



Published in final edited form as:

*Infect Control Hosp Epidemiol.* 2021 January ; 42(1): 110–112. doi:10.1017/ice.2020.1261.

## Serious antibiotic-related adverse effects following unnecessary dental prophylaxis in the United States

Alan E Gross, PharmD, BCPS, BCIDP<sup>1,2</sup>, Katie J Suda, PharmD, MS<sup>3,4,\*</sup>, Jifang Zhou, MD, MPH, PhD<sup>5</sup>, Gregory S Calip, PharmD, MPH, PhD<sup>6</sup>, Susan A. Rowan, DDS, MS<sup>7</sup>, Ronald C. Hershow, MD<sup>8</sup>, Rose Perez, BS<sup>9</sup>, Charlesnika T Evans, MPH, PhD<sup>10,11</sup>, Jessina C McGregor, PhD<sup>12</sup>

<sup>1</sup>University of Illinois at Chicago College of Pharmacy, Dept of Pharmacy Practice, Chicago, IL

<sup>2</sup>University of Illinois Hospital and Health Sciences System, Pharmacy Services, Chicago, IL

<sup>3</sup>Center for Health Equity Research and Promotion, VA Pittsburgh Health Care System, Pittsburgh, Pennsylvania

<sup>4</sup>University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

<sup>5</sup>School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, Jiangsu, China

<sup>6</sup>University of Illinois at Chicago College of Pharmacy, Dept. of Pharmacy Systems, Outcomes and Policy, Chicago, IL

<sup>7</sup>University of Illinois at Chicago College of Dentistry, Department of Restorative Dentistry, Chicago, IL

<sup>8</sup>University of Illinois at Chicago School of Public Health, Chicago, IL

<sup>9</sup>University of Illinois at Chicago College of Medicine, Chicago, IL

<sup>10</sup>Northwestern University Feinberg School of Medicine, Department of Preventive Medicine, Institute for Public Health and Medicine, Chicago, IL

<sup>11</sup>Center of Innovation for Complex Chronic Healthcare, Edward Hines, Jr VA Hospital, Hines, IL

<sup>12</sup>Oregon State University College of Pharmacy, Portland, OR

---

Dentists prescribe 10% of outpatient antibiotics, with a significant portion of these being for infection prophylaxis following dental procedures.<sup>1,2</sup> Current guidelines primarily recommend antibiotic prophylaxis prior to dental procedures that manipulate the gingival tissue, the periapical region of teeth, or perforate the oral mucosa in patient that are at high risk of an adverse outcome should they develop infective endocarditis.<sup>3</sup> Recent data

---

\* Author for Correspondence: Katie J. Suda, PharmD, M.S., Professor, Department of Medicine, University of Pittsburgh, School of Medicine, Research Health Scientist and Associate Director, VA Center for Health Equity Research and Promotion, Phone: (901) 848-5516, ksuda@pitt.edu.

Potential conflicts of interest.

No authors report potential conflicts of interest relevant to this article.

These data were presented in part as the SHEA featured oral abstract at IDWeek 2019

show that 80.9% of antibiotic prophylaxis was unnecessary prior to dental procedures.<sup>2</sup> The objective of this study was to assess the harms of unnecessary antibiotic prophylaxis prior to dental procedures.

## METHODS

We conducted a retrospective cohort study of patients prescribed unnecessary antibiotic prophylaxis for a dental visit from 2011–2015 using the IBM Watson Health MarketScan<sup>®</sup> Commercial Claims/Encounters, Medicare Supplemental, Coordination of Benefits Research databases.<sup>2</sup> Patients were included if they were enrolled in commercial dental insurance and received unnecessary antibiotic prophylaxis. Antibiotic prophylaxis was defined as a 2 day supply of antibiotics dispensed within 7 days before a dental visit. Patients with a hospitalization or extra-oral infection 14 days prior to antibiotic prophylaxis were excluded. Unnecessary antibiotic prophylaxis was defined as prophylaxis in patients who did not undergo a procedure that manipulated the gingiva/tooth periapex and did not have an appropriate cardiac diagnosis. Patients with prosthetic joints were categorized as unnecessary (without a cardiac condition).<sup>2</sup> Patients with multiple eligible visits were allowed to re-enter the cohort if visits were >7 days apart.

