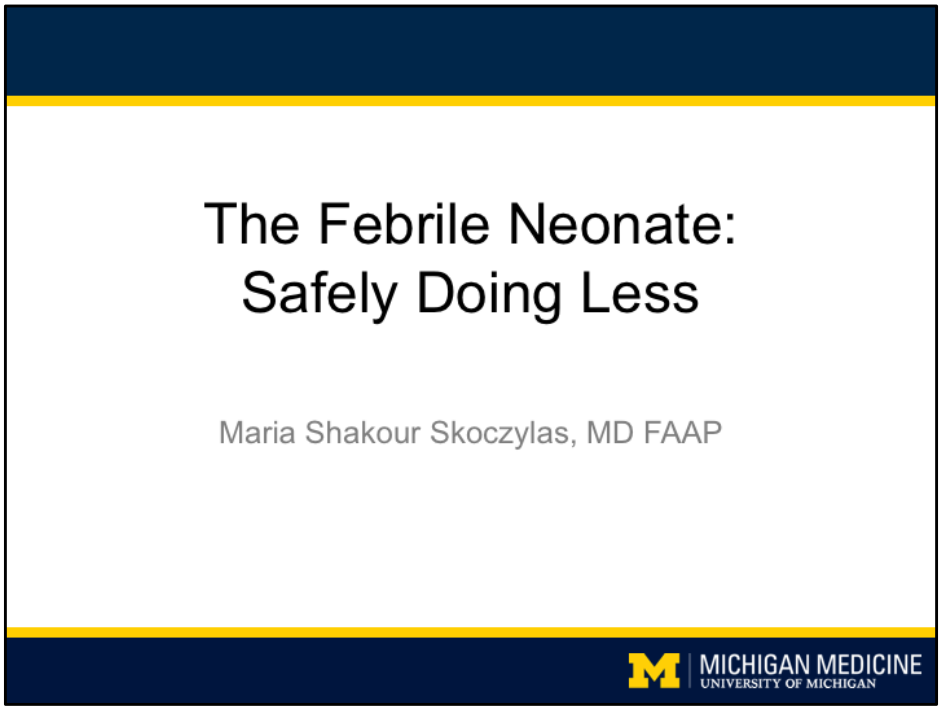

Introduce myself
If small group, ask for background of people in the room
- Practice setting: office, ED, hospital, combination
No more than 5 minutes gathering background of people in the room

Disclosures

- I have nothing to disclose.

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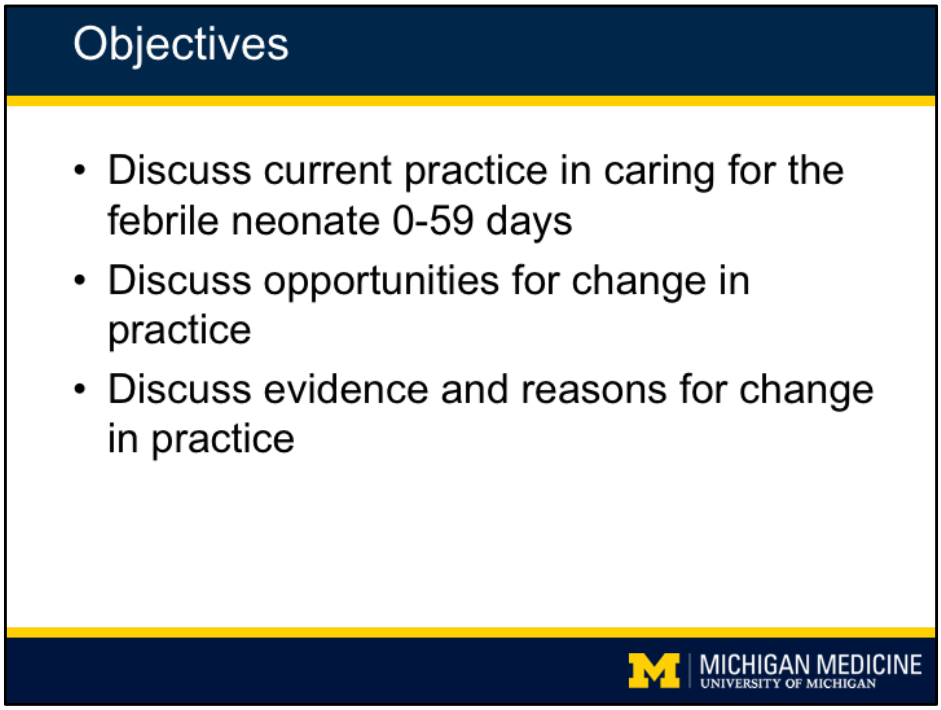
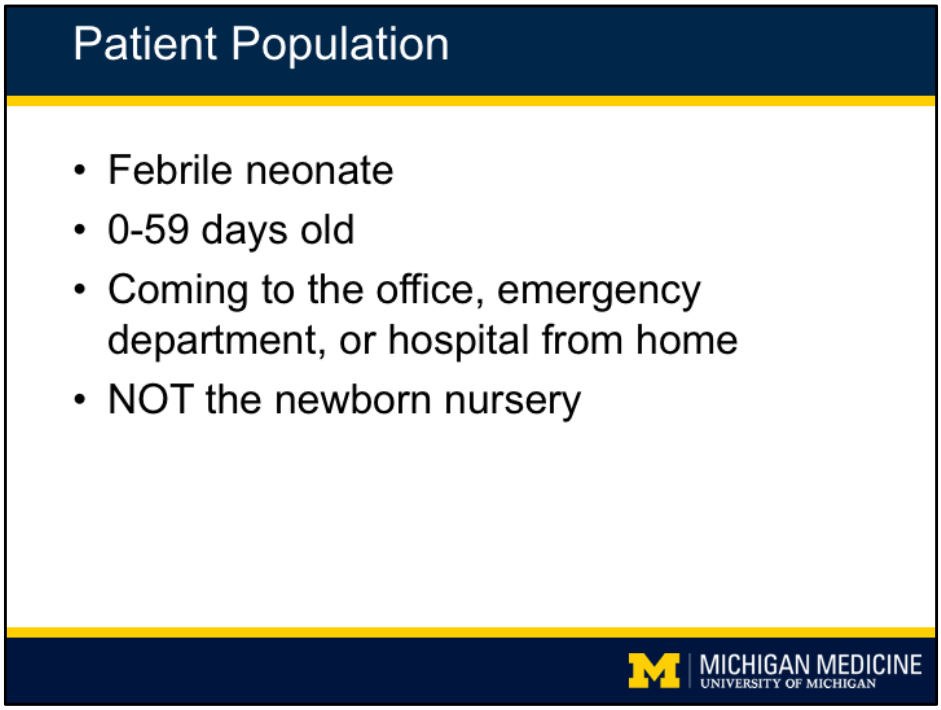


