

Research Paper

Drug utilization pattern and cost-effectiveness analysis of five most common antibiotics used in Saudi Arabia

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Received August 29, 2020; Accepted October 21, 2020.

Abstract

Objectives Inappropriate use of antibiotics is a matter of concern worldwide as that may lead to antimicrobial drug resistance. The objective of current study was to assess drug utilization pattern and cost-effectiveness. Studies are conducted to analyze the pattern of antibiotics prescribing their adherence to standard guidelines and economic impact on the patients in order to promote their rational use.

Methods The study was designed as a single-centred, cross-sectional retrospective pharmacy database study of prescribing patterns and cost-utility analysis of five most common antibiotics used in Saudi Arabia. Data for the period from 1 January 2019 to 31 December 2019 were used in the study. Demographic characteristics were demonstrated as frequencies and percentages (with Wilson 95% confidence intervals for proportions). The chi-square test (for *P*-value calculation) was used to compare the adherence of National Antimicrobial Guidelines for prescribing antibiotics in Saudi Arabia.

Key findings The maximum number of patients was recorded from the age group of 18–35 years (35.97%) and minimum from 72 to 88 years (1.82%). The number of units prescribed was highest for amoxicillin, clavulanic acid (22487) to 42.93% of patients and was lowest for ciprofloxacin (4215) with 8.04%. The longest duration of therapy was for Cefdenir (7.23 days) and lowest for azithromycin (3.58 days). The cost was highest for Cefdenir 38.66SR (10.31USD), and lowest cost was estimated for Cefuroxime 12.43SR (3.31USD).

Conclusions Our study declared that (amoxicillin with clavulanic acid) was used the most as first-line agents in treating bacterial infections due to their broad coverage against different microbes. Conducting laboratory tests to identify the type of microbe before prescribing could prevent the development of drug resistance and save the antibiotic for future. The cost-to-benefit analysis studies of antibiotics must be conducted for each indication that may promote their rational use.

Keywords: prescribing pattern; antibiotics; National Antimicrobial Guidelines; cost analysis; Saudi Arabia

Introduction

The leading cause for deaths during 1900 was mainly due to infectious diseases that dropped down steeply during 2000 as a result of the discovery of antibiotics during this period.^[1] The agents

that work against the pathogenic microbes are antimicrobials. Antibiotics are among the most widely used antimicrobials.^[2] The widespread use of antibiotics may impose a threat of antibiotic resistance that may account for the global rise in deaths.^[3]

World Health Organization (WHO) recommends the appropriate and rational use of antibiotics as they are the reason behind the alarming rise in the global deaths.^[4]

Around 20 new classes of antibiotics were produced globally during the period between 1930 and 1962.^[5] Some common classes of antibiotics based on chemical or molecular structures include beta-lactams, macrolides, tetracycline, quinolones, aminoglycosides, sulphonamides, glycopeptides and oxazolidinones.^[6]

The most well-known drugs of the beta-lactam class include penicillin, cephalosporins, monobactams and carbapenems. Augmentin is a combination of amoxicillin with clavulanic acid which is a chemical that inhibit bacterial penicillinase enzyme, thereby enhancing antibacterial activity of amoxicillin.^[7] Cephalosporins being similar to penicillin in structure and mode of action are found to be the most prescribed by the physicians in the UK.^[8] These cephalosporins are divided into five generations, later ones being more effective against the treatment of infections caused by Gram-negative bacteria.^[9] Azithromycin, erythromycin and clarithromycin belong to the category of macrolide group that acts by inhibition of bacterial protein synthesis.^[10] Tetracyclines act by targeting the ribosomes and disrupting the synthesis of proteins in bacteria. They are grouped into generations based on their synthesis. Antibiotics belonging to this category are chlortetracycline, oxytetracycline, doxycycline and so on.^[6] Quinolones are potent, broad spectrum antibiotics that act by inhibiting bacterial DNA synthesis. They are one of the widely prescribed medications in outpatients and hospital settings for various infections although it has various gastrointestinal and central nervous system side effects.^[11] Aminoglycosides are potent broad spectrum antibiotics that act by inhibition of protein synthesis. Neomycin, kanamycin, gentamycin and tobramycin are some of the drugs belonging to this class. They were first-line agents in chemotherapy during earlier days but later were replaced in 1980s with cephalosporin, fluoroquinolone and carbapenams that were found to be less toxic and had a broad coverage. They are administered by parenteral route due to its poor bioavailability by oral route.^[12]

