Antibiotics-associated pseudomembranous colitis: a disproportionality analysis of the US Food and Drug Administration Adverse Event Reporting System (FAERS) database

Jinhua Chen
The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital
Weijiang Yu
The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital
Cuicui Sun (cuicuisun1@126.com)
Qilu hospital of Shandong University
Wenzhou Zhang
The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital

Article

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Abstract

Antibiotics have been established as an important risk factor for pseudomembranous colitis (PMC), a potential life-threatening complication. Evaluating the antibiotics most commonly associated with PMC is of great significance. In this study, we extracted the data from fourth quarter of 2003 to third quarter of 2023 in the US Food and Drug Administration Adverse Event Reporting System (FAERS). Disproportionality analysis was performed to evaluate the potential association between antibiotics and PMC. The results showed that eighty-one antibiotics which met the three algorithms simultaneously were enrolled. A total of 11737133 adverse event (ADE) reports were identified in the FAERS database, of which 1683 reports were associated with the enrolled antibiotics related PMC. It showed that the elderly and females are more susceptible to the antibiotics-associated PMC, especially for patients aged > 60 years. The top twenty-four antibiotics included four penicillins, eleven cephalosporins, three carbapenems, two lincosamides, one cephamycin, one aminoglycoside, one fosfomycin, and one echinocandin. This study also showed that cefoxitin, streptomycin, fosfomycin, and micafungin have a high risk of PMC, but there are few reports in the literature. This is helpful to reduce the potential damage of antibiotics-associated PMC.

Introduction

Pseudomembranous colitis (PMC) is a severe inflammatory condition of the colon characterized by colonic mucosa with the formation of pseudomembranes, with diarrhea as the main clinical manifestation[1,2]. Many different etiologies can cause PMC, such as *Clostridium* (reclassified as "*Clostridioides*") *difficile* (*C. difficile*) infection, *Staphylococcus aureus* infection, *Cytomegalovirus*, and Behcet's disease[3]. Among these, it is well-known that *C. difficile* infection is the most common cause[4]. Toxin A and toxin B produced by *C. difficile* might cause PMC by activating the immune system to cause inflammation in the colon[5]. Many drugs are associated to PMC, such as antibiotics, immune checkpoint inhibitors and glucocorticoids[6–8]. Antibiotics-induced PMC accounts for 25%-33% of all antibiotics-associated diarrhea, which is mainly associated with dysbacteriosis, thus leading to the overgrowth of *C. difficile*[9].

The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a spontaneous reporting database to collect the adverse events of drugs approved by FDA worldwide[10–12]. This provides a large source of data about drug-induced adverse events (ADEs) in real-world clinical setting[13]. This study was to comprehensively assess the association between antibiotics and PMC by a disproportionality analysis using the FAERS, which can provide a reference for the marketed antibiotics that induced PMC.

Materials and methods

Data sources and processing. This study was a retrospective pharmacovigilance analysis to asses reports of antibiotics-associated PMC based on the FAERS database. OpenVigil 2.1, a validated

pharmacovigilance data extraction, cleaning, and mining tool of the FAERS database, was used to retrieve FAERS database[14]. In this study, drug information was extracted by using PMC (including *C. difficile* colitis) as preferred term (PT) from the fourth quarter of 2003 to third quarter of 2023 in the FAERS database through OpenVigil 2.1. We selected all antibiotics from the extracted drugs. Moreover, this study excluded some antibiotics: (1) they are usually available as combination products, including β-lactamase inhibitors (tazobactam, clavulanate, avibactam, sulbactam), cilastatin, sulfamethoxazole, and trimethoprim. (2) several antibiotics are used to treat *C. difficile* infection and thus highly unlikely to cause PMC as adverse events, including metronidazole, vancomycin and fidaxomicin.

We deduplicated the ADE reports of the enrolled antibiotics-associated PMC from the FAERS database. Reports with the same information including adverse event, ISR number, date received, drug, indication, gender, reporter country and age were identified as duplicate reports and excluded. The remaining reports were further screened by setting the main selection criterion as primary suspect (PS), to eliminating the effects of other factors. After deduplication, the remaining reports were used for follow-up analysis.

