Step-down Therapy with Oral Fluoroquinolones vs. Oral Beta-Lactams for Hospitalized Adult Patients with Community-Acquired Pneumonia: A Multi-Hospital Cohort Study

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BACKGROUND

- Community-acquired pneumonia (CAP) guidelines recommend transition to an oral (PO) beta-lactam (BL) regimen or fluoroquinolone (FQ) when patients are stable.
- Due to the adverse effects (including tendinopathy, neuropathy, confusion, QTc prolongation) and collateral damage (resistance, *Clostridium difficile* infection) associated with FQs, stewardship efforts often focus on reducing initial empiric FQ use for CAP therapy.
- However, less attention is given to antibiotic selection at the transition to a PO regimen.

AIMS

- Determine factors associated with selection of a PO FQ vs PO BL for step-down therapy
- Compare clinical outcomes in patients who transition to a PO FQ vs PO BL for CAP treatment after initial improvement on an intravenous (IV) BL regimen

METHODS

- Design: Retrospective cohort study from January 2016 through February 2018
- Setting: 46 Michigan hospitals (members of the Michigan Hospital Medicine Safety Consortium)
- Participants: Hospitalized medical patients with a diagnosis of CAP who are started on an IV BL (ceftriaxone or ampicillin-sulbactam) + atypical coverage (macrolide/doxycycline/clarithromycin) by hospital day 2
- Exclusions: positive culture, concomitant infection, HCAP, unstable on day 4, ICU admission, or severe immune deficiency
- Data collection: Trained abstractors collected detailed data from chart review and 30 day post-discharge phone call. Abstractors complete an annual survey of detailed stewardship practices.
- Primary outcome: De-escalated to a PO respiratory FQ (levofloxacin, moxifloxacin) vs PO BL (amoxicillin, amoxicillin/clavulanate, cefuroxime, 3rd generation cephalosporins) +/- atypical by day 4
- Predictors: Disease, patient, provider factors
- Secondary outcomes at 30 days: Mortality, readmission, ED visit, *Clostridium difficile* infection, adverse drug events, and hospital length of stay
- Statistical analysis: Data were analyzed using logistic generalized estimating equation models, accounting for hospital level clustering; outcomes were adjusted using inverse probability of treatment weighting by propensity scores. P<0.05 were considered significant.

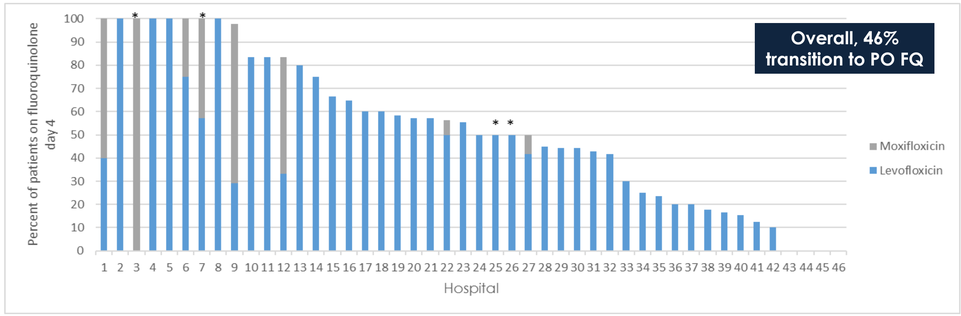
RESULTS

Table 1. Comparison of Clinical and Treatment Characteristics of Oral Fluoroquinolone and Oral Beta-lactam Groups (n=555)

Variable	FQ (n=253)	BL +/- atypical (n=302)	P value
Baseline Characteristics			
Age (Median [IQR])	65 [52-75]	72 [59-81]	0.015
Gender (male)	125 (49.6%)	150 (49.7%)	0.72
Charlson comorbidity index (Median [IQR])	2 (0-4)	2 [1-4]	0.10
Diabetes	72 (28.5%)	69 (22.8%)	0.21
COPD or asthma	107 (42.3%)	153 (50.7%)	0.08
Cardiovascular disease	67 (26.5%)	151 (50.0%)	<0.001
Malignancy	5 (2.0%)	11 (3.6%)	0.58
Moderate or severe chronic kidney disease	55 (21.7%)	73 (24.2%)	0.47
Liver disease	6 (2.4%)	12 (4.0%)	0.50
Current/former alcohol abuse	32 (12.6%)	33 (10.9%)	0.86
Received immunosuppressive therapy[1]	110 (43.5%)	141 (46.7%)	0.95
Antibiotics before admission	39 (15.4%)	43 (14.2%)	0.75
Non-Ambulatory	4 (1.6%)	9 (3.0%)	0.32
Home oxygen	18 (7.1%)	28 (9.3%)	0.59
Severity of Illness			
CURB-65 (≥2)	122 (48.2%)	190 (62.9%)	0.017
CURB-65 (Median [IQR])	1 [1-2]	2 [1-3]	0.005
≥2 SIRS criteria	219 (86.6%)	258 (85.4%)	0.21
Pneumonia Severity Index (Median [IQR])	82 [59-99]	92 [71-115]	0.016
Day clinical stability[2] reached (Mean (SD))	2.5 (0.9)	2.8 (0.7)	0.08
Treatment-related Characteristics			
Antibiotic duration (Median [IQR])	8 [7-9]	8 [7-9]	0.12
Days on IV antibiotics (Mean (SD))	2.4 (0.7)	2.5 (0.6)	0.016

