

ORIGINAL ARTICLE

In-vitro Susceptibility of Levofloxacin against Different Clinical Isolates

Rabia Bushra¹, Mehwish Rizvi², Maqsood Ahmed³, Shazia Alam⁴ and Nusrat Bano⁵

ABSTRACT

Background: Levofloxacin is a broad spectrum quinolone, widely used to treat infections caused by gram negative and gram positive bacteria. Development of resistance by pathogens against different broad-spectrum antibiotics is increasing and now becoming a global issue.

Objectives: The aim of the study is to evaluate the current sensitivity pattern of levofloxacin against various common clinical isolates like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiellapneumoniae*.

Methods: A total of one hundred and ten samples were collected from different pathological laboratories of Karachi, Pakistan. The above mentioned pathogens were isolated from blood, stool/urine, sputum, skin samples.

Results: Results show least resistance of levofloxacin against *E.coli* (27.5%), and *P.aeruginosa* (27%), while *S.aureus* possessed highest resistance (45%).

Conclusion: Study concluded levofloxacin still possesses excellent anti-microbial activity against common pathogens. Routine monitoring and surveillance is further required to ensure effective treatment regimens to community.

KEY WORDS: Levofloxacin, Resistance, Susceptibility, Clinical Isolates, Pathogens.

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INTRODUCTION

In early 1960s the development of quinolones was initiated. Nalidixic acid, was granted a license to be used in the treatment of urinary tract infections (UTIS), mainly caused by gram negative bacteria, in 1967. In the initial days of the usgae, Quinolones were resisted by gram negative bacteria.¹ The first monofluoroquinolone, flumequine, exhibited improved sensitivity against gram positive pathogens in comparison to nalidixic acid due to structural modifications.² Off late, quinolones have been widely used to treat bacterial infections, with ciprofloxacin as an effective member of the class, having excellent bioavailability and active drug efflux.³

Levofloxacin, a broad spectrum antibiotic quinolones, is found to be effective against a variety of the clinical isolates, especially *Enterococcus spp.* and *S. pneumoniae*. Among all quinolones levofloxacin is strongly active against both gram positive and gram negative bacteria. It is two times more effective than ofloxacin against *Enterobacteriaceae* and *Pseudomonas aeruginosa*.^{4,5} Additionally it also bears potential therapeutic response over *Pasteurella species*, *Eikenella*, *Corrodens*, *Legonella*, *Pneumophila* and *BacteroidesFragilis*.⁶ The minimum inhibitory concentration (MIC) of levofloxacin is 4-8 ug/ml against *Pseudomonas aeruginosa* while for *Haemophilus influenza*, *Neisseria gonorrhoeae* and *Moraxella catarrhalis* MIC is around 0.015-0.06 ug/ml.^{7,8,9} The effectiveness of levofloxacin against *Spneumoniae* infections was also reported.^{10,11,12} The antibiotic has been utilized in the treatment of ear infections in children.¹³

The objective of the study was to determine the in-vitro susceptibility of levofloxacin against common pathogens like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* using Baur-Kirby method.

METHODOLOGY

Clinical isolates were collected from different pathological laboratories of Karachi, Pakistan from January 2013 to May 2013. Pathogens were isolated from pus, sputum, stool, urine and blood samples. Susceptibility of levofloxacin was determined using disk diffusion method in laboratory to produce consistent results with bacterial isolates. Commercially prepared disc of levofloxacin (5µg) was purchased from the local market (Oxoid Ltd., England). Muller Hinton Agar (Oxoid, England) and broth were prepared according to standard guidelines provided by CLSI (Clinical and Laboratory Standard Institute).¹⁴ McFarland standard 0.5 was used and prepared.¹⁵ Commercial discs of levofloxacin were placed on dry inoculated streaked plates using sterile forceps, and incubated at 37°C for 18-24 hours. After incubation, the zones of inhibition appeared around the discs were measured using scale. The zones of inhibition for *E.coli*, *K.pneumoniae*, and *P.aeruginosa*, were set as resistant (≤ 13), intermediate resistant (14-16mm), and sensitive (≥ 17 mm). While the zones for *S.aureus* were resistant (≤ 15 mm), intermediate resistant (16-18mm), and sensitive (≥ 19 mm).^{14, 15}

