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RESEARCH TRENDS OF MICROBIOLOGY

Phenotipic resitance of enterobacteriaceae to quinolones in university hospital "Mother Tereza "in Tirana, Albania

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Published Online: Jan 25, 2019

eBook: Research Trends of Microbiology

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Enterobacteriacea; Quinolones; Resistance

Abstract

Background: Resistance to antimicrobials has been reported with a notable frequency in species belonging to the family *Enterobacteriaceae*, among other bacterial families, in sources including animals and food. Quinolones are among the most commonly used antibiotics for oral treatment of community infections. The study aims to highlight the resistance level of Enterobacteriacea isolates to quinolones in Albania, in a tertiary hospital and compare the assessment data with international data

Materials and method: We performed a prospective study during the period 2015-2017. The isolates were obtained from clinical samples obtained from inpatients and outpatients at the University Hospital "Mother Theresa". The microbial organism identification and antimicrobial susceptibility were determined using the Vitek 2 system (BioMérieux,) in accordance with the manufacturer's instruction.

Results: In our study 339 strain were isolated, 115 of were resistance to quinolones. Overall resistance was 33.9%. The most frequently isolated species were Escherichia coli (61.06%), followed by Proteus species (10.91%), Klebsiella pneumoniae (7.96%) and Salmonella species (7.07%).

Conclusions: In Albania there is a high prevalence of enterobacteriaceae to quinolones, but it is within the range of global and European norms. This study suggests the need for appropriate prevention efforts and constant attention to the resistance level to quinolones.

Introduction

The family Enterobacteriaceae is the largest, most heterogeneous collection of medically important gram negative rods. More than 50 genera and hundreds of species and subspecies have been described [1]. Enterobacteriaceae family includes Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii, Morganella morganii, Proteus mirabilis, Salmonela species, Shigella species, Yersenia species, Enterobacter species, and Serratia species, to name a few. They are responsible for various infectious diseases [2]. Since antibiotics began to develop, at the same time in parallel with them, resistance to antibiotics has developed.

There was a time during which the world did not know that antibiotics would cause widespread resistance [3]. Resistance to antimicrobials has been reported with a notable frequency in species belonging to the family Enterobacteriaceae, among other bacterial families, in sources including animals and food [4]. Quinolones are among the most commonly used antibiotics for oral treatment of community infections. Probably they are the most common antibacterial agents for the treatment of urinary infections where E. coli is the most common cause [5]. Quinolones are synthetic antibacterial compounds whose precursor is nalidixic acid. It was described for the first time by Lesher and his co-workers in 1962 [6] and created as a by-product of chloroquine synthesis and introduced into use for the treatment of urinary infections [7]. All molecules have a pyridine cycle. Fluoroquinolones are characterized by the presence of a fluorine atom at position 6 and a piperazine cycle at position 7. The introduction of new molecules (levofloxacin, moxifloxacin, gatifloxacin) has allowed a new expansion of fluoroquinolone indications, especially in respiratory infections due to prominent pneumococcal activity, but without improvement of performance against enterobacteria and other Gram-negative bacteria [6]. The quinolones exert a selective inhibitory effect on bacterial DNA synthesis by acting on two enzymes that participate in this synthesis: DNA topoisomerase II, otherwise called DNA gyrase, and DNA topoisomerase IV [6]. DNA gyrase enzyme is responsible for the 'super-coiled' of the DNA negative type during replication. Topoisomerase IV has the specific function of the daughter DNA release at the end of the replication. Quinolones inhibit these function of enzymes. [6]. Resistance obtained from fluoroquinolones in Gram negative bacilli has been considered to be exclusively caused by chromosomal mutations until the 1998 description of plasmid resistance [8]. Resistance to chromosomal mutations is caused: From the decreasing affinity to the intra-cellular target of DNA-DNA gyrase and DNA-DNA topoisomerase IV complexes. From the decrease of the antibiotic intra-cellular concentration due to the inability of passive penetration and / or active excretion. Plasmid resistance is caused by protecting DNA gyrase from its quinolone linkage [9]. The systematic observation of enterobacteriaceaes resistance to antibiotics is important for the impact of this resistance to health and treatment costs [5]. Besides this, the prevalence and risk factors of fluoroquinolones resistance acquisition have not been well described in Albanian hospitals. Surveillance of fluorquinolones resistance is an important element for the implementation of intervention strategies aimed at preserving the efficacy of antibiotics, as the only possible oral preparations. The study aims to highlight the resistance level of *Enterobacteriacea* isolates to quinolones in Albania, in a tertiary hospital and compare the assessment data with international data.