Sulphonamides are the synthetic antibiotics that stop the growth of bacteria by inhibiting the conversion of *p*-amino benzoic acid to dihydropteroate that mediates in bacterial DNA synthesis. They are available as single drug or in combination for oral use. There are creams, suppositories and ophthalmic dosage forms of sulphonamides available. Sulfonamides are available for oral and topical use. They are used in the treatment of inflammatory bowel disease, burns, urinary tract infections, vaginitis and so on.^[13]

Oral is the most common route for administering antibiotics but in severe systemic infections, they may be administered by parenteral route. Topical route is favoured in the treatment of some skin infections like cellulitis and acne.^[14]

Inappropriate use of antibiotics for instance overuse and misuse in hospitals and community is a matter of concern worldwide as that may lead to antimicrobial drug resistance, adverse effects, hospitalization and economic burden on the patient due to high cost of treatment. Hence, drug utilization and cost-effectiveness studies are conducted to analyse the pattern of drug prescriptions by the physicians' and their economic impact on the patient to promote their rational use. This study is conducted to analyse the pattern of drug utilization of the five most commonly used antibiotics in hospital settings and their cost effectiveness.

Methods

The study was designed as a single-centred, cross-sectional retrospective pharmacy database study of prescribing patterns and

cost-utility analysis of the five most common antibiotics used in Saudi Arabia. Data for the period from 1 January 2019 to 31 December 2019 were retrieved from the electronic pharmacy records in Al-Mana General Hospital Khobar, Saudi Arabia. Together in-patient and out-patient pharmacy department electronic drug dispensing records were retrieved. All retrieved data were archived in Microsoft excel 2013. Among all the retrieved data of patients on antibiotic therapy were categorized according to their frequency of prescribing in decreasing order of highest five different antibiotics, and categorized and labelled as five different antibiotics. It was found that amoxicillin and clavulanic acid, cefuroxime, azithromycin, Cefdenir and ciprofloxacin were the five highly utilized antibiotics in the studied hospital. Patients of both genders, all age groups and different nationality taking any five above-mentioned antibiotics, either alone or together were included in the study. Patients who were not prescribed and dispensed any of the five above-mentioned antibiotics were excluded from the study. Daily price of each drug was computed based on the WHO defined daily dose and National Antimicrobial Guidelines, which was established as a universal measure of drug consumption and provides a rough estimation of the prescribing pattern of different antibiotics taken for the management of different kinds of infectious diseases. The cost analysis of each studied drug was calculated in terms of average prices of each unit dose of each prescription. Lastly, the prescribing patterns were evaluated based on the adherence of guidelines and protocols of the National Antimicrobial Guidelines, which are the followed guidelines at the study centre (hospital) used for the management of different kinds of infectious diseases. All the five above-mentioned antibiotics were categorized on the basis of the availability of dose form and route of administration also coded in WHO anatomical therapeutic chemical classification code/ATC. These are amoxicillin and clavulanic acid (ATC code: J01CR02), azithromycin (J01FA10, S01AA26), Cefdenir (ATC code: J01DD15), cefuroxime (ATC code: J01DC02) and ciprofloxacin (ATC Code: J01MA02, S01AE03, S02AA15).