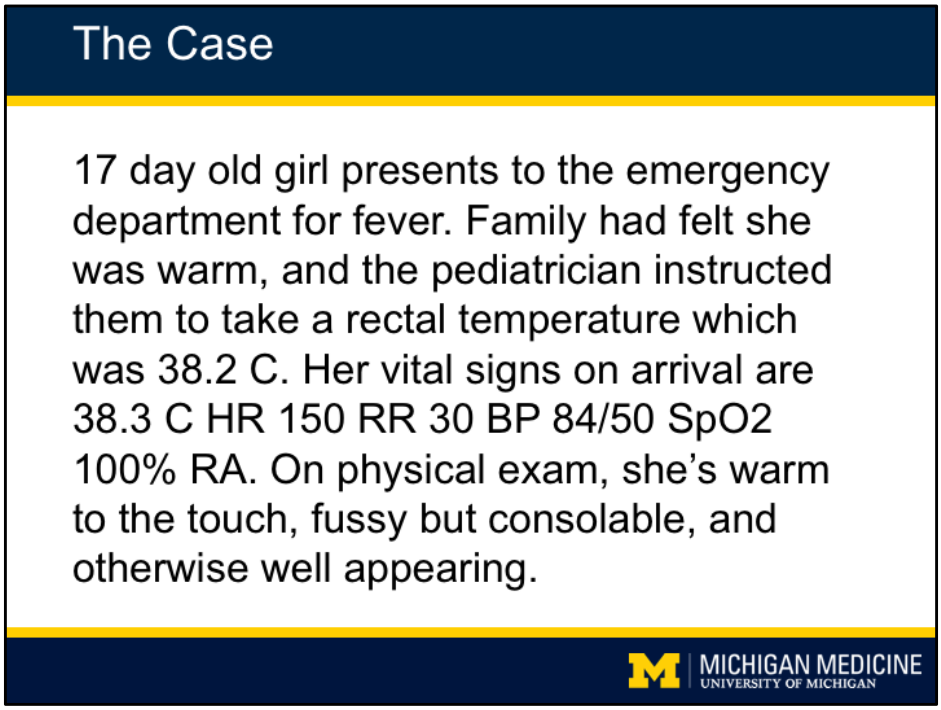
My goals this afternoon are to discuss current practice in caring for the febrile neonate ages 0-59 days as well as to discuss opportunities for change in practice and the evidence and reasons for change in practice.

The AAP does not have any new published guidelines for evaluation of the febrile neonate



These are infants 0-59 days old who present to your office, emergency department, or hospital from home with a temperature of 38.0 or above.

This also does not include infants in the well newborn nursery. These should be risk stratified according to their own criteria in particular evaluating for maternal fever and GBS disease and prophylaxis.



At this point I would like to discuss a typical case.
[read case]

I would consider this a fairly typical presentation for the febrile neonate. Some of them may actually have fevers when they arrive though some may have only had a fever at home.

So the question I pose to you is: what would you do for an infant who presented this way?

the literature tells us that there is variation in practice. In a 2014 study in pediatrics looking at the practice of pediatric emergency department physicians at 36 pediatric emergency departments 1 in 6 infants who presented for a fever would be discharged with varying degrees of evaluation.

In my training I was taught to do a full sepsis work up including CBC, comprehensive metabolic panel, and urinalysis, as well as blood, urine, and CSF cultures on all infants 28 days or younger.
I was not trained to consistently test for HSV. Many times I would check for HSV in the CSF but I did not routinely test for other forms of HSV including viremia or SEM disease if preliminary labs did not show evidence of hepatitis unless the mother had a known history of HSV.

If an infant had respiratory findings, I would get a CXR.
Sometimes I would get a full respiratory viral panel if the infant was symptomatic.

The approach that I learned in my training had holes in it in particular for the well appearing infant which would make it difficult to be confident that I could avoid antibiotics for my patient while I monitored the patient in the hospital

Therefore, I started these infants on ampicillin and cefotaxime or ampicillin and gentamicin and hospitalize the baby for 48 hours until I was confident that bacterial cultures were negative.

Then every now an then, I wouldn't be able to get the LP on the baby even after a few attempts and we would feel obligated to treat them for meningitis for 14-21 days.

These infants who present with fever are difficult. Infants don't show us localizing symptoms as well and they are more susceptible to become sick. We also know though that infants with viral illness can appear as sick as infants with bacterial illness.
We know there are risks to the antibiotics, to being hospitalized and exposed to nosocomial infections, to having PICC lines placed.

In your experience, what percentage of these infants had true SBI that required antibiotics? For me, it was fairly low. We know we were overtreating.
On the other hand, how many of you have either experienced or had a colleague who discovered too late that an infant had an illness such as HSV?

Known that there is wide variation in practice in actually following these recommendations (Jain et al Pediatrics 2014)

- In the study of 36 pediatric EDs, 1 in 6 febrile neonates was discharged from pediatric ED
- In those hospitalized, high rates of serious bacterial infection (SBI); approximately 12%
- In those discharged from ED, the rate of return was low with <1% (0.3%) having an SBI.

