Final Report

EN 601.656 Computer Integrated Surgery II

Spring 2023

CREATION OF A NOVEL REAL-TIME COMMUNICATION SOLUTION FOR TIMELY SEPSIS MANAGEMENT

Team Member

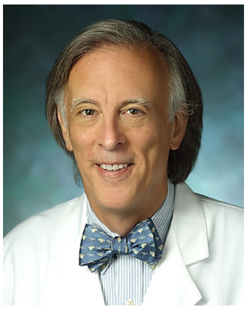
Sofia Posada, Junior

Department of Computer Science

Team Member

Rahul Swaminathan, M.S.E Student

Department of Biomedical Engineering



Mentor

Dr. Jim Fackler, M.D.

Anesthesiology and Critical Care Medicine

Mentor

Dr. Kimia Ghobadi, Ph.D.

Department of Civil and Systems Engineering

Table of Contents

1 Introduction

1.1 Background

Sepsis is the body's extreme reaction to an infection. However, diagnosing a child with sepsis has different criteria than diagnosing an adult with sepsis, which is evident from the bolded text in Figure 1 (1). Regardless of age, sepsis is a life-threatening condition that attacks the body quickly. It is a main cause of global morbidity and mortality, with peak mortality occurring in pediatric and elderly patients (2). Based on a systematic review with 15 studies included in the meta-analysis, they found that there are, on average, 48 sepsis cases in children per 100,000 person-years. Within these cases, mortality ranged from 13 to 54% (2). The majority of deaths from children with severe sepsis occur during the first 24 hours after the children are referred to the pediatric intensive care unit (3).

SIRS[a]
The presence of at least two of the following four criteria, **one of which must be abnormal temperature or leukocyte count:**
- Core[b] temperature of >38.5°C or <36°C.
- Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period **OR for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.**
- Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

Infection
A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

Sepsis
SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis
Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in Table 4.

Septic shock
Sepsis **and cardiovascular organ dysfunction as defined in Table 4.**

Modifications from the adult definitions are highlighted in boldface.
[a]See Table 3 for age-specific ranges for physiologic and laboratory variables; [b]core temperature must be measured by rectal, bladder, oral, or central catheter probe.

Figure 1: Differences in Sepsis Symptoms Between Adults and Children

1.2 Problem and Motivation

Since sepsis attacks the body so quickly, timing is of utmost importance when treating children with sepsis. A child can appear healthy one moment and quickly develop sepsis and need to be put on life support, so detecting sepsis as soon as possible is critical. Once detected, delivering antibiotics to a septic child within one hour is critical, with a noted decrease in mortality by 40% (4). The data showed that the children who received antibiotics within one hour had, on average, a shorter hospital length of stay and shorter in-hospital mortality rate (5). Evidently, timing is critical when treating sepsis.

Though it is known that identifying sepsis early and treating patients within one hour is critical, there is no implementation in place to accomplish this. After speaking with Dr. Fackler and other attending physicians at the Johns Hopkins PICU, it is evident there is a communication issue when it comes to treating children with sepsis.

1.3 Goals

Although a process map exists regarding the team members involved when it comes to treating sepsis, the map is not finalized as it is still missing several members and workflows. We will finalize this map by interviewing providers as well as collect timestamps regarding the people on this map. With this data, we will perform a gap analysis and see where there is the biggest lack of communication. Our goal is to find a viable solution to this problem and indirectly improve treatment outcomes by successfully providing IV antibiotics within an hour to children diagnosed with a serious bacterial infection.

2 Technical Approach

The project workflow was split into the following main components:

1. Augment the Process Map
2. Collect Data and Perform Gap Analysis
3. Develop a Communication Solution
4. Test Efficacy of Solution (if time permits)

2.1 Process Map Augmentation

Augmenting the process map involved conducting clinician and provider interviews with the help of Chen Wang, a Master's student who was currently working with Dr. Fackler. We started by interviewing Dr. Dave Procaccini, a pharmacist at the Children's Pharmacy at the Johns Hopkins Hospital, to learn more about the pharmacy's workflow for delivering antibiotics and any potential room for delays. We then met with David Reisz who manages the Versus Information System (VIS) at the Hopkins Hospital in order to learn about potential tracking technology that we could use to track both antibiotics and personnel. We were also able to meet with Anatoly Gimburg, the Vice President of Facilities Management for the JHHS, and he gave us a tour of the pneumatic tube system that connects all the Hopkins Hospital buildings.

