Impact of a Pharmacy-Driven Antimicrobial "Time-Out" on Duration of Therapy in Community-Acquired Pneumonia

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BACKGROUND

- Community-acquired pneumonia (CAP) is responsible for approximately one million hospitalizations and 50,000 deaths annually. As a common indication for antimicrobial therapy it poses significant potential for overuse. Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) recommend a minimum five days of therapy guided by CAP-associated signs of stability[1]
- Each day of antimicrobial exposure is associated with increased risk of antimicrobial-associated adverse events and development of antimicrobial resistance. In 2017, 30% of *S. pneumoniae* isolates were resistant to ≥ 1 clinically relevant antibiotic[2,3]
- Joint Commission Antimicrobial Stewardship Standards mandate implementation of antimicrobial "time-outs" (ATOs) to prompt assessment of appropriateness of therapy, patient response, and a plan for duration of therapy.[4] Centers for Disease Control and Prevention recognize pharmacist expertise as a Core Element of Antimicrobial Stewardship Programs[5]
- In January 2018, OSF Healthcare System implemented a 48-hour pharmacy-driven ATO in the electronic health record. The ATO also includes features such as culture data, intravenous (IV) to oral interchange, duplicate therapy, and stewardship review communication tool for handoff

Previous studies evaluating ATOs driven by other members of the primary care team	
72-hour best practice alert to providers[6]	▪ Increase in antibiotic de-escalation ▪ Reduction in total antibiotic days and length of hospital stay ▪ No difference in antibiotic-related adverse events
72-hour "ATO" tool for primary team[7]	▪ Increase in modification or discontinuation of regimens ▪ No change in inpatient or total days of antibiotic therapy

SETTING

- OSF Saint Anthony Medical Center, Rockford, IL
  - Antimicrobial stewardship program: One Infectious Disease Pharmacist and One Infectious Disease Physician
- Pharmacy Department: 10 clinical pharmacists
- May 2016- Oct 2017 (PRE) and Apr 2018- Sep 2019 (POST)

OBJECTIVES

Primary	▪ To determine if a pharmacy-driven antimicrobial time-out impacts duration of therapy in patients hospitalized with CAP
Secondary	▪ To determine if a pharmacy-driven antimicrobial time-out impacts: ▪ Length of hospital stay in patients hospitalized with CAP ▪ Efficacy and safety of CAP treatment

METHODS

Study Design
- Retrospective chart review
- Enrollment criteria listed in Table 1
- All patients with ICD-9 diagnosis of CAP pulled from both time periods, then selected for chart review using a random number generator until pre-determined sample size met in both groups

Table 1. Key inclusion and exclusion criteria

Inclusion	▪ Adults ≥18 years old ▪ Patients with CAP diagnosis
Exclusion	▪ Pregnant ▪ Extra-pulmonary infection (bacteremia, cellulitis, urinary tract infection, etc.) ▪ Infection acquired ≥ 48 hours after admission ▪ Mechanical ventilation ▪ Cavitation or tissue necrosis on imaging ▪ Hospitalization in previous 90 days ▪ Neutropenia (ANC ≤ 1000 cells/mm^3) or leukopenia (WBC ≤ 4000 cells/mm^3) ▪ Immunosuppressed patients (HIV and CD4 count < 200 cells/mm^3, active chemotherapy within the past 30 days, organ transplant, prophylactic antibiotics, or prednisone equivalent ≥ 10 mg daily for greater than 2 weeks

METHODS (continued)

Endpoints
- Primary endpoint: Duration of antibiotic therapy (DOT)
  - Total DOT: Inpatient days of therapy and discharge prescriptions
- Secondary endpoints: Length of hospital stay (LOS), duration of IV therapy, 30-day readmission or emergency department (ED) visit, and antibiotic-associated adverse events
- Subgroup analysis: β-lactam and fluoroquinolone-based regimens
- Antibiotic-associated adverse events (as documented by providers or as evidenced in laboratory values): *C. difficile* infection, diarrhea, allergic-type reaction, acute kidney injury (AKI, per KDIGO guidelines), and treatment failure (need for escalation of therapy)

Statistical Analysis

Sample Size:
- Inclusion of 310 patients estimated to provide 80% power to detect a 20% difference in mean duration of antibiotic therapy in adults hospitalized with CAP

Statistical tests:
- Continuous Data: Positive t-test of mean
- Discrete Data: χ2 or Fischer's exact test

RESULTS

- 808 patient charts reviewed to enroll the necessary number of patients (**Figure 1**)
- Baseline characteristics were comparable between treatment arms (**Table 2**)

