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REDUCING TURN-AROUND TIME FOR FIRST-DOSE ANTIBIOTICS

By

PATRICK J BIRNEY

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Reducing turn-around time for first-dose antibiotics

To the Faculty of the University of Houston, College of Pharmacy:

The members of the committee appointed to examine the project of Patrick Birney find it satisfactory and recommend that it be accepted on _____.

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Masters Research Project

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Abstract:

Reducing turn-around time for first-dose antibiotics

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Background: The 2012 update of the Surviving Sepsis Campaign's Guidelines for Management of Severe Sepsis and Septic Shock recommends administration of effective antibiotics within the first hour of disease recognition; however literature describing an effective approach to expedite antibiotic administration is sparse.

Objective: To determine the effectiveness of a multidisciplinary intervention on reducing antibiotic turnaround time.

Methods: A three-arm cohort design was used to assess the impact of the intervention on antibiotic turnaround time. The study consisted of a historical Control taking place in April 2013, Cohort 1 in March 2014 evaluating changes in workflow, and Cohort 2 in April 2014 evaluating activation of a medical logic module (MLM).

Results: Workflow revisions reduced turnaround time for stat orders on acute care units by decreasing the percent of orders delayed greater than 4 hours (19.6 vs. 8.4%, $p = 0.009$), but did not have any effect on any other subpopulation. Activation of the MLM resulted in a 54% decrease in mean turnaround time Cohort 2.

Conclusion: The combined effect of the workflow revisions and activation of MLM improved mean antibiotic turnaround time and the percent of first-doses administered within 60 minutes.

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List of Acronyms:

CPOE: Computerized provider order entry
ED: Emergency department
EHR: Electronic health record
ICU: Intensive care unit
LOS: Length of stay
MAR: Medication administration record
MLM: Medical logic module
SCIP: Surgical care improvement project
SIRS: Severe inflammatory response syndrome

Background:

The 2012 update of the Surviving Sepsis Campaign's Guidelines for Management of Severe Sepsis and Septic Shock recommends administration of effective antibiotics within the first hour of recognition of septic shock. [1] However, the consensus committee recognizes that despite strong evidence supporting the timely administration of antibiotics, achieving this throughout an institution has been elusive. An international guideline-based performance improvement program was initiated by the Surviving Sepsis Campaign, and the results showed a reduction in hospital mortality rates associated with implementing Campaign recommendations. [2] Kumar et al. investigated the effect of antibiotic administration timing and mortality in patients with septic shock, concluding that early administration of effective antibiotic therapy after documented hypotension was associated with higher rates of survival to discharge from a hospital. [3] Patients that received antibiotics within 60 minutes of hypotension survived to discharge in 79.9% of cases, with the survival fraction decreasing for every hour that therapy is delayed. After 6 hours of documented hypotension, every additional hour of delay in therapy resulted in a 7.6% drop in survival; and according to the authors' analysis, delays in effective antimicrobial administration produced 28.1% of the variance in survival. Further evidence that early administration of effective therapy is critical to survival can be seen comparing patients who received appropriate therapy upon sepsis recognition versus patients who received inappropriate therapy. In a retrospective cohort of 5,715 patients, the survival rate was 52.0% for patients receiving effective therapy versus 10.3% for patients receiving inappropriate therapy at onset of hypotension in septic patients. [4]

A number of studies have refuted the claim that delays in antibiotic administration prior to the onset of shock results in deleterious outcomes. Puskarich et al. describe an Emergency Department based resuscitation protocol for patients with septic shock, and found that delays in antibiotic initiation after triage had no discernible effect on in-hospital mortality. However, the authors report that delaying antibiotic administration until after the recognition of shock doubled in-hospital mortality. [5]

