

Recognizing and Treating Neonatal Herpes Simplex Virus in Neonates Presenting to a Pediatric

Emergency Department: Predictors of Acyclovir Use

Research Manuscript

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This project was unfunded

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Abstract

Background

The risk of transmission of Herpes Simplex Virus from infected mothers to newborns is highest in mothers with active, symptomatic lesions. With the proper primary care, this population can be treated prophylactically to greatly reduce the risk of transmission. These babies can then be monitored closely for any sequelae indicating the disease. However, if neonates do not have the known risk factor of a mother carrying HSV, certain signs and symptoms in the neonatal period can alert physicians to the possibility of a neonatal Herpes Simplex Virus infection and prompt empirical treatment.

Methods

A retrospective chart review was done using data from the electronic medical records of Eastern Health. Eligible subjects who met inclusion and exclusion criteria were identified, and data from eligible charts was extracted and analyzed to form a picture of which infants were being treated for NHSV infection.

Results

Due to the small number of eligible subjects available from the time frame of the study, statistical analysis was limited. The mean age of the eligible population (neonates aged 0 to 28 days) was 14 days old. The majority of these presented with fever. Three out of 17 patients were treated presumptively with acyclovir, 2 of whom had presented with fever and 1 with suspected seizure.

Interpretation

Unfortunately, due to the low number of eligible subjects, interpretation regarding which combination of symptoms and other characteristics lead to treatment with acyclovir cannot be completed. A future direction in which to take this research question could involve a larger sample of data from a longer time period.

Introduction

Neonatal Herpes Simplex Virus infections occur when neonates become infected by Herpes Simplex virus. Although the overall incidence of Neonatal Herpes Simplex Virus (NHSV) infections is low, infections can have a high rate of morbidity and even mortality if it is not recognized. The low incidence of these infections is due, in part, to the fact that, if mothers have been symptomatic in the past, their condition will be known during pregnancy and the appropriate preventative measures can be taken (1).

Common presentations of NHSV infections can be divided into 3 categories; mucocutaneous symptoms, central nervous system (CNS) symptoms and septic symptoms. Mucocutaneous symptoms include skin and oral lesions or rashes, CNS symptoms often present as seizure and septic symptoms as fever (1). These symptoms are non-specific to NHSV infections and may easily be attributed to another illness. The most specific of these symptoms that would lead a physician to think of NHSV infection are mucocutaneous lesions. If not recognized and treated, the sequelae of these symptoms can be devastating—when the nervous system is affected, encephalitis may lead to developmental delay and death (1).

Using a retrospective chart review, this research project looks at which combination of these common symptoms and other features prompt treatment of neonates (infants between the ages of 0 and 28 days) with acyclovir in the Emergency Department (ED) setting, to answer the question: What are the predictors of acyclovir use in treating neonates presenting to the ED?

As mucocutaneous lesions are more specific to the diagnosis of NHSV infection compared to fever or seizures (2), and therefore the presence of these characteristic lesions would prompt clinicians to consider the possibility of NHSV infection more readily, neonates with the presence of mucocutaneous lesions were not included in the study.

Methods

In order to address this question, a retrospective chart review was completed during the period of January 2018 through May 2018. The population used included infants aged 0 to 28 days that had presented to the Janeway Emergency Department with a fever or first episode seizure over a three year period (April 1st, 2014 to March 31st 2017). The Janeway is the only pediatric ED in Newfoundland and Labrador.

A list of patients less than 28 days old who had presented to the Janeway ED, and had been successfully seen by a physician (ie: did not leave before being seen), with symptoms of fever or seizure, along with their Health Care Numbers, was obtained from Eastern Health Medical Records. The electronic medical record shows a scanned version of the physician notes from the ED visit, as well as any testing, procedures or treatments they received. This list was screened using a set of Inclusion and Exclusion criteria (see appendix) to determine eligibility

for the review. Eligibility included factors such as presenting symptom (fever or first episode seizure), age and admission as an inpatient. Patients were excluded if they were known to have had interventions for HSV infections in the past. Once determined eligible, each case was issued a study ID and the data was extracted from the Eastern Health Electronic Medical Record using a paper data extraction form (see appendix).

Data collected from patient charts included age, sex, weight, time of triage, presenting symptoms, investigations and results, treatment given and length of admission.

This variety of information allows for a complete picture to compare those patients who received treatment with acyclovir with those who did not. With it, a comparison of variables such as age, sex, weight, type of antibiotics received and time they were given, can be made.

The data analysis for the study was completed using the program SPSS. This program is available for use of medical students at Memorial University. The data was analyzed using descriptive statistics, including mean, median, mode and standard deviation.