Figure 1. Study Analysis Population Flow Chart

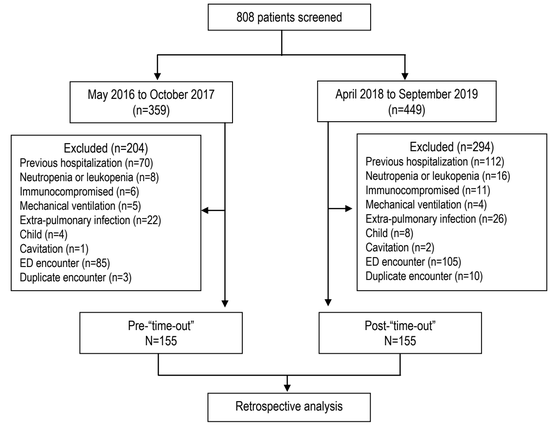

Table 2. Baseline Characteristics

Characteristic	Pre-intervention (n=155)	Post-intervention (n=155)
Median age (years)	70 (19-100)	75 (19-100)
Female	69 (45%)	73 (47%)
Inpatient antibiotics		
β-lactam + macrolide	71%	82%
Fluoroquinolone	19%	11%
Discharge antibiotics		
β-lactam + macrolide	44%	68%
Fluoroquinolone	44%	29%

Efficacy outcomes (**Table 3**; PRE vs. POST)
- DOT was 2.14 days shorter following ATO implementation (10.51 days vs. 8.37 days; P< 0.001)
- Duration of IV therapy (3.86 days vs. 3.21 days; P<0.001) and 30-day ED visit rate (16.13% vs. 3.23%; P<0.001) were also significantly reduced
- Differences in LOS and 30-day readmission rate did not meet statistical significance

RESULTS (continued)

Table 3. Efficacy Outcomes

Endpoint	Pre-intervention	Post-intervention	P-value
Duration of therapy* (days)	10.51 (5-34)	8.37 (4-16)	**P<0.001**
▪ Inpatient duration*	4.48	4.02	**P=0.018**
▪ Outpatient duration*	6.03	4.35	**P<0.001**
Length of stay* (days)	4.60	4.45	P=0.279
Duration of IV therapy* (days)	3.86	3.21	**P<0.001**
30-day readmission rate	14 (9.03%)	7 (4.52%)	P=0.114
30-day ED visit rate	25 (16.13%)	5 (3.23%)	**P<0.001**

Safety outcomes (**Table 4**; PRE vs. POST)
- Rates of diarrhea (28.39% vs. 17.42%; P=0.022) and AKI (17.42% vs. 6.45%; P=0.003) were lower after implementation but *C. difficile* infection and treatment failure were not significantly different

Subgroup Analysis (**Table 5**; β-lactam vs. fluoroquinolone)
- DOT was shorter in both regimens following implementation, but β-lactam regimens were significantly longer than fluoroquinolone regimens (POST: 8.21 days vs. 7.24 days; P=0.020)

Table 4. Safety Outcomes

Endpoint	Pre-intervention	Post-intervention	P-value
C. Difficile infection	4 (2.58)	1 (0.65)	P=0.371
Diarrhea	44 (28.39)	27 (17.42)	**P=0.022**
Acute kidney injury	27 (17.42)	10 (6.45)	**P=0.003**
Allergic-type reaction	1 (0.65)	0 (0)	P=0.317
Treatment failure	5 (3.22)	3 (1.94)	P=0.723

Table 5. Subgroup Analysis

Pre-intervention	β-lactam	Fluoroquinolone	P-value
Duration of therapy* (days)	11.03	10.09	**P=0.097**
Post-intervention			
Duration of therapy* (days)	8.21	7.24	**P=0.020**

* mean

CONCLUSIONS

- Implementation of the pharmacy-driven ATO was associated with a shorter DOT and fewer treatment-associated adverse events but no difference in rates of treatment failure or readmissions, suggesting a safe and effective ATO implementation
- Limitations:
  - Retrospective nature of the study restricted data collection, especially in terms of adverse events
  - We did not address disease severity, completion of discharge therapy, and subsequent resistance
- Pharmacists interventions were not intentionally documented and therefore not measured, representing an opportunity for prospective audit in the future
- Prescribing trends were noted in data collection that did not change with implementation of the ATO
  - Providers prescribing consistent durations on discharge regardless of inpatient DOT
  - Discrepancies between intended DOT and actual duration administered
- The next steps for targeted pharmacist interventions include:
  - Ensuring discharge prescriptions reflect continuity of therapy
  - Intervene earlier to initiate oral therapy
  - Continue to encourage evidence-based DOT

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