In addition to mortality benefits, appropriate sepsis care stands to have a major impact on the cost of healthcare in the United States, with almost 1 million cases of sepsis per year. Shorr et al. compared sepsis care pre- and post-implementation of a sepsis protocol, and found a 27% reduction in median hospital costs ($21985 vs. $16103) and a 5-day reduction in average length of stay. [6] Implementation of a severe sepsis protocol with antimicrobial recommendations resulted in less time to first-dose antibiotic administration (1.77 versus 14.90 hours) and decreased length of stay (9.8 versus 14.7 days) when compared to a historical control group. [7]

The effect of early effective antimicrobial therapy has been proven outside of sepsis as well. Use of mass spectrometry to rapidly identify the causative species in gram negative bacteremia and provide early targeted therapy resulted in reduction in mean length of stay from 11.9 days to 9.3 days, and reduction in mean hospital costs from $45,709 to $26,162. [8]

Despite convincing evidence that early effective antimicrobial therapy increases survival in a number of disease states, literature describing an effective approach to achieve effective antibiotic therapy within 60 minutes of sepsis recognition is lacking. A 2012 article reported that

for patients admitted to a 9-bed ICU, median time to effective antibiotics was 1.7 hours after onset of septic shock. In the population examined, only 19 of 55 patients (34%) received antibiotics within one hour, with a trend towards less delay in the emergency department (1.1 hours in ED vs. 2.3 hours in the ICU). [9]

Initiation of appropriate antibiotic therapy within 60 minutes is an important quality measure of care for patients with sepsis and septic shock. Because of literature supporting prompt antimicrobial administration in non-septic patients, we postulate that all patients with infection stand to benefit from antibiotic administration within 60 minutes of diagnosis and order entry. Thus, after quantifying time to first-dose of antibiotics after order entry and identifying sources of delay within an 800-bed tertiary medical center, a small-scale, multidisciplinary pilot intervention was implemented on two patient care units to improve antibiotic turn-around time for first-dose and antibiotics ordered as stat. After a sustained improvement in turnaround time during the pilot, the intervention was implemented throughout the institution to improve care and outcomes for patients with infectious diseases. The primary objective of this study was to determine the effectiveness of a multidisciplinary intervention on time to first-dose antibiotic administration.

Objective:

To determine the effectiveness of a multidisciplinary intervention on reducing mean antibiotic turnaround time and increasing the percentage of first-doses administered within 60 minutes

Specific Aims

- To assess if the intervention resulted in a decrease in antibiotic turnaround time compared to historical control.
- To assess if a decrease in antibiotic turnaround time results in improved patient outcomes
- Identify areas of the medication use process that cause delays in antibiotic administration

Hypothesis:

A multidisciplinary workflow renovation and improved prescribing practice will reduce antibiotic turnaround time and increase the number of antibiotics administered within 60 minutes of order entry

Study Design:

A three-arm cohort design was used to assess the impact of the intervention on antibiotic turnaround time. The study consisted of a Control taking place in April 2013, Cohort 1 in March 2014, and Cohort 2 in April 2014.

Methods:

