Time to Antibiotic Administration for Neutropenic Fever in the Emergency Department

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Abstract

Neutropenic fever, a common complication in cancer patients, requires prompt antibiotic treatment to prevent mortality. Current guidelines recommend antibiotic administration within 60 minutes of triage completion. However, many emergency departments (EDs) struggle to meet recommended treatment timeframes. This study in an academic medical center's ED analyzed 88 neutropenic fever cases, revealing a median time to antibiotic administration of 146 minutes, with only 7.95% meeting the 60-minute guideline. Factors like door-to-doctor time, time to antibiotic order placement, and antibiotic preparation time were found to affect time to antibiotic administration. No correlations were found between time to antibiotic administration and long-term patient outcomes in this study. Future initiatives should focus on reducing time from triage completion to antibiotic order placement to optimize patient outcomes and improve care for neutropenic fever patients in the ED.

Problem Description

Neutropenia is defined by the American Society of Clinical Oncology as an absolute neutrophil count (ANC) less than 1,000 cells per microliter with severe neutropenia being an ANC less than 500 cells per microliter, and profound neutropenia being an ANC less than 100 cells per microliter (Flowers et al., 2013). Neutropenic fever is a common presenting concern among cancer patients, affecting more than 80% of patients with hematologic malignancies and 10-50% of patients with solid tumors (Kwak et al., 2016). This condition most often results from profound bone marrow suppression (usually caused by chemotherapeutic treatment regimens) increasing cancer patients susceptibility to serious and potentially life threatening infections (Kwak et al., 2016). Neutropenic fever is associated with a 4-10% mortality rate and can reach as high as 58% in patients with multiple comorbidities such as congestive heart failure, lung disease, liver disease, kidney disease, and diabetes (Bruce, 2021; Kuderer et al., 2006). Neutropenic fever is generally defined as a measured oral temperature greater than 38.0°C that lasts longer than one hour or a single measured oral temperature of 38.3°C or greater in patients who have neutropenia (White & Ybarra, 2014).

Current guidelines recommend that antibiotic therapy should be administered within 60 minutes of triage completion for patients presenting to the emergency department (ED) with neutropenic fever (Flowers et al., 2013). Currently, many EDs (especially those of community hospitals that do not treat cancer patients frequently) do not meet the recommended time to antibiotic (TTA) guidelines, which places patients at increased risk of complication and death (Dang et al., 2018). It has been shown that in patients with severe neutropenia and fever, antibiotic administration within one hour of fever onset results in a 70% reduction in mortality (Rosa & Goldani, 2014). Furthermore, for each one hour delay of antibiotic administration, there

is an 18% increased risk of mortality within 28 days (Dang et al., 2018). Therefore, it is necessary for EDs to improve TTA and ensure that patients with neutropenic fever are being treated promptly.

Available Knowledge

Prompt treatment with empiric-broad spectrum antibiotics is necessary to ensure positive outcomes for patients who present to the ED with neutropenic fever. Multiple quality improvement (QI) projects have been conducted on how to improve TTA in EDs with varying degrees of success. However, many of the projects were conducted in pediatric only EDs and still need to be trialed in mixed populations and adult EDs. In one tertiary care hospital's pediatric ED, a QI project found that by implementing a clinical practice guideline (CPG) for the treatment of patients with neutropenic fever, median TTA was reduced from 207 minutes to 44 minutes (Benner et al., 2018). Another QI project at an academic medical center's pediatric ED found that by implementing a rapid ANC test in the hospital's lab, ANC turnaround times decreased from 60 minutes to 10 minutes and the percentage of neutropenic fever patients who met the TTA goal increased from 47% to 60% (Yoshida et al., 2018).

