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CORRELATING ANTIBIOTIC CONSUMPTION WITH ANTIMICROBIAL RESISTANCE OF UROPATHOGENS IN A UNIVERSITY TEACHING HOSPITAL IN LAGOS, NIGERIA

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ABSTRACT

Objective: This study was carried out to correlate the antibiotic consumption rates with the antibiotic resistance rates of uropathogens in Lagos University Teaching Hospital.

Methodology: Urine specimens obtained over 18 months (between January 2005 and June 2006) were processed for microscopy culture and sensitivity, and records of antibiotics dispensed during the same periods were reviewed. Significant bacteriuria was performed by the standard loop method. Isolation and identification of organisms was by standard laboratory methods. The antibiotic consumption calculator of Monnet (ABC calc version 3) was used to classify the antibiotics into ATC classes and to calculate the numbers of daily defined doses. The 6-monthly antibiotic resistance and consumption rates were compared using Pearson's correlation coefficient. For analysis, the period of study was divided into three.

Results: Except for co-trimoxazole the rates of consumption of all antibiotics were higher in the second period than the first period of the study and highest in the 3rd period for ciprofloxacin, and ceftazidime. This correlated with an increase in the rates of resistance for some antibiotics during the 2nd and 3rd periods. While a steady increase in consumption of ciprofloxacin correlated with a steady increase in the resistance rates from the 1st to the 3rd periods, a steady increase in consumption of ceftazidime was associated with an increased resistance rate from the 2nd to 3rd periods.

Conclusion: Increased consumption of the antibiotics tested, most noticeably, ciprofloxacin and ceftazidime correlated with increased resistance rates. There is need for urgent interventions like formulation of antibiotic policies and education of staff on the appropriate use of antibiotics to reduce the development of resistance.

Key words: Antibiotic Resistance, Antibiotic Consumption *(Accepted 19 November 2007)*

INTRODUCTION

The antibiotic classes traditionally used to treat urinary tract infections (UTI) include sulfonamides, broad spectrum penicillin, cephalosporins and aminoglycosides. For a long time trimethoprim-sulphomethoxazole and amocyxillin have been the antibiotics of choice in the community. Due to resistance, these are being gradually replaced by quinolones, and other antibiotics. Aminoglycosides also have been the drugs of choice for hospital acquired UTI, but due to resistance, in recent times, the third generation cephalosporins are also widely used[1-3].

There are three main mechanisms of antimicrobial resistance in uropathogens; natural resistance, selection of resistance mutants and transferable resistance. Of these, transferable resistance is the most common and the most often associated with antibiotic abuse[4]. This type of resistance is mediated by transferable plasmids. Transfer of plasmids from one bacterium to another occurs within the faecal reservoir of patients receiving beta-lactams, trimethoprim-sulphomethoxazole, aminoglycosides and tetracyclines and is particularly problematic in the hospital. Usually the plasmids contain more than one gene that code for resistance to various antibiotics making such bacteria multi-drug resistant[4,5].

Plasmids naturally occur in strains of *E. coli* and other gram negative bacilli, but the incidence is higher in countries where antibiotics are directly available to the general population and many of the bacterial strains spontaneously lose the plasmids in the absence of any antibiotic usage[6]. Thus, the incidence of antibiotic resistance depends not only on the occurrence of plasmids but also on the patterns of use of antibiotics in hospitals or the general population[5]. Several studies have correlated increased antibiotic consumption with increased antibiotic resistance and

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others have shown that reducing antibiotic consumption will reduce resistance to such antibiotics[7-9].

In Nigeria, there have been reports of inappropriate prescribing of antibiotics by health practitioners and anecdotal history of abuse of antibiotics by individuals[10,11], but there has been no attempt to study the rate of use of antibiotics for appropriate indications in our hospitals. Despite the huge information on increasing antibiotic resistance of pathogens especially uropathogens, no attempt has been made to correlate these with the rate of antibiotic consumption[12-14].

To measure drug use, a classification system, the anatomic therapeutic chemical system (ATC) as well as a technical unit of measurement called defined daily doses (DDD) were developed and have been internationally accepted and utilized[15]. The body responsible for coordinating the use of the ATC/DDD methodology is the WHO collaborating centre for Drug statistics and methodology in Oslo[15].

This study was carried out to correlate antibiotic consumption rates with the antibiotic resistance rates of uropathogens in Lagos University Teaching Hospital.

METHODOLOGY

All urine specimens submitted to the Microbiology laboratory of the Lagos University Teaching Hospital from January 2005 to June 2006 were processed for microscopy culture and sensitivity, and records of antibiotics dispensed during the same periods were reviewed. The study was approved by the ethics and research committee of the Lagos University Teaching Hospital.