Pre-study process

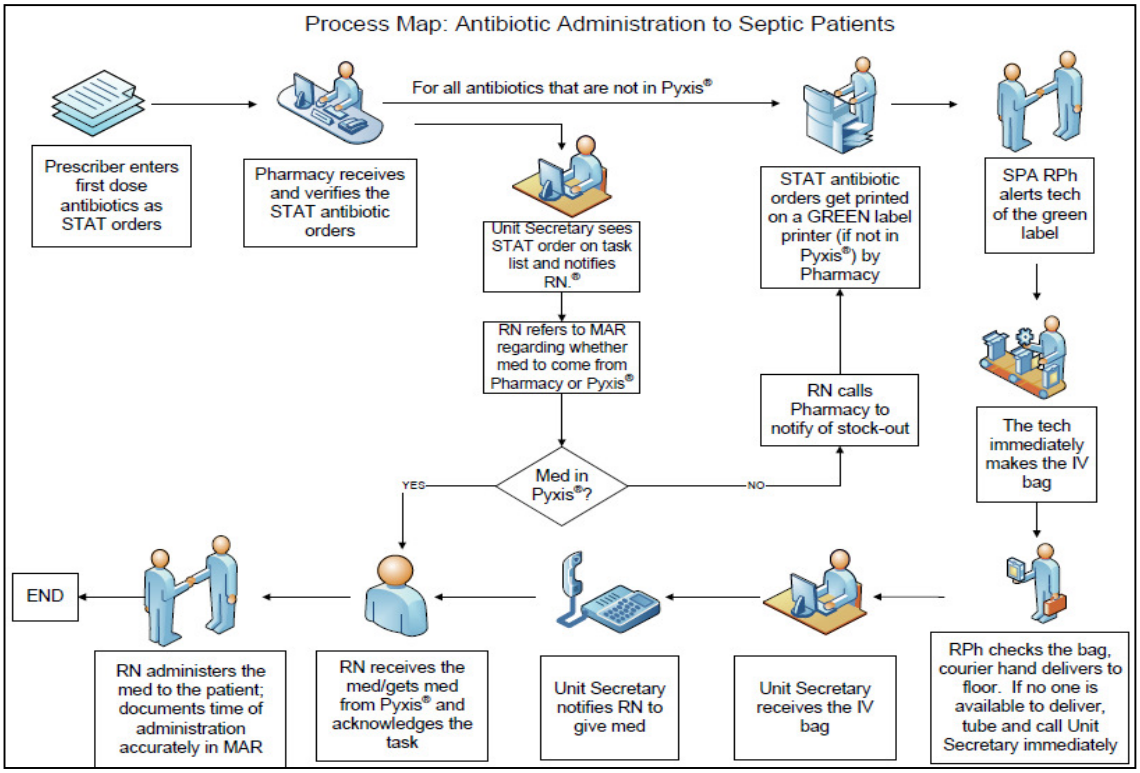
Prior to this study there was no systemic protocol aimed at reducing antibiotic turnaround time within the study institution. Medication orders are submitted via computerized provider order entry (CPOE) and are programmed to a default priority of "Routine," subjecting them to the hospital's standard administration times. Priority could be manually changed to "stat" by the provider, but this was uncommon, occurring in less than 1/3 of first-dose orders. Medication

orders were verified and checked by a pharmacist, at which point they became available in an automated dispensing cabinet from the pharmacy. Nursing practice policy dictates that "flags" for new orders in the medical record must be checked at minimum every two hours. When an order is received the nurse may administer the first dose immediately at his/her discretion; however a mandatory task will not be generated in the medication administration record (MAR) until the next standard administration time.

Development and Pilot of Antibiotic Fast Track

A multidisciplinary team was assembled consisting of three pharmacists, two nursing unit directors, two nurses, and two physicians to assess the rate-limiting factor and other bottlenecks in the medication use process for first-dose antibiotics. A pilot intervention was designed, consisting of (1) education of prescribers to appropriately set priority of first-dose antibiotics to "stat," (2) improved Pharmacy turnaround time by optimizing floor-stock supplied antibiotics and creating a "fast-lane" pathway for stat antibiotics within central pharmacy and the sterile products area, and (3) improving nurse recognition and administration of stat orders with the help of unit secretaries (Figure 1).

Figure 1. Workflow Revision for Stat Antibiotics



The team determined that ordering first dose antibiotics as stat would be a required step to ensure timely administration. Stat orders appear at the top of the pharmacy verification queue, and are prioritized accordingly by Order Verification Pharmacists. A printer with green label paper was installed to use for stat antibiotics. This was to serve as a visual cue for pharmacists, technicians, and nursing unit staff that the labeled medication is stat antibiotic, and promote quick throughput and subsequent administration. Unit Secretaries were instructed to notify nurses of "Stat Flags" – visual cues that are within the electronic medical record. Pharmacy delivery technicians were instructed to deliver medications with a green label directly to the patient's nurse or the unit secretary, who could hand-off to the nurse, rather than delivering the antibiotics to the medication room without any notification.

