

## Differences by patient race in guideline concordant outpatient antibiotic use in adult patients in Michigan

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### Abstract

**Purpose:** To determine if there are significant differences in the rate of guideline concordant antibiotic use by race in adult patients in the state of Michigan.

**Methods:** Using the Collaboration to Harmonize Antimicrobial Registry Measures (CHARM) database, outpatient prescriptions from 6 health systems throughout the state of Michigan in 2021 were reviewed, and the 5 infectious disease diagnoses with the most antibiotic prescriptions were identified. The 2 most common races amongst patients were identified, and the differences in rates of guideline concordance were compared between them.

**Results:** A total of 62,070 outpatient prescriptions were identified for the 2 most common races, White and Black or African American. Of those, 43,519 outpatient prescriptions were identified for the top 5 infectious diagnoses, acute cystitis, acute sinusitis, acute pharyngitis, cellulitis, and otitis media. Antimicrobial choice concordance was higher in patients who are White (71.6% vs. 68.5%;  $p < 0.01$ ), while antibiotic dosing concordance was higher in patients who are Black or African American (65.9% vs 68.4%;  $p = 0.02$ ). Differences in antimicrobial choice concordance was primary driven by acute cystitis with more patients who are Black or African American receiving doxycycline (1.1 % vs 6.0%;  $p < 0.01$ ). Differences in antimicrobial dose concordance was primary driven by acute pharyngitis with fewer patients who are White receiving concordant doses of amoxicillin (45.5 % vs 64.6%;  $p < 0.01$ ).

**Conclusion:** Differences in rates of antibiotic choice and dosing concordance were seen between patients who are White and Black or African American. Further studies investigating the clinical significance of these differences are warranted.

**IRB approval:** This study was evaluated by the local Institutional Review Board and determined to be exempt because it did not involve human subjects research.

**Keywords:** antibiotic tracking; outpatient; antimicrobial stewardship; race; Black or African American; White; social determinants of health

### Introduction

Antibiotic use is a prevailing cause of antibiotic resistance, and the majority of antibiotic use in humans occurs in the outpatient setting.<sup>1</sup> According to the Centers for Disease Control and Prevention (CDC), 236 million outpatient antibiotic prescriptions are dispensed each year, and at least 28% of these were for diagnoses that did not need antibiotics.<sup>2,3</sup> There is limited data investigating differences in antibiotic use based on patient race or ethnicity.

The 2021 Michigan census reported that 79% of citizens identified as White and 14% as Black or African American.<sup>4</sup> Data from the Centers for Medicare & Medicaid Services reported a life expectancy of 76.7 years for patients who are non-Hispanic or Latino White and 71.2 years for patients who are non-Hispanic or Latino Black.<sup>5</sup>

Clinical data has also demonstrated worse outcomes for patients who are Black compared to patients who are White for several decades in disease states such as hypertension, heart disease, stroke, cancer, asthma, diabetes, and COVID-19.<sup>6-15</sup>

Data comparing appropriate antibiotic use in the outpatient setting in adults by race is limited. Overall antibiotics are prescribed at a greater rate for White patients compared to non-White patients in the outpatient setting, without commentary on appropriateness.<sup>16,17</sup> In the inpatient setting, observational data is mixed with some data suggesting patients who are non-Hispanic Black are less likely to received guideline-concordant antibiotics compared to patients who are non-Hispanic White, while other data suggests they are more likely to.<sup>18-20</sup> These data suggest there are differences in antibiotic prescribing by race, but data on appropriate antibiotic use by race in the outpatient setting is limited to pediatric patient populations. These limited data suggest that children who are non-Hispanic White in the outpatient setting were more likely to inappropriately receive an antibiotic for viral respiratory tract infections than children who are non-Hispanic Black or Hispanic or Latino.<sup>21</sup>

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There is a lack of data comparing differences in appropriate antibiotic prescribing by race in the outpatient setting. The purpose of this study was to supplement this lack of data by comparing infectious disease diagnoses and antibiotic prescriptions in adult patients compared between patients who are White and Black or African American in outpatient clinics.

