Factors Associated with Longer than Recommended Durations of Antibiotic Therapy for Uncomplicated Ambulatory Infections in an Integrated Healthcare System

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ABSTRACT

Across the ambulatory care network of an integrated healthcare system, durations of antibiotic therapy prescribed for uncomplicated infections were longer than recommended in 39% of cases. By logistic regression, site of care, prescriber characteristics, and type of infection were independently associated with longer than recommended durations of therapy.

**Keywords:** Outpatient antibiotic stewardship, Healthcare epidemiology, Primary health care, Outpatient infectious diseases
INTRODUCTION

In the United States, at least 30% of antibiotic prescriptions are unnecessary or inappropriate [1]. The majority of national studies of outpatient antibiotic prescribing have focused on the appropriateness of the indication for the prescription or the spectrum of activity. Only recently have such studies evaluated the appropriateness of durations of therapy prescribed [2-4].

In a study from the United Kingdom, about 1.3 million antibiotic-days were in excess of the durations of therapy recommended for uncomplicated ambulatory infections [4]. In the U.S. Veterans Affairs Health Care System, 13% of antibiotics prescribed in primary care were for a longer duration than recommended in national guidelines [3]. Specific conditions such as acute sinusitis, uncomplicated urinary tract infections, cellulitis, and cutaneous abscesses have been associated with excessive durations of therapy [5-8]. Despite these studies, the extent and drivers of excessive durations of therapy in outpatient settings are incompletely understood. Our objectives were to describe durations of therapy prescribed for uncomplicated infections across the ambulatory care network of an integrated healthcare system and identify factors associated with longer than recommended durations.

METHODS

Setting and population

This was a retrospective, cross-sectional evaluation conducted from July 1, 2018 to June 30, 2019 at Denver Health, an integrated healthcare system that serves as the primary safety net institution for the City and County of Denver, Colorado. We identified antibiotic prescriptions for patients ≥ 18 years of age presenting with an uncomplicated infection to an ambulatory care site in the network including three Internal Medicine clinics, six Family Medicine clinics, two urgent care centers, and the emergency department.
Data collection

We identified potentially eligible antibiotic prescriptions linked to a visit with a primary *International Classification of Disease, Tenth Revision* (ICD-10) diagnosis code for the following infections: acute cystitis, pyelonephritis, acute sinusitis, acute otitis media (AOM), community-acquired pneumonia, cellulitis, and cutaneous abscess (Supplemental Table S1). At Denver Health, institutional guidance for these typically uncomplicated infections is for 5 days or less of therapy [9]. Antibiotics prescribed for >5 days were defined as longer than recommended. The following prescriptions were excluded from the analysis: non-fluoroquinolone antibiotics for pyelonephritis, those prescribed for respiratory tract infections where antibiotics are not indicated (e.g. acute bronchitis, non-specific upper respiratory infection), those prescribed for bacterial infections that require >5 days of therapy (e.g., Group A streptococcal pharyngitis, *Helicobacter pylori* infection), and those intended for prophylaxis. Prescriptions for acute sinusitis were included since commonly used ICD-10 codes do not distinguish between viral and bacterial sinusitis (Supplemental Table S1) and the vast majority of patients with acute sinusitis are treated with antibiotics [5, 7].

Analyses were based on the duration prescribed by the provider rather than patient adherence to the prescribed duration. Antibiotic prescriptions for a patient with a primary or secondary diagnosis with the same ICD-10 code in the previous 30 days were considered to potentially reflect a complicated infection and were excluded.

Statistical analysis

Cellulitis and cutaneous abscesses were categorized as skin and soft tissue infections (SSTIs). Cystitis and pyelonephritis treated with a fluoroquinolone were categorized as urinary tract infections (UTIs). Multiple logistic regression was used to evaluate factors associated with longer than recommended duration of therapy. Factors with $P<0.05$ by Chi-square test and $P<0.2$ by univariate
analysis were used to develop the multiple logistic regression model. All statistical analyses were performed using IBM® SPSS® Statistics, version 27.0. (IBM® Corp., Armonk, NY, USA).

Patient Consent Statement

This programmatic evaluation did not include factors necessitating patient consent and it was reviewed by the Quality Improvement Review Committee of Denver Health and Hospital Authority and deemed not to constitute human subjects research.