2.2 Data Gap Analysis

The bulk of our time was focused on this component, where we performed a gap analysis on the dataset of timestamps to determine and create a solution to the lack of communication that occurs when treating pediatric sepsis patients. To do this, our original plan was to re-purpose the existing Versus Information System (VIS) tracking technology in the hospital. VIS is a real-time locating system that was initially introduced to hospitals as a way of tracking the locations of nurses and patients within a hospital. The system uses infrared and radio-frequency-based tracking to identify room-level locations rather than approximate locations. Rather than using it to track nurses, we planned to collaborate with the hospital pharmacy to place VIS tags in the bags containing the antibiotics in order to track their location throughout the delivery process. We hoped this would not only give us an idea of how the antibiotics go from the pharmacy to the patient but also where and when delays happen; and whether there are any specific problem areas within the hospital.

Due to limitations beyond our control, we were unable to get hold of the VIS tags from the hospital. Instead, we were able to access secondary data from the hospital's patient database. The dataset included timestamps of the antibiotics throughout their delivery process. We used this previously existing data to perform our gap analysis. Our findings will be discussed in our Results section. However, a key finding was that the biggest time delay occurred when delivering the antibiotics from the pharmacy to the PICU. This information was critical as we developed our solution.

2.3 Develop a Communication Solution

After the successful collection and analysis of the data, we intended to export the tracked locations and correlate them to team members in charge of transporting or administering the antibiotics at those locations. Essentially, we planned to use the timestamps from our data in relation to our process map to further develop the antibiotic administration workflow. We planned to use this information in combination with either VIS's internal alert system or Epic's secure chat to develop an alert system that would contact relevant personnel and inform them when it is their turn to take over antibiotic delivery. Before implementing our alert system, our first milestone was to develop real-time visibility of the antibiotic delivery process. This entailed researching a way to track the antibiotics.

Initially, our approach was to use VIS tags, which, as mentioned earlier, are small devices that can track the location of items in real time. However, further research revealed that the pneumatic tube system used to transport antibiotics from the pharmacy to the clinic would pose a significant limitation to this approach. Specifically, the VIS tags relied on IR tracking, which required there to be a line-of-sight between the tags and their receiver. Due to the opaque nature of pneumatic tube capsules, IR tracking would be impossible until the antibiotics were taken out of the capsules. However, one main problem we identified through our gap analysis was that there is no way to tell once a capsule containing the antibiotics has reached the PICU through the pneumatic tube. Nurses come by the tube station irregularly to check for deliveries, but there is no formal alert system, so that leaves much room for delays.

Our idea for a solution to this problem was to implement a Bluetooth proximity sensor to detect the arrival of important capsules carrying antibiotics. We aimed to place a Nutale BLE tag inside the pneumatic tube capsule containing the antibiotics and have an ESP32 microprocessor acting as a receiver by the tube station. In this way, when the capsule reaches the PICU, the microprocessor picks up the Bluetooth signal and uses the strength of that signal to estimate proximity. The microprocessor can be programmed to send notifications once the signal has reached a certain strength in order to alert nurses to the fact that the antibiotics have arrived. Placing one microprocessor in the pharmacy and one at the PICU tube station could also allow detailed tracking of individual capsules in order to collect data on how long deliveries take and whether there is any need for alternative policies in the event of stalled deliveries. This new solution entailed using the Bluetooth proximity sensors to track the arrival of antibiotics from the pneumatic tube while the VIS tags could be used to track the location of the antibiotics within the PICU. However, access to the VIS tags was not possible, necessitating a third solution.

After extensive research, we decided to take inspiration from "Implementation of a Web-based medication tracking system in a large academic medical center" (Calabrese and Williams 2012), which describes the implementation and effect of a live tracking system using barcodes for the delivery of medication within the Cleveland Clinic. The paper suggested that just like traditional package delivery through companies like FedEx, where barcodes are scanned at different locations to provide electronic delivery tracking for vendors and the end-user, pharmacies can also use barcodes on medications to track patient-specific medications during the delivery process in order to decrease medication turnaround time and improve overall workflow efficiencies (6). Due to the positive results from this paper, we found it to be a great suggestion for a new way to track antibiotics that we had not yet considered. Hence, our final solution entailed using the Bluetooth proximity hardware to track antibiotics within the pneumatic tube and barcode scanning to track antibiotics within the PICU.

