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Evaluation of time to antibiotic administration for suspected late-onset sepsis in the Neonatal Intensive Care Unit: A quality improvement project

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ABSTRACT

Late-onset sepsis is a significant cause of morbidity and mortality, with mortality increasing by 8–9% for each hour delay in antibiotics. The primary objective of this study is to evaluate the time to antibiotic administration for late-onset sepsis after implementation of a newly developed process for performing sepsis evaluations. A retrospective chart review was conducted utilizing electronic medical records to obtain data for select time points within the sepsis evaluation process. There were 42 patients evaluated prior to the quality improvement project (Group 1) and 59 patients evaluated after (Group 2). The average time to antibiotic administration was 2 h and 48 min in Group 1 and 1 h and 7 min in Group 2 ($p < 0.0001$). Time to antibiotic administration for late-onset sepsis in the Neonatal Intensive Care Unit (NICU) significantly decreased after implementation of a newly developed process, however, several barriers still exist.

1. Introduction

Late-onset sepsis contributes to a high degree of morbidity and mortality if not promptly recognized and treated. Although the incidence of early-onset sepsis has decreased since introduction of Centers for Disease Control and Prevention's recommendations for intrapartum antibiotic prophylaxis, there has been no reduction in the incidence of late-onset sepsis (Ferrieri et al., 2018). In 2013, sepsis was ranked the third leading cause of neonatal death globally, contributing to 15.6% of all neonatal deaths (WHO, 2019). Additionally, sepsis accounted for about 14% of neonatal deaths in the early period (<7 days of life) versus around 50% of neonatal deaths in the late period (≥7 days of life). This illustrates the need for infection prevention strategies and quick recognition of the signs and symptoms of sepsis to promptly initiate antibiotic therapy.

The non-specific signs of infection in neonates make early recognition and treatment challenging for providers in the Neonatal Intensive Care Unit (NICU). With mortality increasing by 8–9% for each hour delay in antibiotic administration, the 2017 American College of Critical Care Medicine (ACCM) guidelines recommend initiating a resuscitation bundle for neonates with suspected sepsis (Bissinger et al., 2013; Davis et al., 2017). The bundle includes administration of antibiotics within 60 min of recognition and obtaining blood cultures if it does not delay the administration of antibiotics. The potential delay in recognition of neonatal sepsis along with the several assessment and diagnostic processes involved in a sepsis evaluation may lead to delayed antibiotic administration, and ultimately, increased risk of mortality.

Delays in antibiotic administration for suspected late-onset sepsis have been recognized across several institutions and countries. Duber and colleagues observed that only 32.3% of patients with a recorded diagnosis of neonatal sepsis received any antibiotic within 2 h of identification, and only 26.6% received an appropriate regimen within that time (Duber et al., 2018). Additionally, Bissinger discusses the efforts made to decrease time to antibiotic administration after observing a delay of antibiotic administration for up to 6 h after initiation of a neonatal sepsis evaluation (Bissinger et al., 2013). At our institution, it was also recognized upon chart review that time to antibiotic administration for suspected late-onset sepsis in the NICU exceeded the 60 min recommendations for 98% of patients assessed during a 6 month time period.

In an attempt to decrease time to antibiotic administration in the NICU, a quality improvement project was implemented to increase timeliness of antibiotic administration and to identify barriers within the current sepsis evaluation process. The primary objective of this study is to evaluate the time to administration of antibiotics for suspected late-onset sepsis after implementation of a newly developed process for performing sepsis evaluations in the NICU. The secondary objective is to assess the barriers associated with administration of antibiotics within

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60 min after initiation of sepsis evaluation and to define the utility of a bedside job aid.