Material and methods

During the period 2015-2017, were collected a total of 339 isolates, obtained from blood cultures, vaginal/urethra swabs, sputum, pus, fecal, urine cultures, from inpatient and outpatient examinations at University Hospital Center "Mother Theresa", with different infections.

The microbial organism identification and antimicrobial susceptibility were determined using the Vitek 2 system (BioMérieux,) in accordance with the manufacturer’s instruction. The bacterial susceptibility to fluoroquinolones was determined based on MIC to Ciprofloxacin in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards where isolates are considered susceptible when MIC<0.25µg/ml, and resistant when MIC>4µg /ml. Data entry and processing was done using the Microsoft Office Excel 10 program and IBM SPSS Statistics version 20. For the comparison of percentages, the Chi-Square goodness-of-fit test was used.

Results

Table 1: Distribution of strains and their resistance.

Isolate	Resistant	Sensible	Total
E. coli	72 (21.2%)	135 (39.8%)	207 (61.1%)
Klebsiella pneumonia	12 (3.5%)	15 (4.4%)	27 (7.9%)
Proteus species	17 (5.0%)	20 (5.9%)	37 (10.9%)
Salmonella species	3 (0.9%)	21 (6.2%)	24 (7.1%)
Shigella species	0 (0%)	3 (0.9%)	3 (0.9%)
Serratia species	0 (0%)	9 (2.6%)	9 (2.6%)
Morganela species	4 (1.2%)	3 (0.9%)	7 (2.1%)
Enterobacter cloacae	5 (1.5%)	16 (4.7%)	21 (6.2%)
Citrobacter freundi	1 (0.3%)	1 (0.3%)	2 (0.6%)
Providencia	1 (0.3%)	1 (0.3%)	2 (0.6%)
Totali	115 (33.9%)	224 (66.1%)	339 (100%)

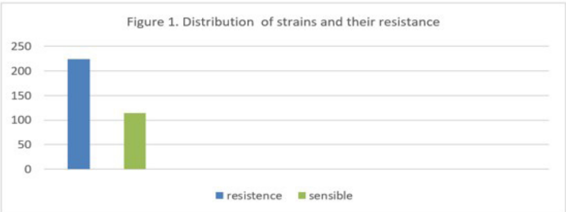

Table & Figure 1 shows resitence strains to fluoroquinolones. Resistance strains was detected in 115 out of 339 clinical samples cultivated. Overall resistance was 33.9%.

Table 1: Distribution of isolates according to clinical samples.

Isolates	Blood culture	Vagina/urethral swab	Sputum	Fecal	Urine	Pus	Total
E.coli	5 (1.5%)	6 (1.8%)	2 (0.6%)	63(18.6%)	125(36.9%)	6 (1.8%)	207 (61.1%)
K.pnemoniae	3 (0.9%)	2 (0.6%)	5 (1.5%)	2 (0.6%)	9 (2.%)	6 (1.8%)	27 (8.0%)
Proteus species	1 (0.3%)	1 (0.3%)		7 (2.1%)	24 (7.1%)	4 (1.2%)	34 (10.0%)
Salmonella species				24 (7.1%)			24(7.1%)
Shigella species				3 (0.9%)			3 (0.9%)
Enteobacter cloacae		4 (1.2%)	1(0.3%)		14 (4.1%)	2 (0.6%)	21 (6.2%)
Morganella morganii			1(0.3%)		5 (1.5%)	1 (0.3%)	7(2.1%)
Citeobacter freundi					1(0.3%)	1 (0.3%)	2 (0.6%)
Providencia rettgeri						2 (0.6%)	2 (0.6%)
Serratia marcescens		1(0.3%)	1(0.3%)	2(0.6%)	1 (0.3%)	4 (1.2%)	9 (2.7%)
Totali	9(2.6%)	14(4.1%)	10(2.9%)	101(29.7%)	179 (52%)	26 (7.7%)	339 (100%)

Data in table No. 2 show the distribution of isolates according to clinical samples. Bases in our data, ten bacterial genera were identified in the clinical samples analyzed during the period of the study, as follows: Escherichia, Klebsiella, Proteus, Citrobacter, Enterobacter, Morganella, Providencia, Serratia, Salmonella and Shigella. The most frequently isolated species were Escherichia coli (61.06%), followed by Proteus species (10.91 %), Klebsiella pneumoniae (7.96%) and Salmonella species (7.07%).

