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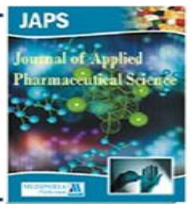

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Bacteraemia in Maiduguri Metropolis, Nigeria: A 2005 to 2009 study of some causative pathogens and fluoroquinolones activities against them

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ABSTRACT

Blood-stream pathogens were investigated between 2005 and 2009 in 262 patients with septicaemia in Maiduguri Metropolis, Nigeria to evaluate trends in fluoroquinolones activities against them. Blood samples were cultured in an enriched nutrient agar while susceptibilities tests were performed using the disc diffusion techniques.*Staphylococcus aureus*, the predominant pathogen accounted for 57.6% and peaking in 2007 with 26.5%. *Salmonella spp* (overall: 20.2%) infectivity increased from 2006-2008 by 15% but *Klebsiella* bacteraemia (14.9%) decreased by 20.7% from 2006-2008. Bacteraemia caused by *Escherichia coli* (7.3%) was the least. The *S. aureus* sensitivity to ciprofloxacin decreased by 25% between 2005 and 2007 while ofloxacin steady decrease from 2005 to 2008 by 33% showed significant correlation ($P<0.05$). Ciprofloxacin activities against norfloxacin-resistant and pefloxacin-resistant *S. aureus* (74.5% and 75% respectively) are both significantly different ($P<0.005$) from ofloxacin (27.7% and 37.5% respectively) but 92%, 81% and 78% of nalidixic acid-resistant *Klebsiella spp* are sensitive to ciprofloxacin, ofloxacin and pefloxacin respectively. The ofloxacin's activities against *E. coli* were superior to ciprofloxacin with 50%, 69% and 94% of nalidixic acid-resistant *E. coli* being sensitive to pefloxacin, ciprofloxacin and ofloxacin respectively. However all ciprofloxacin-resistant *E. coli* are ofloxacin-sensitive. The study found occurrence of continuous and significant loss in activities of most fluoroquinolones against *S. aureus* and *E. coli* but while ciprofloxacin indicated high activities against *S. aureus* and *Klebsiella* bacteraemia, ofloxacin was superior against *E. coli* and *Salmonella* bacteaemia than other agents.

Key words: Bacteraemia, ciprofloxacin, fluoroquinolones, Staphylococcus aureus, Pathogens, nalidixic-acid resistant.

INTRODUCTION

Following their introduction as chemotherapeutic agents against infectious diseases, the fluoroquinolones' empiric choices have gained preferences over most other previously introduced antibiotic agents in many regions (Hooper, 2000). They have become one of the fastest growing antibacterial classes in terms of global revenue and are increasingly being used in both hospital and community sectors (Bhanot et al., 2001). Their uses was reported to have increased by threefold in the emergency room environment between 1995 and 2002 in the US (MacDougall et al., 2005) and have become first line treatment in some serious cases requiring patient hospitalization (Liu and Mulholland, 2005). Most pathogens isolated from various infectious sites were reported to show low levels resistances on the average compare to other existing agents (Ohieku et al., 2010). The ability to add several substituent groups at various sites of the nalidixic acid moiety does not only confer higher activities and potencies against many pathogens (Saeed et al., 2005) but have also led to several congeners making them one of the abundant class of agents

Introduced into the pharmaceutical market in recent times (Saeed et al., 2005). They have wide spectra of activities especially against *Neisseria Spp, Haemophillus influenzae, Morexella catarrhalis, Mycoplasma, Chlamydia spp, Chlamydophila spp, Regionella spp, Enterobacteriaceae, Pseudomonas aeruginosa* (particularly ciprofloxacin), *Mycobacterium tuberculosis*, some atypical mycobacteria, and Methicillin-sensitive *Staphylococci* (The Merck, 2009) thereby expanding their applications in clinical practice. Newer agents like levofloxacin, moxifloxacin and gatifloxacin have extended activities against Gram positive pathogens (Duggirala et al., 2007) while many other fluoroquinolones are developed having activities against some anaerobes (David, 2010). Their pharmacokinetics properties which favor once or twice daily administration have made it convenient and acceptable to patients and therefore justifying their empirical choices and recommendations (Hooper, 2000). All these advantages offer the clinicians with the privilege of choosing from a wide range of agents with similar profile or minor variation in their pharmacological profiles.