It's tough to be a pediatrician. Our patients, especially our youngest patients, are inherently unable to tell us when they are ill and these are the ones who are at highest risk of getting an SBI.
In the febrile neonate, approx 7-11% will have an SBI with the rates being higher in the <28 day population. (Biondi & Byington)

When Intermountain health looked at the febrile neonate they found that 20% of ED visits for infants <90 days were for fever
Like other studies, of those infants only 8-10% had positive SBI (UTI, bacteremia, meningitis).
Overtreatment of the remaining 90% also poses real risks. Infants are subjected to unnecessary antibiotics, interruption of their gut flora, potential nosocomial infection, and interruption of breastfeeding

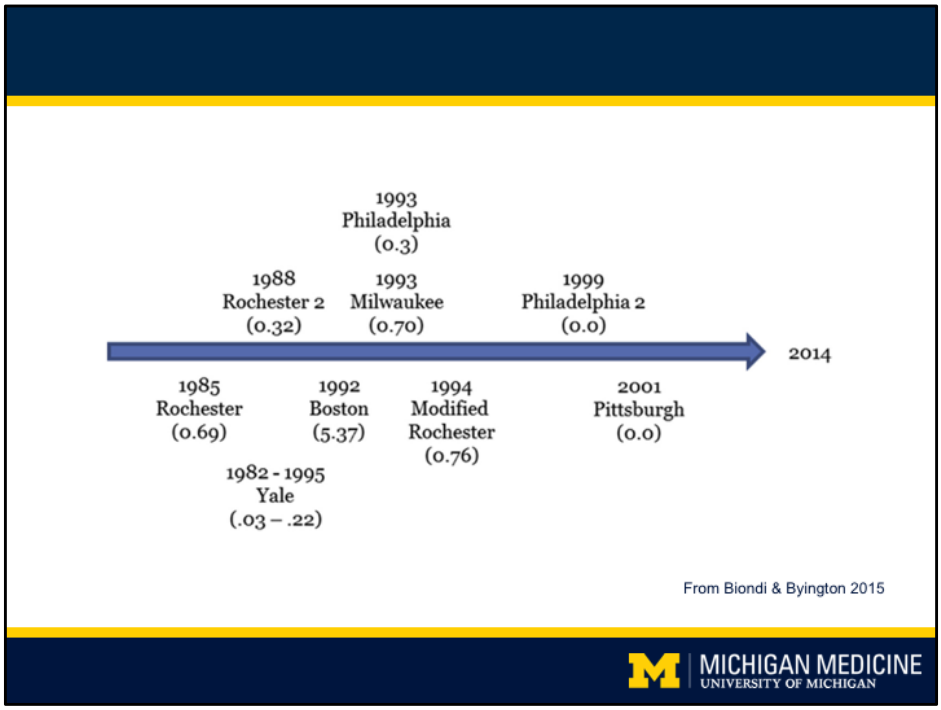
So it's important for us to recognize that we have new data and new standards of care. Medicine has evolved and we work in an era when vaccinations prevent illnesses that historically used to hospitalize or kill children. With vaccinations, we also have an opportunity to decrease treatment of our youngest patients as well. Hib, DTaP, PCV, polio.

Listeria no longer is listed as one of the most common bugs to cause neonatal meningitis.

Our colleagues in obstetrics also routinely evaluate mothers for GBS and provide prophylaxis against GBS disease that reduced the rates of GBS disease in our patients.

The literature has slowly given us reasons to do less for our patients in some ways, decrease LOS, decrease empiric antibiotics, but we can only do this if we reliably follow guidelines to ensure that we are pursuing a complete work up for our patients so that we have all best information we can in order to make our decisions

Our group got involved in the AAP quality improvement project called REVISE. REVISE stands for reducing excessive variability in sepsis evaluation. This has been how are group has been able to work on standardizing our evaluations and thus safely do less for our infants.

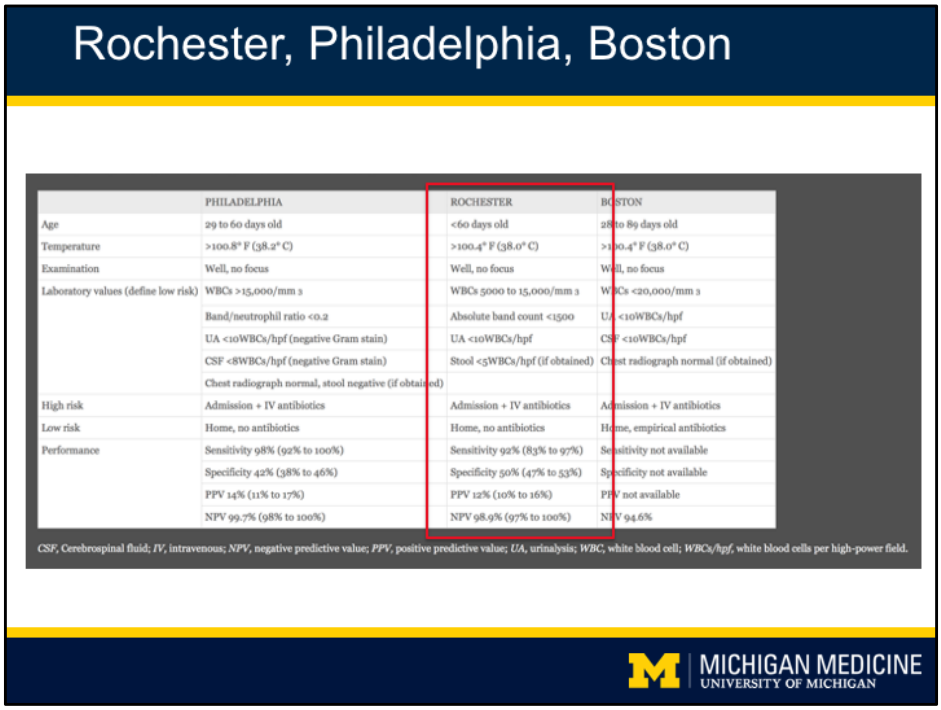


From Biondi and Byington 2015

There has not been one single study that has given us the reason to being changing our practice.

- Multiple separate studies with preponderance of evidence that indicated that we should be able to safely decrease the number of infants who are treated.

- There has been a long history of trying to determine what criteria could be used to risk stratify infants to know who should be evaluated in the hospital and who could safely be discharged home.



The Philadelphia, Boston, and Rochester criteria are guidelines that I'm sure you're all familiar with that have proposed lab criteria to define an infant as low risk.

[next to highlight Rochester criteria]

Using the Rochester criteria, an infant who is low risk has a <2% chance of having an SBI and it is even less likely that a low risk infant will have bacteremia or meningitis.

Using these criteria, we have spared so many children from antibiotics. These infants have been those >28 days.

The new goal, is to allow the same benefit to those children who are even younger and avoid antibiotics in those who are younger while closely monitoring them in a setting that allows us to administer antibiotics quickly.

The intermountain health guidelines also took this management one step further by utilizing appropriate viral testing in addition to labs to evaluate for SBI.

When they looked at the ED visits for infants <90 days, 20% of these were for fever and similar to other studies 8-10% of those infants had SBI including UTI, bacteremia, and meningitis.