[1]Immunosuppressive therapy defined as corticosteroids or immunosuppressive medications on admission or in 30 days prior; [2]Clinical stability: afebrile with ≤ 1 vital sign abnormality by day 5 (HR >100, RR>24, SBP <90, altered mental status, oxygen saturation <90% or new oxygen requirement)

Figure 1. Proportion of Patients with CAP on an Oral FQ by Day 4 by Hospital



*Hospital in the 10th percentile or below for case count of CAP across the collaborative

Table 2. Independent Predictors for Selection of Oral FQ vs Oral BL as Step-down Therapy For CAP

Variable	OR* (95% CI)	P-value
Stewardship shares reports on antibiotic use with providers	0.51 (0.27, 0.97)	0.04
Cardiovascular disease	0.69 (0.54, 0.87)	0.002
CURB-65 (per unit increase)	0.82 (0.71, 0.95)	0.009
Non-white race (vs. White)	1.02 (1.01, 1.04)	0.006
Medicaid	1.08 (1.02, 1.14)	0.011
Diabetes	1.39 (1.00, 1.93)	0.048

OR, Odds ratio; CI, Confidence interval
*Odds ratios > 1 indicates factors associated with treatment with a fluoroquinolone

Table 3. Outcomes in Oral FQ vs Oral BL Cohorts (n=555)

Variable	FQ (n=253)	BL +/- atypical (n=302)	Adjusted Odds Ratio* (95% CI)	Adjusted P-value
30-day all-cause mortality[a]	4 (12%)	2 (1%)	3.4(0.6,19.5)	0.16
30-day all-cause readmission[a]	15 (6%)	29 (10%)	0.8 (0.5, 1.3)	0.29
Urgent care/Emergency Department within 30 days[a]	19 (8%)	29 (10%)	0.7 (0.4, 1.5)	0.37
Clostridium difficile infection[b]	3 (1.2%)	1 (0.3%)	3.5(0.3, 5.0)	0.29
Adverse drug event[c**]	12 (5%)	18 (6%)	0.7 (0.3, 1.4)	0.28
Length of stay (median [IQR])[c]	3 [3-4]	3 [3-4]	1.0 (0.9, 1.0)[d]	0.50

*Odds ratios > 1 indicates outcomes associated with treatment with a fluoroquinolone; *Adverse drug events defined as rash, diarrhea, acute kidney injury, neutropenia, thrombocytopenia, allergic reaction; [a]Adjusted for age, LOS, Charlson, discharge to nursing home, insurance, cardiovascular disease, CURB-65, days to clinical stability, PSI, days on IV therapy, COPD; [b]Adjusted for age, history of antibiotic use (and number of antibiotics), transfer from skilled nursing facility, prior hospitalization, LOS, proton-pump inhibitor use, Charlson, cardiovascular disease, CURB-65, days to clinical stability, PSI, days on IV therapy, COPD; [c]Adjusted for age, Charlson, gender, cardiovascular disease, CURB-65, days to clinical stability, PSI, days on IV therapy, COPD; [d]Relative risk given continuous variable

CONCLUSIONS

- Among CAP patients started on an IV non-pseudomonal BL regimen, nearly half were switched to a PO respiratory FQ by therapy day 4, with significant variation between hospitals.
- Diabetes, Medicaid, and non-white race were associated with transition to FQ therapy.
- Although patients who remained on a BL were more likely to have cardiovascular disease and more severe pneumonia, adverse event rates were low overall, and there were no differences in outcomes compared to the FQ group.
- Given the harms associated with FQ use and similar outcomes between CAP patients treated exclusively with BLs +/- atypical coverage as opposed to those transitioned to FQs, stewardship programs should emphasize transition from IV BL regimens to non-FQ PO therapies in clinically stable patients with CAP.

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