Through our interview with Dr. Procaccini, we found that barcode scanning is already used in the pharmacy to track when medications have been sent to the PICU, but these barcodes are then unused so there isn't any way to track the medications past that. We aimed to identify key points in the delivery process where nurses could be asked to scan the unique barcode on each medication order and automatically update a timesheet. The barcode scanning process worked as follows: A pharmacist would print a barcode sticker onto the antibiotic before sending it out through the pneumatic tube. After being alerted that the antibiotic has arrived at the PICU using the Bluetooth proximity sensor, the next relevant sepsis team member would use a barcode scanner located at different locations within the PICU to scan the antibiotic's barcode. Every time the barcode is scanned, the antibiotic's location would be updated.

2.4 Test Efficacy of Solution (not done)

While the proposed solution has significant potential to improve sepsis treatment, it must be noted that the efficacy of the entire solution altogether could not be tested due to time constraints and unforeseen circumstances.

Despite these limitations, we made considerable progress in identifying an effective approach to tracking antibiotic delivery and administration.

3 Results

3.1 Key Findings

The finalized process map, initially started by Chen Wang, was the main contributing factor that aided us in finding a communication solution. A subset of this process map highlighting decision-making steps with the largest potential for delays is shown in Figure 2 and serves to provide a visualization of what the antibiotic delivery process looks like.