Clinical characteristics in enrolled reports were analyzed, including sex, age, reporting region, outcome and reporting year. Serious outcomes included hospitalization, life-threatening, disability, and death.

Signal mining. To improve the sensitivity, specificity and predictive value, three disproportionality analyses were performed to detect the potential association between ADEs and antibiotics using the reporting odds ratio (ROR), the proportional reporting ratio (PRR), and the information component (IC)[15]. Each algorithm has its own advantages and disadvantages, and they can complement each other to some extent. The ADE signals were considered to be positive when they met three algorithm criterias simultaneously. The equations and corresponding thresholds of the three algorithms are listed in Table 1.

Table 1
Three Algorithms Used for Signal Detection.

Algorithms	Equation	Criteria
ROR	ROR=(a/c)/(b/d)	a ≥ 3, 95%CI ≥ 1
	95%CI = $e^{\ln(ROR)\pm1.96(1/a+1/b+1/c+1/d)^{0.5}}$	
PRR	PRR=[a/(c + d)]/[c/(a + b)]	a ≥ 3, PRR ≥ 2, $\chi^2 \geq 4$
	χ^2=[(ad-bc)^2](a + b + c + d)/[(a + b)(c + d)(a + c)(b + d)]	
BCPNN	IC = $\log_2$a(a + b + c + d)(a + c)(a + b)	IC025 > 0
	95%CI = E(IC) ± 2V(IC)^0.5	

Equation: a, number of reports containing both the target drug and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the target drug; c, number of reports containing the target adverse drug reaction of other drugs; d, number of reports containing other drugs and other adverse drug reactions. 95%CI, 95% confidence interval; χ^2, chi-squared. IC, information component; IC025, the lower limit of 95% CI of the IC; E(IC), the IC expectations; V(IC), the variance of IC.

Statistical analysis. Descriptive analyses were performed to summarize the clinical characteristics in the ADE reports of antibiotics-associated PMC. Risk factors were compared using a Pearson's chi-squared test. All data mining and statistical analyses were performed using Microsoft Excel 2019 and SPSS.

Results

Descriptive analysis. From the fourth quarter of 2003 to third quarter of 2023, there were 11737133 ADE reports in the FAERS database. Of these, there were 1683 reports of PMC associated with the enrolled antibiotics. Clinical characteristics in reports were described in Table 2. There were 836 (49.67%) reports for males, 692 (41.12%) reports for females, and 155 (9.21%) with missing gender information. The number of reports aged < 18 years, 18–40 years, 41–60 years, and > 60 years was 86 (5.11%), 165 (9.80%), 322 (19.13%), and 831 (49.38%), respectively. United States (675, 40.11%) had the highest number of reports, followed by United Kingdom (143, 8.50%), Japan (134, 7.96%), France (123, 7.31%), and Canada (119, 7.07%). Analysis about reporting years showed that the number of antibiotics-associated PMC reports was increasing over time. Moreover, the majority (1229, 73.02%) were serious outcome events, including hospitalization, death, life-threatening, and disability. Hospitalization was the most frequent serious outcome event (805, 47.83%), followed by death (305, 18.12%), life-threatening (110, 6.54%), and disability (9, 0.53%).

Table 2
Clinical Characteristics in Reports with PMC.

Characteristics	Report numbers(n)	Report proportion (%)
Gender		
Male	836	49.67%
Female	692	41.12%
Unknown	155	9.21%
Age		
< 18	86	5.11%
18–40	165	9.80%
41–60	322	19.13%
> 60	831	49.38%
Unknown	279	16.58%
Reporting region		
United States	675	40.11
United Kingdom	143	8.50%
Japan	134	7.96%
France	123	7.31%
Canada	119	7.07%
Spain	70	4.16%
Germany	65	3.86%
Italy	56	3.33%
Poland	35	2.08%
Portugal	28	1.66%
China	26	1.54%
Romania	12	0.71%
Other countries and unknown	197	11.71%
Reporting years		
2004–2008	262	15.57%

Characteristics	Report numbers(n)	Report proportion (%)
Gender		
2009–2013	442	26.26%
2014–2018	451	26.80%
2019–2023	528	31.37%
Outcomes		
Hospitalization	805	47.83%
Death	305	18.12%
Life-Threatening	110	6.54%
Disability	9	0.53%
Others and Unknown	454	26.98%