Rather than implementing only one intervention aimed towards improving TTA, as in the QI projects above, several hospital's QI projects implemented multiple interventions at the same time. One large pediatric facility's ED implemented a QI project with three different interventions aimed to improve workflow for neutropenic fever patients. These interventions were to create a provider order set, create a triage nurse order set, and to administer antibiotics prior to receiving an ANC result (Lukes et al., 2019). These interventions decreased the ED's TTA from 128 minutes to 53 minutes and increased the number of patients who met the TTA goal from 0% to 83% (Lukes et al., 2019). A pediatric level one trauma center's ED identified

several areas for TTA improvement and completed a QI project with five interventions. These interventions were to improve timely identification of neutropenic fever patients, create a streamlined intravascular access process, standardize practice among providers, provide easy access to appropriate empiric antibiotics, and increase staff education (Woods et al., 2022). This project showed an improvement from 73% to 95% achievement of the TTA goal and sustained greater than 90% TTA goal adherence for more than three years after project completion (Woods et al., 2022).

At an adult hospital's ED, a two-phase QI project was implemented to improve the TTA in patients who presented with neutropenic fever. The first phase was to increase staff education about the TTA goal, create a neutropenic fever protocol/order set, and improve ED workflow. This phase decreased TTA from 100 minutes to 67 minutes (Dang et al., 2018). The second phase was to create an ED neutropenic fever response team (similar to cardiac and stroke response teams) to initiate a hospital wide response for the rapid care of the patients and implement 15-minute weekly huddles to review the cases where the TTA goal was not met. This second intervention further decreased TTA time from 67 minutes to 27 minutes (Dang et al., 2018). All the data from the QI projects discussed above suggest that improvement in the care of patients with neutropenic fever through the timely administration of antibiotics may benefit from a multifactorial approach. It is clear that reaching a TTA goal of 60 minutes requires interdisciplinary cooperation, excellent team communication, and coordination between multiple departments within a hospital.

Rationale

This study was guided by the steps laid out in the Model for Improvement (MFI) created by the Associates in Process Improvement. It also incorporated elements of the Define, Measure, Analyze, Improve, Control (DMAIC) process, which is traditionally a part of the Six Sigma initiative, but for this study was used as part of improvement procedures as seen in other QI models (ASQ, 2023). The MFI is based on three foundational questions: "What are we trying to accomplish? How will we know that change is an improvement? What change can we make that will result in improvement?" (Langley et al., 2009). This study aims to answer the three questions posed by the MFI and to address the first three steps in the DMAIC process, as they relate to the treatment of neutropenic fever in the ED, to guide the development of future Plan-Do-Study-Act (PDSA) cycles.

Specific Aims

Specific Aim 1: Understand the current time it takes at an academic medical center's emergency department to identify a patient with neutropenic fever and initiate antibiotic therapy.

Specific Aim 2: Analyze what factors affect TTA for patients with neutropenic fever at the academic medical center including: ESI (emergency severity index) assigned by triage RN, door-to-triage (DTT) time, door-to-doctor (DTD) time, time to antibiotic order placed, time from antibiotic order placed to administration (antibiotic preparation time), time to lab order placed, and time to ANC result.

Specific Aim 3: Analyze if there is a relationship between TTA for patients with neutropenic fever and the following: ED length-of-stay (LOS), total hospital LOS, and 30-day readmission rate.

Specific Aim 4: Propose a target area or variable of interest for improving TTA at the academic medical center in question.

Methods

Context

This study took place in an adult only 576-bed teaching hospital, biomedical research facility, and level 1 trauma center's ED. This hospital has a large, well-funded cancer institute that is ranked among the United States' top cancer centers. Therefore, the ED at this hospital experiences a higher than typical volume of patients who present with neutropenic fever. This hospital is located in an urban setting with an estimated 2,500,000 residents in the metropolitan area and is one of only two level 1 trauma centers in the area (Oregon EMS and Trauma Systems, 2023; U.S. Census Bureau, 2022).

This hospital's 44-bed ED experiences longer than average patient LOS and door-to-doctor (DTD) times. This is likely a result of high patient volumes and the hospital chronically being at capacity, causing a high volume of inpatient boarders in the ED and decreased ED bed availability. In addition to the challenges posed by increased LOS and DTD times, this ED has many temporary staff in the form of travel nurses and resident physicians. Staff inexperience and frequent turnover may contribute to a lack of awareness of the importance of TTA in patients with neutropenic fever. These contextual elements all have the potential to make identifying and immediately treating patients presenting with neutropenic fever difficult.