However, the indiscriminate uses of the fluoroquinolones for minor conditions have generated concern in several regions because of chances of resistance development. Resistances to them is capable of evolving rapidly, even during the course of treatment and many strains of *Staphylococcus aureus*, enterococci, *Streptococcus pyogenes* now exhibited resistances worldwide (Jacobs, 2005). Specifically, resistances to the older generation fluoroquinolones like ciprofloxacin, norfloxacin, pefloxacin and ofloxacin with Enterobacteriaceae, *Neisseria, Pseudomonas aeruginosa, S. pneumonia* are growing due to their increasing uses (The Merck, 2009). Although one of the special abilities of bacteria in spreading resistances is their capacity to exchange resistance genes (plasmid) among similar and dissimilar groups, many other factors like epidemiologic, local antibiotics policies, patient's characteristics, origin of strains, geographical locations are among the factors considered to have increased the resistance rate of the Fluoroquinolones (Acar and Goldstein, 1997).

Resistance problems are associated with life-threatening cases and death. According to the Center for Disease Control (CDC) report in 2005, about 94 000 life-threatening infections and 17650 deaths were reported in the US in 2005 from methicillin-resistant *Staphylococcus aureus* (MRSA) infection (Salynn, 2007). The Extended spectrum beta-lactamases (ESBLs) pathogens; which are mostly *Klebsiella spp* and *E. coli* with the incidences found with most Enterobacteriacea (Kenneth, 2008) are similarly healthcare problems. Concerns have grown over the years with problems like MRSA including those of hospital-acquired and community-acquired MRSA, vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant *enterococci* (VRE) and ESBL which are resistant to cephalosporins and monobactams, and penicillin-resistant *Streptococcus pneumonia*e (PRSP).

Bacteraemia is a condition with high mortality rate and where quick interventions with antibiotics therapy having high activities such as the fluoroquinolones are required. However, the increasing multi-drug resistant pathogens have caused therapeutic problems in many regions. There are worries that the fluoroquinolones which have become first line agents may have created circumstances that increase resistances of pathogens in the region due to their continuous and indiscriminate use since resistances are often associated with previous overuse and misuse of any agent (Austin et al., 1999). We isolated and studied the in-vitro sensitivities of pathogens incriminated in bacteraemia to the fluoroquinolones commonly used in the region from 2005-2009 in patients diagnosed with bacteraemic infections and investigated their resistant status and their inter-activities relationships to some pathogens.

AIMS AND OBJECTIVES

The study aimed at investigating trends in bacteraemic pathogens in the region, the activities of the fluoroquinolones against blood-stream bacterial isolates and to investigate the inter-activities relations of these antibiotics.

MATERIALS AND METHODS

Sampling

262 cases of blood-stream bacterial infections were investigated between 2005 and 2009 in individuals suspected to have septicaemia following the presented clinical signs and symptoms and confirmed with microbiological blood-stream assay.

Blood Culture and Sensitivity Assay

The individual blood sample was cultured in an enriched nutrients agar incubated at 37 ^{o}C for 7 days. Biochemical tests were further carried out to characterize the isolated pathogens. All pathogens are judged clinically significant from the microbiological reports. Susceptibilities tests were performed using the disc diffusion techniques and tested against the disc concentrations of ciprofloxacin (30 µg), pefloxacin (10 µg), ofloxacin (10 µg), norfloxacin (30 µg) and nalidixic acid (30 µg).

Statistical Analysis

Chi square analysis was used to determine levels of activities between two or more agents at 95% confidence interval.