2. Methods

A retrospective chart review was conducted in December 2018 to assess time to antibiotic administration and the barriers associated with administration of antibiotics within 60 min of a late-onset sepsis evaluation. A parallel study design was utilized to compare time to antibiotic administration pre- and post-quality improvement (QI) project implementation. Group 1 data (pre-QI project) included NICU patients aged 3–60 days old who received antibiotics for late-onset sepsis evaluations from March 1, 2017 through September 1, 2017. Group 2 data (post-QI project) included NICU patients of at least 3 days of age who received antibiotics for late-onset sepsis evaluations from September 1, 2018 through December 31, 2018. Patients who received

Septic Work-Up
(Delay in antibiotic administration increases mortality: Goal is to complete labs and begin antibiotics within one hour)

May 2018
Owner: Leanna Magner/Danielle Brooks

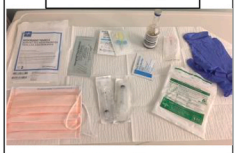
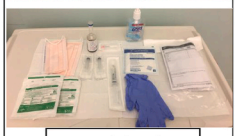
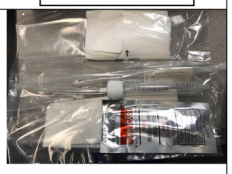
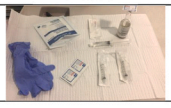
	Job Sequence	Key Steps	Illustration
1.	Patient presents with symptoms of sepsis and septic work up ordered.	Cultures should not be delayed therefore provider will stay at the bedside to enter orders and prepare to obtain blood specimens. Obtain a timer from ANM and set to 1 hour. Clock starts now!	
2.	Gather supplies for Blood Cultures (BC) as ordered.	**BC from a Central Line** • clean gloves • sterile gloves • two syringes • sterile saline flush • culture bottle • blood transfer device • cap change kit • 4 x 4 gauze • mask for each person at the bedside **BC from a Peripheral Stick** • clean gloves • sterile gloves • two syringes • culture bottle • CHG • blood transfer device • two sterile towels/drapes • mask for each person at the bedside • winged collection set • sterile saline (if less than 1500 grams)	Central Line   Peripheral
3.	Gather supplies for Urine Culture if ordered.	• clean gloves • sterile gloves • neonatal catheter kit	
4.	If no IV access, gather supplies for PIV. Refer to Venous Access Algorithm if needed.	• clean gloves • angiocath • CHG • tegaderm • silk tape • tourniquet (if applicable), comfeel •normal saline flush •T-connector	
5.	Prepare patient and work space for specimen collection.	Verify correct patient, acknowledge orders and provide comfort measure or administer pain medication if appropriate.	
6.	Assist MD with BC collection and obtain BC from central line if ordered.	Use blood culture collection cart as a designated work space. In the event that the MD cannot obtain BC immediately due to work load, notify ANM or PICC nurse to draw BC.	
7.	Obtain urine specimen for culture.	Do not advance catheter beyond 4 cm in female infant and beyond 7 cm in male infant. Refer to *policy #6332 Specimen Collection: Urine Culture* for procedure steps if needed. Antibiotics should be administered **within one hour** of initiation of septic work-up therefore inability to obtain urine should not delay treatment. If multiple attempts are required and unable to obtain sample within 1 hour, place UA bag and proceed with antibiotic administration.	
8.	Obtain IV access. Don't delay!	Delay in antibiotic administration increases mortality and the goal is to begin antibiotics within one hour. Priority should be placed on obtaining IV access.	
9.	Once cultures and IV access are completed, begin antibiotics.	If antibiotics are not at bedside *within one hour,* notify pharmacy (629.1410) for an estimated time of arrival.	
10.	Complete evaluation for septic work up process improvement and return to ANM.		

Fig. 1. Septic Work-Up Bedside Job Aid.

antibiotics ordered for a surgical procedure or patients who were transferred from an outside hospital or to the Pediatric Intensive Care Unit (PICU) were excluded from the study.

Patients that met the inclusion criteria were evaluated according to the newly developed process that was created by a multidisciplinary team of NICU physicians, nurse educators, and pharmacists. The process involves the utilization of a bedside job aid to provide detailed information on nursing and provider processes for sepsis evaluation (Fig. 1), an evaluation form to identify barriers (Fig. 2), and the use of a 1 h timer from start of evaluation. Once antibiotics were administered, the evaluation form was to be completed and returned to the pharmacy. The job aid, evaluation form, and a timer were available on all central carts that contain blood culture supplies throughout the NICU. If a timer was not available, the nurses were instructed to utilize a mobile device. Additionally, the NICU sepsis order set was revised and the pharmacists and pharmacy staff were educated regarding importance of delivering these medications to the NICU in a timely manner.