Interventions

To meet the first aim of this project, a retrospective chart review was conducted to identify patients who presented to the ED at the academic medical center in question and were diagnosed with neutropenic fever. Data from the charts of the identified patient was collected to

determine the length of time elapsed between triage completion and first antibiotic administration for these patients. To meet the second aim, further data was on patient specific variables affecting TTA. To meet the third aim, the charts were evaluated to determine ED LOS, total hospital LOS, and 30-day readmission rate. The above data collected was compounded and analyzed to meet the fourth aim of the project, to determine what tool might be used to improve TTA for the ED.

Study of the Interventions

The study of this project's data collection included the monitoring for any new facility-based initiatives or staff education during the collection period that may affect the patient specific measures including: TTA, LOS, DTD, etc. No new education or initiatives were identified during the study period. It is recognized that new resident physicians start annually, in the month of July, and this may affect the data collected for this project as new resident physicians may not identify and treat patients with neutropenic fever as quickly as experienced providers. By including data collected immediately before and after new resident physicians start in the ED, this study aimed to have a more accurate representation of TTA and other patient specific measures.

Measures

The primary measure of this project was TTA in patients who present to the ED with neutropenic fever. Data was collected from November 1st, 2022 to February 28th, 2023 and from May 1st, 2023 to August 31st, 2023. This time period aimed to account for seasonal differences in ED volume as well as resident physician's level of experience. Process measures for this study were the variables thought to be affecting TTA including time for lab work completion, time for antibiotic preparation, DTD time, ESI assigned by triage nurse, etc. All data was collected from

the electronic medical record (EMR) of patients who were given a diagnosis of neutropenic fever during their ED visit. The appropriate EMRs were identified based on ED visits assigned an ICD-10 code for neutropenic fever.

Analysis

The primary analysis for data collected in this project is quantitative and based on inferential statistics. Data collected from the EMR for this project was analyzed using T-tests to determine if there is a statistical significance in variables thought to be affecting TTA, scatter plots that display relationships between the data gathered, and linear regression models to understand the strength of relationships between variables. Exploratory model building was used to determine which variables are the best fit and have the greatest impact on TTA. The project primarily used the median findings to analyze data to mitigate the effects of outliers. Future projects at this facility aimed to address TTA in patients with neutropenic fever will be able to compare the data collected in this project before the implementation of a change with data collected in the future after a change is implemented.

Ethical Considerations

This project protected the anonymity and confidentiality of the patients involved by not collecting any personally identifying information and by ensuring that the facility where data collection occurred was deidentified. The implementation of a proposal created to meet the aim of this project had the potential to affect the care that patients with neutropenic fever received while in the ED. Added process changes could have negatively contributed to increased clinician stress; this project attempted to mitigate these ethical concerns by proposing an intervention for TTA improvement that did not negatively affect patient care or overburden clinicians. Clinician stress can be mitigated in future QI projects by educating ED staff on the importance of

improving TTA for patient outcomes to increase buy-in for any process changes. This project was submitted to the OHSU IRB, assigned the IRB ID: STUDY00025894, and was deemed "not human research". The investigators in this study have no conflict of interest.

Results

There were 97 ED encounters during the six-month study period that were assigned an ICD-10 code corresponding with neutropenic fever. Of these 97 patient visits, eight were excluded because the patient's ANC was greater than 1,000 cells per microliter. One encounter was excluded because the patient presented as a trauma activation, which was determined to skew the data collected. Of the 88 ED encounters included in this study, it was found that the mean TTA was 193.1 minutes and the median TTA was 146 minutes. This study determined that during the data collection period, only 7.95% of patients diagnosed with neutropenic fever were administered antibiotics within 60 minutes of triage completion. The time for triage completion was found to be 15 minutes.