The pilot was implemented on two nursing units in May and June of 2013, and resulted in a significant reduction in time to administration for first-dose antibiotics. This information was

used to secure resources to develop an electronic learning module for unit secretaries to recognize and act on stat orders, and to investigate development of an automatic prioritization tool for first-dose antibiotics.

Antibiotic Medical Logic Module

In addition to the workflow changes to promote order recognition, a Medical Logic Module (MLM) was designed to ensure antibiotic orders are submitted with the appropriate priority selected. An MLM is an electronic algorithm that inputs available data points and suggests a medical decision, in this case, prioritization and timing of first-dose antibiotic administration. Upon prescriber entry of an antibiotic order into the CPOE system, the MLM actively cross-references the MAR for any prior administrations of the selected antibiotic for the patient. If the drug has not been administered within 72 hours, the order priority will be set to "stat". If the drug has been administered to the patient within 72 hours, and the frequency of the new order is identical to the previous order (e.g. 1 gram every 12 hours to 2 grams every 12 hours), the order priority will be "routine" and remain on the original schedule. In cases where the next administration time falls within 3 hours of order entry, the priority will be changed to "stat" to ensure the dose is not delayed. If the drug has been administered within 72 hours, and the frequency of the new order is different than the previous order (e.g. every 12 to every 8 hours, with or without a dose change), then the ordering provider will be prompted to specify the next intended administration time. For all aforementioned scenarios, the order entry screen contains information on the most recent order, including dose, frequency, and time of the most recent administration.

Outcome Variables

The study has two primary outcomes, to (1A) compare the success rate of achieving first-dose antibiotic administration within 60 minutes of order entry before and after intervention and (1B) compare the median time to antibiotic administration for first dose antibiotics before and after intervention. Process outcomes include turnaround time of all medications from central pharmacy, percent of first dose antibiotic orders submitted as "stat", and percent of first doses antibiotics are that are significantly delayed (>240 minutes). Secondary outcomes include mean ICU length of stay (LOS), mean hospital LOS, in-hospital mortality, and composite endpoint of admission to ICU, LOS above 10 days and/or in-hospital mortality. Subgroup analyses include, patients identified as having sepsis, ICU length of stay, hospital length of stay, in-hospital mortality, transfer from acute care to ICU following antibiotic initiation, length of vasopressor use in patients that received them, and change in number of positive SIRS criteria 24 hours after antibiotic initiation.

Data collection

Data collection was completed using an automated query that identified, for each patient discharged from the hospital or deceased within the specified date range, every IV antibiotic order that was entered and administered at least once. For included patients, the first order of each unique antibiotic medication was documented, as well as the electronic timestamp for order entry, order verification, documented drug administration, when this documentation in the MAR was completed, discontinuation of antibiotic order, and the last administration of this antibiotic during the hospital stay. Other variables collected include diagnosis of sepsis, location of patient at the time of each order, total ICU length of stay during admission, hospital length of stay, in

hospital mortality, and use of vasopressors during admission. The following markers of sepsis and severe sepsis were collected as the most recent documented value before order entry and 24 hours after order entry to evaluate change in the patient's condition: white blood cell count, temperature, respiratory rate, heart rate, and blood pressure.

The institutional review board at Houston Methodist Hospital and the University of Houston approved all data points collected in this study.

Inclusion and Exclusion

Adult patients treated in the acute care, intensive care, or emergency department setting and discharged from the study institution from January 2013 through April 2014 that received parenteral antibiotics were eligible for inclusion in this study. Exclusion criteria included orders that were known prophylactic antibiotics or continuation of home antibiotics, antibiotics known to be ordered for non-infectious causes, orders entered in the peri-procedural or outpatient area, and antibiotics ordered as part of a surgical order set and therefore administered according to Surgical Care Improvement Project (SCIP) timing recommendations.