Disproportionality analysis. There were eighty-one antibiotics that met the three algorithms simultaneously and were enrolled. The top twenty-four antibiotics in the descending order were showed in Table 3 according to the lower limit of 95% CI of ROR, PRR value, and the lower limit of 95% CI of the IC (IC025). Of the top twenty-four antibiotics, there were four penicillins, namely dicloxacillin, pivmecillinam, piperacillin, and piperacillin-tazobactam; there were eleven cephalosporins, including one first-generation cephalosporin (cefazolin), two second-generation cephalosporins (cefotiam and cefuroxime), six third-generation cephalosporins (ceftriaxone, cefixoral, ceftizoxime, cefpodoxime, cefditoren, and ceftazidime - avibactam), one fourth-generation cephalosporin (cefepime), and one fifth-generation cephalosporin (cefiderocol); three carbapenems (meropenesm, ertapenem, and imipenem) and two lincosamides (clindamycine and lincomycin) were included; Moreover, there was one cephamycin (cefoxitin), one aminoglycoside (streptomycin), one fosfomycin (fosfomycin), and one echinocandin (micafungin) (Table 4).

Table 3
Top 24 antibiotics Associated with PMC Arranged by ROR, PRR and IC025.

Drugs	Report numbers	ROR (95%CI)	PRR (95%CI)	IC(IC025)
Pivmecillinam	12	120.12(67.16,119.54)	114.09(65.69,198.13)	6.83(5.26)
Cefotiam	5	119.64(48.64,294.25)	113.65(48.35,267.10)	6.83(5.38)
Lincomycin	8	74.70(36.92, 151.17)	72.34(36.56, 143.11)	6.17(4.66)
Ceftazidime - avibactam	3	67.45(21.38, 212.76)	65.51(21.48,199.86)	6.03(4.74)
Micafungin	66	53.21(41.63, 68.03)	52.02(40.92, 66.13)	5.68(4.04)
Cefpodoxime	19	43.90(27.86, 69.18)	43.08(27.58, 67.31)	5.42(3.83)
Cefoxitin	11	43.00(23.67, 78.13)	42.21(23.49,75.85)	5.40(3.85)
Cefixoral	33	41.52(29.39, 58.65)	40.79(29.06, 57.26)	5.07(3.71)
Cefazolin	91	41.33(33.53, 50.94)	40.62(33.07, 49.88)	5.32(3.67)
Dicloxacillin	7	38.79(18.37, 81.93)	38.15(18.29, 79.57)	5.25(3.77)
Fosfomycin	25	36.67(24.68, 54.50)	36.10(24.45, 53.31)	5.17(3.55)
Ertapenem	64	34.11(26.61, 43.72)	33.62(26.32, 42.94)	5.05(3.41)
Cefiderocol	4	34.07(12.69, 91.49)	33.58(12.69,88.85)	5.07(3.71)
Streptomycin	11	32.76(18.05, 59.45)	32.31(17.96, 58.13)	5.01(3.46)
Cefditoren	9	32.05(16.59, 61.92)	31.62(16.52, 60.52)	4.98(3.46)
Clindamycine	269	31.14(27.52, 35.23)	30.75(27.22, 34.73)	4.87(3.21)
Cefuroxime	114	27.87(23.12, 33.59)	27.55(22.90, 33.13)	4.75(3.10)
Ceftriaxone	228	26.88(23.53, 30.72)	26.59(23.30,30.34)	4.67(3.01)
Meropenem	119	24.66(20.54, 29.61)	24.41(20.37,29.25)	4.58(2.92)
Imipenem	53	24.64(18.77, 32.34)	24.39(18.63, 31.92)	4.59(2.95)
Ceftizoxime	30	24.44(17.03, 35.05)	24.19(16.92, 34.56)	4.59(2.97)
Piperacillin-tazobactam	39	24.32(17.72, 33.39)	24.07(17.60, 32.93)	4.58(2.95)
Cefepime	63	23.41(18.23, 30.04)	23.18(18.10, 29.68)	4.52(2.87)
Piperacillin	157	22.99(19.60, 26.97)	22.77(19.44, 26.67)	4.47(2.81)

ROR, reporting odds ratio; PRR, proportional reporting ratio; 95%CI, 95% confidence interval; IC, information component; IC025, the lower limit of 95% CI of the IC.