RESULTS

From July 2018 to June 2019, there were a total of 17,775 antibiotic prescriptions for patients ≥18 years of age. Of these, 5,331 prescriptions met inclusion criteria (Supplemental Figure S1). The duration of therapy was longer than recommended (>5 days) for 2,100 (39%). The overall median duration of therapy was 5 days (interquartile range [IQR], 5 – 7 days). Median duration of therapy was 5 days (IQR, 5 – 7 days) for each type of infection, with the exception of acute sinusitis and AOM where the median was 7 days (IQR, 7 – 10 days). Prescribed durations varied significantly by ambulatory care site, sex of patient, provider type, and type of infection (Table 1). Of the 2,100 longer than recommended prescriptions, the urgent care centers accounted for 52.8%, followed by Family Medicine clinics (29%) and Internal Medicine clinics (11.4%). Acute sinusitis and AOM together accounted for 43.7% of all longer than recommended prescriptions, followed by SSTIs (33.5%), and UTIs (20%). There was not an association between longer than recommended durations of therapy and patient age or race/ethnicity (Table 1).
Prescriptions by advanced practice providers were more likely to be for a longer than recommended duration than those by physicians (41.7% vs 37.3%, \( P<0.001 \)). Similarly, men were more likely to be prescribed a longer than recommended duration of therapy than women (46.8% vs 35.6%, \( P<0.001 \)). When stratifying by sex, 40.1% of men with a UTI received an antibiotic prescription for >5 days in comparison to only 19.2% of females (Supplemental Table S2). The association between men receiving longer durations of antibiotic therapy is driven due to a significant interaction between sex of patient and UTIs (Supplemental Table S3). In comparison with the emergency department, providers from the urgent care centers, Family Medicine clinics, and Internal Medicine clinics more often prescribed longer than recommended durations. Family Medicine clinics had the highest proportion of longer than recommended durations (46%) (Supplemental Figure S2). For cellulitis, acute sinusitis, and AOM, the duration was longer than recommended in 50%, 54%, and 75% of cases, respectively (Supplemental Figure S3).

By logistic regression, factors independently associated with longer than recommended durations of therapy, after adjusting for the interaction between sex of patient and UTIs, included prescriptions by advanced practice providers (adjusted odds ratio [aOR], 1.24; 95% confidence interval [CI], 1.09 – 1.41), prescriptions in urgent care centers (aOR, 1.51; 95% CI, 1.20 – 1.89) or Family Medicine clinics (aOR, 2.24; 95% CI 1.76 – 2.86), and prescriptions for SSTIs (aOR, 3.82; 95% CI, 2.84 – 5.14), acute sinusitis (aOR, 4.66; 95% CI, 3.41 – 6.36), and AOM (aOR, 12.41; 95% CI, 8.68 – 17.73) (Table 2).

**DISCUSSION**

A recent national study by King and colleagues showed that for common outpatient infections, the median duration of therapy was 10 days and nearly three quarters of prescriptions exceeded guideline-recommended durations [2]. Our findings differ from those by King and colleagues in that the overall median duration of therapy was 5 days and a substantially lower proportion of
prescriptions (39%) were for longer than recommended durations. The shorter durations we observed may in part be the result of a long-standing antimicrobial stewardship program and the provision of syndrome-specific treatment guidance via a widely utilized smartphone application [9, 10]; however, there is still substantial opportunity to improve adherence to recommended treatment durations. Within our system, universal adherence to the recommended 5-day duration of therapy would have averted 6,657 antibiotic-days over the 1-year period or 20% of the total antibiotic-days prescribed.

At a system level, excessive durations were common across all sites of care but particularly among the urgent care centers and Family Medicine clinics. Since the same prescribing guidance is available to all providers in our organization, there is a need to better understand why adherence is substantially better in some care locations than others. Although prescriptions by advanced practice providers were independently associated with longer than recommended durations, it is worth noting that excessive durations were common among physicians as well. Specific conditions including SSTIs, acute sinusitis, and AOM – among the most common indications for outpatient antibiotics [1] – were about 4-, 5-, and 12-times more likely, respectively, to be prescribed with excessive durations of therapy. This highlights the potential value of syndrome-specific antimicrobial stewardship interventions emphasizing appropriate durations of therapy. For example, among older children with AOM, we were able to markedly increase adherence to 5-day durations of therapy with a multifaceted intervention [11].

This work has several limitations. First, these data are from a single healthcare system, and thus, the findings are not generalizable. However, based on national data, it may be that there is even greater opportunity to reduce excessive durations of therapy in other institutions [2]. Second, the use of
ICD-10 codes to identify conditions for which antibiotics were prescribed has inherent limitations including the potential for misclassification or miscoding of clinical conditions. Third, a large proportion of antibiotics prescribed were excluded from the analysis and antibiotics prescribed for concomitant infections were not evaluated. This is likely in large part due to the use of a limited set of ICD-10 codes in an attempt to include only uncomplicated infections. Fourth, we did not evaluate clinical outcomes and were unable to assess whether longer than recommended durations impacted the likelihood of treatment success or antibiotic-related adverse events. Fifth, we did not evaluate the appropriateness of the duration prescribed in individual cases. However, given our large sample size, we suspect that the 5-day or less outcome measure was a reasonable surrogate for appropriateness in most cases. A strength is the inclusion of a wide breadth of ambulatory care sites that allowed us to assess variability in and factors associated with longer durations of therapy across sites.

In summary, across the ambulatory care network of an integrated healthcare system, nearly 40% of antibiotic prescriptions for uncomplicated infections were for longer than recommended durations. Several system-level, provider-level, and patient-level factors were associated with longer than recommended durations of therapy. These data add to recent evidence that reducing excessive durations of therapy is an essential component of outpatient antimicrobial stewardship and highlight areas of focus that may be high yield.

