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Successful Implementation of an Inpatient Fluoroquinolone (FQ) Pre-Authorization (PA) Policy at a Tertiary Care Academic Center and Associated Changes in Antibiotic Use, Antibiogram Susceptibility, and Provider Behavioral Changes

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BACKGROUND

- Multiple warnings about FQ toxicity, adverse effects, and risk of *C. difficile* infection have been released in the past 2 decades including 6 FDA warnings and black box warnings.
- FQ are often overused for many infectious disease syndromes.
- Given the above information, we implemented a PA policy for FQ use for inpatients within our main academic hospital as described below in methods.
- We evaluated the effectiveness in decreasing FQ use as well as possible secondary effects including changes in the antibiogram and behavioral changes in provider use of FQ at an unrestricted site.

METHODS

Site: University Hospital is the main adult-care hospital for UW Health. It is a tertiary care regional referral center in the Upper Midwest, a level 1 trauma center, an American College of Surgeons-verified Burn Center, a national leader in solid and bone marrow transplant, and a National Cancer Institute-designated center with ~25,000 patient admissions per year.

EMR: UW Health uses EPIC Systems EMR. Restriction policy was instituted within the EMR to direct providers on obtaining approval and/or using alternatives.

Time period: Pre-implementation period was January 2014 to May 2016. In June 2016, FQ restriction was piloted on 2 wards (the Intensive Care Unit and the Hematology/BMT unit). This wash-in period lasted 9 months. In March 2017, the policy went hospital wide for all adult patients on all wards/services.

PA policy: PA was comprehensive. All FQs required approval from the Antimicrobial Stewardship (AMS) service, staffed by ID Attendings, or the ID consult service. Exemptions to the policy included: 1) Hematology/BMT prophylaxis use for patients at high-risk febrile neutropenia, 2) Single peri-procedural use for urological procedures or in selected procedures for patients with documented severe or immediate IgE-mediated beta-lactam allergy, and 3) single one-time use was allowed between 10pm-6am. Even if patients were on FQ prior to admission, approval had to be granted.

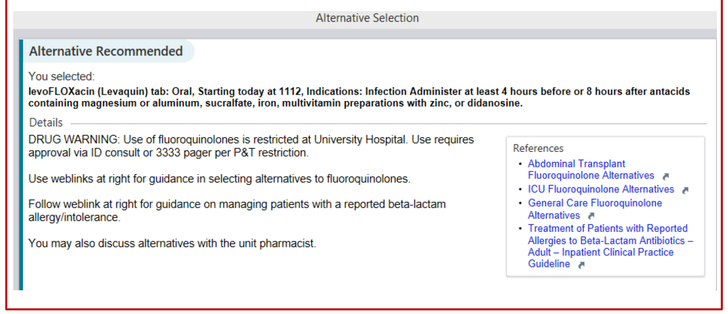
FQ alternative clinical decision support: The AMS team developed FQ-alternative clinical decision support documents that were available on the intra-net as well as hyperlink included in the EMR FQ order screen.

Data collection: Monthly antibiotic use was collected in DOT/KPD. Antibiogram data was collected from all inpatient cultures, restricted to first culture per patient per site per 7-d period. Finally, data on FQ use was obtained from a separate hospital that is part of the UW Health organization and staffed by physicians (primarily hospitalists) from the University Hospital, but for which a FQ restriction was not in place. Hospital onset CDI was determined using CDC/NHSN criteria and data collected from our infection control monitoring program.

Statistical analysis: Changes in antibiotic use and susceptibility over time were compared pre-/post-implementation of the PA using *t*-test, Mann-Whitney Rank Sum, and z-test.

RESULTS

EMR Restriction and Alternatives Clinical Decision Support Tool: Below is a screen shot of the EMR alert to clinicians that FQ use is restricted to PA only, how to obtain PA, and references to seek alternatives.



RESULTS (cont.)

FQ use trends - NOTE: Blue lines = 95% confidence band for trend line; Red lines= 95% prediction band for data points.