This study identified that 54.5% of patients during the collection period were given an ESI of 2, while the rest were given an ESI of 3. However, ESI was not determined to be a relevant factor based on T-tests for statistical significance (see Appendix A). The DTD time was found to be 47 minutes and the time from triage completion to antibiotic order placement was 72 minutes. The antibiotic preparation time was determined to be 68 minutes. T-tests performed to determine the association between different variables and the primary outcome of TTA within 60 minutes found that DTD, time to antibiotic order, and antibiotic preparation time all had statistically significant P-values (see Appendix B). The effects of the variables on TTA were confirmed using continuous-by-continuous data through basic scatterplots with a linear trend line (see Appendix C). The variable with the greatest effect on TTA was time to antibiotic order (R

squared: 0.75), followed by DTD (R squared: 0.38), and antibiotic preparation time (R squared: 0.26). The best fit linear regression model based on ED LOS, DTD, time to antibiotic order, and time to lab order (adjusted R squared: 0.752) determined that the primary variable effecting TTA was time from triage completion to antibiotic order placement. The correlation coefficient for this variable was 0.92 with a 95% confidence interval (CI) [0.75, 1.09] (see Appendix D).

The time for lab order placement during the study period was 2 minutes and the time to lab work collected was 22 minutes. It was found that 12.5% of patients who presented for neutropenic fever had been referred by an oncology clinic and had lab work draw prior to arrival with a new ANC result from that day. The remaining 87.5% of patients had a time from triage to ANC result of 128 minutes. Of the patients included, 36.4% were given antibiotics prior to having an ANC result. All the variables regarding lab work and ANC results were not found to be statistically significant based on results from the best fitting linear regression model and T-tests.

This project was also able to determine that the median ED LOS during the study period was 25 hours, hospital LOS was 6 days, and the 30-day readmission rate was 35%. Of note this study found that 15% of patients in this study were deceased within 30 days of their ED visit. None of these factors were found to have any statistically significant connection with TTA during the study period.

Discussion

Summary

In summary, this study found that during the study period only 7.95% of patients received antibiotics within the recommended 60 minutes from triage completion. The median TTA for the academic medical center in question was 146 minutes, which is 2.4 times greater than the

national standard. This means that this academic medical center would benefit from an intervention aimed at improving the TTA for neutropenic patients presenting to its ED. It was determined that the time from triage completion to first antibiotic order placed is the most significant factor affecting TTA and would likely be a good target for improvement in future PDSA cycles. This project did not find any significant relationship between TTA and ED LOS, hospital LOS, or 30-day readmission rates.

Interpretation

This study has shown that the academic medical center in question is currently not meeting national recommendations for the TTA administration in patients who present to its ED with neutropenic fever. This is not surprising as there are many EDs that are not currently meeting the antibiotic administration within 60 minutes from triage completion recommendation. As mentioned above, there are many factors that may be affecting this finding at this facility including a lack of staff education, high staff turnover, and large volumes of boarding patients. Given the findings of this study, it seems that this academic medical center would make a good candidate for future QI projects to trial interventions aimed at improvement using PDSA cycles.

There are many variables that contribute to TTA in emergency departments and there have been various QI projects at other institutions that target different variables. This study found that DTD time, time to antibiotic order, and antibiotic preparation time all had statistically significant effects on the total TTA. However, the variable with the greatest effect was found to be time to antibiotic order placement. The findings of this study are similar to those of the QI project conducted by Benner et al. (2018); implementation of a CPG was successful in decreasing median TTA by 163 minutes for the treatment of patients with neutopenic fever. Another large pediatric facility's ED was able to improve TTA to within the 60 minute

recommendation by creating a provider order set, creating a triage nurse order set, and administering antibiotics prior to receiving an ANC result (Lukes et al., 2019). Based on the results of this QI project, implementing a similar intervention would likely greatly improve TTA.

Limitations

This study was limited by the small sample size who met the recommended TTA goal. It was difficult to compare the differences between the variables in two groups when one group was very small. The use of continuous-by-continuous data as opposed to discrete data was used to help mitigate the effects of few patients meeting recommended TTA goals and meaningful conclusions were still able to be drawn. Future projects may choose to review a full year of data rather than six months. The data analysis in this project was affected by significant outliers. However, the effects of these outliers were mitigated by using median values and various statistical tools. The data collected about 30-day readmission rates, hospital LOS, and ED LOS was confounded by patients who were readmitted within 30 days for scheduled cancer treatments and the significant time spent boarding in this ED. This prevented any useful data interpretation about the long-term effects of TTA; this limitation was largely unavoidable because of the site chosen for this study.

