloxacin pharmacokinetic profile and efficacy evaluation in empiric treatment of community-acquired pneumonia. *Antimicrob Agents Chemother.* 2015; 59:2398 –2404
9. Niederman, M., Church, D., Haverstock, M. &Springsklee, M. Does appropriate antibiotic therapy influence outcome in community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB)? *Journal of Respiratory Medicine.* 2000; *Suppl. A*, E23.
10. Christina Krasemann, Jutta Meyer, and Glenn Tillotson. Evaluation of the Clinical Microbiology Profile of Moxifloxacin. *Clinical Infectious Diseases* 2001; 32(Suppl 1):S51–63.
11. Tillotson G, Blondeau J. Today's community respiratory tract infections: a challenge appropriate for moxifloxacin. In: Adam D, Finch R, eds. *Moxifloxacin in practice.* Vol 1. Oxford: Maxim Medical, 1999: 1–11.
12. Gerald L. Murray, Catriona S. Bradshaw, Melanie Bissessor, Jennifer Danielewski, Suzanne M. Garland, Jørgen S. Jensen, Christopher K. Fairley, Sepehr N. Tabrizi. Increasing Macrolide and Fluoroquinolone Resistance in *Mycoplasma genitalium*. *Emerging Infectious Diseases.* 2017; 23 (5).
13. Dalhoff A. Global fluoroquinolone resistance epidemiology and implications for clinical use. *InterdiscipPerspect Infect Dis.* 2012; 2012:976273.
14. Pillar C. M., Thornsberry C., and Sahm D. F. "Susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* collected across Europe and Asia to levofloxacin and other respiratory agents; results from GLOBAL surveillance (1997–2007)." *Penetration,* 2010; 14–22.
15. Ali I, Butt MA. Antibiotic Susceptibility Pattern of Bacterial Isolates from Patients of Respiratory Tract Infection at 43 Centers in Punjab, Pakistan. *ClinExpPharmacol.* 2017; 7: 229.
16. Anderson H, Esmail A, Hollowell J, Littlejohns P, Strachen D. Epidemiologically based needs assessment: lower respiratory disease. DHA Project Research Programme. 1993; 6-12.