Statistical Analysis

Three separate time periods were analyzed for the study: April 2013 served as the historical control, Cohort 1 took place in March 2014 to account for the change of workflow for pharmacy and unit secretary involvement in stat order identification and nurse notification, and lastly Cohort 2 was a single-day trial run of the MLM in April 2014. Comparison of antibiotic turnaround time before and after the education and workflow intervention and implementation of

the MLM was completed using a Chi-squared test for outcome 1A, and a student's t-test for outcome 1B. To detect a difference of 30% in the success rate of "Less than 60 minutes" goal, a sample size of 44 per group was required. To detect a reduction in median turnaround time of 75 minutes with a standard deviation of 210 minutes, a sample size of 166 per group required. Each parameter was calculated with an alpha of 0.05 and power of 90%.

Results:

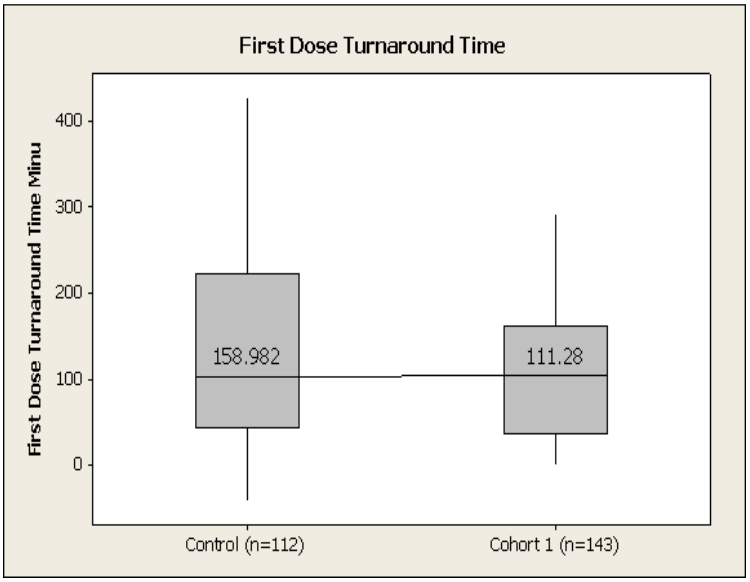
Data was collected for 9438 orders in total, 3651 of those met inclusion criteria. 1735 included orders were in the Control group, 1890 orders in Cohort 1, and 26 orders in Cohort 2. A more detailed breakdown of order characteristics can be found in Table 1.

Table 1: Included orders by setting and priority

	Control N=1735	**Cohort 1 N=1890**	**Cohort 2 N=26**
ICU Orders	480 (27.6%)	346 (18.3%)	4 (15.3%)
Stat	25.6%	19.9%	75%
Acute care orders	791 (45.5%)	916 (48.5%)	10 (38.5%)
Stat	14.2%	15.6%	100%
ED orders	464 (26.7%)	628 (33.2%)	12 (46.2%)
Stat	69.1%	74.4%	100%

Between the Control group and Cohort 1, there was no statistically significant difference found in mean antibiotic turnaround time (204 vs. 200 minutes, $p = 0.650$) or percent of orders administered within 60 minutes of order entry (27.2 vs. 28.5%, $p = 0.342$). Further, there was no significant difference found in a subgroup of stat orders, orders submitted for patients in the ICU, stat orders for patients in the ICU, or orders of any priority submitted for patients in an acute care setting. The only patient population that did show a significant difference in mean turnaround time between the Control and Cohort 1 was stat orders submitted for patients in an acute care unit (Figure 2).

Figure 2: First dose antibiotic turnaround time for STAT orders submitted on acute care units



Within this subgroup, there was no significant difference in the percent of orders administered within 60 minutes of order entry (31 vs. 29%, p = 0.746; Figure 3), rather; the difference in mean TAT can be traced to a reduction in the rate of administrations that were delayed beyond 4 hours (19.6 vs. 8.4%, p = 0.009; Figure 4).