Table 4
Classification of Top 24 Drugs Associated with PMC.

Classifications		Drug names
Penicillins	Penicillinase-resistant penicillin	Dicloxacillin
	Broad-spectrum penicillins	Pivmecillinam; Piperacillin; Piperacillin-tazobactam;
Cephalosporins	First generation	Cefazolin
	Second generation	Cefotiam; Cefuroxime
	Third generation	Ceftriaxone; Cefixoral; Ceftizoxime; Cefpodoxime; Cefditoren; Ceftazidime - avibactam
	Fourth generation	Cefepime
	Fifth generation	Cefiderocol
Carbapenems		Meropenem; Ertapenem; Imipenem
Cephamycin		Cefoxitin
Lincosamides		Clindamycine; Lincomycin
Aminoglycoside		Streptomycin
Fosfomycin		Fosfomycin
Echinocandin		Micafungin

Serious versus Non-Serious Cases. We explored the risk factors of antibiotics-associated PMC by comparing between serious and non-serious cases (Table 5). A higher proportion of female exhibited serious and non-serious ADEs than males, and the difference was statistically significant ($\chi2 = 13.79$, $P = 0.0002$). Additionally, there was statistically difference in age ($\chi2 = 50.03$, $P < 0.0001$). It showed that the elderly had a significantly higher incidence of serious ADEs.

Table 5
Differences in clinical characteristics between severe and non-severe reports.

Clinical characteristics	Serious cases(N = 1229)	Non-serious cases(N = 427)	χ2	*P*-value
Gender				
Male	547(44.51%)	134(31.38%)	13.79	0.0002
Female	594(48.33%)	230(53.86%)		
Age				
< 18	57(4.64%)	28(6.56%)	50.03	< 0.0001
18–40	105(8.54%)	59(13.82%)		
41–60	229(18.63%)	87(20.37%)		
> 60	692(56.31%)	128(29.98%)		
Reporting region				
United States	475(38.65%)	174(40.75%)		
United Kingdom	113(9.19%)	5(1.17%)		
Japan	69(5.61%)	65(15.22%)		
France	95(7.73%)	28(6.56%)		
Canada	103(8.38%)	16(3.75%)		
Spain	57(4.64%)	13(3.04%)		
Germany	46(3.74%)	44(10.30%)		
Italy	53(4.31%)	3(0.70%)		
Poland	29(2.36%)	6(1.41%)		
Portugal	19(1.55%)	9(2.11%)		
China	16(1.30%)	9(2.11%)		
Romania	6(0.49%)	6(1.41%)		
Other countries and unknown	148(12.04%)	49(11.48%)		
Reporting years				
2004–2008	171(13.91%)	86(20.14%)		
2009–2013	319(25.96%)	109(25.53%)		

Clinical characteristics	Serious cases(N = 1229)	Non-serious cases(N = 427)	χ2	*P*-value
Gender				
2014–2018	329(26.77%)	116(27.17%)		
2019–2023	410(33.36%)	116(27.17%)		

Discussion

PMC is a potential life-threatening complication. Drugs are an important etiology of PMC, such as antibiotics and proton pump inhibitors[6]. Antibiotics-associated PMC has been widely reported, but there is no large-scale case study[16,17]. To our knowledge, this study is the first pharmacovigilance study on ADEs of antibiotics-associated PMC using the real-world data from the FAERS database.

Currently, the main mechanism by which antibiotics cause PMC is that they suppress the growth of some normal micro-organisms, resulting in the increased colonization and proliferation of toxinogenic strains of *C. difficile* and the enhanced cytotoxin synthesis of *C. difficile*[18–21]. Moreover, production of antibiotics-resistance *C. difficile* is also an important risk factor for PMC[22–24]. Accumulating evidence suggests that *C. difficile* infection is the most common cause of PMC[1]. Therefore, to ensure a more comprehensive data related to antibiotics-associated PMC, we included *C. difficile colitis* in this study.