RESULTS

Pathogens were isolated by blood, stool, urine, pus and sputum. The detail of sources is given in Table 1. Percent susceptibility of *E.coli* (72.5%), *S.aureus* (55%), *P.aeruginosa* (73%), and *K.pneumoniae* (66%) showed *P.aeruginosa* to be more susceptible towards levofloxacin as compared to other tested pathogens. Table 2 presents the number of pathogens resistant (isolates not inhibited by normal dose of the anti-microbial agent or lack of insignificant zone around experimental disc), intermediately resistant (lower than susceptible response of isolates with smaller diameter zones around the experimental discs; clinically disregarded as higher doses can be used to treat infections and susceptible (isolates inhibited by normal concentration of drug and significant zones are appeared around the experimental disc).¹⁴

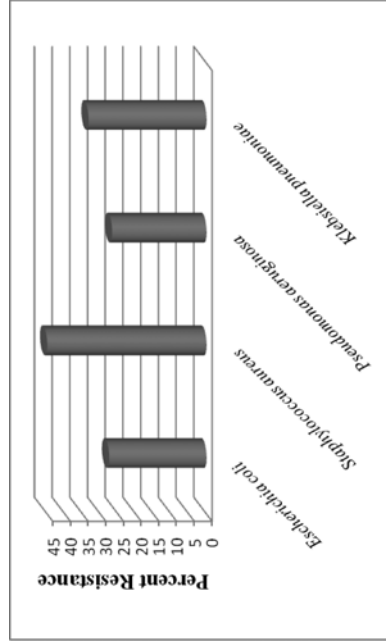
Table 1: Sources of Clinical Isolates

S. No.	Pathogens	Sources				Sample Size
		Blood	Stool/Urine	Skin Pus	Sputum	
1	<i>Escherichia coli</i>	14	23	3	-	40
2	<i>Staphylococcus aureus</i>	12	20	8	-	40
3	<i>Pseudomonas aeruginosa</i>	3	5	3	4	15
4	<i>Klebsiellapneumonia</i>	3	3	2	7	15

Table 2: Sensitivity of Levofloxacin against Clinical Isolates

S. No.	Pathogens	Resistant (R)	Intermediate Resistant (IR)	Sensitive (S)
1	<i>Escherichia coli</i>	08	03	29
2	<i>Staphylococcus aureus</i>	10	08	22
3	<i>Pseudomonas aeruginosa</i>	02	02	11
4	<i>Klebsiellapneumoniae</i>	02	03	10

Figure 1: Percentile Resistance of Levofloxacin against Clinical Isolates



DISCUSSION

Resistance to a variety of antimicrobial drugs is rising throughout the world.¹⁶ The emergence of antibiotic resistance is mainly due to needless use of antibiotics in humans and animals. Risk factors for the increase of resistant bacteria in hospitals and the community can be summarized as over-crowding, lapses in hygiene or poor infection control practices.¹⁷ In present study sensitivity pattern of levofloxacin was determined against 40 samples of *Escherichia coli*, 40 of *Staphylococcus aureus*, 15 of *Klebsiellapneumoniae* and 15 of *Pseudomonas aeruginosa*. In a previous study,

200 clinical isolates were tested including the species *Escherichia coli*, *Klebsiellapneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providenciairetgeri*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*.¹⁸ Findings indicated all isolates of *E.coli* were susceptible to levofloxacin with similar results.^{17,19} The sensitivity of levofloxacin against *S. aureus* was 55%. While past studies have shown good activity of Levofloxacin and ofloxacin against staphylococcal strains²⁰ compared with the majority of other antibiotics. Researchers reported 60.43% susceptibility of *S.aureus* to levofloxacin.²¹ The comparatively lower

susceptibility shows resistance has emergence against this fluoro-quinolone possibly due to irrational use of antibiotic, incomplete course of therapy and the self-medication.

The present study revealed only 2 pathogens of *K.pneumoniae* resistant to levofloxacin while reports depict *K.pneumoniae* to be 100% susceptible to levofloxacin.²² Another study showed 98% sensitivity of *K.pneumonia* towards levofloxacin,²³ using CLSI disk diffusion technique.

Current susceptibility of *Pseudomonas aeruginosa* was 66% with a previous finding depicting greater anti-bacterial response than ciprofloxacin.²⁴ Comparable results of levofloxacin and ciprofloxacin against 300 *Pseudomonas aeruginosa* isolated from hospitalized patients are also available.²⁵ These results showed that the newer quinolones possessed good antimicrobial activity against various strains of gram positive and gram negative bacteria, however, rational and correct monitoring programs for its sensitivity should be conducted regularly in order to control the emergence of its resistance.