Data analysis

Demographic characteristics were demonstrated as frequencies and percentages (with Wilson 95% confidence intervals for proportions). The chi-square test (for *P*-value calculation) was used to compare the adherence of National Antimicrobial Guidelines for prescribing antibiotics in Saudi Arabia. All statistical analyses were conducted using SPSS version 26 (SPSS Institute Inc., Cary, NC, USA) and Microsoft Excel 2013. *P*-value ≤ 0.05 was considered as statistically significant.

Results

Baseline demographic data (Table 1) suggested that from the studied 52 372 patients, with prescribed antibiotics, males contributed to 51.64% (CI: 51.21–52.07; *n* = 27 046) and females 48.36% (CI: 47.93–48.79; *n* = 25 326). The maximum number of patients were recorded from the age set of 18–35 years 35.97% (CI: 35.57–36.39; *n* = 18 842) followed by 0–17 years 29.51% (CI: 29.13–29.91; *n* = 15 459), 36–53 years 21.93% (CI: 21.59–22.3; *n* = 11 489) and 54–71 years 10.73% (CI: 10.48–11.01; *n* = 5624). The number was considerably low for the age group 72–88 years 1.82% (CI: 1.72–1.95; *n* = 958). Bigger number constituted Saudis 58.21% (CI: 57.8–58.64; *n* = 30 490) compared with non-Saudis 41.78% (CI: 41.36–42.2; *n* = 21 882).

As shown in Figure 1, for the five most common antibiotics, the number of units prescribed was highest for amoxicillin, clavulanic acid (22 487) and lowest was for ciprofloxacin (4215).

The other antibiotics were prescribed in the following decreasing order of units as cefuroxime (12 737), azithromycin (8349) and Cefdenir (4546).

Table 2 describes prescribing patterns for antibiotics among diverse age group patients and adherence on National Antimicrobial Guidelines, Ministry of Health, Saudi Arabia. The drug amoxicillin, clavulanic acid (ATC code-J01CR02), exists in oral solid and liquid, parenteral dosage form with standard dose of 6.67–20 mg/kg, 1.67–5 mg/kg was given to the highest percentage of patients 42.93% (CI: 42.52–43.36; $n = 22\,487$) with following distribution among the various age groups: 0–17 years 17.89% (CI: 17.56–18.22; $n = 9371$), 18–35 years 12.89% (CI: 12.62–13.19; $n = 6754$), 36–53 years 8.05% (CI: 7.83–8.30; $n = 4219$), 54–71 years 3.57% (CI: 3.42–3.74; $n = 1873$) and 72–88 years 0.51% (CI: 0.46–0.59; $n = 270$) with significant P value <0.05 .

Cefuroxime (ATC Code:J01DC02) exists in oral solid and liquid dosage form with a standard dose of adult 0.75–1.5 g by the gap of 8 h/day for 5–10 days paediatric 50–150 mg/kg/day was given to 24.38% (CI: 24.02–24.76; $n = 12\,773$) patients with following distribution among the various age groups: 0–17 years 1.40% (CI: 1.30; $n = 735$), 18–35 years 12.82% (CI: 12.54–13.11; $n = 6716$), 36–53 years 6.88% (CI: 6.67–7.1; $n = 3605$), 54–71 years 32.82% (CI: 26.8–2.97; $n = 1479$) and 72–88 years 0.45% (CI: 0.4–0.51; $n = 238$) with significant P value <0.05 .