The primary endpoint was any antibiotic adverse effect (AAE) within 14 days post-prescription (composite of: allergy, anaphylaxis, *C. difficile* infection [CDI], or emergency department [ED] visit). Allergies and CDI were defined based on previously validated ICD-9/10 codes and ED visits were identified by provider and place of service codes (Supplemental Table 1). Subjects were censored at the occurrence of event, loss-to-follow-up and end of enrollment.

### Statistical analysis

The primary endpoint of composite AAE incidence rate was measured as events per 1000 person-days (PD) in the overall cohort and stratified by amoxicillin and clindamycin; corresponding 95% confidence intervals were calculated. Secondary endpoints included the risk difference of the primary endpoint between amoxicillin and clindamycin per 1000 PD, and the incidence of CDI 30 days after the antibiotic and the corresponding 95% CI for each. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R software 3.3.1 (fmsb package), version 0.7.0.

## RESULTS

Of the 168,420 dental visits with antibiotic prophylaxis, 136,177 (80.9%) were unnecessary and included for analysis (median patient age: 62 years, interquartile range 55–71; 58% female). Antibiotics prescribed included: amoxicillin (67.9%), clindamycin (15.5%), cephalexin (8.6%), azithromycin (2.8%), penicillin (1.5%), and others (3%). 1.4% of unnecessary prescriptions were associated with an AAE within 14 days; the incidence of AAE was 1.01/1000 PD. ED visits (83%) and allergies (16%) were the most frequent (Table 1). CDI incidence was 0.009/1000 PD (95%CI 0.006 – 0.012). Overall AAE were more common with clindamycin (1.167 incidence rate/1000 PD) than amoxicillin (0.958

incidence rate/1000 PD) (risk difference 0.209/1000 PD, 95% CI: 0.108 – 0.33), including a higher risk of ED visit and allergy (Table 1, Supplemental Table 2)

## DISCUSSION

This is the first study to characterize adverse effects related to unnecessary dental prophylaxis. We found that although the occurrence of AAE was rare (1.4%), serious AAEs (anaphylaxis, CDI) occurred. A limited number of studies and case reports describe the adverse effects of dental prophylaxis regardless of appropriateness.<sup>4–8</sup> A French database of voluntarily reported adverse effects found 17 reports of anaphylaxis due to amoxicillin prophylaxis prior to dental procedures.<sup>4</sup> Another study using a United Kingdom database assessed adverse reactions following single doses of amoxicillin or clindamycin.<sup>5</sup> Of 2.7 million amoxicillin prescriptions, 67 adverse reactions were reported (16 anaphylaxis, 38 other allergies). Of 1.2 million clindamycin prescriptions, 193 adverse reactions were reported, 15 of which were fatal (12 due to CDI) and the remaining primarily gastrointestinal or allergy-related skin disorders. The only study in the U.S., outside of the current report, was an evaluation of community-acquired CDI cases in Minnesota that found 8% (136/1626) of CDI cases were related to antibiotic prophylaxis for dental procedures.<sup>6</sup> Consistent with the study from Thornhill et al, we observed a significantly greater rate of AAE with clindamycin compared to amoxicillin.<sup>5</sup> Also consistent with our findings, a previous study found clindamycin was associated with a greater rate of emergency department visits than amoxicillin.<sup>9</sup> Collectively, these studies show that even short courses used for antibiotic prophylaxis, regardless of appropriateness of use, are associated with patient harm.

Our study has some limitations. Comparisons were not performed to patients unexposed to antibiotics, thus the risk associated with inappropriate antibiotic prophylaxis cannot be ascertained. Only patients with commercial dental insurance were included. ED visits could not be definitively attributed to AAEs. Patients with adverse reactions but who did not seek medical care are not captured in this study because our endpoint is based on medical coding. However, our study did not rely on voluntary reporting by medical professionals to ascertain outcomes. Therefore, we may have been able to identify and more comprehensively characterize AAE rates than previous studies.