RESULTS AND DISCUSSION

The blood is though a sterile zone; but bacteria can gain access to it through many routes to cause bacteraemia. The distribution of pathogens isolated from the blood stream of patients with bacteraemia (Table 1) indicated a general increase in incidence by 6.1% between 2006 and 2009. *Staphylococcus aureus* (57.6%), was the only encountered gram-positive bacteria with its infectivity peaking in 2007. The *Salmonella spp* bacteraemic infectivity increased from 2006-2008 by about 15% peaking in 2008 but showed no correlation between levels of isolates during these periods. The decrease in *Klebsiella spp* bacteraemic incidences between 2006 and 2008 recorded significant correlation ($P<0.01$) as the year increased. *Escherichia coli* blood infections was consistently lower than other pathogens but its recorded

increase between 2007 and 2009 (26.8%) was not found to be significant (Table 1).

Table 1: Isolated pathogens in blood-streams of patients between 2005 and 2009.

Pathogens	Frequency of bacterial isolates					TOTAL
	2005	2006	2007	2008	2009	
S. aureus	30 (19.9%)	23 (15.2%)	40 (26.5%)	19 (12.9%)	39 (25.8%)	**151 (57.6%)**
Salmonella spp	9 (17%)	8 (15.1%)	11 (20.8%)	13 (24.5%)	12 (22.6%)	**53 (20.2%)**
Klebsiella spp	6 (15.4%)	13 (33.3%)	9 (23.15)	5 (12.8%)	6 (15.4%)	**39 (14.9%)**
E. coli	3 (15.8%)	4 (21.1%)	2 (10.5%)	3 (15.8)	7 (36.8%)	**19 (7.3%)**
TOTAL	**48 (18.3%)**	**48 (18.3%)**	**62 (23.7%)**	**40 (15.3%)**	**64 (24.4%)**	**262 (100%)**

Although there are many possible risk factors for *S. aureus* infections (Marwick et al., 2007; Kenneth, 2008), this high incidence is not surprising since high resistance rates of *S. aureus* isolates from many infectious sites to many classes of antibiotics in the region were previously reported (Ohieku et al., 2010) contributing to increasing hospital visits. The result is in agreement with other authors who reported *S. aureus* as one of the predominant pathogens causing bacteraemia (Enabulele et al., 2008) but is in contrast to what was reported in England between 2004 and 2008 where *E.coli* (23%) was the most common bacteraemic pathogen followed by *S. aureus* (Wilson et al., 2008). In Gambia, the 18.3% reported incidence of *S. aureus* was second to *Streptococcus pneumoniae* and lower than our result while *E.coli* bacteraemic isolates was a little higher than obtained in our result (Hill et al., 2007). Khan and Associates (2010) reported in Qatar that *E. coli* blood isolates (21.5%) was the predominant pathogen but bacteraemia caused by *E. coli* (7%) in Kenya (Thomas et al., 2009) showed similar proportion with our findings (7.3%).

Although there was an increase in *E. coli* infectivity by 26.3% between 2007 and 2009 but the recorded overall incidence is lower than the 27% of *E. coli* bacteraemic cases reported in Spain (Ortega et al., 2009). The reason for these differences is attributable to variation in environment and health-care practice including variation in antibiotic resistance since antibiotics may have been misuse for several extra-vascular infections before pathogen gain access to the blood stream. These increasing trends in bacteraemia caused by *S. aureus* and other pathogens are worrisome when compared with the declining incidence of *S. aureus* associated bacteraemia reported in some regions in England during similar period (Wilson et al., 2010). There is therefore the need to focus attention to curtail these rises.

The overall gram-negative bacteraemia recorded is 42.4% but the *Klebsiella* bacteraemia incidence recorded in this study is slightly lower than the 15.5% previously reported in the region (Ohieku et al., 2010). The higher rate of gram-positive incidence (57.6%) over gram-negative bacteraemia (42.4%) in the study showed similar trends with the 58.5% and 38.5% respectively reported in Greece (Starakis et al., 2010) but were in contrast to lower trends reported in Israel (Marchaim et al., 2008). Generally, gram-positive bacteraemia are increasing in many regions (Pontecelli, 2008). Similarly, *Salmonella* bacteraemia increases by 9.4% between 2006 and 2008 in our study due to environmental exposure and food-borne conditions as equally reported in some regions (Timothy et al., 2006). All these variations are naturally associated with many factors including those of epidemiologic, local antibiotics policies, patient's characteristics, individual and environmental hygiene, and geographical locations.