### Methods

Data for this research was obtained from the Collaboration to Harmonize Antimicrobial Registry Measures (CHARM) database. The CHARM project was developed to help quantify and assess the appropriateness of outpatient antibiotic use by partnering with health systems throughout the United States of America. The CHARM project and this current evaluation has been approved by the local Institutional Review Board. Antibiotic prescribing data from partnering health systems are sent to the CHARM database for outpatient clinics, urgent care centers, emergency department, and dental practices. Data is shared through a data use agreement that states these data will not be shared with entities outside of CHARM. For this reason, granular data for this study cannot be shared.

Antibiotic prescriptions are linked to International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes that were either directly linked to the antibiotic prescription or were associated with the outpatient visit recorded on the same day as the antibiotic prescription. The antibiotic prescription and ICD-10 code are evaluated for concordant drug choice based societal guidelines. If the antibiotic choice is determined to be guideline concordant, the dose, frequency, and duration are then assessed further for guideline concordant dosing. Guideline concordant antimicrobial dosing is assessed using recommended therapeutic range (RTR) and prescribed therapeutic regimen (PTR) system described in a previous manuscript.<sup>22</sup>

These data are transformed into interactive, user-friendly dashboards that are used by partner institutions to track and report outpatient antimicrobial use. Each CHARM dashboard is equipped with filters that allow for viewing the data according to timeframe, diagnosis, prescriber group/individual prescriber, antimicrobial, guideline concordance, and patient demographics. CHARM also publishes a multi-system dashboard for Michigan using aggregate data from all partnering health-systems in the state. The data from this statewide Michigan dashboard was utilized for this evaluation. Antimicrobial agents that were prescribed from January 1, 2021, through December 31, 2021 were included. During this timeframe, there were 6 partnering health systems with prescription information in the statewide Michigan CHARM database. A full explanation of the CHARM database including how it identifies antibiotic prescriptions, identifies associated diagnoses, and categorizes antibiotic concordance is available in Appendix A.

Through these data within CHARM, the 2 races with the largest number of outpatient prescriptions were identified (White and Black or African American). Differences in the rate of concordant antimicrobial choice and concordant antimicrobial dosing were compared between these groups. Differences were compared with chi-square test, and the margin of significance was defined as a two-tailed p-value less than 0.05.

The CHARM project is funded in part with a grant from the Michigan Department of Health and Human Services. This particular evaluation is not supported by any additional funding.

### Results

The most common infectious diagnoses reported by CHARM as well as patient demographic information for those specific diagnoses are reported in Table 1. Overall antimicrobial choice concordance for these 5 disease states was higher in the White group (28,775/40 161 [71.6%]) compared to the Black or African American group (2,300/3,358 [68.5%];  $p < 0.01$ ). Antimicrobial choice concordance was higher in patients who are White for acute cystitis ( $p < 0.01$ ), but antimicrobial choice concordance was higher in patients who are Black or African American for acute sinusitis ( $p = 0.02$ ) and acute pharyngitis ( $p < 0.01$ ). No significant difference in concordant antibiotic choice was seen between the patients who were White and the patients who were Black or African American for cellulitis ( $p = 0.091$ ) or otitis media ( $p = 0.83$ ). Full details on antimicrobial choice concordance is reported in Table 2.

For acute cystitis, this difference in concordant antimicrobial choice was primarily driven by a difference in doxycycline prescribing. Patients who are White were prescribed doxycycline less commonly than patients who are Black or African American (159/14,057 [1.1%] vs 85/1,368 [6.0%];  $p < 0.01$ ). For acute sinusitis, the majority of non-concordant antibiotic choices were from azithromycin, but more patients who are White received azithromycin than patients who are Black or African American (2,027/10,696 [19.0%] vs 85/1,368 [6.0%];  $p < 0.01$ ). For pharyngitis, amoxicillin/clavulanate was the most common non-concordant antibiotic choice for both groups, but more patients who are White patients than who are Black or African American received this medication (541/3,652 [14.81%] vs 39/534 [7.3%];  $p < 0.01$ ).