They also looked at how using a standard pathway increases the appropriate lab evaluation.
- when the intermountain guidelines were implemented appropriate labs to risk stratify increased from 57% to 87%
- appropriate use of viral testing which also helps us appropriately risk stratify increased from 56% to 74%
- this is important, because we need to be able to have the right labs in order to appropriately risk stratify the infants. We don't want to assume that an infant is not sick and inappropriately discharge the infant.

https://intermountainhealthcare.org/ext/Dcmnt%3Fncid%3D520441555

As I already mentioned, there was not one defining study that allowed us to pursue this change in practice.

I was taught to monitor cultures in even well-appearing, low risk patients for 48 hours before calling them negative.

A 2011 publication from Guerti and a separate study from Kumar demonstrated that outside of the critically ill patients, if you ignore CoNS, >90% of positive cultures will grow by 24 hours—these studies unfortunately didn't include infants <28 days

A pilot study in the <28 day population done at the university of Rochester by Biondi et al demonstrated that true positive cultures became positive well before 24 hours. These were mostly E. Coli and definitely no listeria.

We also now have more reliable viral PCR studies.
Infants with a positive viral study for parechovirus, RSV, echovirus, enterovirus, and influenza (especially if they have clinical bronchiolitis) are even less likely to have a serious bacterial infection

Rhinovirus is tough to be sure that it's a true positive as the PCR will remain positive for 90 days following true illness.

When you apply risk factors, of those infants at higher risk, <20% will have positive cultures.

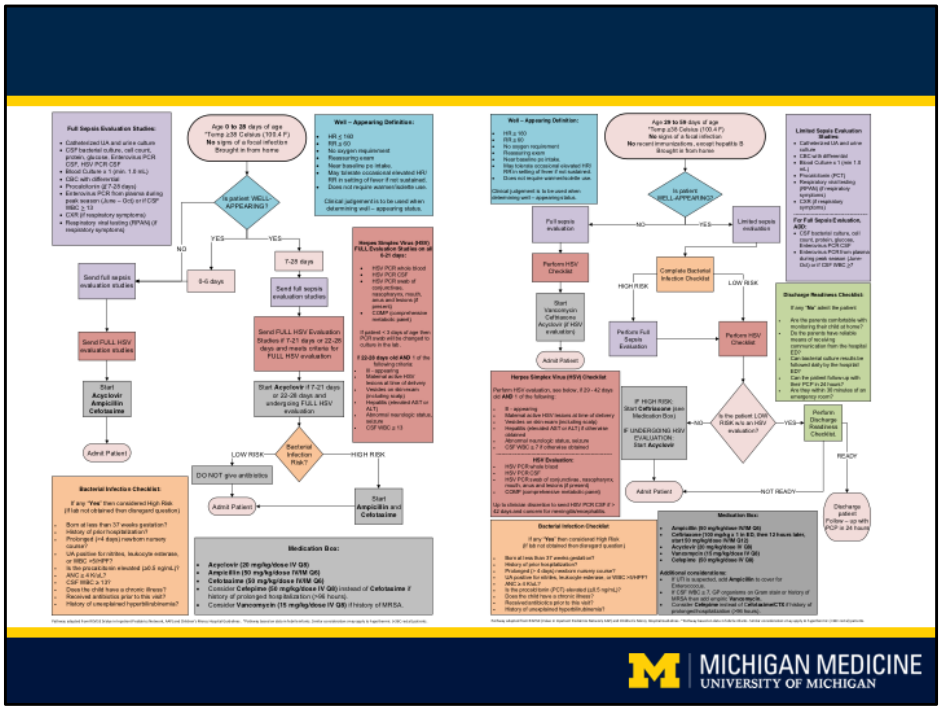
Rates of SBI (or IBI) in different age groups
Rates of IBI in infants with viral infection
Rates to time of positive culture and true disease—discuss Biondi et al in peds in review 2013
Biondi and Byington evaluation and management of the febrile neonate 2015
2011 Guerti if you take out CoNS then 93% of positive cultures will be positive at 24 hours
Intermountain Healthcare System outcomes 2012

None of us want to miss a serious infection in an infant either.

When the inter mountain healthcare system implemented their guideline, they Allowed infants who were low risk or who tested positive for a viral pathogen who had negative cultures at 24 hours to be discharged. Other culture negative infants were eligible for discharge at 36 hours.

- No missed SBI
- Stable readmission rate again implying that when they discharged infants earlier (at the 24 or 36 hour mark) with appropriate follow up they were not causing more harm to infants.

- Those infants who are low risk <90 days old who were managed in the outpatient setting have similar outcomes to those who are managed in the inpatient setting in particular when the ultimate diagnosis is UTI (which is the most common causes)



Variability in care has been shown to lead to both over- and under-treatment. Care pathways allow us to provide consistent high-quality care. They also help us to recognize when a patient is not following the expected pattern which then prompts us to investigate why the patient is deviating from expectations.

These are the guidelines that we are following at the university of michigan, they were adapted from the guidelines in the REVISE trial as well as from

the guidelines at Kansas City Children's mercy Hospital.

[Hand out fever pathways here!]

For me this was a huge change in practice in particular for the infants 28 days and younger. Some of us in our group at the time had already decreased LOS until the culture was negative for 36 hours though many of us were still monitoring cultures for 48 hours.

One big change was not initiating antibiotics in all infants.
For infants up to 6 days, they are still so close to birth and the exposure to vaginal flora that they are managed with empiric antibiotics.