Figure 3: Percent of acute care STAT orders administered within 60 minutes

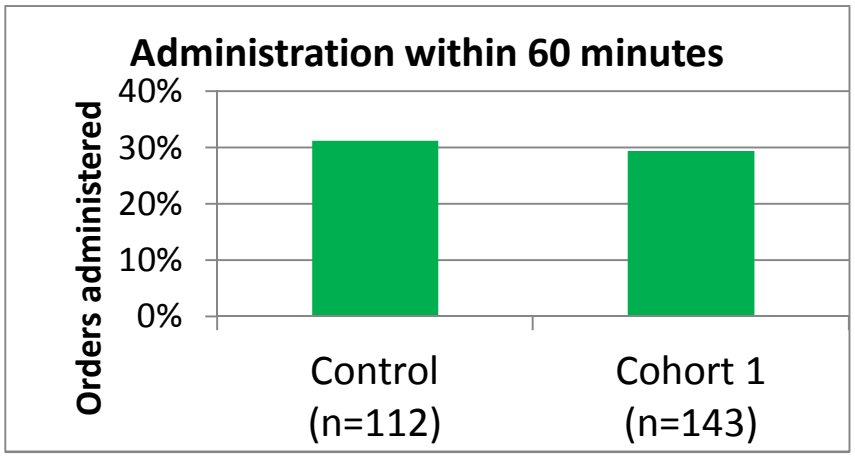
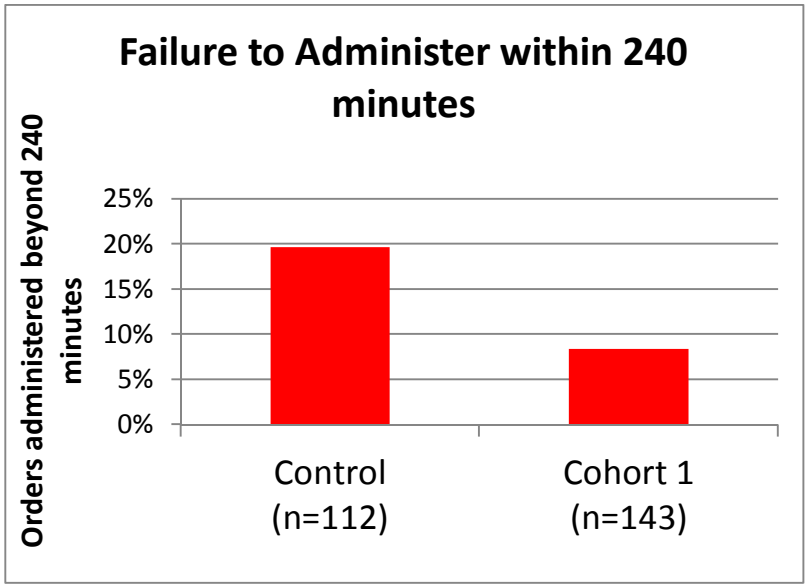


Figure 4: Percent of acute care STAT orders administered beyond 240 minutes



A 3-way ANOVA comparing the Control group, Cohort 1 and Cohort 2 for mean turnaround time highlighted a 54% reduction in mean turnaround time from baseline to Cohort 2 ($p = 0.043$; Figure 5), and Chi-squared analysis revealed a 23% increase in the rate of orders administered within 60 minutes ($p = 0.030$; Figure 6) along with a non-statistically significant trend towards a decreased number of orders delayed greater than 4 hours. As the Control group and Cohort 1 were statistically similar in all aspects on the whole, these two groups were combined for the purpose of comparison to Cohort 2. In this two-tailed analysis, Cohort 2 showed statistically significant reductions in mean turnaround time ($p = 0.0134$) and frequency of antibiotic orders administered within 60 minutes ($p=0.012$), as well as a trend towards reduction in administrations delayed greater than 4 hours ($p = 0.048$).