More strains are isolate in urine sample (52.0%), followed by fecal sample (29.7%) and lower strain are detected in blood culture 2.6% and sputum 2.9%.

Table 3: Distribution of strains isolate according to service.

Service	resistant isolates	sensible isolates	Total
Pediatric	12 (3.5%)	62 (18.3%)	78(23%)
Infantile surgery	1 (0.3%)	-	1(0.29%)
Urology	13 (3.8%)	11 (3.2%)	24(7%)
Oncology	3 (0.9%)	2 (0.6%)	5(1.47%)
Out patients	28 (8.2%)	56 (16.6%)	84(24.7%)
Gastro-hepatology	5 (1.47%)	2 (0.6%)	7(2.06%)
Internal medicine	2 (0.6%)	6 (1.8%)	8(2.35%)
Neurology	7 (2.1%)	9 (2.7%)	16(4.7%)
Infectology	25 (7.4 %)	46 (13.6%)	71(20.9%)
Prison Hospital	4 (1.2%)	-	4(1.17%)
Surgery emergency	5 (1.5%)	4 (1.2%)	9(2.65%)
Nephrology & Dialysis	6 (1.8%)	5 (1.5%)	11(3.24%)
Hematology	1(0.3%)	-	1(0.29%)
Allergy	1(0.3%)	5 (1.5%)	6(1.76%)
Intensive care unit of cardiology	2(0.6%)	-	2(0.5%)
Endocrinology	-	3 (0.9%)	3(0.88%)
Dermatology	-	5 (1.5%)	5(1.47%)
Plastic surgery	1(0.3%)	10 (2.9%)	11(3.24%)
Total	115 (33.9%)	224 (66.1%)	339

Our data in Table & Figure 3 show distribution of isolates according to services. From outpatient clinical sample are isolated 24.8% of strains, followed by pediatric service (23%) infectology service (20.9%). While resistance strains are detected more in out patients (8.2%) followed by infectology service 7.4% and urology service 3.8%.

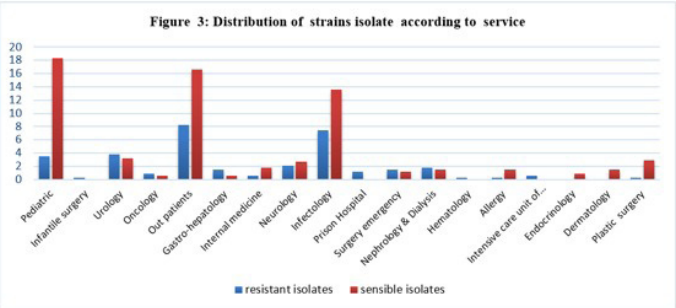

Table 4: Distribution of E.coli according to service.

Service	resistant isolates	sensible isolates	Total
Pediatric	11 (5.3%)	43 (20.8%)	54 (26%)
Infantile surgery	1 (0.5%)	-	1 (0.48%)
Urology	4 (1.9%)	3 (1.4%)	7 (3.38%)
Oncology	2 (0.9%)	-	2 (0.96%)
Out patients	20 (9.6%)	45 (21.7%)	65 (31.4%)
Gastro-hepatology	5 (2.4%)	2 (0.9%)	7 (3.38%)
Internal medicine	1 (0.5%)	2 (0.9%)	3 (1.44%)
Neurology	5 (2.4%)	7 (3.4%)	12 (5.79%)
Infectology	17 (8.2%)	21 (10.1%)	38 (18.35%)
Prison Hospital	2 (0.9%)	-	2 (0.96%)
Surgery emergency	2 (0.9%)	1 (0.5%)	3 (1.44%)
Nephrology & Dialysis	2 (0.9%)	1 (0.5%)	3 (1.44%)
Hematology	1 (0.5%)	-	1 (0.48%)
Allergy	1 (0.5%)	3 (1.4%)	4(1.93%)
Intensive care unit of cardiology	1 (0.5%)	-	1 (0.48%)
Endocrinology	-	2 (0.9%)	2 (0.96%)
Dermatology	-	3 (1.4%)	3 (1.44%)
Plastic surgery	-	2 (0.9%)	2 (0.96%)
Total	72 (34.7%)	135 (65.3%)	207

Data from table No. 4 to table No.14 show distribution of each strains isolated according to service.