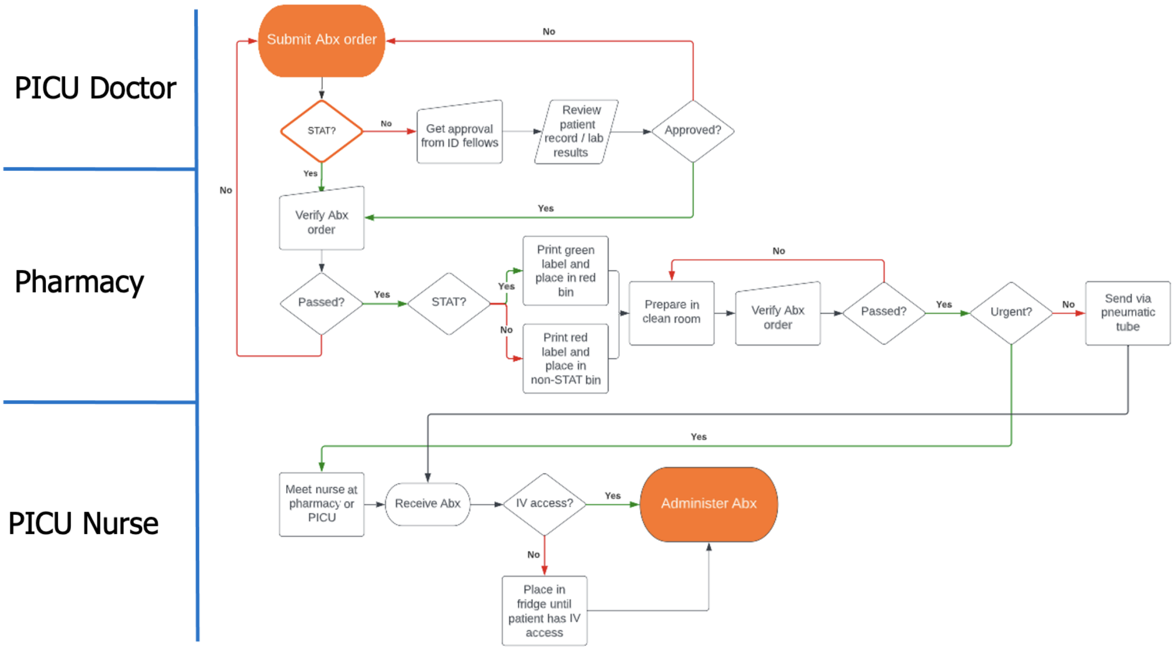


Figure 2: Process Map of Sepsis Management

We were able to acquire some but not all data needed for our gap analysis, as the dataset we were provided contained timestamps for when orders were placed and administered, but there was not much information on the steps in between. In fact, after interviewing Tom Kaszmetskie, a senior business intelligence developer for JHHS Quality and Clinical Analytics, we learned that the pharmacy does not have a standardized workflow for how to report rejected or cancelled orders, so none of the available datasets are organized clearly enough to derive a linear timeline for each order. Moreover, he showed us that in the thirteen months of data available to him of all PICU antibiotics orders, a timestamp for when an order was received was only recorded for 221 orders, as opposed to the 6472 timestamps available for when an order was sent. Essentially, once an order is marked as sent, regardelss of whether it is sent via the tube system or brought by a runner, we only know when the medication was received 3% of the time.

To address the lack of quantitative data, we conducted our gap analysis using a combination of the available timestamps and our interviews from shadowing Dr. Fackler in the PICU. We suspected that the biggest unknown in the delivery process was the transition from the pharmacy to the PICU through the pneumatic tube, as there is no alert system for when the antibiotics have arrived at the tube stations in the PICU, and that is also where the dataset is largely lacking. Although shipments from the pharmacy to the PICU only take around 2.4 minutes on average, there are about 140 cases per month where it takes longer than 3 minutes, with the longest delivery taking more than 23 minutes. This information can be found in Figure 3.

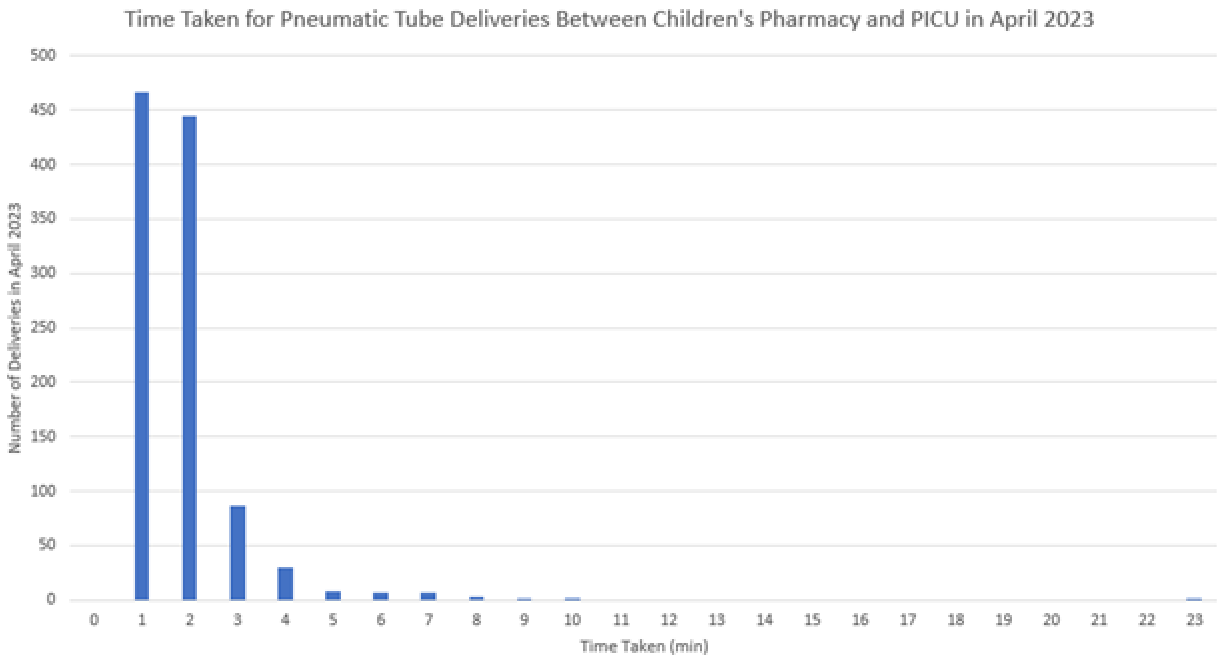


Figure 3: Time Taken for Pneumatic Tube Deliveries between the Children's Pharmacy and PICU in April 2023

According to Mr. Gimburg, the pneumatic tube system that Hopkins uses is very old and can run into issues with ghost carriers, where a capsule may get stuck, but the system won't recognize that and will send another capsule, causing the desired delivery locations to all be offset by one. Problems like these require a complete shutdown of the system and manual delivery during that time. Even when shipments do arrive within a couple minutes, the lack of an alert system leads to infrequent checking of the tube station, and we observed that nurses took up to 10 minutes to pick up a capsule from the PICU tube station once it had arrived.