In conclusion, the risk of harm with unnecessary antibiotic prophylaxis is non-trivial. Since most AAEs are diagnosed in medical settings, dentists may not be aware of these adverse effects. These data provide further impetus to optimize prescribing of antibiotic prophylaxis prior to dental procedures and improved prescribing may be facilitated via comprehensive, multidisciplinary antimicrobial stewardship programs in dental clinics.<sup>10</sup>

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

Financial support.

Research was funded by Agency for Healthcare Research and Quality (AHRQ) R01 HS025177 (PI: Suda). The opinions expressed are those of the authors and do not represent those of AHRQ, the Department of Veterans Affairs or the U.S. government.

## REFERENCES

1. King LM, Bartoces M, Fleming-Dutra KE, Roberts RM, Hicks LA. Changes in US Outpatient Antibiotic Prescriptions From 2011–2016. *Clin Infect Dis* 2020;70:370–377. [PubMed: 30882145]
2. Suda KJ, Calip GS, Zhou J, et al. Assessment of the Appropriateness of Antibiotic Prescriptions for Infection Prophylaxis Before Dental Procedures, 2011 to 2015. *JAMA Netw Open* 2019;2:e193909. [PubMed: 31150071]
3. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007;116:1736–1754. [PubMed: 17446442]
4. Cloitre A, Duval X, Tubiana S, et al. Antibiotic prophylaxis for the prevention of infective endocarditis for dental procedures is not associated with fatal adverse drug reactions in France. *Med Oral Patol Oral Cir Bucal* 2019;24:e296–e304. [PubMed: 31011140]
5. Thornhill MH, Dayer MJ, Prendergast B, Baddour LM, Jones S, Lockhart PB. Incidence and nature of adverse reactions to antibiotics used as endocarditis prophylaxis. *J Antimicrob Chemother* 2015;70:2382–2388. [PubMed: 25925595]
6. Bye M Antibiotic Prescribing for Dental Procedures in Community-Associated *Clostridium difficile* cases, Minnesota, 2009–2015. *Open Forum Infectious Diseases* 2017;4.
7. Lochmann O, Kohout P, Vymola F. Anaphylactic shock following the administration of clindamycin. *J Hyg Epidemiol Microbiol Immunol* 1977;21:441–447.
8. Bombassaro AM, Wetmore SJ, John MA. *Clostridium difficile* colitis following antibiotic prophylaxis for dental procedures. *J Can Dent Assoc* 2001;67:20–22. [PubMed: 11209501]
9. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis* 2008;47:735–743. [PubMed: 18694344]
10. Gross AE, Hanna D, Rowan SA, Bleasdale SC, Suda KJ. Successful Implementation of an Antibiotic Stewardship Program in an Academic Dental Practice. *Open Forum Infect Dis* 2019;6:ofz067. [PubMed: 30895206]

**Table 1.**

Occurrence of adverse effects within 14 days of unnecessary antibiotic prophylaxis

Overall								
	Number of events	Total follow-up time, <sup>2</sup> person-years	Incidence rate Per 1000 person-days	95% CI				
Any allergy	319	5213.46	0.168	0.150	0.185			
Anaphylaxis only	5	5219.57	0.003	0.0003	0.005			
<i>C. difficile</i> infection	14	5219.43	0.007	0.004	0.011			
ED visit	1629	5188.93	0.860	0.825	0.894			
Visits associated with any adverse effect <sup>1</sup>	1916	5183.39	1.012	0.976	1.048			
By Antibiotic Agent								
	Number of adverse events	Total follow-up time, <sup>2</sup> person-years	Incidence rate Per 1000 person-days	95% CI		Risk difference Per 1000 person-days	95% CI	
Amoxicillin	1220	3486.74	0.958	0.915	1.001	Reference	Reference	
Clindamycin	356	835.06	1.167	1.075	1.259	0.209	0.108	0.311
Others	340	861.60	1.080	0.991	1.170	0.122	0.023	0.222

<sup>1</sup>Primary endpoint defined as 14 days post-prescription (composite endpoint of allergy, anaphylaxis, *C. difficile* infection, or ED visit).

<sup>2</sup>Subjects were censored at the occurrence of event of interest, loss-to-follow-up and at end of enrollment