ORIGINAL ARTICLE

# Descriptive Analysis of Reported Adverse Events Associated with Amoxicillin/ Clavulanate potassium

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## Abstract

**Aim:** Amoxicillin/clavulanate use leads to different adverse effects such as diarrhea, loose stools, skin rashes, nausea, and urticaria. The aim of the study was to describe the reported adverse events associated with the use of amoxicillin/clavulanate potassium. **Materials and Methods:** The study included a descriptive analysis of the reports that were submitted to the FDA Adverse Event Reporting System (FAERS). **Results:** Between 1994 and 2022, 2203 reports about amoxicillin/clavulanate potassium adverse events were submitted to FAERS. The most reported adverse events were diarrhea (9.03%), pruritus (8.81%), hypersensitivity (7.67%), pyrexia (7.31%), rash (6.95%), dyspnea (5.99%), vomiting (5.54%), drug ineffective (5.08%), and nausea (4.31%).The present study showed also that amoxicillin/clavulanate potassium use leads to several adverse events that could be serious events. **Conclusion**: It is important to increase the awareness of healthcare providers about the adverse events of broad-spectrum antibiotics such as amoxicillin/clavulanate potassium. The health-care providers should educate their patients about the adverse events of using amoxicillin/clavulanate potassium and about how to manage and how to report these events.

**Key words:** Adverse events, amoxicillin/clavulanate potassium, FDA adverse event reporting system, reporting

## INTRODUCTION

Amoxicillin/clavulanate is a broad-spectrum antibiotic that has been available for treatment in a wide range of infections in the previous years.[1] It is a combination of two separate agents: Amoxicillin and clavulanic acid.[2] Amoxicillin has activity against several Gram-negative and Gram-positive bacteria.[3,4] The addition of clavulanic acid increases the spectrum to include beta-lactamase-producing bacteria and broadens the coverage to include other organisms such as *Neisseria* species, methicillin-sensitive *Staphylococcus aureus*, and *Proteus* species.[3,4]

Amoxicillin/clavulanate potassium is well tolerated but its use could lead to several adverse effects. The most frequently reported adverse effects were diarrhea, loose stools, skin rashes, nausea, and urticaria.[5] It interacts with several medications such probenecid, oral Anticoagulants, allopurinol, and oral contraceptives.[2]

Post-marketing surveillance is essential to ensure the long-term safety of medications and to study rare adverse events and adverse reactions.[6] The US FDA Adverse Event Reporting System (FAERS) is a post-marketing surveillance program seeking inputs on adverse events to monitor medications safety.[7] It is one of the world's largest reporting systems that enclosemillions of reports and contains valuable information that is of interest to toxicology, pharmacovigilance, and post-marketing surveillance researchers.[8]

There is a lack of studying the adverse events reporting of several medications, particularly the most used medications such as amoxicillin/clavulanate. The present study aimed to describe the reported adverse events associated with the use of amoxicillin/clavulanate potassium.

## MATERIALS AND METHODS

This was a descriptive analysis of the reported adverse events associated with the use of amoxicillin/clavulanate

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**Received:** 23-06-2022
**Revised:** 24-08-2022
**Accepted:** 08-09-2022

potassium which is used to manage numerous infections. The study included a descriptive analysis of the reports that were submitted to the FAERS.

The reports about amoxicillin/clavulanate potassium that were submitted to FAERS from 1994 to 2021 were included in the study. Hence, the reports of other drugs and amoxicillin/clavulanate potassium reports that were submitted in 2022 were excluded from the study.

The collected data included the total number of amoxicillin/clavulanate potassium reports that were submitted to FAERS, the specialty of the reporters, the gender of the patients, the age of the patients, and the most reported adverse events of amoxicillin/clavulanate potassium. The descriptive data were represented as numbers and percentages.

## RESULTS

Between 1994 and 2022, 2203 reports about amoxicillin/clavulanate potassium adverse events were submitted to FAERS. More than 37% of the reports were submitted in the period between 2007 and 2011 and 26.65% of the reports were submitted between 2017 and 2021. The total number of amoxicillin/clavulanate potassium reports that were submitted to FAERS is shown in Table 1.

Table 2 showed the specialty of the reporters. More than 63% of the reporters were healthcare professionals (63.37%).

Table 3 showed the gender of the patients who developed an adverse event associated with the use of amoxicillin/clavulanate potassium. About 52.93% of the patients were female patients.

Table 4 showed the age of the patients who developed an adverse event associated with the use of amoxicillin/clavulanate potassium. The age of 51.79% of the patients was between 18 and 64 years.

Table 5 shows the most reported adverse events of amoxicillin/clavulanate potassium. The most reported adverse events were diarrhea (9.03%), pruritus (8.81%), hypersensitivity (7.67%), pyrexia (7.31%), rash (6.95%), dyspnea (5.99%), vomiting (5.54%), drug ineffective (5.08%), and nausea (4.31%).