Significant bacteriuria was performed by the standard loop method. Specimens were cultured on MacConkey agar (Oxoid) and blood agar base (Oxoid) to which 5-7% blood has been added. Incubation was in air and 5-10% CO_2 for 24-48 hours. Isolates were identified by standard laboratory methods[16].

Antibiotic sensitivity was performed on all pathogens isolated on Mueller-Hinton agar using the disc diffusion method and the zone sizes obtained were interpreted based on recommendations of the Clinical Laboratory Standards Institutes (CLSI formerly National Committee for Clinical Laboratory Standards (NCCLS)[17] All antibiotics were Oxoid products and included: gentamicin 10µg, ofloxacin 5µg, amoxicillin-clavulanic acid 30µg ciprofloxacin 5µg, cotrimoxazole 30µg, ceftazidime 30µg, and cefuroxime 30µg. .Reference strains *Staphylococcus aureus* ATTC 29213, *E. coli* ATTC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used for quality control of procedures.

The antibiotic consumption calculator of Monnet (ABC calc version 3) was used to classify the antibiotics in ATC classes and to calculate the numbers of DDDs[18]. The names of antibiotics normally used to treat UTI in the hospital and their corresponding number of grams per unit per package were entered into the spreadsheet. The number of packages of each antibiotic which was consumed between January and June 2005, July and December 2005, and January and June 2006 were entered. The numbers of DDDs for each of the antibiotics for each 6-monthly period were thus generated. It was then possible to compare the 6-monthly antibiotic resistance and consumption rates using Pearson's correlation coefficient.

RESULTS

For analysis, the period of study was divided into three. The pathogens isolated at various periods are shown on table 1. *E .coli* was the organism most commonly isolated throughout. The only antibiotics dispensed in the hospital during this period are listed on table 2. Ciprofloxacin and amoxicillin-clavulanate were the most commonly used while cotrimoxazole was the least commonly used. Resistance rates were highest with cotrimoxazole, followed by amoxicillin-clavulanic acid.

Except for co-trimoxazole the rates of consumption of all antibiotics were higher in the second period than the first period of the study and highest in the 3rd period for ciprofloxacin, and ceftazidime. This correlated with an increase in the rates of resistance for some antibiotics during the 2nd and 3rd periods. While a steady increase in consumption of ciprofloxacin correlated with a steady increase in the resistance rates from the 1st to the 3rd periods, a steady increase in consumption of ceftazidime was associated with an increased resistance rate from the 2nd to 3rd periods.

DISCUSSION

Although the study was for a short period, for most antibiotics, correlation between resistance and consumption could be seen. Such an association has been demonstrated in various studies[13,14]. This picture of antibiotic overuse will be painted even more clearly if the study is continued for a few more years. Large scale use of ciprofloxacin is a recent event in the hospital of study as its use in Nigeria started in the early nineties. In a study of multi-resistant strains of *Pseudomonas aeruginosa* carried out in the same hospital between 1994 and 1996, as many as 96.2% of isolates were sensitive to ciprofloxacin[18]. In this study, a steady increase in its use was accompanied by a steady increase in resistance to it, confirming that over time, antibiotic use leads to resistance.

A similar trend has been observed in previous studies[13-15]. Resting antibiotics by discontinuing their use for some time often reverses the resistance trend. In another tertiary hospital in 2004 and 2005, after instituting a program to reduce ciprofloxacin use, a reduced resistance rate was observed[20]. The consequences of resistance include increased treatment cost due to therapeutic failure and increased length of hospital stay. This will impact negatively on the economic budget for the patient, the hospital, as well as the country.

Resistance rates of uropathogens to cotrimoxazole and amoxicillin clavulanic acid in this study were consistently high in all the periods of this study, raging from 78 to 98%. Since they were inactive against uropathogens, they should no longer be used to treat urinary tract infections in the hospital until this trend in resistance has been reversed.

In addition, the hospital needs to develop antibiotic policy to reduce or restrict the use of the other antibiotics which may have become suboptimal as a result of overuse. This done, it will be necessary to continue to monitor the resistance patterns of the discontinued and restricted antibiotics in order to demonstrate the reduction in resistance in response to reduced consumption.

DDD as a unit of measurement of drug consumption gives only a rough estimate of consumption and not an exact picture of actual use. Nevertheless it makes possible assessment of trends in drug consumption which should necessarily accompany formulation of antibiotic policies and education of staff[15,16]. These are all necessary interventions to solve the ongoing resistance problem in the hospital of study.

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