The susceptibility trends of blood-stream bacteria to the quinolones from 2005 to 2009 are shown in Table 2.

Table 2: Quinolones activities against isolated blood-stream pathogens between 2005 and 2009.

Antibiotics	Quinolones Percentage activities against **Staph aureus**					Quinolones Percentage activities against **Salmonella spp**				
	2005	**2006**	**2007**	**2008**	**2009**	**2005**	**2006**	**2007**	**2008**	**2009**
Ciprofloxacin	93	74	69	100	84	100	86	100	100	100
Ofloxacin	90	80	70	67	80	100	100	100	100	100
Pefloxacin	70	62	93	78	0	100	100	100	92	100
Norfloxacin	57	56.2	47	37.5	43	75	-	-	75	-
Nalidixic acid	0	0	50	0	33	86	50	45	33	33

Table 3: Comparison of activities of Quinolones to resistant bacteraemic *Staph aureus*.

No. of *Staph aureus* Resistance to	Nos (%) of Resistance *Staph aureus* that are sensitive to other quinolones				
	Nal. acid	Norfloxacin	Pefloxacin	Ciprofloxacin	Ofloxacin
Nalidixic acid(n=5)	XXX	0	5 (100)	4 (80)	5 (100)
Norfloxacin (n=47)	0	XXX	8 (17.0)	35 (74.5)	13 (27.7)
Pefloxacin (n=8)	0	2 (25)	XXX	6 (75)	3 (37.5)
Ciprofloxacin(n=20)	1 (5)	5 (25)	5 (25)	XXX	6 (30)
Ofloxacin (n=11)	1(9.1)	1 (9.1)	2 (18.2)	6 (54.5)	XXX

S. aureus sensitivity to ciprofloxacin decreased by 19% between 2005 and 2006 and by further 6% in 2007, but these decreases are not significant (P>0.050) and no resistances were recorded in 2008 with all the pathogens. The ofloxacin activities against *S. aureus* which recorded steady decline between 2005 and 2008 indicated significant correlation as the year increases (P<0.05). This sensitivity trends recorded with ofloxacin in 2008 is similar to the reported in Eastern part of Nigeria (Ikeogwu et al., 2008). Activities of pefloxacin against *S. aureus* similarly decreased from 2007 to 2009 by similar margin and are attributed to variation in previous utilization rates although cross resistance may be contributory.

The Ciprofloxacin's high activities against norfloxacin-resistant *S. aureus* (74.5%) compare to ofloxacin (27.7%) (Table 3) indicated significant difference (P<0.005) between the two agents. Similarly, ciprofloxacin activities (75%) were higher than ofloxacin (37.5%) among pefloxacin-resistant *S. aureus* bacteraemia though the reverse was the case with nalidixic acid-resistant *S. aureus* cases (Table 3). Only 30% of ciprofloxacin-resistant *S. aureus* were sensitive to ofloxacin whereas 54.5% of ofloxacin-resistant *S. aureus* are sensitive to ciprofloxacin. All the nalidixic acid-resistant *S. aureus* are sensitive to ofloxacin. Although the resistances of *Staphylococcus aureus* to the fluoroquinolones are reported worldwide (Jacobs, 2005) with newer generation fluoroquinolones demonstrating higher activities than these older ones (John et al., 2008), but the general, rapid decline in sensitivity patterns of *S. aureus* recorded with all the

fluoroquinolones compare to other pathogens in this study (Table 2) is worrisome. These results demonstrated that some strains of *S. aureus* untreatable with the available fluoroquinolones in the zone have emerged. Ciprofloxacin however appeared to be the treatment option for most quinolone-resistant *S. aureus* bacteraemia while there is an urgent need to introduce other agents in order to resolve resistance strains in the region.