Results

Measures of central tendency, as well as standard deviation for continuous variables describing baseline characteristics, such as age in days and weight in kg and the frequency values for categorical variables were compiled using the program SPSS and are outlined below.

Table 1: Baseline characteristics (age, sex, weight and presenting symptom) of eligible patients

	Age of patient in days	Sex of patient		Weight of patient in kg	Presenting Symptom	
		Male	Female		Fever	Seizure
N	17	9	8	17	13	4
Mean	14.1			3.5		
Median	12.0			3.6		
Mode	8.0			4.0		
Standard Deviation	7.8			0.5		

Table 2: Frequency values of outcomes

Variable	Frequency	Percent
Type of antibiotic given		
Ampicillin	2	11.8
Ampicillin & Cefotaxime	1	5.9
Ampicillin & Gentamicin	6	35.3
Cefotaxime & Gentamicin	6	35.3
None	2	11.8
Time to Antibiotics in hours		
None given	2	11.8
< .40	1	5.9
0.40 - 2.0	2	11.8
2.0 - 2.5	1	5.9
2.5 - 3.0	2	11.8
3.0 - 3.2	1	5.9
3.4 - 3.5	1	5.9
3.5 - 4.0	3	17.6
4.0 - 5.0	1	5.9
5.0 - 9.0	3	17.6
Lumbar Puncture Given		
Yes	9	52.9
No	8	47.1
Acyclovir Given		
No	14	82.4
Yes	3	17.6

Out of the 17 cases that were eligible to be included in the study, three of those patients received treatment with acyclovir. These cases are outlined below:

Case 1

Age: 8 days

Weight: 4.0 kg

Sex: Male

Presenting Symptom: Fever

Investigations: Complete blood count

Lumbar puncture: small amount of white blood cells, many red blood cells, no bacteria visible under microscopy, no growth on culture

PCR: no HSV DNA detected

Urine studies: E. coli growth on culture

Chest x-ray: clear

Blood culture: no growth

Stool culture: no growth

Acyclovir: Administered at 07:00 (5.5 hours from triage). Dose of 80 mg

Antibiotics: Ampicillin (dose of 200 mg) administered 4 hours after triage.
Gentamycin (dose of 16 mg) administered 4.5 hours after triage.

Case 2

Age: 6 days

Weight: 3.5 kg

Sex: Female

Presenting Symptom: Seizure

Investigations: Complete blood count

Lumbar puncture: Occasional white blood cell, no bacteria seen under microscopy, *Streptococcus viridans* grown on culture (likely due to contamination)

PCR: no HSV DNA detected

Urine studies: E. coli grown on culture

Cranial ultrasound: normal

Blood culture: no growth

Acyclovir: Dose of 70 mg administered at 08:00 (15 hours from triage)

Antibiotics: Gentamycin (dose of 14 mg) administered 10 hours from triage, Ampicillin (dose of 175) administered 9 hours from triage

Case 3

Age: 3 days

Weight: 3.02 kg

Sex: Male

Presenting Symptom: Fever

Investigations: Complete blood count

Lumbar puncture: Occasional white blood cells, no bacteria seen under microscopy, no growth on culture

PCR: No HSV DNA detected

Urine studies: Coagulase-negative staphylococci grown on culture (suspected contamination)

Chest x-ray: clear

Blood culture: no growth

Acyclovir: Dose of 60 mg administered at 07:20 (15 hours from triage)

Antibiotics: Ampicillin (dose of 300 mg) administered at 12 hours from triage, Gentamycin (dose of 14 mg) administered at 7.5 hours from triage.

Interpretation

The majority of neonates that presented to the ED during the study period presented with fever (n=13), while a fewer number presented with first episode seizure (n=4). This is to be

expected, as fever in the neonatal population is much more common than seizure-like activity. The symptoms of fever and seizure were mutually exclusive in these cases: there were no patients that presented with both symptoms. The mean age of patient presentation was 14 days, while the male to female ratio of the patients was roughly equal.

The most commonly given combinations of antibiotics were ampicillin and gentamicin (n=6) and cefotaxime and gentamicin (n=6). Two of the eligible patients did not receive antibiotics. The mean time to antibiotic administration was 3.7 hours from triage. Only one of the patients treated with antibiotics received them within an hour of triage.

52.9 % of the presenting neonates received a lumbar puncture while 47.1 % did not. Of the 9 neonates that received a lumbar puncture, 3 of them were treated with acyclovir. Two of those patients presented with fever, while the other presented with seizure.