Table 1 Baseline demographic characteristics of the studied patients

Characteristics	Total 52 372, % (95% CI) (n)
Gender	
Male	51.64 (51.21–52.07) (27 046)
Female	48.36 (47.93–48.79) (25 326)
Age (years)	
0–17	29.51 (29.13–29.91) (15 459)
18–35	35.97 (35.57–36.39) (18 842)
36–53	21.93 (21.59–22.3) (11 489)
54–71	10.73 (10.48–11.01) (5624)
72–88	1.82 (1.72–1.95) (958)
Nationality	
Saudi	58.21 (57.8–58.64) (30 490)
Non-Saudi	41.78 (41.36–42.2) (21 882)

Azithromycin (ATC Code: J01FA10, S01AA26) exists in oral solid and liquid, eye and ear drop, parenteral dosage form with standard dose of adult 500 mg OD, or 10 mg/kg OD, one drop of 1% solution BD was given to 15.94% (CI: 15.64–16.27; $n = 8351$) patients with following distribution among the various age groups: 0–17 years 5.41 (CI: 5.23–5.62; $n = 2838$), 18–35 years 5.51% (CI: 5.32–5.71; $n = 2888$), 36–53 years 3.04% (CI: 2.91–3.20; $n = 1597$), 54–71 years 1.57% (CI: 1.48–1.69; $n = 827$) and 72–88 years 0.38% (CI: 0.33–0.44; $n = 201$) with significant P value <0.05 .

Cefdenir (ATC Code: J01DD15) exists in oral solid and liquid dosage form with a standard dose of 300–600 mg OD or 14 mg/kg was given to 8.68% (CI: 8.44–8.93; $n = 4546$) patients with following distribution among the various age groups: 0–17 years 4.53% (CI: 4.36–4.71; $n = 2375$), 18–35 years 1.91% (CI: 1.81–2.04; $n = 1003$), 36–53 years 1.31% (CI: 1.22–1.41; $n = 688$), 54–71 years 0.81% (CI: 0.74–0.89; $n = 425$) and 72–88 years 0.10% (CI: 0.09–0.14; $n = 55$) with significant P value <0.05 .

The antibiotic, ciprofloxacin (ATC Code: J01MA02, S01AE03, S02AA15), exists in oral solid and liquid, eye and ear drop, parenteral dosage form with a standard dose of 14–40 mg/kg, two drops hourly in the affected eye was given to 8.04% (CI: 7.82–8.29; $n = 4215$) patients with following distribution among the various age groups: 0–17 years 0.26% (CI: 0.23–0.32; $n = 140$), 18–35 years 2.82% (CI: 2.69–2.98; $n = 1481$), 36–53 years 2.63% (CI: 2.50–2.77; $n = 1380$), 54–71 years 1.94% (CI: 1.84–2.07; $n = 1020$) and 72–88 years 0.37% (CI: 0.32–0.43; $n = 194$) with significant P value <0.05 .

As shown in **Table 3**, among the studied common antibiotics, when compared the average therapy of duration, longest duration was for Cefdenir (7.23 days), followed by ciprofloxacin (7.09 days), amoxicillin, clavulanic acid (6.44 days), cefuroxime (3.88 days) and least for azithromycin (3.58 days).

The cost-utility analysis showed that the cost was highest for Cefdenir 38.66SR (10.31 USD) followed by azithromycin 22.26SR (5.94 USD), amoxicillin, clavulanic acid 17.75SR (4.73 USD) and ciprofloxacin 15.15SR (4.04 USD). The lowest cost estimated was for cefuroxime 12.43SR (3.31 USD).

Discussion

Our study revealed that there was not much difference in the numbers of males/females and adults/children who were prescribed