Figure 5: Mean antibiotic turnaround time

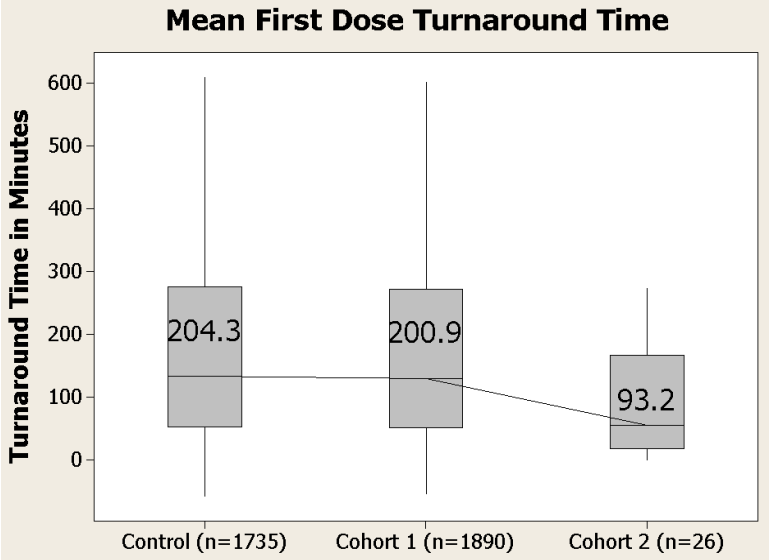
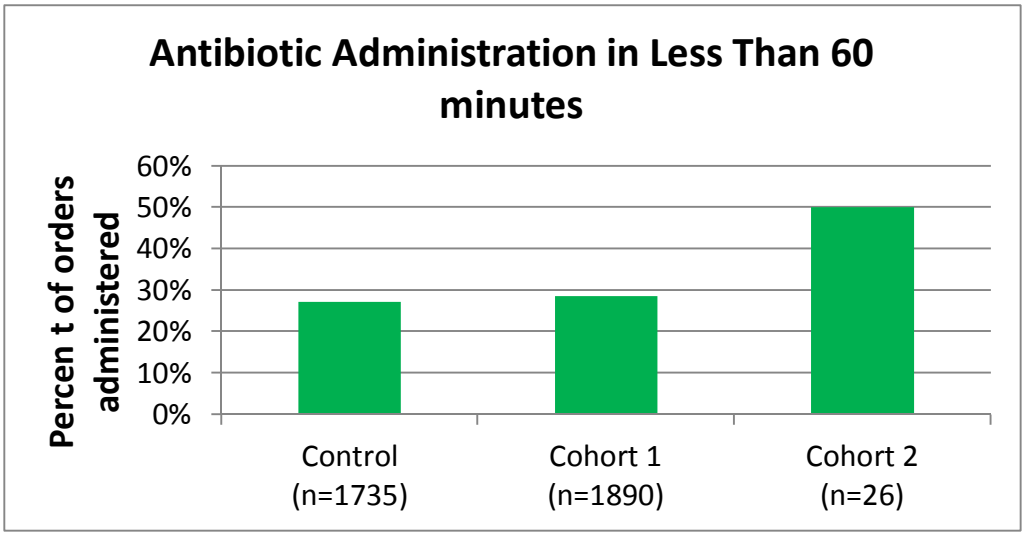


Figure 6: Orders administered within 60 minutes



Discussion:

The workflow changes from the Control group to Cohort 1 did not produce statistically significant improvements in mean turnaround time, success rate of achieving administration within 60 minutes, or reduction in delays greater than 4 hours. However, a number of positive

results in the small scale pilot intervention were yielded. We believe the primary reason for this is the nature of the intervention in Cohort 1, that it is dependent on healthcare worker education and vigilance, two notably impractical and unsustainable interventions on a large scale. The pilot, upon which Cohort 1 was based, was performed on two acute care units, each approximately 30 beds in size. The interdisciplinary team that was assembled to design the intervention consisted of the clinical pharmacist, nurse director, and a staff nurse from each of these units. In addition, physician groups that frequented these units were provided in-services from Pharmacy staff to utilize a stat priority for first dose antibiotics, and unit secretaries were sought out by their managers for engagement in identifying stat orders. During Cohort 1, this intervention was scaled to approximately 775 beds across 35 units of varying size and acuity. Communication about the project was delivered to nursing leaders at the institution's monthly Nursing Leadership Assembly meeting. Consequently, this information was only reaching front-line nursing staff at the unit director's discretion. Rather than being directly engaged by their managers, Unit Secretaries were given materials on acknowledging and notifying nurses of stat orders through an online learning module. Institution-wide completion rates were unable to be assessed, and compliance with both the learning module and actively notifying unit staff of stat orders is enforceable at the discretion of their manager and charge nurse, respectively.