All of these findings from the gap analysis served to substantiate the need for Bluetooth proximity sensing in order to detect the arrival of antibiotics through the pneumatic tube system. Using the ESP32 microprocessor and BLE tags mentioned earlier and shown in Figure 4, we tested the accuracy of proximity sensing at the PICU pneumatic tube station with assistance from Dr. Fackler. Figure 5 shows the PICU pneumatic tube station along with two of the plastic capsules insulated with foam. After initial benchtop testing to see whether the microprocessor could detect the presence of the BLE tag and track it using its MAC address, we placed the tag inside a capsule and placed the microprocessor on the table next to the tube station. Although we were a little worried that the plastic and foam insulation would drastically weaken the Bluetooth signal strength, we were happily surprised to find that the signal strength consistently stayed between -63 and -70 while the capsule was in the tube station holding area. Moving the capsule away from the tube station caused the signal strength to weaken to between -85 and -95 before the signal was eventually lost. The smaller the negative number, the stronger the signal, so we updated the code to reflect these findings and print out a statement confirming the arrival of the capsule with the tag if the signal strength was greater than -70. This could also be modified to send an SMS to my phone upon arrival or update a timesheet with the arrival information.

Figure 4: ESP32 Microprocessor (Left) and Nutale BLE Tag (right) Used for Bluetooth Proximity Sensing

Figure 5: PICU Pneumatic Tube Station No. 845

3.2 Significance

Our proposed communication solution of real-time tracking of antibiotics has the potential to significantly enhance the communication and coordination among sepsis team members involved in the antibiotic delivery process. This, in turn, can reduce the time required for antibiotic administration, thereby improving patient outcomes. As mentioned earlier, timely administration of antibiotics is crucial in sepsis treatment and can significantly reduce morbidity and mortality rates. With our proposed solution, any reduction in the time required for antibiotic administration can have a positive impact on patient outcomes, ultimately improving the quality of care provided to sepsis patients. Furthermore, our solution will allow for more data regarding how much time each step of the delivery process takes, providing justification for policy changes in how medications are delivered and received. Overall, the significance of our solution lies in its potential to visualize the antibiotic delivery process and alert relevant sepsis team members in order to improve communication and coordination, and ultimately enhance the efficiency and effectiveness of sepsis treatment.

4 Management

4.1 Team Member Roles

We each contributed our unique skills and expertise to ensure the success of the project. The tasks completed by each of us are listed explicitly as follows:

Sofia:

- Met with Dr. Fackler to get a full walkthrough of the PICU, pharmacy, and antibiotic fridge
- Met with pharmacists at JHMI to get an in-depth look at the antibiotic's journey in the pharmacy before being sent off to the PICU
- Met weekly with Chen, Dr. Fackler, and Dr. Ghobadi to provide updates and brainstorm next steps
- Investigated e-alerts used at other hospitals and summarized relevant papers
- Further researched the barcode scanning system and created design specifications
- Conducted gap analysis using patient data
- Created mock-up of antibiotic tracking display

Rahul:

- Met weekly with Chen, Dr. Fackler, and Dr. Ghobadi to provide updates and brainstorm next steps
- Interviewed Dr. Dave Procaccini, David Reisz, and Anatoly Gimburg to learn about the pharmacy workflow, tracking technology, and the pneumatic tube system as well as help finalize the process map
- Met with Michael Cook and Tom Kaszmetskie to learn about the dataset containing antibiotic delivery and administration timestamps.

- Identified barcode scanning solution and summarized relevant papers
- Conducted gap analysis using pneumatic tube delivery data
- Created mock-up of antibiotic tracking display
- Brainstormed, designed, and tested Bluetooth proximity sensing solution

4.2 Dependencies

As shown in the table of dependencies in Figure 6, green signifies that the dependency was successfully resolved, yellow signifies that the dependency was partially resolved, and red signifies that the dependency was never met, so the contingency plan was followed.