Many practice fields have enacted guidelines regarding the fluoroquinolones utilization to safeguard the continuous resistance against them. For example, agents like the macrolides or doxycyclines are recommended as first line rather than the fluoroquinolones by the American Thoracic Association (Wikipedia, 2011). Similarly the drug resistant *Streptococcus pneumoniae* Working Group recommends that fluoroquinolones be used only after other antibiotics have been tried and failed while others have made recommended interventions to reduce their excessive prescription in the U.S. (MacDougall et al., 2005). It is hopeful that appropriate antibiotic policy in the region will be of immense therapeutic benefit.

Ciprofloxacin, ofloxacin and pefloxacin activities against *Salmonella spp* are high and almost uniform (Table 2). The pathogen recorded no resistances to ofloxacin and the decrease in activities of ciprofloxacin in 2006 and pefloxacin in 2008 were not found to be significant. The activities of these drugs do not vary significantly from their previously reported status in the region (Ohieku et al., 2010). All the strains of *Salmonella spp* isolates in 2005 and 2006 were resistant to nalidixic acid but about 92% activities each were recorded by ciprofloxacin and pefloxacin against nalidixic acid-resistant *Salmonella* bacteraemia while 100% were recorded with ofloxacin (Table 4).

Table 4: Comparison of activities of Quinolones to resistant bacteraemic *Salmonella spp.*

No. of Salmonella spp resistance to	No. (%) of Resistance *Salmonella spp* that are sensitive to other quinolones				
	Nal. acid	Norfloxacin	Pefloxacin	Ciprofloxacin	Ofloxacin
Nalidixic acid(n=26)	XXX	0	24(92.3)	24 (92.3)	26 (100)
Norfloxacin (n=1)	0	XXX	0	1 (100)	0
Pefloxacin	0	0	XXX	0	0
Ciprofloxacin(n=1)	1 (100)	0	1 (100)	XXX	1(100)
Ofloxacin (n=0)	0	0	0	0	XXX

The study found these three agents still relevant in bacteraemia conditions caused by *Salmonella* pathogens in the regions suggesting that they may have a high cure rate against typhoid fever and other non-typhoidal or Salmonellosis diseases in the region. Our result confirmed the report that *Salmonella spp* whether nalidixic acid-sensitive or nalidixic acid-resistant are usually sensitive to most fluoroquinolones (Asperilla et al., 1990).

Ciprofloxacin's activities against *Klebsiella spp* showed no observable resistance during the period except in 2006 (Table 5). These recorded activities are better when compared with higher resistance rates recorded by the pathogen in England, Wales and North Ireland between 2005 and 2009 (Health Protection Report, 2010). The ciprofloxacin activities against *Klebsiella spp* were consistently higher than ofloxacin except in 2006 (Table 5) suggesting that it is the treatment option where empiric choices are required.

Table 5: Quinolones activities against isolated blood-stream pathogens between 2005 and 2009.

Antibiotics	Quinolones Percentage activities against ***Klebsiella spp***					Quinolones percentage activities against ***E. coli***				
	2005	**2006**	**2007**	**2008**	**2009**	**2005**	**2006**	**2007**	**2008**	**2009**
Ciprofloxacin	100	92	100	100	100	67	50	50	100	83
Ofloxacin	60	100	87.5	75	100	100	100	100	100	80
Pefloxacin	70	85	87.5	100	83	67	50	100	67	50
Norfloxacin	-	-	-	100	-	-	-	-	-	50
Nalidixic acid	0	20	71	0	33	0	0	0	0	20

This finding is in agreement with that of Duggirala and colleagues (2007) where superior activities of ciprofloxacin over ofloxacin against gram negative pathogens was reported, but is in contrast to the work of Jones and colleagues (1992) who reported ofloxacin's high activities against *Klebsiella spp* for many years. The variation in their utilization from one region to another and the level of adopted antibiotics policies may contribute to these observed differences. However, *Klebsiella spp* appeared to have recorded an improved sensitivity to pefloxacin between 2005 and 2008 (Table 5). These increases however, showed no correlation during the study periods ($P>0.05$) but there was an overall increase in resistance of this pathogen over the previous report (Ohieku et al., 2010). 91%, 83% and 78% of nalidixic acid-resistant *Klebsiella* bacteraemia were sensitive to ciprofloxacin, ofloxacin and pefloxacin respectively (Table 6).