We expected an improvement in stat orders turnaround time in the ICU setting due to the 1:1 or 1:2 nurse-to-patient ratio due to the familiarity with sepsis-related mortality and hyper-vigilance of the staff, but a different scenario was observed. We are interested to see that the only subgroup that experienced a significant difference in turnaround time was stat orders submitted for patients on an acute care unit, as that closely resembles the environment that the pilot was

designed for and tested in with notable success. Even after this group was identified, we predicted an improvement in the number of orders administered within 60 minutes, but the primary source of the reduced average time was a decrease in the number of orders that were delayed greater than 4 hours.

Design and development of the first-dose antibiotic MLM proved to be extremely complex and time-consuming due to the technical challenges of creating the function and the organizational challenges of gaining approval and buy-in. With the build of the MLM came difficulties in maintaining compliance with SCIP measures in the perioperative period, scheduling of first-doses for previously administered medications, and difficulties in scheduling follow-up doses, as it negated previously established standard administration times. The approval process was particularly difficult to navigate, as the MLM affected every physician, nurse, and pharmacist in the hospital. This led to significant delays in receiving approval to move forward with implementing the MLM as it did not fall neatly within any existing committee's charter. In the time since the MLM design, a formal pathway for Clinical Decision Support approval and implementation has been developed by the pharmacy and system quality leaders.

Despite having an extremely small sample size of 26, Cohort 2 showed statistically significant improvements compared to Control and Cohort 1 in median turnaround time and percentage of orders administered within the 60 minute target, as well as a trend towards reduced rate of orders delayed greater than 4 hours. This confirms our theory that order priority is the critical determinant to turnaround time for these orders, and serves as additional justification for the

Information Technology resources that were devoted to the development and revision of this program.

The findings from this study support allocation of resources towards the development and implementation of infrastructure that will hard-wire an action or reminder. An intervention dependent on healthcare workers' hyper-vigilance and recognition of clinical scenarios was not predictable or reliable enough to produce a significant improvement across the entire institution. This information challenges education-based adaptations, and suggests that a more holistic approach utilizing advances in technology and logic-based, automated algorithms offer the greatest opportunity for sustained improvement.

On a more global scale, this study illustrates expansion of technology from traditional clinical decision support messages to a logic-based algorithm that interprets provider intent and alters a medical action accordingly. Medicare EHR Incentive Programs require CPOE to meet Meaningful Use objectives, and with this comes remote order entry capabilities and decreased face-to-face communication between physicians and unit-based nursing staff. Use of antibiotic stewardship is expanding throughout the United States, with the intent of promoting appropriate use of antibiotics – this includes time of administration. We believe this technology can serve as a template for how antibiotics are ordered and administered in all healthcare institutions, as well as a model for the creation and expansion of applications that leverage existing data at the individual patient level to guide healthcare providers to an appropriate medical action in line with their working diagnosis and treatment plan.

Conclusion:

The medication use process workflow renovation did not produce a significant improvement in first-dose antibiotic turnaround time throughout the institution; but when paired with an advanced Medical Logic Module, reduced administration times were documented across the spectrum among other improvements, including the rate of orders meeting the 60 minute target and a reduction in orders that were extremely delayed.

Disclosures:

Patrick Birney: Nothing to disclose

Rebeca Halfon: Nothing to disclose

Julianna Fernandez: Nothing to disclose

Faisal Masud: Nothing to disclose

Shaikh Hai: Nothing to disclose

Alex Varkey: Nothing to disclose

Kevin Garey: Nothing to disclose

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