Conclusions

There are few QI projects in adult-only hospitals that aim to improve the care of neutropenic fever patients in the ED. The results of this study may be useful in providing generalizable knowledge to other academic medical centers with similar patient demographics and ED volumes that are aiming to improve TTA for patients with neutropenic fever. This study has been able to lay the foundation for future QI projects that will focus on the implementation of interventions aimed at improving TTA. Future projects will be able to compare data from

before and after intervention implementation using the data presented in this study. Future QI projects should be aimed at decreasing time from triage completion to antibiotic order placement to have the greatest effect on reducing TTA.

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Appendix A

T-test Data for ESI

T-test data for statisitcal significance of assigned ESI level effects on DTT, DTD, time to antibiotics ordered, time to antibiotics prepared, time to labs ordered, and time to lab work resulted.

ESI Level	DTT (min)	DTD (min)	Antibiotics Order (min)	Antibiotics Prepared (min)	Labs Ordered (min)	Lab Result (min)
2	17	60	86	77	4	128
3	18	75	136	93	19	154
P-value	0.36093078	0.30951558	0.04920311	0.28101674	0.13713224	0.0619818

Appendix B

T-test Data for TTA

T-test data for statisitcal significance of ED LOS, hospital LOS, DTT, DTD, time to antibiotics ordered, time to antibiotics prepared, time to labs ordered, and time to lab work resulted on TTA.

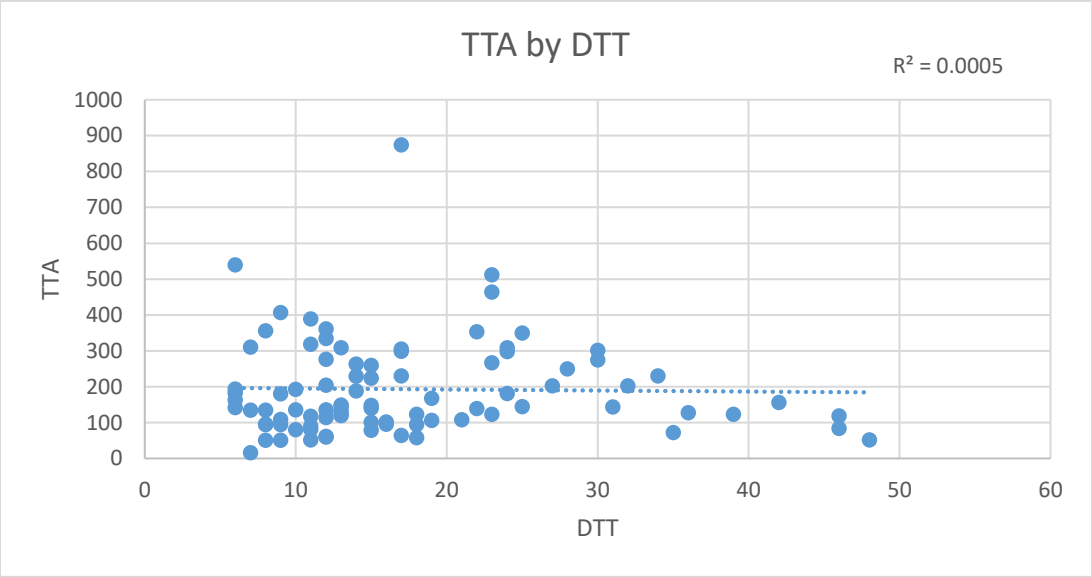
Antibiotics given within 60 minutes	ED LOS (min)	Hospital LOS (min)	DTT (min)	DTD (min)	Antibiotics Order (min)	Antibiotics Prepared (min)
Yes	1474	10	16	30	19	29
No	1994	8	18	68	109	88
p-value	0.38736475	0.74731412	0.81560261	0.00201332	2.82107E-10	6.97541E-09