Table 6: Comparison of activities of Quinolones to resistant bacteraemic *Klebsiella spp.*

No. of *Klebsiella spp* Resistance to	Nos (%) of Resistance *Klebsiella spp* that are sensitive to other quinolones				
	Nal. acid	Norfloxacin	Pefloxacin	Ciprofloxacin	Ofloxacin
Nalidixic acid(n=23)	XXX	0	18 (78,3)	21(91.3)	19(82.6)
Norfloxacin (n=1)	0	XXX	1(100)	0	0
Pefloxacin (n=6)	0	0	XXX	5 (83.3)	5 (83.3)
Ciprofloxacin(n=1)	0	0	0	XXX	1(100)
Ofloxacin (n=5)	2 (40)	0	5 (100)	5 (100)	XXX

Surprisingly, ofloxacin activities against *E. coli*, another gram negative pathogen were superior to ciprofloxacin though uniform activities were recorded by both agents in 2008 (Table 5). The higher resistant rates of *E. coli* to ciprofloxacin are in agreement with the work of Starakis and colleagues (2010) in Greece and is attributable to the higher utilization rate of ciprofloxacin over ofloxacin in the region though acquire resistance to the fluoroquinolones or other classes of antimicrobial agents may play a role (Weiner et al., 1999). The 17% loss in activities of ciprofloxacin in the study is lower than the 22% of ciprofloxacin-resistant cases reported by Blazquez and colleagues (2002) in Spain.

The pefloxacin activities against *E. coli* were consistently lower than its activities against other pathogens during the year

except in 2005 and are also lower than that of other fluoroquinolones except in 2008 (Tables 2 and 5). However, 50%, 69% and 94% of nalidixic acid-resistant *E. coli* were sensitive to pefloxacin, ciprofloxacin and ofloxacin respectively (Table 7). Similarly 37.5% and 87.5% of pefloxacin-resistant *E. coli* bacteraemic pathogens were sensitive to ciprofloxacin and ofloxacin respectively while all the ciprofloxacin-resistant *E. coli* bacteraemic isolates were sensitive to ofloxain (Table 7) thus making ofloxacin the treatment option against *E. coli* bacteraemia in the region. 11.4% of ciprofloxacin-resistant *E. coli* bacteraemia were reported in Korea (Chung et al., 1999).

Table 7: Comparison of activities of Quinolones to resistant bacteraemic *Escherichia coli*.

No. of *E, coli* Resistance to	No. (%) of Resistance *Escherichia coli* that are sensitive to other quinolones				
	Nal. acid	Norfloxacin	Pefloxacin	Ciprofloxacin	Ofloxacin
Nalidixic acid(n=16)	XXX	0	8 (50)	11(68.8)	15 (93.7)
Norfloxacin	0	XXX	0		0
Pefloxacin (n=8)	0	0	XXX	3 (37.5)	7 (87.5)
Ciprofloxacin(n=5)	0	0	0	XXX	5 (100)
Ofloxacin (n=1)	0	0	0	1(100)	XXX

CONCLUSION

Our study indicated occurrence of continuous and significant loss of activities of most fluoroquinolones against *S. aureus* and *E. coli* bacteraemic pathogens. Although ciprofloxacin was better than other agents against *S. aureus* and *Klebsiella* bacteraemia with ofloxacin serving as the treatment option against *E. coli* and *salmonella* bacteraemia, resistance strains untreated with available fluoroquinolon**es** appeared to have emerged in the region.

REFERENCES

Acar JF., Goldstein FW. Trends in bacterial resistance to fluoroquinolones. *Clin. Infect. Dis.*1997; (Suppl 1): S67-73

Asperilla MO., Smego RA., Scott LK. Quinolones activities in the treatment of *Salmonella* infections. *Rev. Infect. Dis.* 1990; 12: 873-889

Austin DJ., Kristinsson KG., Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *Proc. Natl. Acad. Sci. U.S.A.* 1999; 96(3):1152-6.