Select time points within the sepsis evaluation process were obtained by reviewing electronic medical records. Post-conceptual age (day of life), time that blood cultures were ordered and obtained, time that antibiotics were ordered and verified in EPIC, time that antibiotics were prepared and administered, and culture results (positive or negative) were recorded for each patient included in the study. The evaluation form completed by the bedside nurse included questions regarding IV access at initiation of sepsis evaluation, identification of type of cultures ordered by the provider and successfully obtained, and steps successfully completed within 1 h of the sepsis evaluation process (Fig. 2).

Descriptive statistics were utilized to determine the mean time to antibiotic administration post-QI project. An unpaired *t*-test was then utilized to compare the mean time to antibiotic administration of group 1 (pre-QI project) versus group 2 (post-QI project). Descriptive statistics were also utilized to determine the percentage of patients who lacked IV access at the time of sepsis evaluation, as this was previously identified as a potential barrier with administration of antibiotics within 60 min.

This study was reviewed by The University of Louisville Institutional Review Board and determined to be exempt due to the quality improvement nature of the study. Ethical approval was not required.

Form completed by: _____

Patient Label

Norton Children's Hospital Late Onset Sepsis Evaluation Review

To be completed by bedside nurse before the end of shift during which the initiation of a sepsis work-up occurred. Please return completed forms to ANM.

Date: _____ Room: _____

Evaluation Data:

1. Time sepsis work-up was initiated: _____ Time ended (antibiotics administered): _____

2. Reason for initiation of sepsis work-up: _____

3. Prior IV access?: ☐ Yes ☐ No

4. Cultures obtained:
☐ Blood (peripheral)
☐ Blood (central)
☐ Urine
☐ Other _____

5. After an hour, what did you complete?
☐ IV access (if none prior)
☐ Blood culture obtained (peripheral and/or central)
☐ Urine culture obtained
☐ Antibiotics received at bedside
☐ Antibiotics administered

6. If any of these boxes were not checked, what were identified barriers? (please explain below):
_____
_____
_____

7. Was the job aid for sepsis evaluation available?
☐ Yes
☐ No

8. Was the job aid for sepsis evaluation helpful?
☐ Yes
☐ No
☐ Comments _____

Fig. 2. Late-Onset Sepsis Evaluation Form.

3. Results

Fifty nine patients met inclusion criteria and were included for final analysis. The average day of life at time of sepsis evaluation was 53 days (range 3–212 days). Overall, the time from which the blood culture was ordered to the time that antibiotics were administered in group 2 was 1 h and 7 min compared with 2 h and 48 min in group 1 ($p < 0.0001$). For the patients in group 2 who had completed evaluation forms, the time from which the blood culture was ordered to the time that antibiotics were administered was 52 min, compared to 1 h and 17 min for those who had not completed an evaluation form ($p = 0.03$). The time to antibiotic administration for patients without IV access at the initiation of sepsis evaluation was 1 h and 32 min, compared to 53 min for those patients with prior IV access ($p = 0.005$). The remainder of results for select time points within the sepsis evaluation process are displayed in Table 1.

Of the 59 patients included for final analysis, 24 had a completed evaluation form (40.1%). There were 9/24 patients (37.5%) who did not have IV access at the time of sepsis evaluation. Of the 9 patients without prior IV access, 7/9 (77.8%) were able to obtain IV access within 1 h. Within the first hour of sepsis evaluation, 2/24 patients (8.3%) did not have blood cultures obtained, 4/24 patients (16.4%) had urine cultures ordered but not obtained, 4/24 patients (16.4%) did not receive antibiotics at bedside, and 6/24 patients (25%) did not have antibiotics administered. The bedside job aid was available for 21/24 patients (87.5%), and 15/21 (71.4%) nurses reported the job aid to be helpful, 3/21 (14.3%) reported the job aid was not helpful, and 3/21 (14.3%) reported it was either not used or too lengthy for a procedure that is relatively common.