All febrile infants <60 days old get at least a limited sepsis workup:

CBCPD, blood culture, UA, urine culture, procalcitonin (other hospitals are using a CRP)

HSV studies are indicated in:

All infants 0-21 days old or 22-42 days and: ill-

appearing, seizures, HSV risk factors, or evidence on labs

Add: CMP, HSV PCR of blood and CSF, HSV PCR of conjunctiva, nasopharynx, mouth, anus (single swab) and vesicles (if present)

High risk infants (0-28 days old, risk factors, ill-appearing, or abnormal labs) get a full sepsis workup:

Add CSF culture, cell count, protein, glucose, enterovirus CSF PCR

Add plasma enterovirus PCR from June-October or if elevated CSF WBC for age

Key changes:
Decreased LOS (watching cultures for a mere 24 hours instead of 48)
Not all infants will get antibiotics
Not all infants >28 days will get an LP or be admitted (not a huge change)
More HSV testing (this was a big change in practice for us; we standardized HSV testing to reduce variability, increase quality of care and individualize care)

https://en.wikipedia.org/wiki/Herpes_simplex_virus

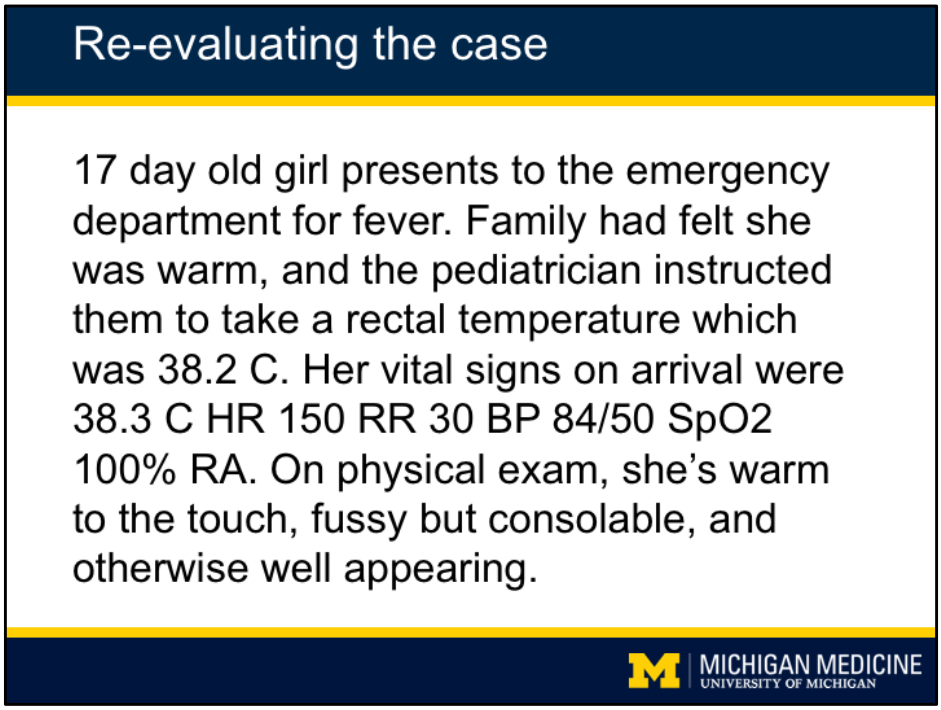
As I mentioned earlier, I was guilty of not testing consistently for HSV. I considered maternal history, patient history, and lab values. When Curfman et al looked at infants with HSV, 16% of them lacked the classic signs at presentation (seizures or elevated transaminases) though they developed these things later. Most infants with HSV will have SEM disease (which I wasn't testing for with any regularity) but the mortality from the disease is high 15%.

With this, our group increased testing of whole blood HSV and swabbing for SEM disease in addition to sending the HSV PCR on the CSF. The risk is highest in those 21 days or younger so we began testing all of those infants for HSV and allowing clinical appearance, maternal history, and lab values to guide evaluating for HSV in older infants.

Evidence to increase whole blood HSV testing
Curfman et al J pediatrics 2016–

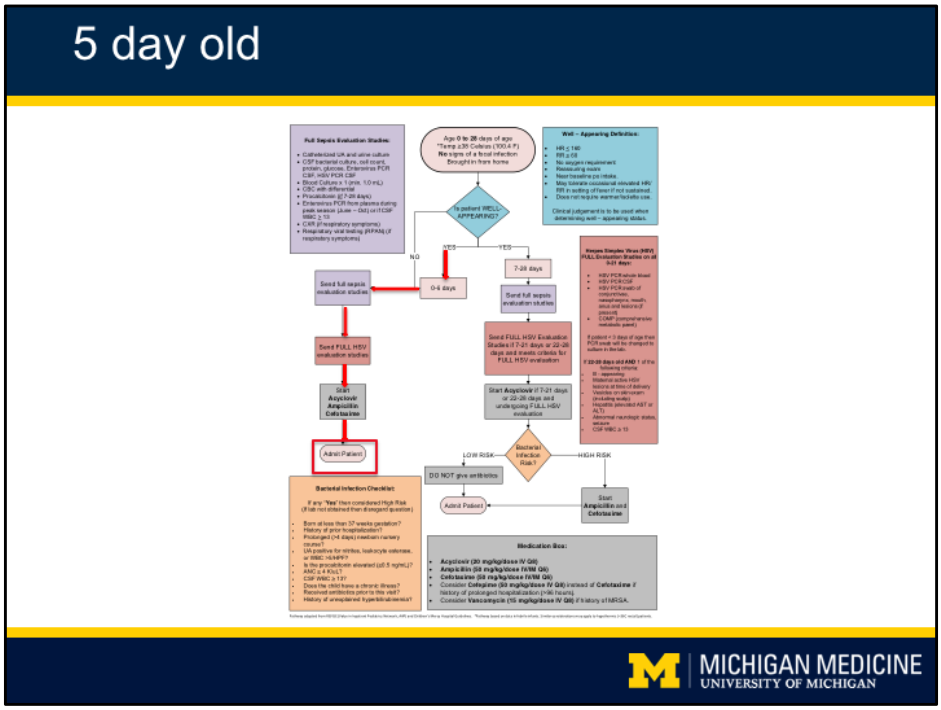
16% lacked classic signs at presentation (seizures or elevated transaminases) but developed later which can be too late

Biondi and Byington: <1% ill have HSV, most infants with HSV will have SEM disease, BUT mortality from the disease is high (15%)

