

## **The Adverse Effects Reporting of Antibiotic Induced Diarrhea**

### **ABSTRACT**

**Introduction:** In Saudi Food and Drug Authority, there is a center called National Pharmacovigilance and Drug Safety Center responsible for adverse events reporting. This study aims to demonstrate the antibiotic induced diarrhea reporting by National Pharmacovigilance and Drug Safety Center in Saudi Arabia.

**Methodology:** This is a retrospective study about the reporting of diarrhea adverse effects caused by antibiotics. The data were collected from the adverse effects reports that were submitted to Saudi Food and Drug Authority in 2017 and 2018.

**Results:** Gastrointestinal adverse effects reports were mainly for penicillin antibiotics. The major gastrointestinal adverse effect of penicillin was diarrhea (100 reports out of 147 reports for penicillin include diarrhea). Most of the diarrhea reports were caused by Amoxicillin/Clavulanate followed by Amoxicillin.

**Conclusion:** One of the major adverse effects for antibiotics is diarrhea that is mainly occurred by penicillin antibiotics. The majority of cases of antibiotics-associated diarrhea are not serious, but still affect the patients' quality of life. Therefore, it is important to increase the awareness regarding medications adverse effects and their reporting.

**Keywords:** *Adverse Effects Reporting, ADEs Reporting, Antibiotic, Diarrhea.*

## 1. INTRODUCTION

Antibiotics save lives, but any time antibiotics are used, they can lead to many side effects and if used excessively, they increase the development antibiotic resistance. The Excessive usage of antibiotics could result in several adverse events including diarrhea. Centers for Disease Control and Prevention reported that the common side effects of antibiotics include diarrhea, rash, yeast infections and nausea. [1]

Diarrhea is a common adverse effect of antibiotic therapy. Antibiotic associated diarrhea occurs in about 5-30% of patients, it includes the diarrhea that occurred either early during antibiotic therapy or that occurred up to two months after the end of the treatment. [2-4]

Antibiotic-associated diarrhea can be defined as passing loose, watery stools three or more times a day after taking antibiotics. Most often, the diarrhea that is resulted by antibiotic is mild, requires no treatment and it typically clears up within a few days if the patient stop taking the antibiotic. [5]

One of the most serious causes of antibiotic-associated diarrhea is infection with *Clostridium difficile* (*C. difficile*) bacterium. *C. difficile* infections are common, with approximately 500,000 cases in the United States annually. [6] Other infectious organisms causing antibiotic-associated diarrhea include *Staphylococcus aureus*, *Clostridium perfringens*, *Candida species*, *Salmonella species* and *Klebsiella oxytoca*. [7]

The majority of antibiotics have been associated with *C. difficile* diarrhea and with colitis but the antibiotics that are most frequently associated with it include clindamycin, cephalosporins, amoxicillin and ampicillin. [8]

Clinical trials generally aim to establish the efficacy of a medication and to reveal common adverse events, but there are many limitations in identifying safety concerns. For example, study participants may not be representative to the real world patients receiving the medication once it is on the market. [9] Therefore, it is important to report any unexpected adverse effects to the department in Food and Drug Administration (FDA) that are responsible for adverse effects reporting, this reporting maybe done by the public, health care professionals or by pharmaceutical companies.

Pharmacovigilance plays an essential role in ensuring that patients are using safe medications. In Saudi Arabia, Saudi Food and Drug Authority, health institutions, healthcare professionals and marketing authorization holders are involved in the activities of pharmacovigilance regardless of the level of the involvement. The pharmacovigilance is considered as a new concept in Saudi Arabia. [10]

In Saudi FDA, there is a center called National Pharmacovigilance and Drug Safety Center responsible for adverse events reporting. This study aims to demonstrate the prevalence of antibiotic induced diarrhea reporting by National Pharmacovigilance and Drug Safety Center in Saudi Arabia.

## **2. METHODOLOGY**

This is a retrospective study about the reporting of diarrhea adverse effects caused by antibiotics. The data were collected from the adverse effects reports that were submitted to Saudi Food and Drug Authority.

The data include only gastrointestinal side effects and limited to many antibiotics related to the most common prescribed antibiotic classes, which are Aminoglycoside, Penicillin, Cephalosporin, Macrolide and Quinolones in 2017 and 2018.

The other antibiotic classes were excluded. Moreover, the adverse effects reporting other than gastrointestinal adverse effects were excluded and the reports before 2017 or after 2018 were excluded.

The data were collected using excel software and the Descriptive data were represented by frequencies and percentages.