All patients that received treatment with acyclovir were also treated with Ampicillin and Gentamycin; however, the timeliness of antibiotic administration varied. It was determined from the results of the PCR of the cerebrospinal fluid, that out of the three patients that were treated prophylactically with acyclovir, none were infected with Herpes Simplex Virus.

From the sample of 17 eligible patients, three patients were treated with acyclovir. Out of those three patients, two presented with fever while the other presented with seizure. All of the patients treated with acyclovir were less than 9 days old. Before administration of acyclovir, all patients were treated with both Ampicillin and Gentamycin. No HSV DNA was detected by PCR in any of the patients that received acyclovir.

It is interesting that in the study sample, the mean time to administration of antibiotics was 3.7 hours. Research within the field shows that it is ideal to treat febrile neonates within the first hour of presentation (3). Only one patient from this population received antibiotics within that ideal time frame. It is also interesting to note that only approximately half of patients received a lumbar puncture, where guidelines suggest all febrile neonates to be worked up with a lumbar puncture, unless unstable (4).

This study was conducted using a population of infants aged 0 to 28 days who presented to the Janeway ED in a 3 year period. Of this population, 17 patients were deemed eligible based on the Inclusion and Exclusion criteria. Seventeen patients is a relatively small sample size for a chart review comprised of 3 years of ER visits, and suggests to the investigators that all eligible patients were not identified. This small sample size is a major limit to the study. With a larger sample size, more meaningful comparisons could have been made. As only 3 infants in the population were ultimately treated with acyclovir, no trends can be drawn from this data.

This small sample size also affects the statistics available to analyze the data. Additionally, it is limited by the time frame allowed for this project within the medical school curriculum. Given more time, a larger number of charts could be reviewed to obtain a larger sample size

In conclusion, the data obtained for this project was insufficient to answer the research question. If this research were to be taken further, it would be feasible to use the data from 5 years of ED visits, and perhaps use other methods to ensure identification of all eligible patients, to obtain a more useful sample size.

References

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Appendix

**Recognizing and treating Neonatal Herpes Simplex Virus in Neonates Presenting to a Pediatric
Emergency Department: Predictors of Acyclovir Use**

Inclusion/Exclusion Criteria

Screening ID: _____

Inclusion Criteria:

Age <28 days: _____ Y _____ N

Presented to the Janeway Emergency Department and seen by an Emergency Department
physician: _____ Y _____ N

Confirmed fever or unexplained seizures: _____ Y _____ N

Admitted to the Janeway as an inpatient: _____ Y _____ N

Exclusion Criteria:

Neonatal Intensive Care Unit interventions for HSV prior to Emergency Department presentations:
_____ Y _____ N

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Eligible _____ Y _____ N

Study Enrolment ID #: _____

Data Extraction Form

Study Enrolment ID: _____

Age (in days): _____

Sex: _____ Male _____ Female

Weight (kg): _____

Triage Code: _____ Time of Triage (24 hr clock): _____

Presenting Symptoms: _____ Fever _____ Seizure

Onset of Symptoms (hours): _____ or > 24hrs: _____

Investigations and Results:

Complete Blood Count: _____ Y _____ N

Results: WBC (10^9 /L) _____ Neutrophils (10^9 /L) _____

Lymphocytes (10^9 /L) _____ Monocytes (10^9 /L) _____

Lumbar Puncture: _____ Y _____ N

Done before antibiotic administration: _____ Y _____ N

Results: WBC (10^9 /L) _____ RBC (10^9 /L) _____

Neutrophils (10^9 /L) _____ Lymphocytes (10^9 /L) _____

Monocytes (10^9 /L) _____ Other (10^9 /L) _____

Glucose (mmol/L) _____ Protein (g/L) _____

Gram stain: _____

Culture: _____

PCR: _____ Y _____ N

Results: _____

Urine Studies: _____ Y _____ N

Results: _____

Imaging: _____ Y _____ N

Type: _____

Results: _____

Blood Culture: _____ Y _____ N

Results: _____

Nasopharyngeal Swab: _____ Y _____ N

Results: _____

Other: _____

Treatment:

Acyclovir Administered: _____ Y _____ N

Dose (in mg): _____

Time of first dose (minutes from triage): _____

Location of First Dose: _____ ED _____ Ward _____ PICU/NICU

Antibiotics Administered: _____ Y _____ N

Antibiotic 1: _____

Dose (in mg): _____

Time of first dose (minutes from triage): _____

Location of First Dose: _____ ED _____ Ward _____ PICU/NICU

Antibiotic 2: _____

Dose (in mg): _____

Time of first dose (minutes from triage): _____

Location of First Dose: _____ ED _____ Ward _____ PICU/NICU

Length of Admission (days): _____