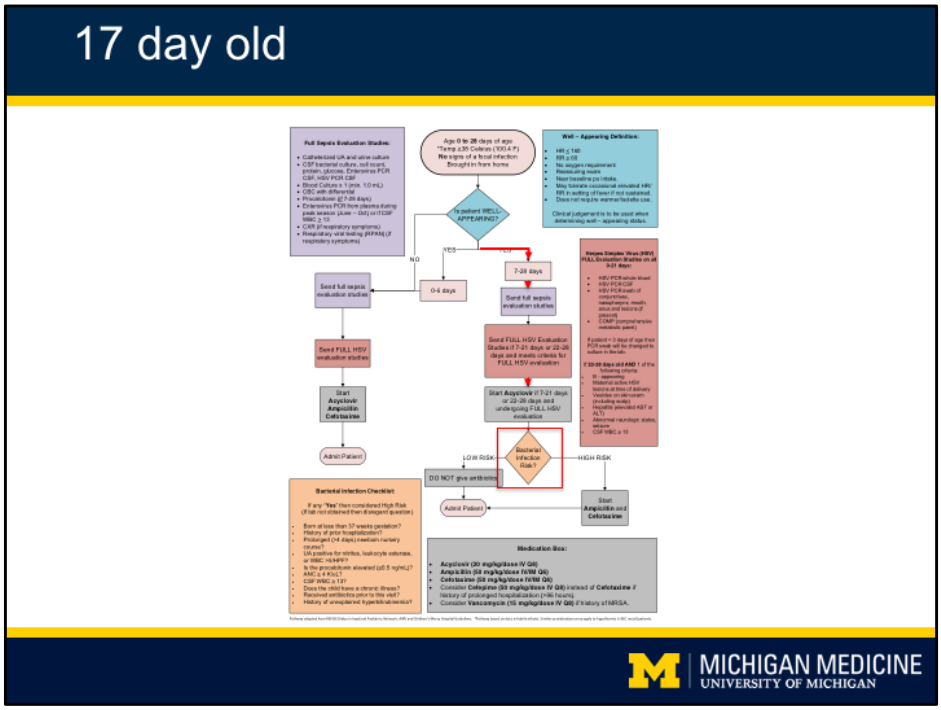


Now I'd like to re-evaluate the case using the new sepsis guidelines

5 day old: full sepsis evaluation, antibiotics (amp and cefotax or amp and gent, acyclovir)
17 day old:
27 day old
37 day old
Ill-appearing infant



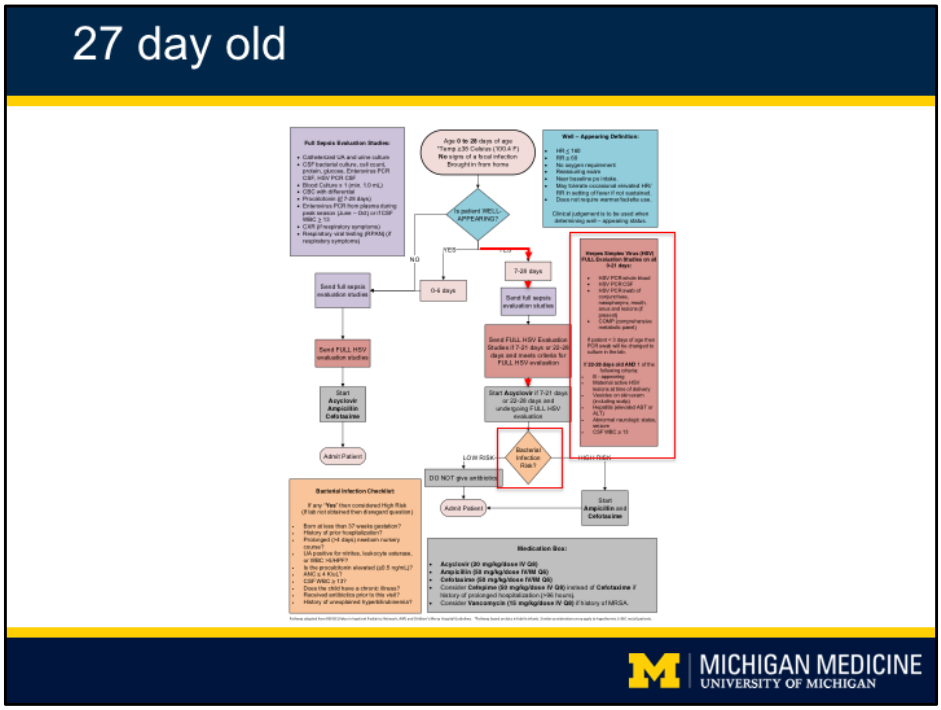
A 5 day old who was discharged from the newborn nursery at 48 hours would full sepsis evaluation, antibiotics (amp and cefotax or amp and gent, acyclovir). This infant has very recent exposure to vaginal flora etc and therefore the risk is high enough that we would start empiric antibiotics in all infants at this age while we monitor cultures.



In infants ages 7-28 days 10% will have a UTI, 3% will have bacteremia, and 1% will have meningitis.

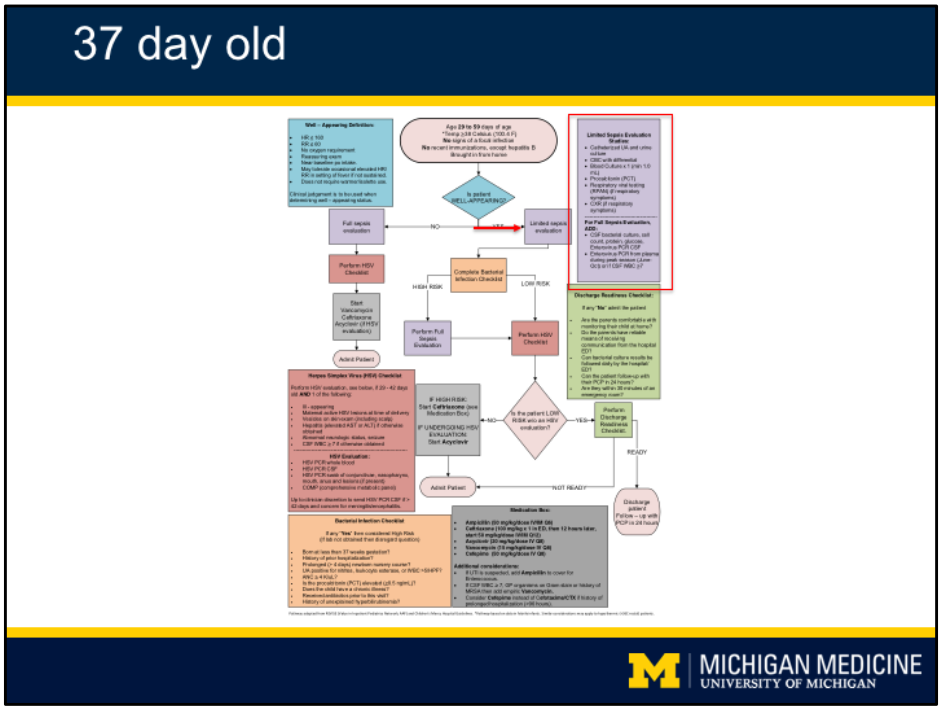
For a 17 day old, this infant would be started on acyclovir due to the risk of HSV being high enough to warrant treatment while awaiting testing but may not get antibiotics until if labs were low risk. With the improved availability of inflammatory markers to evaluate for the presence of infection, we can stratify our risk even more than we could with the Rochester or Philadelphia criteria that would allow us to determine if we need to begin empiric antibiotics.
Depending on your lab, HSV testing may take longer.