Of the 59 patients reviewed, there were 18 patients with a positive culture (30.5%). The most frequent positive culture result was from a urine culture (8/18, 44.4%) followed by a blood culture (6/18, 33.3%). Other positive cultures resulted from sputum, abdominal fluid, wounds, and peritoneal dialysis fluids. There were two patients who had both positive urine and blood cultures, and one patient had a positive blood culture indicative of a central line infection. Details regarding positive cultures and organisms are displayed in Table 2. There were also two patients who were expired at time of record review, of which both were on broad spectrum antibiotics and being treated for a documented infection. However, neither patient had cultures obtained on day of expiration and both had significant co-morbidities relating to prematurity, so it is unclear if these infections were the sole cause of death.

4. Discussion

Newborn deaths now account for 44% of all deaths among children less than 5 years of age, with sepsis/meningitis being the third leading cause and accounting for 15% of neonatal deaths (WHO, 2019). In 2014, the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) developed a proposal entitled "Every Newborn: an action plan to end preventable deaths," which includes 10 core indicators for tracking coverage of effective interventions for women and newborns and the quality of care provided. The three major categories include *Impact, Coverage: Care for all mothers & newborns, and Coverage: Complications & extra care.* The treatment of neonatal sepsis is included as a core indicator under the category of *Coverage: Complications & extra care*. Therefore, it is essential to build research capacity and disseminate findings and best practices to provide better care for patients, especially in low- and middle-income countries. The results from this study, however, indicate that barriers may be present in first world countries. It is the responsibility of healthcare providers to identify and address these potential barriers to aid in decreasing death due to neonatal sepsis.

One identified barrier observed from this study is the lack of timing awareness when performing a sepsis evaluation. This was identified by a significant time to antibiotic administration difference between nurses who utilized the evaluation form and were instructed to utilize a timer or clock, compared to those who had not (52 min vs. 1 h and 17 min, respectively). Timing of initial therapy should be guided by the urgency of the situation, in which case septic shock is considered to be an urgent situation and empiric therapy should be initiated immediately after or concurrently with the obtainment of cultures (Leekha et al., 2011). The request to complete these evaluation forms was with the intention of increasing the sense of urgency among provider and nursing staff and to encourage antibiotic administration within 60 min of sepsis evaluation initiation. This urgency should continue to be utilized for sepsis evaluations despite use of the sepsis evaluation form.

Another barrier that was commonly identified is the difficulty with obtaining IV access for those patients who lacked IV access at the initiation of the sepsis evaluation. Lack of access has also been a barrier identified by other sepsis and time to antibiotic administration studies, and poses a great challenge when striving to meet institutional metrics (Brar et al., 2019; Boutlin, 2017). Although efforts have been made to streamline the IV access process, additional improvements should be made to further narrow the gap in time to antibiotic administration between those with existing vascular access and those without. Institutions should also ensure compliance with venous access algorithms or create a standardized process if one is not in place.

The surveillance of late-onset sepsis evaluations within our institution uncovered several additional barriers aiding to delayed antibiotic administration, including but not limited to, missing equipment on blood culture carts, inability to obtain urine cultures within 1 h, and failure to locate antibiotics after being sent from the pharmacy via pneumatic tube system. These barriers were identified by review of the completed evaluation forms that were located on the blood culture carts, which helped to identify areas for further improvement. Aside from the changes that were implemented as part of this quality improvement project, additional changes should be made including proper and timely

Table 1
Selected time points within the sepsis evaluation process.

Time Points	2017	2018	P value
BC ordered to BC obtained	63 min	28 min	.001
AB ordered to AB verified	11 min	6 min	0.06
AB verified to AB prepared	17 min	14 min	0.22
AB prepared to AB administered	1 h 59 min	49 min	<0.0001
BC ordered to AB administered (ALL)	2 h 48 min	1 h 7 min	<0.0001

BC = blood culture; AB = antibiotics.