CONCLUSION

The present study shows that levofloxacin is still considered as a good choice for the treatment of infections caused by *E.coli*, *P.aeruginosa* and *K.pneumonia*. However, more investigations are required for *S.aureus*. Authors also suggested that the surveillance against such widely prescribed antibiotics must be done periodically to evaluate the current status of resistance against microbes

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ORIGINAL ARTICLE

Risk Factors for Nutritional Rickets in Children under 36 months: A Civil Hospital Case Study

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ABSTRACT

Background: Nutritional rickets is a common problem in Pakistan especially in Karachi with majority of the population living in enclosed housing and slums having limited or no sun exposure. There is a dearth of significant data regarding rickets in Pakistan especially in Sindh which emphasizes the need for further research. This study can be a foundation for other studies regarding strategies for prevention and early diagnosis of rickets.

Objectives: To determine the clinical presentation and identify risk factors for nutritional rickets in children less than three years of age.

Methods: A cross sectional study conducted in the department of pediatrics DUHS/CHK from June 11, 2007 to December 10, 2007. Fifty patients aged two months to thirty six months presenting with the clinical manifestation of rickets were included in the study. Information recorded included symptoms, socioeconomic status, feeding patterns, sun exposure, clothing, housing and malnutrition. Diagnosis was based on clinical signs, serum levels of alkaline phosphatase, calcium, phosphorus and radiological changes in X-ray wrist joint.

Results: Approximately 60% reported a weight for height less than ISD criteria set by WHO. Of the total assessed 58% percent were exclusively breast fed, 30% partial breast fed and 12% on formula milk. Weaning age was not reached in 20% of the children. Complementary feeding initiated late for 40% of the children with 78% percent exposed to sunlight less than 30 minutes per day and. Gross motor delay existed in 30% of children and hypocalcaemia convulsions in 14%. Past H/O repeated was in 32% had 22% had persistent/recurrent diarrhea.

Conclusion: Exclusivity breast feeding to complementary feed, inadequate exposure to sunlight and delayed introduction of complementary foods are the main risk factors for the development of nutritional rickets which can manifest itself in the form of ARI and diarrhea.

KEY WORDS: Rickets, Vit-D Deficiency, Biochemical Abnormalities.

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INTRODUCTION

Rickets is a term signifying failure of mineralization of growing bone or osteoid tissue with characteristic changes of growth plate cartilage among children before closure of growth plate. There are many causes of rickets; among them nutritional vitamin D deficiency remains the most common cause globally.¹ Independent research conducted in Lahore,² Abbottabad,³ and Peshawar^{4,5} also found nutritional deficiency of vitamin D as the most often cited cause of rickets.

Among ethnic minorities in the UK, 1.6% (77% of them of Southeast Asian descent) showed prevalence of rickets. The Center for Disease Control and Prevention places prevalence of nutritional rickets at 5 cases per 1 million children of six months to five years of age.⁶ Multiple studies highlight most black children to be the most affected.⁷

Review of studies conducted between 1986 and 2003 highlighted 166 pediatric cases of rickets USA. Among the affected children, majority were less than 30 months old at presentation, of which 83% were black and 96% were breast-fed.⁸

Nutritional rickets is a common problem in Pakistan as highlighted in different studies. In Peshawar rickets was observed in 2.25% children.⁵ There is dearth of significant data regarding rickets in Pakistan especially in Sindh which emphasizes the need for further research on this preventable disease. This study was undertaken to further evaluate the clinical presentation and risk factors of rickets. This can provide baseline data for other studies targeting early diagnosis and prevention of rickets.

METHODOLOGY

This cross-sectional study was conducted in the department of Pediatrics, CHK from June 2007 to December 2007. Clinical examination and laboratory investigations were used to assess the condition. Keeping the prevalence of rickets 2.25% with a CI of 95% and precision required 0.05 the sample size estimated was 39 using WHO sample size software. The study however

involved 50 children as subjects. The sampling technique used was non-probability, convenience based. Children under three years of age, presenting symptoms of rickets and biochemical abnormalities regardless of gender were included. Those having chronic illness like hepatic or renal disease, on anticonvulsant medicines for more than six months, having evidence of skeletal dysplasia and pre-term children with hypocalcemia were excluded from the study.

Written permission was sought from the ERC of CHK and informed consent was acquired from parents or attendants of the patients. Their anonymity, autonomy, confidentiality and beneficence were given top priority. The respondents were provided complete liberty not to answer any question or leave the study at any time.

