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IMPROVING SURVEILLANCE FOR HYPERAMMONEMIA IN THE NEWBORN

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Abstract

Objective—Prompt ascertainment is crucial for the management of hyperammonemic infants.

Because these patients are rare and recognition of hyperammonemia is often delayed, we designed and implemented an electronic medical record (EMR)-based tool to assist physicians in the detection of hyperammonemia.

Methods—We retrospectively evaluated the hospitalizations of prior hyperammonemic infants to identify codable elements that could trigger an EMR-based warning. An alert was designed and implemented and its utilization was prospectively analyzed.

Results—Blood gas studies were obtained universally and early in the retrospectively evaluated infants ($\bar{x}$ = 26 hours before ammonia level). Prompting physicians to evaluate ammonia after ordering blood gas studies would have accelerated the initial ammonia order in 89% of retrospective cases. The alert has activated 184 times over the first six months of operation leading to 63 laboratory evaluations and detection of one hyperammonemic infant.

Conclusion—Implementation of an EMR-based warning system can improve surveillance for hyperammonemia in a susceptible population.

Keywords

screening; infant; urea cycle defect; electronic medical record

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The authors have no competing interests to declare.

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1. INTRODUCTION

Hyperammonemia is a rare, life-threatening problem in the neonatal period that requires prompt intervention. The clinical presentation of neonatal hyperammonemia may include lethargy, poor feeding, emesis and respiratory distress, all fairly non-specific patterns that can be seen in sepsis or cardiac anomalies. The causes of hyperammonemia are diverse, and include liver failure, infection, medications, and inborn errors of metabolism (IEM).[1] The latter can be the most difficult to recognize, given an overall prevalence of IEMs at approximately 10–15 in every 100,000 births.[2, 3] IEMs that can cause hyperammonemia occur even less frequently and include urea cycle disorders (UCDs), organic acidopathies, disorders of pyruvate metabolism and mitochondrial fatty acid oxidation defects. Several of these disorders can present in the first few days of life, before newborn screening results are available. Some UCDs, including ornithine transcarbamylase deficiency, are not reliably detected by newborn screening.[4]

Elevated ammonia levels result in long-term brain injury, with the severity of damage dependent on the duration of the hyperammonemic coma.[5,6] If detected early, medical management with nitrogen-scavenging medications such as sodium benzoate and sodium phenylacetate and administration of high-glucose and lipid reduce catabolism and ammonia levels to improve outcomes in UCDs.[7] With higher ammonia levels at presentation, hemodialysis provides an effective method for the resolution of hyperammonemia, although at the cost of significant dialysis-associated morbidity.[8] Thus, the time to recognition is critically important to the intellectual outcome of infants with hyperammonemia.

In order to better understand barriers to detection, we examined the medical records of consecutively ascertained hyperammonemic infants to identify patterns of care in their presentation. We used this information to create a tool within our EMR that assists in the recognition of clinical scenarios in which an ammonia level should be obtained.

2. MATERIALS AND METHODS

We identified all children cared for at our institution between January 2002 and December 2011 who had an ammonia level $>400 \mu\text{M}$ during the course of their care regardless of whether hyperammonemia was first observed at our institution or a referring hospital. The value of $400 \mu\text{M}$ was selected so that infants with spurious elevations in ammonia due to technical factors of sample acquisition and processing would not be included in the data set. [1] This search yielded 27 patients (the discovery cohort) for whom we performed a retrospective chart review.

Age (in hours) at presentation to a medical facility, reason for presentation, age at first ammonia draw, and level of first ammonia level were all obtained for each infant in the discovery cohort through available medical records. We examined the chronology of orders obtained around the time of the first ammonia including blood glucose or dextrose-stick, comprehensive metabolic panel (CMP), plasma lactate, blood gas, complete blood count, C-reactive protein, specialized metabolic labs (plasma amino acids, acylcarnitine profile, urine organic acids, orotic acid), and cerebrospinal fluid culture.

A clinical alert tool was generated within in the Inpatient EMR system (Epic, Verona, Wisconsin) to assist physicians in recognizing high-risk infants. To assess the performance of our clinical alert we compared hospital-wide laboratory studies sent between January and July of 2011, with those sent after implementation of the alert (January-December 2012).

The study received an exemption from the Institutional Review Board because only existing data and records were reviewed in a fashion that could not be linked by identifiers to the subjects.