Table 2
Positive culture results and organisms.

Positive Culture	Number of Patients
Urine	8/18 (44.4%)
Blood	6/18 (33.3%)
Sputum	2/18 (11.1%)
Abdominal Fluid	2/18 (11.1%)
Wound	2/18 (11.1%)
PD Fluid	1/18 (5.6%)
Resulting Organism	
Klebsiella pneumoniae	5/18 (27.8%)
Methicillin-resistant *Staphylococcus aureus*	4/18 (22.2%)
Enterococcus faecalis	3/18 (16.7%)
Coagulase-negative staphylococci (CoNS)	2/18 (11.1%)
Staphylococcus epidermidis	2 (11.1%)
Escherichia coli	1 (5.6%)
Methicillin-susceptible *Staphylococcus aureus*	1 (5.6%)
Enterobacter cloacae	1 (5.6%)
Klebsiella oxytoca	1 (5.6%)
Staphylococcus hominis[a]	1 (5.6%)
Corynebacterium	1 (5.6%)

PD = peritoneal dialysis.
[a] Indicated as "possible contaminant" in charting notes, antibiotics only continued for 72 h.

re-stocking of the blood culture carts, prompt delivery of antibiotics to bedside, and education to providers and nurses regarding delayed antibiotic administration due to inability to obtain urine cultures.

There have been several studies that demonstrate improved outcomes with timely antibiotic administration, resulting in decreased mortality, shorter hospital length of stay, and reversal of organ failure for patients with severe sepsis and septic shock (Joo et al., 2014; Ferrer et al., 2014; Seymour et al., 2017). However, robust literature supporting improved outcomes with timely antibiotic administration in neonates are lacking. This study illustrated that about one third of patients who underwent a sepsis evaluation had a positive culture, indicating that many of the patients with suspected sepsis were in fact critically ill. The two patients reviewed in our study who expired also had a positive culture at the time of sepsis evaluation, further supporting the risk of mortality with neonatal infections.According to published literature, Weiner and colleagues were the first to evaluate timeliness of antibiotic administration in the NICU, and observed that all infants with a positive culture (n = 11) survived to discharge with an average interval of time to antibiotic administration of 1.4 h (Weiner et al., 1998). Although not directly observed in either our study or Weiner and colleagues', the decrease in time to antibiotic administration may have prevented additional mortalities and co-morbidities, and is an important outcome that should be addressed in future studies.

To ensure sustainability of these results, it will be essential to continue monitoring antibiotic administration times, provide on-going education for new orientees, develop a sepsis evaluation simulation, and further streamline the process for obtaining IV access. Additional improvement may also be attained by providing individual real-time feedback to nursing and provider staff when 1 h antibiotic administration time is not achieved (Weiner et al., 1998). These objectives will be monitored by performing monthly surveillance on 5 patients who received antibiotics for late-onset sepsis in the NICU, and then reporting results at quarterly multidisciplinary clinical practice team meetings. The sustainability of these results is essential to improving patient care and outcomes, and will therefore require continuous efforts by all healthcare providers and members of the multidisciplinary team.

5. Conclusion

Implementation of a newly developed late-onset sepsis evaluation process led to a decrease in time to antibiotic administration from 2 h 48 min to 1 h 7 min, more closely adhering to recommendations that antibiotics should be administered within 1 h of sepsis recognition. Additionally, several barriers were identified and addressed, which has enabled sustainability of improved sepsis evaluation processes and time to antibiotic administration. The success of this project relied heavily on the efforts of a multidisciplinary team, and should encourage other NICUs to internally evaluate their sepsis evaluation process to decrease time to antibiotic administration for patients with suspected sepsis.

Statement of ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This project does not meet the "Common Rule" definition of human subjects' research and is therefore exempt from Institutional Review Board Review.

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Author contributions

All authors provided substantial contributions to the design of the research, the acquisition, analysis and interpretation of data for the work, the critical revision of the work for important intellectual content, approved the final version of the manuscript to be published, and agreed to be accountable for all aspects of the work.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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