A thorough history including, socioeconomic status, feeding pattern, weaning practices, sun exposure, type of clothing and housing condition were taken followed by a complete examination. Nutritional assessment of children was done using WHO Classification of normal, mild, moderate and severe malnutrition. Intake of vitamin D rich food was assessed in children by inquiring about the average intake of vitamin D rich food. Sun exposure in children was estimated approximately on average weekly exposure. The following investigations were done to confirm rickets, 1) serum calcium 2) serum phosphorus 3) Serum alkaline phosphatase 4) X-ray wrist joint.

Data was entered into SPSS version 16. Mean and SD were calculated for continuous variables. Frequencies were calculated for categorical variables and were exhibited through graphs

RESULTS

Out of the total 50 children with the rickets, 29 (58%) were male and 21 (42%) were female. Mean age was 15.13±9.6 months with mean age of male children at 13.3±9.1 months female at 17.6±10 months. The number of children in the age group 0-12 months were 25 (50%), with those belonging to the groups of 13-24 months and 25-36 months being 18 (36%) and 7 (14%) respectively. The Low socioeconomic group

constituted of 32 (64%) cases, while 17 (34%) belonged to middle and 1 (1%) to the high socioeconomic group. Children who were malnourished were 30 (60%) depicting levels of mild in 10 (20%), moderate in 13 (26%) and severity in 7 (14%) cases having weight for height below 3SD. Exclusive breast feeding was noted in 29 (58%) cases whereas 15 (30%) got supplemented with top feeding out of which 5 (10%) with formula feed, 10 (20%) with fresh milk and 6 (12%) were never been breast fed. Weaning age not reached in 10 (20%) children (Table 1). Vitamin D rich food was not being taken by 60% (24) children who had started weaning while 40% (16) partook egg or fish. In majority of the cases (78%) children had sunlight exposure less than 30 min/week and only 11 (22%) had the required proper sun exposure. Rickets was more prevalent in families residing in apartments with limited or no sun exposure. Main clinical presentation revealed gross motor delay for 15 (30%) cases, hypocalcemic convulsions in 7 (14%), acute gastroenteritis in 6 (12%) and pneumonia in 4 (8%) (Table 2). The most common clinical signs were wide wrist and wide anterior fontanelle (Table 3). The children who had low serum calcium levels were 33 (66%). Hypophosphatemia was observed in 23 but alkaline phosphatase was markedly elevated in all.

Presented of rickets in the present study seems to be the tip of the iceberg as 50 cases with apparent signs of rickets were documented in a 6 month period at single tertiary care teaching hospital.

In the present study majority of the cases (50%) involved children less than one year of age. Kreiter in USA¹⁰ reported high prevalence of rickets in 5-25 month age. In Pakistan Khan et al² reported that 74% of rachitic children were aged below 12 months. The reason for increased incidence in this age group is the

Table 1: Complementary Feeding (n=50)

S. No.	Complementary Feeding	n	%
1	Children below weaning age (<6 months)	10	20
2	Appropriate Onset	17	34
3	Inappropriate Onset	23	46
	Not Started	3	6
	Started Late	20	40
Total		50	100

Figure 1: Factor Relating Sun Light Exposure i.e. Housing (n=50)

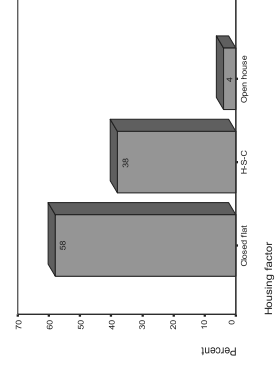


Table 2: Clinical Presentation (n=50)

S. No.	Clinical Presentation	n	%
1	Delayed motor development	15	30
2	Hypocalcaemic seizure	7	14
3	Skeletal deformity	1	2
4	Acute gastroenteritis	6	12
5	Pneumonia	4	8
6	Co-morbid	8	16
7	Incidental finding	9	18
Total		50	100

Table 3: Clinical Presentation (n=50)

S. No.	Clinical Sign	n	%
1	Wide wrists	38	76
2	Wide anterior fontanel	34	68
3	Frontal bossing of skull	18	36
4	Rachiticrosy	10	20
5	Bowing of legs	5	8
6	Kyphosis	4	8
7	Cranioabables	3	6
8	Caput caudratum	3	6
9	Harrison's groove	1	2

DISCUSSION

Presented of rickets in the present study seems to be the tip of the iceberg as 50 cases with apparent signs of rickets were documented in a 6 month period at single tertiary care teaching hospital.