Fig 1. All FQ Use

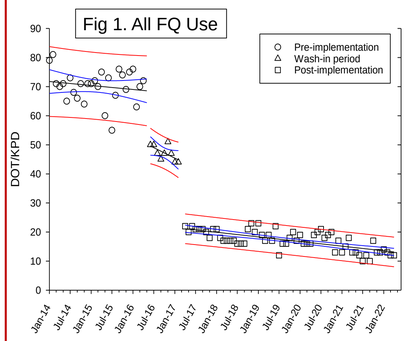
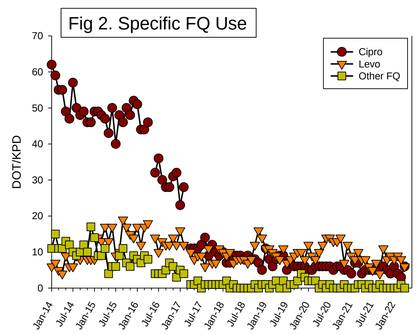


Fig 2. Specific FQ Use



Other GNR agents use trends: Blue lines = 95% confidence band for trend line; Red lines= 95% prediction band for data points. NOTE: blank period in cefepime and piperacillin-tazobactam use from 2015-2017 is due to successive shortages in each drug making the data on use not evaluable.

Fig 3. 3rd Gen Cephalosporins

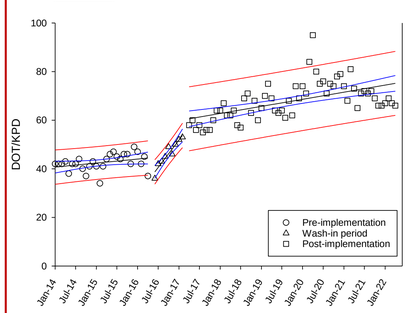


Fig 4. Cefepime and Piperacillin-Tazobactam

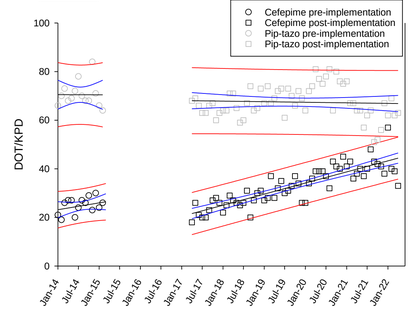


Fig 5. Carbapenems

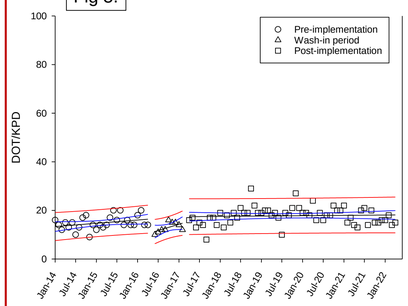


Table 1. Mean (range) use of GNR agents pre/post-implementation of an inpatient FQ PA policy.

Drug	Inpatient Use in DOT/KPD (range)			Pre/ Post p-value
	Pre	Wash-in	Post	
FQ	70.3 (55-81)	47.2 (44-51)	17.1 (10-23)	<0.001
Ceftriaxone	42.6 (34-49)	46.2 (36-53)	67.9 (55-95)	<0.001
Cefepime	24.9 (19-30)	NA*	33 (18-57)	<0.001
Piperacillin-Tazobactam	70.5 (64-84)	NA	67.5 (51-81)	0.109
Carbapenems	14.9 (9-20)	13.0 (10-16)	17.8 (8-18)	<0.001

*NA, data not included due to successive shortages in cefepime and piperacillin-tazobactam occurred during this period affecting use

Associated effects: FQ use at an unrestricted hospital staffed by physicians (primarily hospitalists) from the restricted site is shown in Figure 6. This hospital opened in July 2015, therefore data does not exist prior to this. In Figure 7, changes in hospital onset *C. difficile* infection over the time period is shown.