**Table 1:** The total number of amoxicillin/clavulanate potassium reports that were submitted FAERS

| Category | Number of cases | Percentage |
|---|---|---|
| 2017–2021 | 587 | 26.65 |
| 2012–2016 | 400 | 18.16 |
| 2007–2011 | 824 | 37.40 |
| 2002–2006 | 326 | 14.79 |
| Before 2002 | 66 | 3.00 |
| Total | 2203 | 100.00 |

**Table 2:** The specialty of the reporters

| Category | Number of cases | Percentage |
|---|---|---|
| Health-care Professional | 1396 | 63.37 |
| Consumer | 807 | 36.63 |
| Total | 2203 | 100.00 |

**Table 3:** The gender of the patients

| Category | Number of cases | Percentage |
|---|---|---|
| Female | 1166 | 52.93 |
| Male | 1037 | 47.07 |
| Total | 2203 | 100.00 |

**Table 4:** The age of the patients

| Category | Number of cases | Percentage |
|---|---|---|
| 0–1 month | 7 | 0.32 |
| 2 months–2 years | 108 | 4.90 |
| 3–11 years | 124 | 5.63 |
| 12–17 years | 66 | 3.00 |
| 18–64 years | 1141 | 51.79 |
| 65–85 years | 647 | 29.37 |
| More than 85 years | 110 | 4.99 |
| Total | 2203 | 100.00 |

## DISCUSSION

The present study showed that the most reported adverse events of were diarrhea, pruritus, hypersensitivity, pyrexia, rash, dyspnea, vomiting, drug ineffective, nausea, erythema, jaundice, and urticaria. Evans *et al.* reported that the most adverse effects of amoxicillin/clavulanate potassium were mild gastrointestinal disturbances such as diarrhea, loose stools, nausea, abdominal discomfort, and vomiting.[2] Easton *et al* informed that the most reported adverse events of amoxicillin/clavulanic acid in pediatric patients with acute otitis media were mild gastrointestinal symptoms.[9] Salvo *et al.* reported that the occurrence of gastrointestinal, hematological, and hepatic events was significantly higher for amoxicillin/clavulanic acid than for amoxicillin.[10] Moreover, Uto and Gerriets reported that clavulanic acid can cause some mild gastrointestinal adverse effects when administered with amoxicillin includes nausea, vomiting, discomfort, and loose stools.[11] Furthermore, Matho *et al*. reported that the most frequent adverse effects of amoxicillin/clavulanate were diarrhea and, in females, vaginal discharge and itching.[12] Barry reported that in patients with otitis media, the rates of generalized rash and diarrhea were highest

**Table 5:** The most reported adverse events of amoxicillin/clavulanate potassium

| Category | Number of cases | Percentage |
|---|---|---|
| Diarrhea | 199 | 9.03 |
| Pruritus | 194 | 8.81 |
| Hypersensitivity | 169 | 7.67 |
| Pyrexia | 161 | 7.31 |
| Rash | 153 | 6.95 |
| Dyspnea | 132 | 5.99 |
| Vomiting | 122 | 5.54 |
| Drug ineffective | 112 | 5.08 |
| Nausea | 95 | 4.31 |
| Erythema | 88 | 3.99 |
| Jaundice | 88 | 3.99 |
| Urticaria | 84 | 3.81 |
| Malaise | 80 | 3.63 |
| Condition aggravated | 75 | 3.40 |
| Asthenia | 72 | 3.27 |
| Acute kidney injury | 71 | 3.22 |
| Anaphylactic reaction | 69 | 1.72 |
| Pneumonia | 64 | 2.91 |
| *Clostridium difficile* colitis | 63 | 2.85 |
| Abdominal pain | 60 | 2.72 |
| Fatigue | 58 | 2.63 |
| Hypotension | 58 | 2.63 |
| Cholestasis | 56 | 2.54 |
| Drug interaction | 53 | 2.41 |
| Abdominal pain upper | 51 | 2.32 |
| Hepatitis cholestatic | 51 | 2.32 |
| Drug-induced liver injury | 50 | 2.27 |

with amoxicillin/clavulanate and high-dose amoxicillin, and lowest with azithromycin.[13]

In addition to these common adverse events, amoxicillin-clavulanate use could lead to serious adverse events related to *Clostridium difficile* infection and anaphylactic reaction. Rovelsky *et al.*, Bignardi *et al.*, and Huttner *et al.* reported that gastrointestinal adverse events particularly diarrhea and *Clostridioides difficile* were significantly higher in patients who used amoxicillin/clavulanate as compared with amoxicillin alone.[14-16] Evans *et al.* reported that there is a moderately increased risk of *C. difficile* colitis in patients treated with amoxicillin clavulanate when compared with other classes of antimicrobials.[2] Moreover, the previous studies reported that penicillin allergy is the most reported medication allergy.[17-19] Regateiro *et al*. stated that penicillins are among the leading causes of drug-induced anaphylaxis.[20] Syrigou and Syrigos reported that side effects following skin tests with amoxicillin/clavulanate, and amoxicillin mainly include urticarial rash, but rare cases of anaphylactic shock have also been described.[21]

The first limitation of the study was that there were 1662 different adverse events reported so the study included the most reported adverse events. The 2nd limitation was that the report submitted by the health-care professionals and consumers was voluntary so, not all adverse events were reported. The 3rd limitation was that the number of adverse events may be not accurate because some adverse events were submitted by different names; for example, regarding the reporting of *C.difficile* infection, some reporters wrote the term *C. difficile*, and other reporters wrote *C. difficile* or *C. difficile* infection.

## CONCLUSION

The present study showed that amoxicillin/clavulanate potassium use leads to several adverse events that could be serious events. It is important to increase the awareness of health-care providers about the adverse events of broad-spectrum antibiotics such as amoxicillin/clavulanate potassium. Health-care providers should educate their patients about the adverse events of using amoxicillin/clavulanate potassium and about how to manage and how to report these events.

## ACKNOWLEDGMENT

This Publication was supported by the Deanship of Scientific Research at Prince Sattam bin Abdulaziz University. The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number (IF-PSAU-2021/03/19105).

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**Source of Support:** Nil. **Conflicts of Interest:** None declared.