### 3. RESULTS and DISCUSSION

Table 1 shows the number of Gastrointestinal adverse effects reports of the most common antibiotic classes. Gastrointestinal adverse effects reports were mainly for penicillin antibiotics (63.36 %). Jung IY et al reported that penicillin and quinolones are the most common causative antibiotics for Adverse drug reactions and reported that 29.9 % of penicillin adverse effects were gastrointestinal and 32.4 % of quinolones adverse effects were gastrointestinal effects. [11]

**Table 1. Number of Gastrointestinal adverse effects reports of the most common antibiotic classes**

Antibiotic class	Number of Gastrointestinal adverse effects reports	Percentage
Aminoglycoside	0	0
Penicillin	147	63.36
Cephalosporin	23	9.91
Macrolide	29	12.5
Quinolones	33	14.22

Number and percentage of diarrhea reports of the most common antibiotic classes are shown in table 2.

The major gastrointestinal adverse effect of penicillin was diarrhea 100 report out of 147 reports for penicillin include diarrhea (68.02%). This result is rational because diarrhea is the most common adverse effects of antibiotics in general. For example, for Amoxicillin/Clavulanate potassium diarrhea is occurred commonly (2.9 %to 14.5 %). For amoxicillin, diarrhea occur in greater than 1 % and for other penicillin antibiotics, diarrhea is classified as common adverse effects. [12] Generally, only in one case the diarrhea reported as clostridium difficile diarrhea.

**Table 2. Number of Diarrhea reports of the most common antibiotic classes**

Antibiotic class	Number of Diarrhea reports	Percentage
Aminoglycoside	0	0
Penicillin	100	71.94
Cephalosporin	11	7.91
Macrolide	15	10.79
Quinolones	13	9.35

Most of the diarrhea reports were resulted from the use of Amoxicillin/Clavulanate (61.87%). Table 3 shows the number of Diarrhea reports of the most common antibiotics.

**Table 3. Number of Diarrhea reports of the most common antibiotics**

Antibiotic	Number of Diarrhea reports	Percentage
Amikacin	0	0
Amoxicillin	13	9.35
Amoxicillin/Clavulanate	86	61.87
Ampicillin	1	0.71
Azithromycin	10	7.19
Benzympenicillin	0	0
Cefalexin	1	0.71
Cefepime	0	0
Cefuroxime	10	7.19
Ciprofloxacin	12	8.62
Clarithromycin	5	3.6

Erythromycin	0	0
Gentamicin	0	0
Levofloxacin	1	0.71
Tobramycin	0	0

Most of the diarrhea reports were caused by Amoxicillin/Clavulanate (61.87%) followed by Amoxicillin (9.35%) and Ciprofloxacin (8.62%). Up to 14.5 % of the patients who receive Amoxicillin/Clavulanate developed diarrhea. Generally, about 2.5 % of adult patients who received ciprofloxacin hydrochloride developed diarrhea. Similarly, FDA reported that for Amoxicillin/Clavulanate the most frequently reported adverse effects were diarrhea/loose stools (9%). [13] Similar results were found by Kuehn J at al who reported that there is a substantially increased incidence of antibiotic – associated diarrhea following use of amoxicillin/clavulanate, compared to use of amoxicillin and penicillin V and reported that the antibiotic – associated diarrhea incidence was 19.8% for amoxicillin/clavulanate, 8.1% for amoxicillin, and 1.2% for penicillin V. [14]

Moreover, there were many ciprofloxacin associated diarrhea reports (8.62%). FDA stated that the most frequently reported adverse reactions, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea followed by diarrhea. [15]

#### **4. CONCLUSION**

As a result of current safety concerns surrounding commonly used medications, there is an increasing focus on drug safety. One of the major adverse effects for antibiotics is diarrhea that is mainly occurred by penicillin antibiotics. The majority of cases of antibiotics-associated diarrhea are not serious, but still affect the patients' quality of life. Therefore, it is important to report any adverse effects including diarrhea by the patients, health care providers or by pharmaceutical companies. Moreover, it is important to increase the awareness regarding medications adverse effects (including how to prevent or treat these effects) and regarding how to report an adverse effect if it is happened.

## LIMITATION

This data include the number of reports but not include the number of the different consumed antibiotics, for example the reports were mainly for amoxicillin or amoxicillin/clavulanic acid but these antibiotics is the most commonly used antibiotics, so the increased number of reports may be due to an increased the number of antibiotics used.

Moreover, the gastrointestinal side effects include also nausea, vomiting and other effects and also the consequences for these effects were not mentioned such as the decreased absorption and the decreased level of some vitamin that are caused by gastrointestinal problems.

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