The FAERS database is a global database of ADE reports and collects ADE reports of drugs approved by FDA. The data from the FAERS database showed that the median age of antibiotics-associated PMC patients was 61 years. The distribution of age groups showed that the elderly are more susceptible to the antibiotics-associated PMC, especially for patients aged > 60 years. Currently, most studies on antibiotics-associated PMC are case reports, which lack of comprehensive analysis of age factor[24–26]. *C. difficile* is considered as the pathogenic microorganism in 90–100% of patients with antibiotics-associated PMC[27]. A 3-year cross-sectional study in eastern China showed that 55 years or older was a risk factor for *C. difficile* infection, while several studies surveyed *C. difficile* infection in Europe and United States and found that 65 years or older was its risk factor[28–30]. This study showed that United States had the highest number of antibiotics-associated PMC reports, followed by United Kingdom, Japan, and France. These reports were mainly from United States and Europe, thus it has a similar age to *C. difficile* infection in United States and Europe. Moreover, 73.02% of the patients with antibiotics-associated PMC had serious outcome events. Further risk factor analysis by comparing between serious and non-serious cases showed that sex and age may be related to the severity of ADEs. Female and the elderly had a significantly higher incidence of serious ADEs.

In this study, there were eighty-one antibiotics that met the three algorithms simultaneously. Using the lower limit of 95% CI of ROR, PRR value, and the lower limit of 95% CI of the IC (IC025) in descending order, the top twenty-four drugs are the same, but in a slightly different order. The top twenty-four

antibiotics included four penicillins, elven cephalosporins, three carbapenems, two lincosamides, one cephamycin, one aminoglycoside, one fosfomycin, and one echinocandin. Consistent with our results of antibiotics-associated PMC, studies have demonstrated that penicillins, cephalosporins, carbapenems, and clindamycin have higher risk of *C. difficile* infection than other antibiotics[31]. This study showed that pivmecillinam had the strongest correlation with PMC. Pivmecillinam was been used widely in Nordic countries, but not used extensively in other countries. Thus, this may be related to patient population, and more comprehensive evaluation is needed. Khanafer et al found that second-generation and third-generation cephalosporins have been up to 3 times less active for *C. difficile* than first-generation cephalosporins by culture-based susceptibility studies, indicating that second-generation and third-generation cephalosporins have higher risk for *C. difficile* infection[32]. In this study, cephalosporins made up eleven of the top twenty-four antibiotics, and there were two second-generation cephalosporins (cefotiam and cefuroxime) and six third-generation cephalosporins (ceftriaxone, cefixoral, ceftizoxime, cefpodoxime, cefditoren, and ceftazidime - avibactam). Lincosamides is broad-spectrum activity against Gram-positive and obligate anaerobic bacteria. Many reports have indicated that lincosamides (clindamycine and lincomycin) predisposes patients to PMC[33,34]. It is noteworthy that cefoxitin, streptomycin, fosfomycin, and micafungin have a high risk of PMC in this study, but there are few reports in the literature.

This study had several limitations. Firstly, only cases with PMC were reported to FAERS, but the total populations taking antibiotics were unknown, thus the true incidence rate of PMC of each antibiotic was not estimated based on the FAERS database. Secondly, disproportionality analysis based on the FAERS database statistically evaluated signal strength, but it did not reveal whether there was a causal relationship between PMC and drugs. This needs to be confirmed by further clinical studies.

Conclusion

Our pharmacovigilance analysis indicated that broad-spectrum penicillins, cephalosporins, carbapenems, lincomycin, and clindamycin have higher risk of PMC, which is roughly consistent with studies about *C. difficile* infection. This study found that cefoxitin, streptomycin, fosfomycin, and micafungin had a high risk of PMC, but there are few reports in the literature, and it needs further clinical studies to confirm. This study provided a clue on the relationship between antibiotics and the risk of PMC.

Declarations

Ethical approval. This study didn't contain any studies with human participants or animals performed by any of the authors.

Author contributions. J.C., W.Z. and W.Y. designed the analysis. J.C. and C.S. collected the data and performed the analysis. J.C. wrote the paper. W.Z and C.S. revised the manuscript.

Data availability. The datasets used and analyzed during the current study are available from the corresponding author at a reasonable request.

Competing interests. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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