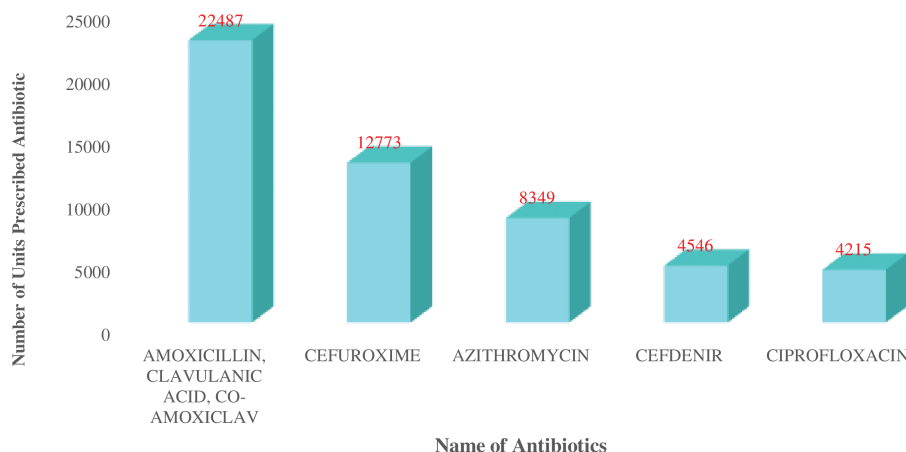


Figure 1 Five different most common prescribed antibiotics in studied hospital.

Table 2 Prescribing patterns for the five most common different antibiotics among different age group patients and adherence on National Antimicrobial Guidelines, MOH, Saudi Arabia (n = 52 372)

Drug	ATC Code	Dosages form	Dose	Total 52 372, % (95% CI) (n)	0–17 years % (95% CI) (n)	18–35 years % (95% CI) (n)	36–53 years % (95% CI) (n)	54–71 years % (95% CI) (n)	72–88 years % (95% CI) (n)	P-value
Amoxicillin, clavulanic acid	J01CR02	Oral solid and liquid, Parenteral	6.67–20 mg/kg 1.67–5 mg/kg	42.93 (42.52–43.36) (22 487)	17.89 (17.56–18.22) (9371)	12.89 (12.62–13.19) (6754)	8.05 (7.83–8.30) (4219)	3.57 (3.42–3.74) (1873)	0.51 (0.46–0.59) (270)	<0.05
Azithromycin	J01FA10, S01AA26	Oral solid and liquid, eye and ear drop, parenteral	Adult 500 mg OD, or 10 mg/kg OD 1 drop of 1% solution BD 300–600 mg OD or 14 mg/kg	15.94 (15.64–16.27) (8351)	5.41 (5.23–5.62) (2838)	5.51 (5.32–5.71) (2888)	3.04 (2.91–3.20) (1597)	1.57 (1.48–1.69) (827)	0.38 (0.33–0.44) (201)	<0.05
Cefdenir	J01DD15	Oral solid and liquid	Adult 0.75–1.5 g every 8 h for 5–10 days Paediatric 50–150 mg/kg/day	8.68 (8.44–8.93) (4546)	4.53 (4.36–4.71) (2375)	1.91 (1.81–2.04) (1003)	1.31 (1.22–1.41) (688)	0.81 (0.74–0.89) (425)	0.10 (0.09–0.14) (55)	<0.05
Cefuroxime	J01DC02	Oral solid and liquid	Adult 0.75–1.5 g every 8 h for 5–10 days Paediatric 50–150 mg/kg/day	24.38 (24.02–24.76) (12 773)	1.40 (1.30) (735)	12.82 (12.54–13.11) (6716)	6.88 (6.67–7.1) (3605)	2.82 (2.68–2.97) (1479)	0.45 (0.4–0.51) (238)	<0.05
Ciprofloxacin	J01MA02, S01AE03, S02AA15	Oral solid and liquid, eye and ear drop, Parenteral	14–40 mg/kg, two drops hourly in the affected eye	8.04 (7.82–8.29) (4215)	0.26 (0.23–0.32) (140)	2.82 (2.69–2.98) (1481)	2.63 (2.50–2.77) (1380)	1.94 (1.84–2.07) (1020)	0.37 (0.32–0.43) (194)	<0.05

Table 3 Prescribing patterns for the five most common antibiotics and their cost-utility analysis prescription wise in the studied hospital