Data in table No. 4 show that resistant strains of E coli are 9.6 % in outpatients isolates followed by infectology service with 8.2%, pediatric service 5.3% and in lower percent in other service.

Table 5: Distribution of Proteus species according to service.

Service	resistant isolates	sensible isolates	Total
Pediatric	-	2 (5.4%)	2 (5.41%)
Urology	3 (8.1%)	2 (5.4%)	5 (13.51%)
Outpatient	2 (5.4%)	4 (10.8%)	6 (16.21%)
Internal Medicine	1 (2.7%)	2 (5.4%)	3 (8.1%)
Neurology	2 (5.4%)	2 (5.4%)	4 (10.81%)
Infectology	3 (8.1%)	4 (10.8%)	7 (18.91%)
Prison Hospital	1 (2.7%)	-	1 (2.73%)
Surgery Emergency	2 (5.4%)	2 (5.4%)	4 (10.81%)
Nephrology & Dialysis	2 (5.4%)	1 (2.7%)	3 (8.1%)
Plastic surgery	1 (2.7%)	1 (2.7%)	2 (5.41%)
Total	17 (45.9%)	20 (54.1%)	37(100%)

Data in table No. 5 show that resistant strains of Proteus species are 8.1% in infectology and urology service, followed by outpatients, neurology, surgery emergence and nephrology & dialysis with 5.4% and other services have quiet an equal distribution of resistance.

Table 6: Distribution of Salmonella species according to service.

Service	resistant isolates	sensible isolates	Total
Pediatric	-	8 (33.3%)	8 (33.33%)
Infectology	3 (12.5%)	13 (54.2%)	16 (66.67%)
Total	3 (12.5%)	21 (87.5%)	24 (100%)

Data in Table No.6 show that resistant strains of Salmonella species are 12.5% in infectology service.

Table 7: Distribution of Shigella species according to service.

Service	resistant isolates	sensible isolates	Total
Pediatric	-	3 (100%)	3
Total	-	3 (100%)	3

Data in Table No.7 show that there are not isolated resistant strains of Shigella species.

Table 8: Distribution of Klebsiella pneumoniae species according to service.

Service	resistant isolates	sensible isolates	Total
Pediatric		3 (11.1%)	3(11.11%)
Urology	2 (7.4%)	3 (11.1%)	5(18.52%)
Onkology	1 (3.7%)	-	1(3.7%)
Outpatient	2 (7.4%)	2 (7.4%)	4(14.81%)
Infectology	2 (7.4%)	3	5(18.52%)
Internal Medicine		1 (3.7%)	1(3.7%)
Prison Hospital	1 (3.7%)	-	1(3.7%)
Surgery Emergency	1 (3.7%)	1 (3.7%)	2(7.4%)
Nephrology & Dialysis	2 (7.4%)	1 (3.7%)	3(11.11%)
Intensive care unit of cardiology	1 (3.7%)	-	1(3.7%)
Plastic surgery	-	1 (3.7%)	1(3.7%)
Total	12 (44.4%)	15 (55.6%)	27(%)

Data in Table No.8 show that resistant strains of Klebsiella pneumoniae are distributed quite equally in all services.

Table 9: Distribution of Enterobacter cloacea according to service.

Service	resistant isolates	sensible isolates	Total
Pediatric	1 (4.8%)	2 (9.5%)	3 (14.28%)
Urology	1 (4.8%)	2 (9.5%)	3 (14.28%)
Onkology		2 (9.5%)	2 (9.52%)
Outpatient	3 (14.3%)	3 (14.3%)	6 (28.57%)
Infectology		4 (19.0%)	4 (19.04%)
Nephrology & Dialysis		1 (4.8%)	1 (4.76%)
Endocrinology	-	1 (4.8%)	1 (4.76%)
Plastic surgery	-	1 (4.8%)	1 (4.76%)
Total	5 (23.8%)	16 (76.2%)	21 (%)

Data in Table No. 9 show that resistant strains of Enterobacter cloacae are 14.3% in outpatients isolates.