In the present study majority of the cases (50%) involved children less than one year of age. Kreiter in USA¹⁰ reported high prevalence of rickets in 5-25 month age. In Pakistan Khan et al² reported that 74% of rachitic children were aged below 12 months. The reason for increased incidence in this age group is the

increased metabolic demand due to rapid growth.

In the present study there was a male preponderance with a male to female ratio of 1.3. A male predominance has been reported in previous studies conducted in Australia, Ethiopia, and Sydney.^{11,12,13} Comparatively a Copenhagen based study depicted a large female predominance¹⁴, whereas a 1:1 ratio was reported from Saudi Arabia¹⁵. The reason of high incidence of nutritional rickets in female sex is not clearly understood, this may reflect preferential treatment given to male children in some societies and cultures. Additional research is required to identify the reasons for the disparity.

In the present study, rickets was associated with children suffering from malnutrition. In Ethiopia most of the patients with rickets were also malnourished.¹¹ The positive association of malnutrition with rickets is based on the prevalence of nutrient deficiencies and presence of other risk factors in their families. Lack of exposure to sunlight exposure was found as a major contributing factor for rickets in children (78%). A study based in Saudi Arabia also cited lack of sunlight exposure as a major cause of nutritional rickets.¹² Nutritional rickets was strongly associated with families living in apartments. In a study conducted in slum areas of Karachi most of the affected children resided in apartments.¹³

Nutritional rickets was more associated with exclusively breast fed children in this study. This finding is consistent with other studies in Pakistan, in which Haitun et al observed that 83% infants who had vitamin D deficiency were exclusively breast-fed.¹⁴ Fresh milk, because of its high phosphorus content, can also lead to hypocalcaemia.¹⁵ Other factors that play significant a role include cultural beliefs and religious orientation, where conservative clothing is donned by those observing pariah which limits sun exposure of sunlight.

In this study prevalence of nutritional rickets was observed in children who had not yet been weaned, or were weaned at a delayed stage. This finding is consistent with research conducted in Kuwait¹⁶ that cited delayed weaning as a factor for rickets in children.

Children with delayed weaning miss the opportunity of obtaining vitamin D from solid foods.

The study revealed intake of vitamin D rich food in children to be low (40%) which is consistent with previous studies^{17,18} that cite vitamin D poor foods as one of the cause of nutritional rickets. Majority of children suffering from nutritional rickets were from low and middle socioeconomic classes. Contrary to the findings, research conducted in India¹⁹ and Pakistan²⁰ showed high prevalence of vitamin D deficiency in infants and nursing mothers belonging to upper socioeconomic class as well.

Hypocalcaemic fits were present in 7 (14%) cases. Findings by Ladhani et al attribute symptomatic hypocalcaemia in almost half of children to nutritional vitamin D deficiency.²¹ In the present study, all children presenting with fits were aged less than 6 months. Pal reported 9 cases of symptomatic hypocalcaemia in young infants, more than half of whom were under 5 months of age.²² Thirty two percent of these children had history of recurrent respiratory tract infections. 1,25(OH)2D acts as an immune system modulator. Yener et al have reported more episodes of bacterial infections in children with vitamin D deficiency as compared to healthy children.²³ Recurrent diarrhea was present in 11 (22%) cases which is congruent with previous studies^{3,13,5} reporting positive association of rickets with recurrent and chronic diarrhea.

Present study identified 39 (78%) children having radiological findings of rickets, while these findings were detected as 73.84%,²¹ 38.09%,¹² and 100%¹⁰ in different studies. Elevated levels of serum alkaline phosphatase were a consistent finding in all rachitic children. Joiner et al²⁴ suggested a more cost effective approach of targeted screening of high-risk groups with alkaline phosphatase levels to detect asymptomatic affected infants.

CONCLUSION

Infants under 2 years of age are liable to have vitamin D deficiency rickets if they are exclusively breast fed and having inadequate exposure to sunlight. Delayed introduction of complementary foods and malnutrition are also

important contributing factors in nutritional rickets. Vitamin D deficiency can present with variety of symptoms other than musculoskeletal symptoms like recurrent ARI, diarrhea and seizures. These are under recognized features of vitamin D deficiency. It is therefore recommended that rickets should be investigated for patients reporting these complaints. It is also possible for clinical signs and symptoms to be present with no radiographic evidence of rickets.

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