Additionally, by having the infant in the inpatient setting, we have the ability to initiate antibiotics if the infant becomes ill appearing at any time or if the labs turn positive



In a 27 day old, the risk of HSV is even lower which allows us to decrease use of acyclovir while monitoring the patient in the hospital

This infant may or may not be started on acyclovir due to the risk of HSV depending on history and labs
This infant even if well and low risk would still be admitted while awaiting culture

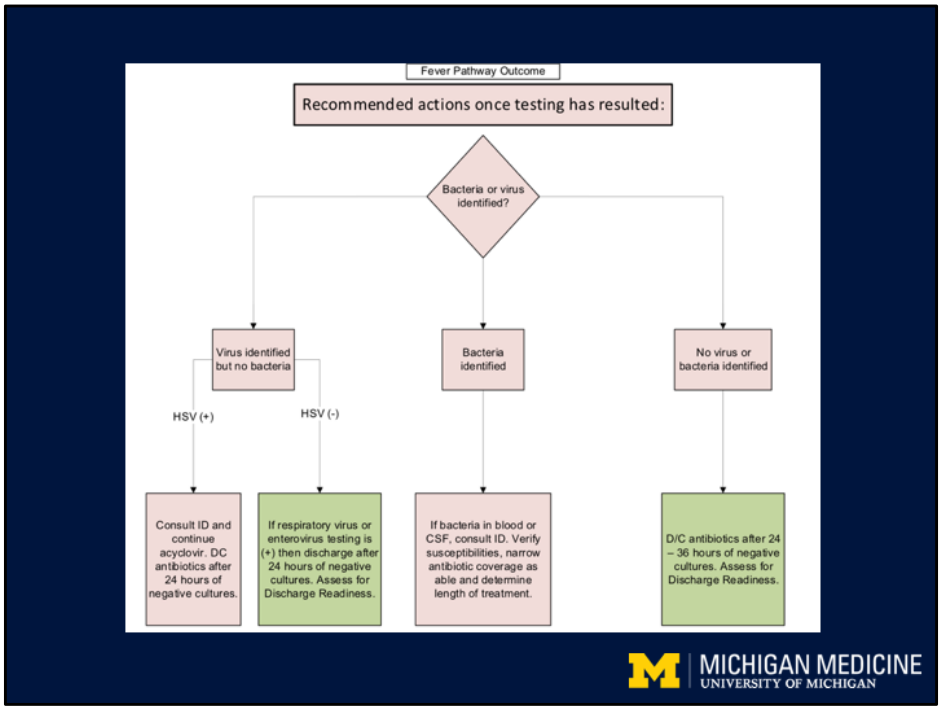


An older infant who is >28 days but well appearing would be able to start the evaluation with a more limited sepsis evaluation. Though up to 10% of infants in this age group might have a bacterial infection, when low risk criteria is met on a limited sepsis evaluation, <5% will have any bacterial infection and <0.5% will have meningitis. The majority of these infants if they have anything will have a UTI.

This infant could potentially be discharged straight from the emergency department without antibiotics after preliminary results.

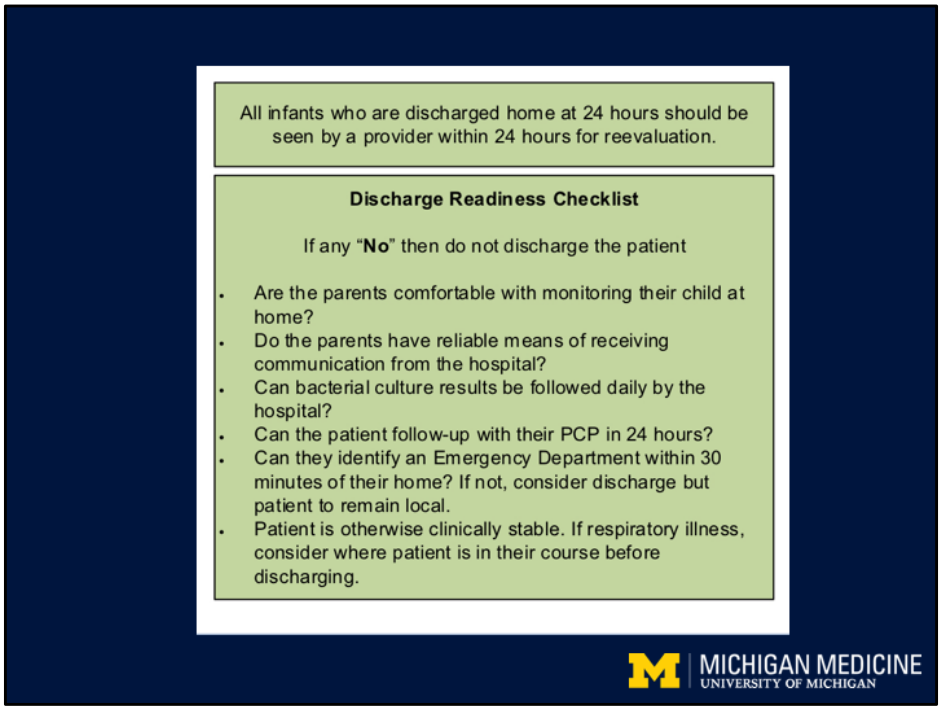
Of note, if the decision is make to give a dose of antibiotics before sending home, a lumbar puncture should be done.

I'd also like to point out that we began doing more enterovirus testing in season empirically. For us, we decided that this was important in order to have the data for those cases when we really weren't able to obtain a lumbar puncture for example since we know that if an infant has a viral illness (with the exception of rhinovirus), the likelihood of concurrent bacterial illness is much lower.