Table 10: Distribution of Citrobacter freundi according to service.

Service	resistant isolates	sensible isolates	total
Plastic surgery	-	1 (50%)	1 (50%)
Urology	1 (50%)	-	1 (50%)
Total	1 (50%)	1 (50%)	2 (100%)

Data in Table No 10 show that resistant strain of Citrobacter freundi is 50% in urology service.

Table 11: Distribution of Providencia rettgeri according to service.

Service	resistant isolates	sensible isolates	Total
Neurology	1 (50%)	-	1 (50%)
Internal Medicine	-	1 (50%)	1 (50%)
Total	1 (50%)	1 (50%)	2

Data in Table No 11 show that resistant strain of Providencia rettgeri is 50% in neurology service.

Table 12: Distribution of Morganella morganii according to service.

Service	resistant isolates	sensible isolates	Total
Urology	3 (42.8%)	-	3 (42.85%)
Outpatient	1 (14.3%)	2 (28.6%)	3 (42.85%)
Allergy	-	1 (14.3%)	1 (14.28%)
Total	4 (57.1%)	3 (42.9%)	7 (100%)

Data in Table No 12 show that rezistant strains of Moganella morganii are 42.8% in urology service.

Table 13: Distribution of Serratia marcescens according to service.

Service	resistant isolates	sensible isolates	Total
Plastic surgery	-	4 (44.4%)	3 (42.85%)
Dermatology	-	2 (22.2%)	3 (42.85%)
Pediatric		1 (11.1%)	1 (14.28%)
Allergy		1 (11.1%)	
Infectology		1 (11.1%)	
Total	0	9 (100%)	7 (100%)

Data in Table No 13 show that there are not isolated resistant strain of Serratia marcescens.

Discussion

In Albania, fluoroquinolones are the fourth group of the most widely used antibiotics after penicillin, tetracycline and macrolide. Their use has an upward trend, namely from 1.72 to 2.51 DID (daily dose per 1000 inhabitants) during 2011-2012 [10]. Together with their use resistance has increased. Increased and sometimes unsuitable use of fluoroquinolones is associated with increased bacterial resistance.

Indeed, Albania has no official data on the resistance of quinolones to enterobacteria [5]. In some studies by Albanian authors, we have some data for this resistance. So, the E. coli isolate resistance from nosocomial infections of the urinary tract to ciprofloxacin is 50%, while for outpatients it is 41% [11]. For intestinal carriers of resistant isolates of Enterobacteriacae and non-fermenters, resistance to ciprofloxacosis is 30% [12] and for non - ESBL isolated E. coli and Klebsiella spp in urine, the resistance to ciprofloxacin is 39.7% [13].

In our study, the resistance of enterobacteria to fluorocinolones is 33.9%. This is a high resistance to a country with a small population as ours, but this result complies with the WHO report on this microbial resistance in the region, Europe and beyond. So, WHO Report informs the following rate ranges: European region 8-48%, Eastern Mediterranean region 21-62%, South East Asia region 32-64%, Western Pacific region 3-96%, The African region results 14-71%, the American region 8-58%. Referring to related regional data, the evidences show the following rates: Serbia 16%, Croatia 14%, Greece 26.6%, Italy 40.5% [5].

Ten bacterial genera were identified in the clinical samples analyzed during the period of the study, as follows: Escherichia, Klebsiella, Proteus, Citrobacter, Enterobacter, Morganella, Providencia, Serratia, Salmonella and Shigella. The most frequently isolated species were Escherichia coli (61.06%), followed by Proteus species (10.91 %), Klebsiella pneumoniae (7.96%) and Salmonella species (7.1%).

Clinical specimens from which more isolate are isolated are urine (52.0%%), followed by the fecal samples (29.7%). In the end there is the blood culture (2.6%), where according to literature all over the world, the possibility of isolation of the blood culture strains is very small. It is noted that the prevalence of sputum strain isolation is small, almost the same as that of blood cultures, because of UHC” Mother Theresa” is not directly oriented in the pulmonary diseases, and sputum examination is required when there have been pulmonary complications of the main disease.

