

Research Paper

Clostridium difficile Infection Risk with Important Antibiotic Classes: An Analysis of the FDA Adverse Event Reporting System

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Abstract

Introduction: Antibiotic use is an important risk factor for *Clostridium difficile* infection (CDI). Prior meta-analyses have identified antibiotics and antibiotic classes that pose the greatest risk for CDI however, CDI epidemiology is constantly changing and contemporary analyses are needed.

Objectives: The objective of this study was to evaluate the association between CDI and important antibiotic classes in recent years using the FDA Adverse Event Report System (FAERS).

Methods: FAERS reports from January 1, 2015 to December 31, 2017 were analyzed. The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify CDI cases. We computed the Reporting Odds Ratios (RORs) and corresponding 95% confidence intervals (95%CI) for the association between antibiotics and CDI. An association was considered statistically significant when the lower limit of the 95%CI was greater than 1.

Results: A total of 2,042,801 reports (including 5,187 CDI reports) were considered, after inclusion criteria were applied. Lincosamides (e.g., clindamycin) had the greatest proportion of CDI reports, representing 10.4% of all lincosamide reports. CDI RORs (95%CI) for the antibiotic classes were (in descending order): lincosamides 46.95 (39.49-55.82), monobactams 29.97 (14.60-61.54), penicillin combinations 20.05 (17.39-23.12), carbapenems 19.16 (15.52-23.67), cephalosporins/monobactams/carbapenems 17.28 (14.95-19.97), cephalosporins 15.33 (12.60-18.65), tetracyclines 7.54 (5.42-10.50), macrolides 5.80 (4.48-7.51), fluoroquinolones 4.94 (4.20-5.81), and trimethoprim-sulfonamides 3.32 (2.03-5.43).

Conclusion: All antibiotic classes included in the study were significantly associated with CDI. Lincosamides (e.g., clindamycin) had the highest CDI ROR among the antibiotics evaluated in this study.

Key words: *Clostridium difficile*, adverse drug events, antibiotics, antimicrobial stewardship

Introduction

Clostridium difficile infection (CDI) is a great public health concern in hospital and community settings. In the first decade of the twenty-first century, United States hospitals noted a profound increase in CDI incidence [1]. Since then, national standards required hospitals to implement effective infection

control interventions and antimicrobial stewardship programs to prevent CDI. Nationally-representative studies now indicate that CDI rates among hospitalized patients might be declining [2]. With the decline in CDI incidence in hospitals, there appears to have been a concurrent shift to community-onset CDI [3].

A rich and diverse intestinal microbiota prevents CDI; disruption of microbiota, especially due to antibiotic use, can lead to loss of colonization resistance and proliferation of *C. difficile* [4,5]. Antibiotic exposure is the most important risk factor in both hospital and community-onset CDI [6-8]. In previous meta-analyses conducted between 1988 and 2009, clindamycin, fluoroquinolones, and cephalosporins had the highest CDI risks [6-8].

Given the change in CDI epidemiology in recent years, more recent data are needed to evaluate the current CDI associations with various antibiotics. The FDA Adverse Event Reporting System (FAERS) provides recent data on CDI and antibiotics [9]. The objective of this study is to evaluate CDI associations with antibiotics using FAERS data from 2015 to 2017.

Methods

Data Source

FAERS is a publicly available database organized into Quarterly Data Files, which contain adverse event reports that were submitted to United States Food and Drug Administration (FDA) [9]. FAERS data include patient demographic information (age and sex), drug information (drug name, active ingredient, route of administration, and drug's reported role in the event), and reaction information. Each report lists a primary suspected drug with one or more adverse reactions and may include other drugs. Clinical outcomes, such as death and hospitalization, may also be reported.

Study Design

FAERS data from January 1, 2015 to December 31, 2017 were obtained from the FDA. Some adverse event reports were submitted multiple times with updated information. Therefore, duplicate reports were removed by case number, with the most recent submission included in the study. Reports containing drugs which were administered in oral, subcutaneous, intramuscular, intravenous, and parenteral routes were included in the study, while other routes of administration were excluded.

Drug Exposure Definition

Each antibiotic was identified in the FAERS drug files by generic and brand names listed in the Drugs@FDA Database [10]. Only drugs with a reported role coded as "PS" (Primary Suspect Drug) or "SS" (Secondary Suspect Drug) were included in this study [11]. Antibiotics with less than three CDI reports were excluded from the data analysis [12].

Adverse Drug Reaction Definition

FAERS defines adverse drug reactions using

Preferred Terms from the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA includes a hierarchy of terms, which are (from the highest to the lowest) System Organ Classes (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Lowest Level Term (LLT). Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, usually at the PT level, which relate to an adverse drug reaction. Pseudomembranous colitis (SMQ), including Preferred Terms "Clostridial infection", "Clostridial sepsis", "Clostridium bacteraemia", "Clostridium colitis", "Clostridium difficile colitis", "Clostridium difficile infection", "Clostridium test positive", "Gastroenteritis clostridial", and "Pseudomembranous colitis" were used to identify CDI cases [13]. "Clostridium difficile sepsis", which is a Lowest Level Term, was also used in the study.

Statistical Analysis

A disproportionality analysis was performed by calculating Reporting Odds Ratios (RORs) and corresponding 95% confidence intervals (95%CI) for the association between CDI and each antibiotic class or individual antibiotic [14]. ROR was calculated as the ratio of the odds of reporting CDI versus all other events for a given drug, compared with these reporting odds for other drugs present in FAERS [14]. An association was considered to be statistically significant if the 95%CI did not include 1.0 (see Table 1 for the calculation of ROR and CI) [14]. A higher ROR suggests a stronger association between the antibiotic and CDI. A subgroup analysis was performed on patients who were 65 years or older and patients less than 65 years old. The Cochran-Armitage Trend Test was used to assess a change in the trend of CDI reports in patients who took fluoroquinolones from 2004 to 2017. Data analysis was performed using Microsoft Access 2016, Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), SAS 9.4, and JMP Pro 13.2.1 (SAS Institute, Cary, NC).

Table 1. A two by two contingency table for a drug (A) – ADR (X) combination

| | ADR (X) | Other ADRs | Total |
|-------------|---------|------------|---------|
| Drug (A) | a | b | a+b |
| Other drugs | c | d | c+d |
| Total | a+c | b+d | a+b+c+d |

† ADR = adverse drug reaction; ROR = (a/b)/(c/d); 95% Confidence Interval (CI) = $e^{\ln(ROR) \pm 1.96 \cdot (1/a + 1/b + 1/c + 1/d)}$

Results

After inclusion and exclusion criteria were applied and duplicate reports were removed, FAERS contained a total of 2,042,801 reports from January 1,