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Table 1. Antibiotic Duration of Therapy for Uncomplicated Outpatient Infections

| Factor                        | Guideline-concordant duration (≤5 days) | Longer than recommended duration (>5 days) | P-value |
|-------------------------------|----------------------------------------|-------------------------------------------|---------|
|                               | (n = 3231)                             | (n = 2100)                                |         |
| **Age (years)**               |                                        |                                           |         |
| 18-49                         | 1979 (61.2)                            | 1291 (61.5)                               | 0.420   |
| 50-64                         | 840 (26)                               | 565 (26.9)                                |         |
| ≥65                           | 412 (12.8)                             | 244 (11.6)                                |         |
| **Race/Ethnicity**            |                                        |                                           | 0.427   |
| Hispanic/Latino               | 1664 (51.5)                            | 1071 (51)                                 |         |
| White                         | 1049 (32.5)                            | 697 (33.2)                                |         |
| Black                         | 371 (11.5)                             | 254 (12.1)                                |         |
| Other b                       | 147 (4.5)                              | 78 (3.7)                                  |         |
| **Sex**                       |                                        |                                           | <0.001  |
| Female                        | 2299 (71.2)                            | 1279 (60.9)                               |         |
| Male                          | 932 (28.8)                             | 821 (39.1)                                |         |
| **Provider type**             |                                        |                                           | <0.001  |
| Physician                     | 1735 (53.7)                            | 1031 (49.1)                               |         |
| Advanced practice provider c  | 1496 (46.3)                            | 1069 (50.9)                               |         |
| **Site of care**              |                                        |                                           | <0.001  |
| Adult urgent care center      | 1740 (53.8)                            | 1109 (52.8)                               |         |
| Family Medicine clinic        | 700 (21.7)                             | 609 (29)                                  |         |
| Emergency department          | 424 (13.1)                             | 143 (6.8)                                 |         |
| Internal Medicine clinic      | 367 (11.4)                             | 239 (11.4)                                |         |
| **Infection**                 |                                        |                                           | <0.001  |
| Urinary tract infection e     | 1541 (47.7)                            | 420 (20)                                  |         |
| Skin and soft tissue infection d | 800 (24.8)                         | 703 (33.5)                                |         |
| Acute sinusitis               | 493 (15.2)                             | 589 (28)                                  |         |
| Acute otitis media            | 109 (3.4)                              | 327 (15.6)                                |         |
| Community-acquired pneumonia  | 288 (8.9)                              | 61 (2.9)                                  |         |

* Uncomplicated outpatient infections include purulent and non-purulent skin cellulitis, cutaneous abscess, acute sinusitis, acute otitis media, community-acquired pneumonia, cystitis, and pyelonephritis treated with a fluoroquinolone

b American Indian or Alaskan Native, Asian, and unknown race/ethnicity

Physician assistant, nurse practitioner, and midwife

Purulent and non-purulent skin cellulitis and subcutaneous abscess

Pyelonephritis treated with a fluoroquinolone and cystitis
Table 2. Logistic Regression Model of Factors Associated with Antibiotic Prescriptions for a Longer than Recommended Duration of Therapy

| Variable                          | Odds Ratio (OR) (95% Confidence interval [CI]) | Adjusted Analysis OR (95% CI) \(^a\) |
|-----------------------------------|-----------------------------------------------|--------------------------------------|
| Advanced practice provider \(^b\) (vs. physician) | 1.20 (1.08 – 1.34)                           | 1.24 (1.09 – 1.41)                   |
| Male patient (vs. female)         | 1.58 (1.41 – 1.78)                           | 1.07 (0.92 – 1.25)                   |
| **Site of care**                  |                                               |                                      |
| Emergency department              |                                               |                                      |
| Family Medicine clinic            | 2.58 (2.07 – 3.21)                           | 2.24 (1.76 – 2.86)                   |
| Adult urgent care center          | 1.89 (1.54 – 2.32)                           | 1.51 (1.20 – 1.89)                   |
| Internal Medicine clinic          | 1.93 (1.50 – 2.48)                           | 1.29 (0.98 – 1.69)                   |
| **Infection**                     |                                               |                                      |
| Community-acquired pneumonia      |                                               |                                      |
| Acute otitis media                | 14.16 (9.97 – 20.12)                         | 12.41 (8.68 – 17.73)                 |
| Acute sinusitis                   | 5.64 (4.17 – 7.62)                           | 4.66 (3.41 – 6.36)                   |
| Skin and soft tissue infection \(^c\) | 4.15 (3.09 – 5.57)                           | 3.82 (2.84 – 5.14)                   |
| Urinary tract infection \(^d\)    | 1.29 (0.96 – 1.73)                           | 0.97 (0.70 – 1.33)                   |

\(^a\) Multiple logistic regression model is adjusted for the interaction between urinary tract infection diagnosis and sex of patient

\(^b\) Physician assistant, nurse practitioner, or nurse midwife

\(^c\) Cellulitis or cutaneous abscess

\(^d\) Pyelonephritis treated with a fluoroquinolone or cystitis