Fig 6. FQ Use at Unrestricted Hospital

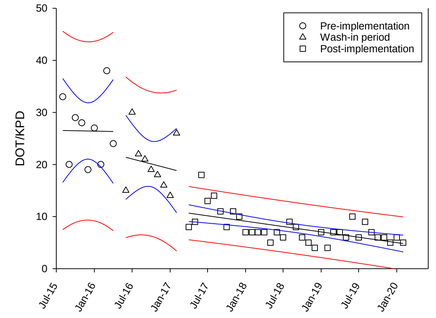
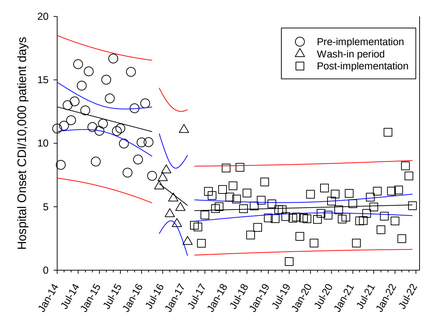


Fig 7. Hospital Onset CDI



Antibiogram changes: Changes in inpatient antibiogram were examined pre- and post-intervention (i.e. the wash-in period was excluded) for all *Enterobacterales* spp., and specifically for *E. coli, K. pneumoniae*, and *P. aeruginosa*. These results are shown below in Table 2.

Table 2. Antimicrobial susceptibility changes for common GNR pathogens pre/post-implementation of an inpatient FQ PA policy.

Drug	*Enterobacterales* spp.		*E. Coli*		*K. pneumoniae* (n)		*P. aeruginosa* (n)	
	%S (n) Pre	%S (n) Post	%S (n) Pre	%S (n) Post	%S (n) Pre	%S (n) Post	%S (n) Pre	%S (n) Post
Ciprofloxacin	80.0 (4297)	84.7* (10007)	72.9 (2420)	79.1* (5392)	90.2 (838)	90.8 (1680)	76.2 (1371)	81.2* (3097)
Ceftriaxone	86.9 (4091)	85.0¥ (9923)	89.1 (2283)	89.0 (5331)	90.9 (800)	90.1 (1664)	R	R
Cefepime	93.7 (4078)	92.7¥ (9905)	92.2 (2283)	91.6 (5331)	92.6 (801)	91.5 (1664)	87.6 (1375)	89.9* (3097)
Pip-Tazo	93.3 (4288)	93.8 (10007)	95.4 (2420)	96.7* (5400)	95.5 (840)	95.4 (1681)	85.3 (1375)	86.7 (3097)
Meropenem	99.7 (4287)	99.7 (9830)	99.8 (2420)	99.9 (5400)	99.9 (839)	99.8 (1457)	84.7 (1375)	84.6 (3096)

%S, the percent susceptible for each period; * significant improvement and ¥ significant decline ($p<0.05$) pre vs post, R indicates intrinsic resistance

CONCLUSION

1] FQ PA was highly effective with a substantial sustained decrease (>70% decrease in use) in inpatient FQ use, primarily driven by decreases in ciprofloxacin use.

2] As has been noted before with restriction of certain classes of antimicrobials, there is a "squeezing the balloon" effect with associated increases in other GNR active agents.

3] We noted significant declines in FQ use at a hospital in which there was no restriction or PA policy, but was staffed with physicians from the University Hospital where the restriction was instituted. This suggests there is a positive "carry-over" behavioral effect whereby providers may become more comfortable with managing patients without FQs leading to practice change.

4] There was an associated decline in hospital onset CDI over this period, though multiple interventions including improved testing algorithms and infection control practices were also introduced.

5] Significant improvements were noted in ciprofloxacin susceptibility against numerous gram-negatives including *P. aeruginosa*, whereas smaller but still significant declines were noted in cephalosporin susceptibility for *Enterobacterales*.

6] Other patient-level outcomes deserve examination such as LOS, mortality, etc.