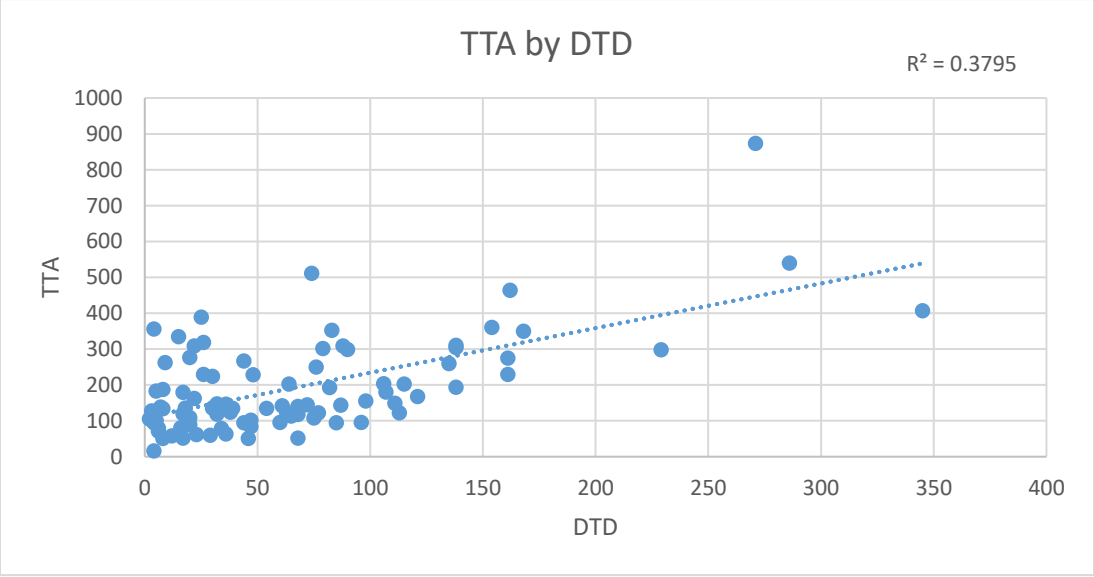
Antibiotics given within 60 minutes	Labs Ordered (min)	Lab Result (min)
Yes	0	146
No	12	139
p-value	0.816354416	0.739702512