In our study we identified as the most common E. coli strain, with 61.1%. Clinical specimens where it was most often isolated is urine 36.9%, because E. coli is the most common cause of the community-acquired and hospital urinary tract infections, [5] which is consistent with the literature [14-16]. The service where it was more frequent was outpatients 31.4 %, followed by pediatric service with 26% and infectology service with 18.35%, which is explained by the largest number of samples taken in these services. Resistance to fluoroquinolones in E. coli develops through mutations of genes [5,8,9]. E. coli strains resistant in our study form 21.2% of all strains isolated, being thus the most frequent resistant strain against ciprofloxacin, which is explained by the largest number of E. coli isolates in the total number of microbial strains taken in the study (Table 1). While E. coli resistance to fluoroquinolones resulted 34.78% of all the E. coli strains of our study. Most of resistants strains are in outpatient (9.6%) followed by infectology service (8.2%) and pediatric service with 5.3% (Table 4).

E. coli is followed by Proteus species with 10.9% of all isolated strains. The strains of P. mirabilis strains cause 10% of uncomplicated urinary infections [17]. They are the fifth most common cause of urinary tract infections and sepsis in hospitalized individuals [18,19]. Proteus species resistant strains make up 5.01% of all isolated strains and 45.9% the all Proteus species strains of our study (Table 1&5)

Klebsiella pneumonia is the third most isolated strain in our study, 7.9% (Table 1). There is an almost uniform distribution in all clinical trials tested with a slight urinary predominance 2.0%. Like E. coli, Klebsiella species are common colonists of the gastrointestinal tract in humans and animals. K. pneumonia infections are particularly common among vulnerable persons such as pre-term children, patients with immune system disorders, diabetics and alcohol users [5]. K. pneumonia gains resistance mainly through the horizontal transfer of mobile genetic elements such as transposons or plasmids [5,9,20,21]. Resistance to fluoroquinolones is 44.4% of all K. pneumonia isolated in our study.

During the study, isolation of a significant number of Salmonella species was observed, 7.1%. Fortunately, they are sensitive to fluoroquinolones 87.5%. Bacteria of the genus Salmonella are a major cause of foodborne illness throughout the world [5]. The incidence of Non-Typhoid Salmonella (NTS) infections has increased markedly in recent years, for reasons that are unclear. Infections caused by NTS are common and usually self-limiting. In severe cases antibacterial treatment may be warranted. Reduced susceptibility to oral drugs such as ciprofloxacin, and increasing numbers of treatment failures, are of concern [5]. Resistance of Salmonella species in our study is 12.5% (Table 6).

Shigella species was also isolated 0.88%. These are also sensitive to fluoroquinolones. Shigella species are a major cause of diarrhea and dysentery throughout the world. The annual number of Shigella episodes worldwide is estimated to be 165 million, of which more than 100 million occur in the developing world, causing more than 1 million deaths [5]. Antibacterial drugs have a proven effect in the management of Shigella infections. Emerging resistance has been reported as a concern from some countries [5]. Mobile genetic units (including plasmids, gene cassettes in integrons and transposons) are important in the spread of resistance determinants among Shigella isolates, as well as in other enterobacteria such as Klebsiella and E. coli [5,9,20,21].

Resistance to ciprofloxacin was found in 50% of Citrobacter freundi and Providencia strains, but the very small number of isolated strains (from 2 strains respectively) makes this result statistically negligible.

Conclusion

The resistance of enterobacteria to fluorocinolones in Albania is 33.9%. The rate of resistance in Albania is within the range of global and European norms.

Antibiotic resistance in general is a major global problem, the impact of each is enormous in the health of all of us. The use of fluoroquinolones has increased greatly, as a very good oral treatment option. This also led to the emergence of resistance to them. Thus, there is a need to intervene with new strategies to reduce this tendency. But, to the design of these new strategies, we can help prevent resistance through control measures that limit the spread of resistance and use with antibiotic criteria. Fluoroquinolones should only be used after they have been confirmed by sensitivity tests and if it is necessary to find alternatives to empiric medication.

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