**Table 1.** Patient Demographics for the Outpatient Infectious Diagnoses Most Commonly Prescribed Antibiotics by Race: Michigan, 2021

	White (N = 56 533)	Black or African American (N = 5 537)	P-values
Acute Cystitis	14 057 (24.9%)	1 368 (24.7%)	0.79
Acute Sinusitis	10 696 (18.9%)	573 (10.3%)	<0.01
Acute Pharyngitis	3 652 (6.5%)	534 (9.6%)	<0.01
Cellulitis	7 656 (13.5%)	484 (8.7%)	<0.01
Otitis Media	5 163 (9.1%)	441 (8.0%)	<0.01
<b>Demographics for Above Diagnoses</b>			
	White (N = 41 224)	Black or African American (N = 3 400)	P-values
Female Gender	29 884 (72.5%)	2 518 (74.1%)	0.05
Age $\geq$ 65 years	11 981 (29.0%)	485 (14.3%)	<0.01

[NOTE: When calculating the percentage of antibiotic prescriptions for these 5 disease states, the total number of antibiotic prescriptions for the study period were evaluated. When calculating patient demographics, only antibiotic prescriptions for the 5 disease states were included.]

**Table 2.** Percent of Outpatient Antibiotic Prescriptions with Concordant Antibiotic Choice by Race: Michigan, 2021

	White	Black or African American	P-value
Acute Cystitis	9 796/14 057 (69.7%)	799/1 368 (58.4%)	<0.01
Acute Sinusitis	7 638/10 696 (71.4%)	436/573 (76.1%)	0.02
Acute Pharyngitis	2 529/3 652 (69.2%)	429/534 (80.3%)	<0.01
Cellulitis	6 321/7 656 (82.6%)	385/484 (79.5%)	0.09
Otitis Media	3 176/5 163 (61.5%)	269/441 (61.0%)	0.83
Total	28 775/40 161 (71.6%)	2 300/3 358 (68.5%)	<0.01

**Legend:** Prescriptions associated with ICD-10 codes for more than 1 of the above diagnoses are reported separately for each individual diagnosis but are reported as a single prescription in the Total row.

Overall antimicrobial dosing concordance for these 5 disease states was lower in patients who are White (16,356/24,823 [65.9%]) compared to patients who are Black or African American (1,440/2,105 [68.4%];  $p = 0.02$ ). Lower concordant

dosing was seen in the White group for acute pharyngitis ( $p < 0.01$ ) and cellulitis ( $p < 0.01$ ). No difference in concordant dosing was seen between patients who were White and Black or African American for acute cystitis ( $p = 0.90$ ), acute sinusitis ( $p = 0.66$ ), or otitis media ( $p = 0.36$ ). Full details on antimicrobial dose concordance are reported in Table 3.

**Table 3.** Percent of Outpatient Antibiotic Prescriptions with Concordant Dosing by Race: Michigan, 2021

	White	Black or African American	P-value
Acute Cystitis	5 248/8 661 (60.6%)	472/776 (60.8%)	0.90
Acute Sinusitis	5 508/5 776 (95.4%)	331/349 (94.8%)	0.66
Acute Pharyngitis	1 146/2 091 (54.8%)	272/399 (68.2%)	<0.01
Cellulitis	2 060/5 698 (36.2%)	151/348 (43.4%)	<0.01
Otitis Media	2 604/2 933 (88.8%)	224/247 (90.7%)	0.36
Total	16 356/24 823 (65.9%)	1 440/2 105 (68.4%)	0.02

[NOTE: Evaluation of concordant antibiotic dosing was only conducted for prescriptions identified as concordant antibiotic choice. Prescriptions without dosing information were excluded from the concordant dosing evaluation.]