Bhanot SK., Singh M., Chatterjee NR. The Chemical and Biological Aspects of Fluoroquinolones: Reality and Dreams *Current Pharmaceutical design* 2001; 7: 313-337

Brazquez A., Munoz P., Gil M., Sanchez M., Rodiguez M., Cercenado E., Bruza E., Alonzo R. Escherichia coli blood stream infection (BSI) caused by ciprofloxacin-resistant bacteria (Cip-R): Impact of incorrect empirical therapy. *Intersci. Conf. Antimicrob. Chemother.* 2002; K-1085.

Chung HU., Yu CW., Park KH., Sohn JW., Kim WJ., Park SC. Quinolone-resistant *E. coli* from one university hospital in Korea. *Intersci. Conf. Antimicrob. Chemother.* 1999;39:179

David CH. Fluoroquinolones, 2010 [cited 2011 Jan 20]. Available from: http://www.uptodate.com

Duggirala A., Joseph J., Sharma S., Nutheti R., Garg P., Das T. Activities of Newer fluoroquinolones against gram positive and gram negative bacteria isolated from ocular infections: An In-vitro comparison. *Indian Journal of Ophthamol* 2007; 55 (10):15-19

Enabulele OI., Aliyu HAS., Omokao O. Incidence of bacteraemia following teeth extraction at the dental clinic of the university of Benin Teaching Hospital, Benin-City, Nigeria, 2008. *Afr. J. Biotech* 2007; 7(10):1390-1393

Health protection Report: *Klebsiella, Enterobacter, Citrobacter and Serretia* Bacteremia- England, Wales and Norther Ireland, 2005-2009. Health Protection Weekly Report 2010, 4 (41); [Published 2010, Oct 15; Cited 2011, Jan 26]; Available from: http://www.hpa.org.uk/hpr/infections/bacteraemia.htm

Hill PC., Onyeama CO., Ikumapayi UNA., Secka O., Ameyaw S., Simmonde N., Donkor S., Howie SR., Tapgun M., Corrah T., Adegbola RA. Bacteraemia in Patients admitted to an urban hospital in West Africa. *BMC Infectious Disease* 2007; **7**:2

Hooper DC. New uses of new and old quinolones and challenges of resistance. *Clin. Infect. Dis.* 2000;30:243-54

Ikeogwu IJ., Amadi ES., Iroha IR. Antibiotic Sensitivity pattern of Staphylococcus aureus Abakiliki, Nigeria. *Pakistan journal of Medical Science* 2008; 24(2): 231-235

Jacobs M. Worldwide overview of antimicrobial Resistance. International Symposium of Antimicrobial Agents and Resistance, 2005

John T., Nalini R., Feng-Yee C., Vance GF., Susan MK., Sandra A., Bruce YL., Anne T. *Staphylococcus aureus.* 2008; [cited 2011, Jan 20]. Available from: http://www.antimicrobe.org/sample_*staphylococcu*s.asp

Jones RN., Reller LB., Roseti LA., Erwin ME., Sanchez ML. Ofloxacin, a new broad spectrum fluoroquinolones. Result from multicenter, National Activity Surveillance study,The ofloxacin surveillance group. *Diagn. Microbiol. Infect. Dis.* 1992 15(5): 425-34

Kenneth T: *Staphylococcus*: In Kenneth Todar's Online Textbook of bacteriology, 2008[cited 2011 Jan 20]. Available from: http://textbookofbacteriology.net/staph_2.html

Khan FY., ElShafie SS., Almaslamani M., Abu-Kattab M., ElHidav AH., Erravis M., Almaslamani E. Epidemiology of bacteraemia in Hamad General Hospital, Qatar: A one year Hospital based study. *Elsevier Tavel Medicine and Infectious Disease* 2010; 8(6):377-387

Liu H., Mulholland SG. Appropriate antibiotic treatment of genitourinary infection in hospitalized patients. *Am. J. Med.* 2005; 118 (suppl 7A): 14S-20S