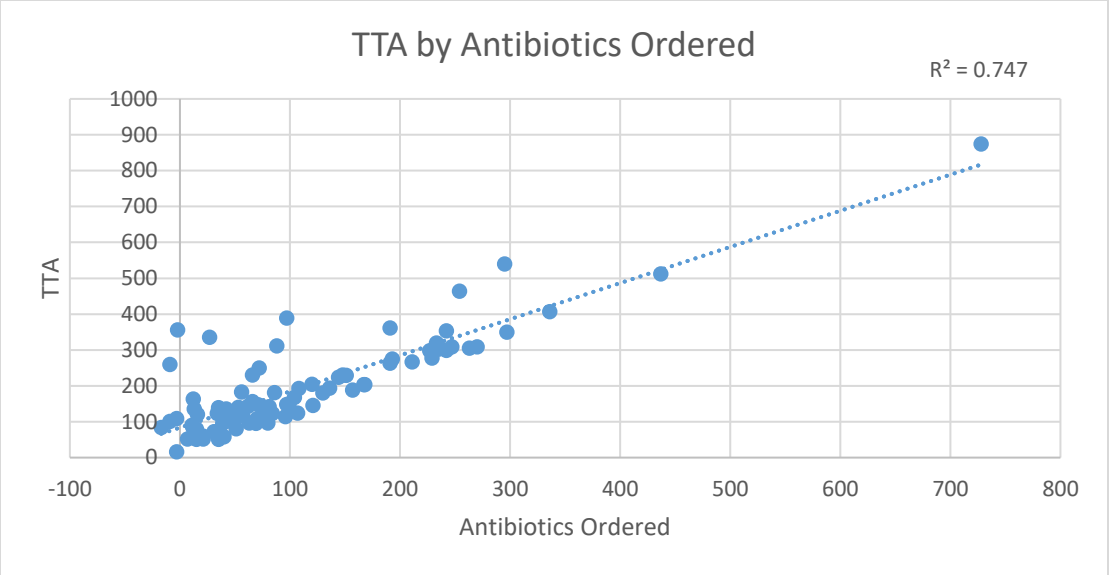
Appendix C

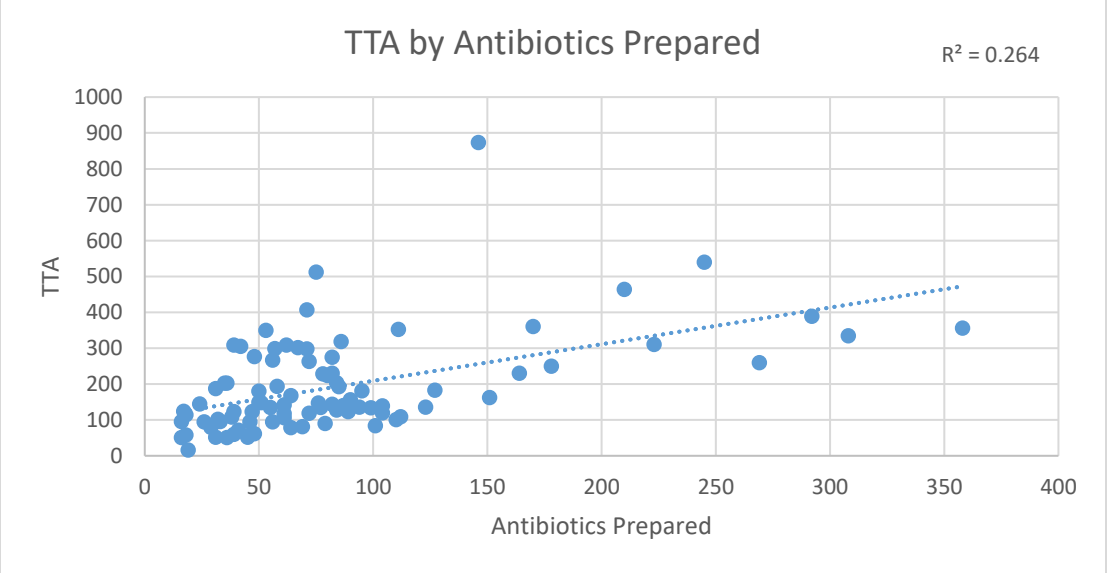
Scatter Plots

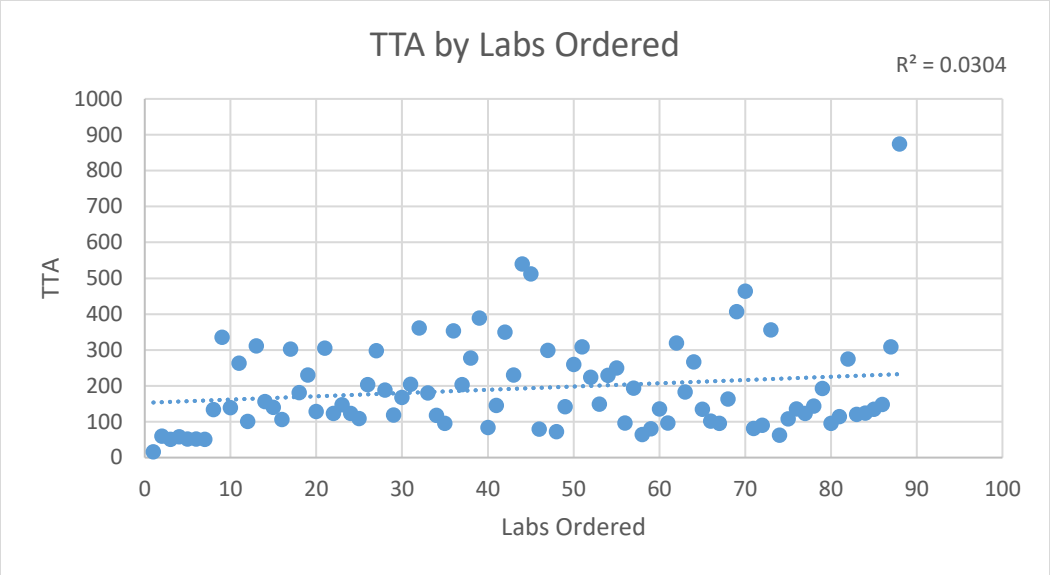
Scatter plots with linear trend lines for the effects of DTT, DTD, time to antibiotics ordered, time to antibiotics prepared, time to labs ordered, and time to lab work resulted on TTA.