For acute pharyngitis, the most common antibiotic associated with non-concordant dosing was amoxicillin for both patients who are White (654/1,436 [45.5%]) and patients who are Black or African American (204/316 [64.6%];  $p < 0.01$ ). For acute pharyngitis, the average total daily dose for amoxicillin was 1.6 g for patients who are White and 1.2 g for patients who are Black or African American. This conflicts with the CDC recommendations of a maximum amoxicillin total daily dose of 1000 mg/day when treating bacterial pharyngitis.<sup>23</sup>

For cellulitis, antibiotic concordant dosing was low across both groups. This low concordant dosing was primarily seen in prescriptions for cephalexin and doxycycline. For cephalexin, concordant dosing was seen less for patients who are White compared to patients who are Black or African American (102/1,362 [7.5%] vs 71/197 [36.0%];  $p < 0.01$ ). For doxycycline, concordant dosing was seen more for patients who are White compared to patients who are Black or African American (1,138/3,278 [34.7%] vs 6/58 [10.3%];  $p < 0.01$ ). The average duration of therapy for cephalexin and doxycycline for both patients who are White and patients who are Black or African American was 7 days, while the Infectious Diseases Society of America (IDSA) guidelines on skin and soft tissue infections recommend a total of 5 days of treatment for cellulitis.<sup>24</sup>

## Discussion

These data highlight that there is a small overall difference between patients who are White and Black or African American in terms of antibiotic choice and antibiotic dosing

when all 5 disease states were taken as a whole. Overall, patients who are White were more likely to receive concordant choice of antibiotics, while patients who are Black or African American were more likely to receive concordant antibiotic dosing. This small difference is of unclear clinical significance. Despite this small difference between groups overall, there are more significant differences seen in individual disease state. There are also confounders between the groups, which could contribute to the differences seen. The White group included more patients who were over the age of 65. As patients age, they are at higher risk for developing other comorbid conditions or requiring additional treatments such as urinary catheterization, which may contribute to providers prescribing broader spectrum antibiotics at higher doses and for longer durations of therapy.

CHARM's evaluation of antibiotic choice concordance and dosing concordance is primarily based on best practice statements from societal guidelines and the CDC. For acute cystitis, the IDSA guidelines recommend against the use of oral 1<sup>st</sup> generation cephalosporins such as cephalexin due to a concern for increased rates of resistance.<sup>25</sup> More recent data suggests cephalexin is safe and effective in the treatment of uncomplicated cystitis when the bacteria grown in culture is susceptible, but these data excluded patients with resistant bacteria.<sup>25</sup> In the majority of outpatient infectious disease cases, culture data is unavailable. Given the rising rates of *E. coli* resistance to 1<sup>st</sup> generation cephalosporins, the use of cephalexin in this evaluation would represent a clinically relevant inappropriate practice.<sup>27</sup>

Similarly, for acute pharyngitis, poor dosing concordance was due to patients receiving a dose higher than what is recommended by CDC guidance. For most disease states, amoxicillin is commonly dosed for 500-1,000 mg every 8 hours, which is higher than the CDC recommendation of 1,000 mg/day as a maximum total daily dose for acute pharyngitis.<sup>19</sup> The average daily dose of amoxicillin for acute pharyngitis in this cohort was 1.5 g/day, which suggests providers were not dosing based on the CDC recommendations for pharyngitis and instead dosing amoxicillin as is recommended for most other disease states. This could also represent a clinically relevant inappropriate practice, as patients receiving higher than recommended doses of antibiotics could result in an increased risk of adverse events such as nausea and diarrhea, which could result in an increase in emergency department visits.

This study also highlighted a higher use of doxycycline for acute cystitis in patients who are Black or African American compared to patients who are White. It is unclear why this was seen, as doxycycline is not routinely recommended or used in the treatment of acute cystitis. It is possible some of these patients had a miscoded sexually transmitted infection, but this cannot be confirmed using the population-level data available within CHARM.

The results of this study also highlighted antimicrobial dosing concordance was low in both groups for cellulitis. The CHARM dashboard highlights that the reason for non-concordant antibiotic dosing was due to prescribing 7 total days of antibiotics instead of 5 days, as is recommended by the IDSA guidelines on Skin and Soft Tissue Infections.<sup>20</sup> This is similar to what was seen in the White group. Figure 1 shows a photo of the CHARM dashboard that highlights the identified non-concordance. Similarly to the pharyngitis prescriptions, this could represent a clinically relevant inappropriate practice, as patients receiving longer durations of antibiotics than recommended could result in an increased risk of adverse events such as nausea and diarrhea, which could result in an increase in emergency department visits.