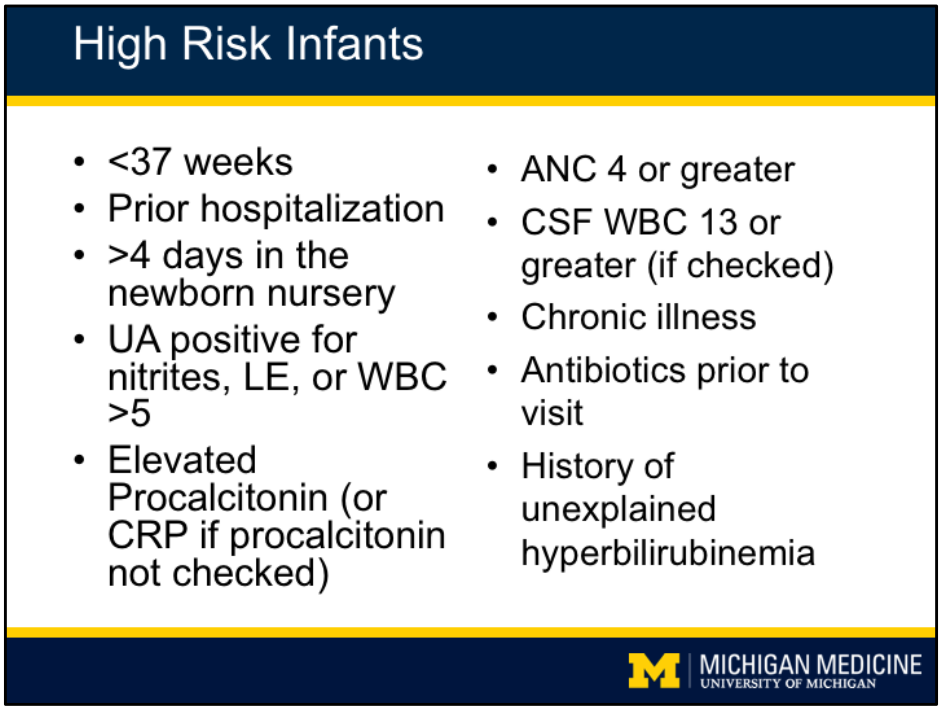
Then we determine our disposition by looking at blood, urine, and CSF cultures at 24 hours. By this time, our HSV PCR has resulted reliably.

Earlier this week, I was very grateful for the standardized approach to evaluation of these patients. I had a 5 day old admitted for fever just this week. The baby continued to fever while inpatient, but the family was pushing to be discharged after 24 hours. The ED had sent HSV studies but the HSV on the blood did not have an adequate sample. I sat down with the family and discussed that with continued fevers, I would prefer to keep the baby overnight to ensure that he was able to continue to feed adequately and did not develop new symptoms and likely recheck labs. The baby actually really looked well and continued to breastfeed well with adequate urine output. Shortly before the 24 hour mark for the cultures, the enterovirus PCR from the CSF returned positive giving me a reason for continued fevers. It was helpful for me to have an etiology for his fevers.

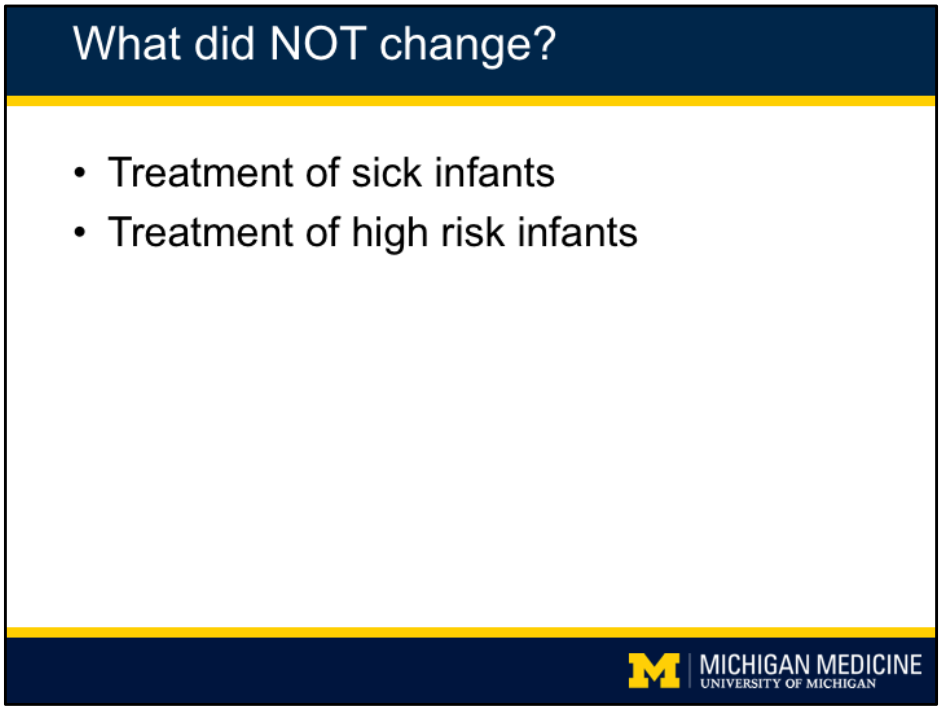


Discharging patients from the ED or hospital setting so early though can only be done with a robust primary care network. As we continue to transition more and more care to the outpatient setting, we need excellent PCPs to be aware of changes in hospital practice. For infants who are discharged home at 24 hours, they need to be seen within 24 hours for re-evaluation.

Obviously in infants who have a respiratory illness, this becomes another factor to consider when considering disposition.



These are the criteria we use to classify an infant as high risk.
- prematurity
- prior hospitalization or long stay in the nursery



Infants who appear ill should be managed with empiric antibiotics.
We just had world sepsis day yesterday. We know that sepsis kills patients of all ages and we need to be aware of it and treat with antibiotics early for those patients who appear ill, have historical factors that put them at higher risk , and in those patients whose labs indicate to us that they risk stratify to a higher risk level.

As I mentioned before, the AAP does not have any updated guidelines for the management of the febrile neonate. This lack of national guidelines has likely led to the variation in care that has been published previously.

Additionally, these guidelines were not specifically designed with the hypothermic neonate in mind.
If an infant has a single low temp but then appears well, you could consider using similar guidelines as well.

This in an app that was developed Children's Mercy Hospital. It walks through the steps of the clinical pathway for the the febrile infant. Their app includes looking at CRP or procalcitonin. It also gives suggestions on appropriate antibiotics and dosing.

Discussion

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Acknowledgments

- Thanks to Kim Monroe, MD

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