3. RESULTS

Of the 27 infants in the discovery cohort, 14 were subsequently diagnosed with specific UCDs, five with transient hyperammonemia of the newborn, four with organic acidemias, one with carnitine palmitoyl transferase-2 deficiency and three with sepsis (Table 1). The most frequent documented presenting complaint included (in order) respiratory distress or failure, hypothermia, poor feeding, and seizures. The time of initial ammonia analysis ranged from 24 to 552 hours (23 days) of life. Of the labs examined, complete blood count, C-reactive protein, and blood gas were obtained in all 27 infants. CMP and lactate were obtained for 25 and 23 infants respectively.

Lab studies were evaluated to see if they would be effective triggers for an alert system designed to detect hyperammonemia. We excluded the use of complete blood count and C-reactive protein because these studies are performed nearly universally on newborns at our institution and did not provide additional specificity. We compared the timing of the remaining studies to determine which was obtained earliest in the clinical course. We found that blood gas studies were generally obtained first, on average 26 hours prior to the ammonia level (std. dev. = 38 hours) (Figure 1).

Since blood gas studies are a relatively common test (3618 individuals tested over the past year at our institution), we wanted to limit the number of times a clinical alert would be triggered, but still maintain sensitivity for hyperammonemic newborns. To accomplish this, we identified additional common features within our target population. We noted that in confining the notification to infants beyond the first day of life and up to the age of one week (24 hours – 7 days of age), based on the age of presentation of UCDs in the newborn period, and limiting it to the first blood gas drawn within the hospital encounter, all hyperammonemic infants in the discovery cohort but three would have been identified (89%). Of these, one presented due to a positive newborn screen for propionic acidemia and the ammonia level was ordered prior to blood gas studies. The two other exceptions had blood gas studies performed beyond seven days and had a final pathologic diagnosis of sepsis complicated by liver failure – no metabolic etiology was suggested for their clinical course. To further limit the number of intrusive clinical alerts, infants with a resulted ammonia level drawn before the ordering of a blood gas could also be excluded from this algorithm. When these two criteria were applied to all patients seen in our facility in the last year, the warning would have triggered 482 times, just over once per day. Therefore, the positive predictive value of the tool over this time frame would have been 0.41%.

In the first twelve months that the alert was installed in the EMR at our institution (see Figure 2), it activated in 184 patient records, resulting in 63 separate orders of ammonia levels (34% of episodes led to screening). One of these infants was found to have hyperammonemia (376.8 μ M) and was ultimately diagnosed with methylmalonic aciduria, confirmed by mutation testing. Hyperammonemia was not detected during the hospital stay of any of the other 121 infants who were not screened. We compared the rate of surveillance to patients that would have activated the flag during six months of the previous year. For these 147 patients who would have triggered the alert, ammonia levels were ordered only eight times during the period from 24 hours-7 days of age (5.4% of episodes led to screening). Twice over this time period, patients with UCDs had blood gas values obtained before the detection of hyperammonemia, delaying the initiation of care.

4. DISCUSSION

While the best solution to any clinical quality improvement is increased clinical vigilance, the scarcity of newborns presenting with hyperammonemia makes this a particular challenge. There is a common cognitive association between anion gap acidosis and neonatal-onset inborn errors, but the lack of routine acidosis (or indeed, the frequent presence of alkalosis) makes it particularly difficult for front-line clinicians to suspect UCDs. To improve the detection and outcomes of newborns presenting with hyperammonemia, we examined the history of patients presenting to our institution over the past ten years with critically elevated ammonia ($>400\mu\text{M}$) and identified simple and easily identifiable features from these cases that may assist in ascertainment.

The objective of this tool is to improve surveillance for hyperammonemia and to speed the recognition of patients so that ammonia elevations can be identified at an earlier stage. It is likely that most detected patients will still require dialysis, since profound hyperammonemia cannot usually be managed with ammonia scavenging medications. However, a reduction in hyperammonemia time of approximately one day, which could reasonably be expected with the adoption of this tool, could have a significant effect on patient outcome. Previous longitudinal studies of hyperammonemic cohorts demonstrate differences in development and intelligence quotient that are appreciable over mere hours of delay.[5,6]

We have designed and installed the tool to assist clinicians in the recognition of situations in which an ammonia level should be considered. The alert appears as text in a pop-up window after an initial blood gas is ordered on infants aged 2–7 days where no prior ammonia studies have been obtained. This warning is based upon unambiguous EMR data rather than clinical judgments of patient condition. From the warning screen, the clinician can directly open the order for ammonia testing. If the clinician chooses not to place the order, the alert will close and will not reappear. The clinician can also defer consideration of the test until later.