Dosing concordance could also be affected by patients who fall out of the normal patient profile (e.g. morbidly obese, kidney dysfunction, slow resolution of infection, or immunocompromised status). This could account for some of the low concordance seen in this cohort, as data regarding these details were not available. These situations should be the minority and should be similar between groups, but these represent possible confounders.

The primary strength of this research is the utilization of the large volume of data within the CHARM project to answer a thus underexplored question. While there are data describing antibiotic use in adults in the outpatient setting by race, this is the first study the authors are aware of that evaluate whether antibiotics prescribed are concordant with guideline recommendations. Another strength of this evaluation is the ability to report both overarching trends along with more granular data explaining these trends. With these more granular data, targeted interventions can be developed in order to address specific issues highlighted in the study population.

The main weakness within CHARM is that its data is retrospective and beholden to what was previously collected into the electronic health record of partner health systems. If a health system did not collect a specific piece of data (e.g. patient race or antibiotic dosing information), that data will not be transmitted to CHARM. This results in many visits lacking important demographic information. CHARM does have an internally validated method of identifying the infectious diagnosis given to the patient on the same day as the antibiotic prescription, but there are still some antibiotic prescriptions without an associated diagnosis that are not reported in the CHARM dashboard, and therefore not captured by this study. Also, the data evaluated for this study did not include information on history of medication allergies or kidney function. These data points could account for some guideline discordant medication choices, but medication allergies should occur in equal amounts in both study groups. Conversely, rates of chronic kidney disease appear to be higher in patients who are Black compared to patients who are

White, which could result in differences in antibiotic prescribing.<sup>15</sup>

Additionally, diagnosis data within CHARM is derived from ICD-10 codes. It is possible that a patient had an ICD-10 code for an infection but did not actually have that infection. CHARM has conducted manual chart review to validate its diagnostic data and has found that the vast majority of prescriptions within CHARM are associated with the diagnosis identified by CHARM. Additionally, the accuracy of the actual diagnosis itself cannot be evaluated using only ICD-10 codes. For example, some disease states, such as acute sinusitis, are most commonly caused by viral pathogens. CHARM is unable to determine if a patient with an acute sinusitis ICD-10 code has a viral infection or bacterial infection.

ICD-10 codes also do not allow for granular identification of some disease states. When evaluating cystitis, there are not separate ICD-10 codes for uncomplicated cystitis and complicated cystitis. CHARM bases concordant antibiotic dosing for cystitis based on recommendations for uncomplicated cystitis. There were likely several prescriptions written for patients with complicated cystitis (e.g. men with acute cystitis), which would be categorized as non-concordant when they may have actually been appropriate. Given the larger percentage of patients in the White group who were over the age of 65, it is possible that more patients in that group had a complicated infection, which could have contributed for the lower rates of concordant dosing in that subgroup.

In conclusion, these data suggest there are statistical differences in guideline-concordant antibiotic prescribing by race. As a whole, these differences are relatively small with unclear clinical significance, but marked differences are seen for individual disease states such as acute cystitis and acute pharyngitis. Studies evaluating clinical outcomes for patients with infections by race will elucidate the clinical significance of the results of this data set. These differences in concordance could result in more treatment failures or an increased rate of adverse drug reactions. Interventions targeted for specific disease states in specific patient populations could prove to be impactful in the future. Future evaluations that also consider potential confounders not included in this data set such as geographic location, socioeconomic status, other social determinants of health, as well as races and ethnicities outside of White and Black or African American would be beneficial.

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**Conflicts of Interest:** Dr. Minji Sohn has received research funding from Emergent Biosolutions, Inc, which is unrelated to the topic of this paper. No other authors have potential or actual conflicts of interest.

**Treatment of Human Subjects:** The CHARM project, where the data for this study originated, was evaluated by the local IRB and deemed to not be human subjects research. This specific research was also evaluated by the local IRB and deemed to not be human subjects research.

**Disclaimer:** The statements, opinions, and data contained in all publications are those of the authors.

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**Figure 1.** CHARM Dashboard Picture Highlighting Dosing Concordance for Encounters with Black or African American Patients for Cellulitis