Drug (ATC code)	Average therapy of duration in days	Average cost in unit dose, prescription wise in SR (USD)
Amoxicillin, clavulanic acid (J01CR02)	6.44	17.75 (4.73)
Azithromycin (J01FA10, S01AA26)	3.58	22.26 (5.94)
Cefdenir (J01DD15)	7.23	38.66 (10.31)
Cefuroxime (J01DC02)	3.88	12.43 (3.31)
Ciprofloxacin (J01MA02, S01AE03, S02AA15)	7.09	15.15 (4.04)

antibiotics except the elderly patients above 72–88 years. Similar fact quoted in a report by the WHO, which states that a serious threat is occurring in every region of the world regarding antibiotic resistance, and it has the potential to affect anyone, of any age, in any country.^[15]

Among the five most commonly used antibiotics, the numbers of units prescribed were highest for amoxicillin, clavulanic acid; this is similar to the earlier findings reported.^[16] This could be due to its effectiveness and safest as a first-line preferred antimicrobial agent for dental infections, ear infection and mild or major upper respiratory tract infection, as found in earlier study also showing adherence to the guidelines given by National Antimicrobial Guidelines, MOH, Saudi Arabia.^[17, 18]

Cefuroxime, the second choice as per our study may be considered as an empirical therapy for a range of community-acquired infections having similarity with the past findings.^[19] Treatment with azithromycin was as effective as cefuroxime in the pragmatic controlling of community-developed pneumonia; also, it is well tolerated.^[20]

Clinical evidence indicates that Cefdenir is an operative and generally well bore drug a worthy choice for the treatment of children, adults and youngsters with precise minor-to-severe skin or respiratory tract toxicities, particularly among common community-acquired pathogens.^[21]

Ciprofloxacin is an FDA-approved antibiotic agent in the fluoroquinolone class appropriate treatment option in patients with mixed infections or patients with predisposing factors for Gram-negative infections. It is used to cure bacterial infections such as urinary tract infections and pneumonia. However, due to serious side effects associated with antibiotics used, it should not be used for treating infections unless there are no other alternatives.

The cost-utility analysis showed that the cost was highest for Cefdenir with highest duration of therapy, where it was moderate for amoxicillin, clavulanic acid with moderate duration of therapy. This is in concurrence with the earlier comparison analysis, which showed that age or gender did not influence the cost of antibiotic medicine treatment, but the choice of antibiotic(s) used had an influence on the treatment cost.

Conclusions

Beta-lactam and beta-lactamase inhibitor combination (amoxicillin with clavulanic acid) were used as the most first-line agents in treating bacterial infections due to their broad coverage against different microbes. The dose of amoxicillin with clavulanic acid

combination should be monitored in case of renal and hepatic dysfunction. Fluoroquinolone (ciprofloxacin) was least preferred due to their toxicity and threat of bacterial resistance. They are not recommended as first-line agents for antimicrobial therapy in children.

Appropriate prescription of drug and their doses should be monitored for its adherence to the national guidelines. Inappropriate and unnecessary prescription of antibiotics may cause the development of drug resistance and adverse effects which may ultimately prolong the hospitalization of the patients and add to the economic burden. Conducting laboratory tests to identify the type of microbe before prescribing could prevent the development of drug resistance and save the antibiotic for future.

Because there is growing concern over the development of drug resistance and lower budgets in developing newer antibiotics, the cost-to-benefit analysis studies of antibiotics must be conducted for each indication that may promote their appropriate use.

Study Place

A retrospective observational study was carried out in the Al-Mana Group of Hospital (AGH), Saudi Arabia. AGH Al-Khobar is a 250-bedded teaching private hospital with 74 out-patient clinic to provide health care facilities to the community of Saudi Arabia.

Acknowledgements

My special thanks to Dr. Aisha Al-Mana, Head of Board of trustee MACHS, for giving me an opportunity for research publication, providing unpublished data, her kind support and encouragement. I would also like to express my thanks to Prof. Emad AlShwaimi, Dean, MACHS to facilitate in obtaining research data.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None declared.

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