Dependency	Need	Status	Planned Deadline	Hard Deadline	Contingency Plan
IRB approval for tracking	Tracking location of antibiotics from the pharmacy	No approval needed for sticking a gps tag in the antibiotics bag because someone from the pharmacy is on the existing IRB	2/16	2/28	N/A
Access to Versus Information System technology	Tracking location of antibiotics from the pharmacy	Still need access to the API Cannot get ahold of the tags	2/28	3/16	Use combination of Bluetooth proximity sensing and barcode system
Access to timestamp data	Gap analysis for identifying solution space	We have some of the data but not all. IRB change was approved!	2/20	3/16	Conduct gap analysis using limited available data in combination with nurse interviews
HIPAA Training	Access to certain datasets and Epic Secure Chat	All trainings are complete	2/28	4/13	May be able to use anonymized data for all analysis purposes

Figure 6: Dependencies and Plans for Resolving

4.3 Adherence to Deliverables

At the beginning of this project, we planned to finalize the process map, collect antibiotic tracking data, conduct a gap analysis, and create a prototype to track the antibiotics from the pharmacy to the PICU, with our maximum deliverables being the implementation and testing of that prototype. However, over the course of this project, we realized that some of these deliverables were infeasible for different reasons, some simply due to time constraints and some due to factors out of our control. For antibiotic tracking data, we were held up for several weeks due to uncertainty regarding the availability and functionality of the VIS tracking technology, and we were eventually unable to acquire the VIS tags for testing, so we were unable to collect that data. On the other hand, for the gap analysis, we were delayed for more than a month due to several issues, including a family emergency, change of staff, and problems with data access. In fact, some of the pharmacy data we expected to have by March is now only scheduled to arrive in mid-May, so we had to change a lot of our plans for how to conduct the gap analysis.

Overall, we still managed to accomplish most of our minimum and expected deliverables, with the remainder in a good place to be continued by whoever picks up this project next. To summarize:

Minimum (by 3/17/2023):

- Finalized process map of sepsis management workflow (Complete)
- Short report of gap analysis showing where a communication solution is most needed (Complete)

Expected (by 4/28/2023):

- Physical prototype of communication solution that allows providers to visualize where the antibiotics are within the hospital (Complete for pneumatic tube deliveries)

Maximum (by 5/18/2023):

- Implemented prototype of communication solution that uses a monitor to display the location of the antibiotics and whose turn it is within the process map (Unable to complete)
- Dataset of timestamps and locations for antibiotic delivery after the solution is implemented (Determined to be infeasible due to time constraints)

5 Conclusion

5.1 Next Steps

Moving forward, our proposed solution for improving communication among sepsis team members has the potential to be further developed and refined. The immediate next step is to test the Bluetooth proximity sensor by placing receivers in the pharmacy and PICU and seeing how well it is able to track a BLE tag as it moves with the antibiotics. Ideally, this will provide three data points. First, the signal strength will increase as the tag passes the pharmacy receiver before being sent through the pneumatic tube, which will allow us to know when exactly the antibiotics were sent. Second, the signal strength will increase as the tag arrives and gets close to the PICU receiver, allowing us to record the timestamp at which the antibiotics arrive. Finally, the signal strength will decrease as the antibiotics and tag are removed from the pneumatic tube capsule and taken to the patient room, which will provide us with a timestamp of when the antibiotics were picked up from the tube station. These three timestamps are currently missing from all existing datasets, so being able to collect this data would provide an accurate measure of the delay between sending and receiving medications through the pneumatic tubes in order to inform procedural improvements. Rahul will work on this testing until the end of May and have everything documented so that it can be picked up by future team members working on this project.

Another possible next step would be to integrate our tracking solution with the hospital's electronic health record (EHR) system, such as Epic, to enable automatic alerts to be sent to the sepsis team members when the antibiotic has arrived at their department. This integration could further streamline the communication process and improve the efficiency of sepsis antibiotic administration, potentially leading to better patient outcomes.

Eventually, we also envision setting up monitors or displays in key locations throughout the hospital to visualize the tracking progress of sepsis antibiotics in real-time. This could include displays in the pharmacy, the PICU, and the sepsis team's workstations, for example. This approach would enable team members to quickly and easily view the location of antibiotics and identify any potential bottlenecks or delays in the delivery process. We envision this display to look like the mock-up shown in Figure 7.