TTA by Antibiotics Ordered
R² = 0.747
TTA
Antibiotics Ordered
1000
900
800
700
600
500
400
300
200
100
0
-100
0
100
200
300
400
500
600
700
800


TTA by Antibiotics Prepared
R² = 0.264
TTA
Antibiotics Prepared
1000
900
800
700
600
500
400
300
200
100
0
0
50
100
150
200
250
300
350
400


TTA by Labs Ordered
R² = 0.0304
TTA
Labs Ordered
0
100
200
300
400
500
600
700
800
900
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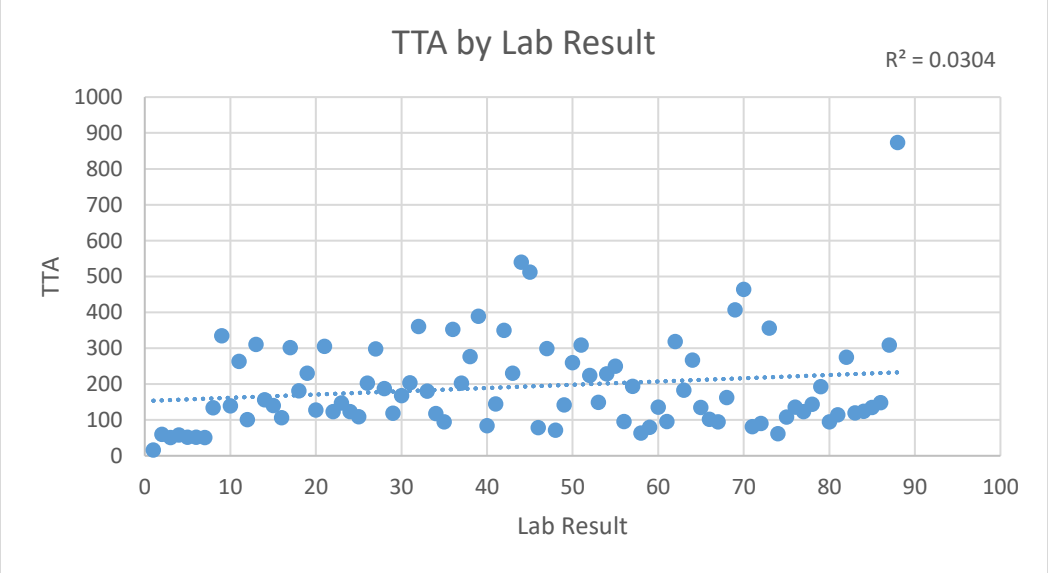
10
20
30
40
50
60
70
80
90
100


TTA by Lab Result
R² = 0.0304
TTA
Lab Result
0
100
200
300
400
500
600
700
800
900
1000
0
10
20
30
40
50
60
70
80
90
100

Appendix D

Linear Regression Model

The best fit linear regression model based on ED LOS, DTD, time to antibiotic order, and time to lab order exhibiting that the primary variable effecting TTA is time from triage completion to antibiotic order placement.

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.873504876
R Square	0.763010769
Adjusted R Square	0.751589601
Standard Error	66.26152269
Observations	88

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	4	1173283.524	293320.881	66.80672115	3.67552E-25
Residual	83	364418.9193	4390.589389		
Total	87	1537702.443			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	77.07740073	13.11843973	5.875500618	8.46141E-08	50.98535173	103.1694497
ED LOS	-0.000986877	0.005008472	-0.197041605	0.844276694	-0.010948526	0.008974771
DTD	0.225157506	0.139837274	1.610139412	0.111164333	-0.052973208	0.503288219
Antibiotics Ordered	0.918516114	0.085196268	10.78117785	1.87373E-17	0.749064164	1.087968063
Labs Ordered	-0.318219602	0.190446188	-1.670916105	0.098504996	-0.060570205	0.697009409