Interruptive alerts in the EMR have been shown to increase nearly two-fold the use of the function they promote but also run the risk of being dismissed when they appear unnecessarily frequently.[9] Low specificity of the “trigger” contributes to clinician fatigue and increased likelihood to bypass the alert.[10] By limiting the frequency of firing using age range and exceptions such as prior testing, we hope to reduce this possibility. Studies have shown that EMR-based alerts are more likely to be accepted when the alert contained explanatory details, was linked directly to the order and excluded patients for whom the alert is irrelevant.[11,12] The designed warning notes the link between hyperammonemia and respiratory distress in newborns, and describes the reasons to include a UCD in the differential.

The positive predictive value of this alert over the first year of use remained low ($<1\%$) confirming that many additional ammonia levels will be obtained in order to improve care for one symptomatic infant. However, the risk and expense of a single additional laboratory study for hospitalized infants requiring blood gas studies is minimal. We suggest that it is justified due to particular difficulties with the diagnosis of hyperammonemia, which has a non-specific presentation that can often be mistaken for more common crises of the newborn. This is also consistent with our view that obtaining ammonia levels in distressed newborns without obvious etiology is generally indicated. Another limitation of this alert system is that it cannot detect children with hyperammonemia who present outside the window of detection. In order to reduce intrusiveness and increase the effectiveness of the alert, it has been restricted to the age group where the yield would have been highest over the ten years studied.

5. CONCLUSIONS

With proper implementation of this tool, we can decrease the time to diagnosis of hyperammonemia in affected infants. We may also identify additional newborns whose hyperammonemia may have otherwise gone undiagnosed. Based upon prior studies of the timing of dialysis, length of hyperammonemic coma and intellectual outcome, we predict that this tool will lead to faster initiation of therapy and improved outcomes for children with hyperammonemia.

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Abbreviations

IEM	Inborn error of metabolism
UCD	urea cycle disorder
CMP	comprehensive metabolic panel
EMR	electronic medical record

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Highlights

- Hyperammonemic infants often escape early detection.
- Prolonged hyperammonemia has serious consequences.
- Many hyperammonemic infants have blood gas studies prior to ammonia level.
- An electronic medical record based tool improved surveillance for hyperammonemia.

Figure 1.

Characteristics of lab studies ordered early in the hospital course of hyperammonemic infants. Histograms plotting the timing of basic metabolic panels (A), lactate levels (B) and blood gas studies (C) were compared to the timing of first ammonia ascertainment, which was adjusted to a zero time point. Studies performed at negative times were performed prior to the detection of hyperammonemia; studies at positive times were performed after detection.

Figure 2. Appearance of the designed clinical alert. The physician can place an order for ammonia level directly from the screen.

TABLE 1

Hyperammonemic infants reviewed in the study

Case	Age at presentation (days)	Time of initial ammonia level (hours)	Presenting symptom	Final Diagnosis
1	2	60	irritability	Methylmalonic acidemia
2	1	203	congenital anomalies	Carnitine palmitoyl transferase II
3	3	69	seizures	Citrullinemia
4	3	69	respiratory distress	Ornithine transcarbamylase def.
5	4	100	respiratory distress	Arginosuccinate lyase def.
6	2	72	poor feeding	Propionic acidemia
7	2	47	respiratory distress	Trans. hyperammonemia of newborn
8	1	48	respiratory distress	Trans. hyperammonemia of newborn
9	2	204	altered mental status	Trans. hyperammonemia of newborn
10	0	278	jaundice	E.coli sepsis
11	3	67	respiratory distress	Ornithine transcarbamylase def.
12	0	24	respiratory distress	Trans. hyperammonemia of newborn
13	0	64	respiratory distress	Trans. hyperammonemia of newborn
14	5	124	abnormal newborn screen	Propionic acidemia
15	2	58	seizures	Ornithine transcarbamylase def.
16	3	86	tachypnea	Citrullinemia
17	4	101	decreased feeding	Propionic acidemia
18	13	300	respiratory arrest	Staph aureus sepsis
19	2	72	decreased feeding	Ornithine transcarbamylase def.
20	0	552	liver failure	Enteroviral sepsis
21	2	42	hypothermia	Ornithine transcarbamylase def.
22	2	71	respiratory distress	Ornithine transcarbamylase def.
23	0	117	hypothermia	Ornithine transcarbamylase def.
24	6	140	poor feeding	Ornithine transcarbamylase def.
25	4	101	irritability	Citrullinemia
26	2	53	hypothermia	Ornithine transcarbamylase def.
27	2	69	respiratory distress	Carbamoyl phosphate synth def.