Further research and testing will be necessary to determine the feasibility and effectiveness of these next steps.

Order #	Current status	Location	Team member responsible	Next step	ETA (Estimated Time of Administration)	On track?
001	Ordered - in progress	Pharmacy	Pharmacist	Send through tube	1:30 pm	
002	Sent-in tube	Pneumatic tube		Pick up from the PICU tube station	2:00 pm	
003	Arrived - waiting to be picked up	PICU Pneumatic tube station #1	Nurse	Check that patient has IV access - deliver to patient room	2:30 pm	
004	Arrived - waiting to be picked up	PICU Pneumatic tube station #2	Travel nurse	Check that patient has IV access - deliver to patient room	3:00 pm	
005	Picked up - waiting for IV access	PICU fridge	Charge nurse	Administer antibiotics	3:30 pm	
006	Administered	Patient room			4:00 pm	

Figure 7: Mock-up of Antibiotic Tracking Display

5.2 Takeaways

Undertaking this project has been a valuable learning experience, both academically and professionally. From an academic standpoint, we gained a deeper understanding of sepsis and the importance of timely administration of antibiotics. We also learned a great deal about hardware and tracking solutions, including the limitations and benefits of different tracking methods.

More importantly, this project has helped improve our research skills and taught us valuable lessons about working with setbacks and challenges. In particular, we learned how to work effectively in a team, collaborating with each other and others to develop and refine our proposed solution. Through our discussions and feedback, we were able to identify potential issues and find creative solutions to overcome them.

5.3 Acknowledgements

We would like to express our gratitude to all the individuals who have contributed to the completion of this research project. We extend our sincere thanks to the healthcare professionals and clinicians who participated in the interviews and provided valuable insights on the challenges faced in sepsis treatment. Their expertise and experience played a critical role in shaping our proposed solution.

We especially would like to thank Dr. Fackler and Dr. Ghobadi for providing guidance and support throughout this research project. Their expertise and feedback were instrumental in shaping the direction of this study.

Without the contributions of these individuals, this research project would not have been possible.

6 References

1. Goldstein, B. , Giroir, B. Randolph, A. (2005). International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics*. Pediatric Critical Care Medicine, 6 (1), 2-8. doi: 10.1097/01.PCC.0000149131.72248.E6.

2. Fleischmann-Struzek, C., Goldfarb, D. M., Schlattmann, P., Schlapbach, L. J., Reinhart, K., Kissoon, N. (2018). The global burden of pediatric and neonatal sepsis: a systematic review. The Lancet. Respiratory medicine, 6(3), 223–230. https://doi.org/10.1016/S2-213-2600(18)30063-8

3. Cvetkovic, M., Lutman, D., Ramnarayan, P., Pathan, N., Inwald, D. P., Peters, M. J. (2015). Timing of death in children referred for intensive care with severe sepsis: implications for interventional studies. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 16(5), 410–417. https://doi.org/10.1097/PCC.0000000000000385

4. Qian, J.1; Wang, Y.I.N.G.1; Zhang, Y.2; Rong, Q.2; Zhu, X.3. ABSTRACT 696: AN EVALUATION OF SIMULATION ON THE FIRST HOUR BASIC CARE TASKS OF THE SEPTIC SHOCK IN PEDIATRIC PATIENTS. Pediatric Critical Care Medicine 15(4_suppl):p 157, May 2014. | DOI: 10.1097/01.pcc.0000449422.48869.74

5. Cowart, M. C., Heath, T. S., Shipman, A. (2022). The Effect of Rapid Initiation Versus Delayed Initiation of Antibiotics in Pediatric Patients With Sepsis. The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG, 27(1), 45–50. https://doi.org/10.5863/1551-6776-27.1.45

6. Sam V. Calabrese, B.S.Pharm., M.B.A., Jonathan P. Williams, Pharm.D., M.S., Implementation of a Web-based medication tracking system in a large academic medical center, American Journal of Health-System Pharmacy, Volume 69, Issue 19, 1 October 2012, Pages 1651–1658, https://doi.org/10.2146/ajhp110527