MacDougall C., Duoglielmo BJ., Maselli J., Gonzales R. Antimicrobial drug prescribing for pneumonia in ambulatory care. *Emerging Infect. Dis*. 2005;11(3):380-384

Marchaim D., Zaidenstein R., Lazaronvitch T., Karpuch Y., Ziv T., Weinberger M. Increase Epidemiology of bacteraemia episodes in a single center: Increase in gram negative isolates, antibiotics resistance and patient age. *Eur. J. Clin. Microbiol. Infect. Dis.* 2008; 27:1045-1051

Marwick CA., Ziglam HH., Nathwani D. Your patient has a blood culture Positive for Staphylococcus aureus-what do you do? 2007 [cited 2011, Jan 20] Available from: http://www.rcpe.ac.uk/education/cme/infect-dis/nathwani/nathwani_2.html

Medication guide [Internet]: Fluoroquinolones;[updated 2008 Dec 20; cited 2011 Jan 26]; Available from: http://ratguide.com/meds/antimicrobial_agents/fluoroquinolones.php

Ohieku JD., Nnolim MI., Gadzama BG., Bassi PU. Bacteraemia among In-Patients of University of Maiduguri Teaching Hospital: The pathogens Involved, Their Susceptibilities to Antibacterial Agents and Multi-drugs Resistance patterns. *Journal of Medical and Applied Biosciences* 2010; 2:1-8

Ortega M., Marco F., Soraiano A., Almela M., Martinez JA., Minoz A., Mensa J. Analysis of 4758 *E. coli* bacteraemia episodes: Predictive factors for isolation of an antibiotic resistant strain and their impact on the outcome. *J Antimicrob Chemother* 2009; (63) 3: 568-574

Pontecelli C. New recommendations in the treatment of gram positive bacteraemia in dialysis patients. *Nephrolog Dial Transplant* 2008;23(1):27-32.

Saeed E., Abbas S., Alireza F. Quinolones recent structures and clinical development. *J. Pharm. Research* 2005; 3:123-136.

Salynn B., More US. deaths from MRSA than AIDS, 2007[cited 2011 Jan 20]. Available from: http://www.webmd.com/skin-problems-and-treatments/news/20071016/more-us-deaths-from-mrsa-than-aids

Starakis I., Mazokopakis EE., Siagris D., I Tsantoula., Gogos CA. Comparison of community and hospital acquired bacteraemia in a Greek university hospital: One year experience. *Medical Practice and Review* 2010;1(1):1-8

The Merck [Internet]. Matthew EL (MD): The Manual Online Medical Library (US) Fluoroquinolones; [updated 2009 July; cited 2011 Jan 20]; Available from: http://www.merckmanuals.com/ professional/ sec14/ch170/ch170f.html.

Thomas NW., Sophie U., Alex M., Calolyne N., Charlotte FM., Daniel HO., Salim M., Julie M., Albert K., Shanaaz KS et al: Bacteraemia in Kenyan children with sicled-cell anaemia: a retrospective cohort and case control study. *Lancet 2009*; 374(9698):1364-70

Timothy FJ., Ingram LA., Kathleen EF., Ruthanne M., Bridget JA., Patrick VM., Duc V et al. A case-control study of epidemiology of sporadic *Salmonella* infection in Infants. *Pediatrics* 2006;118(6):2380-2387

Weiner J., Quinn JP., Bradford PA., Goering RV., Nathan C., Bush K., Weinstein RA. Multiple antibiotics-resistant *Klebsiella and Escherichia coli* in Nursing Homes *JAMA* 1999;281(6):563-4

Wikipedia [Internet] [updated 2011 Jan; cited 2011, Jan 20]: Available from: http://en.wikipedia.org/wiki/Quinolone

Wilson J., Elgohan S., Livermore DM., Cookson B., Johnson A., Lamagni T., Chronias, Sheridan S. Trends among pathogens reported as Causing bacteraemia in England, 2004-2008. *Clinical Microbiology and Infection* 2010, [cited 2011 Jan 20]; Available from: http://onlinelibrary.wiley.com