Reappraisal of Guidelines for Management of Neonates with Suspected Early-Onset Sepsis

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Since 1992, professional societies or public health agencies in the US[1-12] and elsewhere[13-17] have issued several generations of recommendations for prevention or management of early-onset neonatal sepsis (EOS). Despite those efforts, recommendations remain inconsistent, clarifications are necessary,[18] local adaptations are common,[19] and compliance rates are low.[20] We postulate that lack of consensus, especially regarding postnatal management of the neonate, is largely a result of 2 sets of factors. First, obstetrical prevention strategies have reduced substantially the incidence of EOS, potentially changing the utility of predictive strategies based on risk factors. Second, recent data better delineate relationships among risk factors, clinical signs, and EOS, suggesting that risk predictors may have different utilities in different groups. The purpose of this commentary is to explore these questions and to suggest new approaches to management of newborns who may be at risk for EOS.

The Evolution of Neonatal Sepsis Risk Assessment

Adoption of intrapartum antibiotic prophylaxis for the prevention of early-onset group B streptococcal (GBS) sepsis since 1995 has resulted in an 85% reduction in the rate of culture-proven early-onset GBS sepsis, from approximately 1.8 per 1000 live births in the early 1990s[21] to fewer than 0.25 per 1000 live births[22] since 2010. Comparable data for EOS of all causes also reflect a reduction in attack rate, from 2.0 to 2.5 in the late 1980s and 1990s[23-25] to 0.8 to 1.0 per 1000 live births since 2005.[26,27] Among infants ≥34[28] or ≥35[29,30] weeks' gestation or with birth weights >2500 g,[26] recent EOS rates are only 0.5-0.8 per 1000 live births. These much lower attack rates reflect a landscape that is fundamentally different from that extant when consensus guidelines for neonatal sepsis management were being developed 20 years ago. These changes prompt the question of whether predictive tools that had utility in the past might be less valuable now. If so, the development of novel approaches better suited to current circumstances may be necessary.

AAP	American Academy of Pediatrics
CDC	Centers for Disease Control and Prevention
EOS	Early-onset neonatal sepsis
GBS	Group B streptococcal
HCA	Histopathologic chorioamnionitis
NNT	Number needed to treat

Current guidelines from the Centers for Disease Control and Prevention (CDC) recommend diagnostic evaluation, including blood and cerebrospinal fluid cultures, and treatment with broad-spectrum antibiotics for infants who show clinical signs of sepsis.[8] Current American Academy of Pediatrics (AAP) guidelines advocate the same approach for critically ill infants but are less prescriptive with respect to infants with relatively mild findings.[12] The nature and severity of clinical findings that constitute a threshold for treatment remain problematic. Many infants with mild illness become asymptomatic over the first 6 hours and can be observed safely without treatment, unless signs worsen or fail to improve. Although 80%-100% of infants with blood cultures positive for a pathogenic organism exhibit clinical signs consistent with sepsis in the first 48 hours after birth,[26,31-34] those signs are nonspecific.

Rates of EOS among newborn infants with such clinical signs are low, ranging from 2.7% to 5.6%,[32,34,35] corresponding to numbers needed to treat (NNTs) to potentially benefit the one child with bacterial infection between 18 and 38. Thus, clinical signs of illness are reliable but inefficient for the identification of infants with EOS. Reduction of unnecessary treatment in this subpopulation will require development of a rapid, sensitive diagnostic test (likely based on early components of the innate immune response) with a strong negative predictive value for EOS. Until such a test is available, infants with significant clinical signs of possible EOS should continue to have diagnostic cultures and should be treated with antibiotics. Currently available laboratory tests (such as blood cell counts, C-reactive protein, and procalcitonin levels) are not sufficiently sensitive or specific to justify their use to decide whether to initiate or withhold empiric treatment of infants with clinical signs of illness. The use of these laboratory tests should be limited to reliance on the utility of serial normal results for identification of infants without sepsis[36-39] to support early discontinuation of empiric treatment.

Maternal chorioamnionitis is the second risk criterion in both the CDC[8] and AAP[12] guidelines. Both recommend treatment with broad-spectrum antibiotics when this

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diagnosis is made and acknowledge challenges in the use of this obstetrical diagnosis to guide neonatal therapy. Early studies that linked EOS to chorioamnionitis used strict diagnostic criteria, requiring 1 or 2 clinical findings in addition to maternal fever.[40] It has proven difficult to incorporate strict criteria into routine clinical practice, and the diagnosis now often is based on observation of maternal fever alone.[20] Lack of precision in diagnosing chorioamnionitis seriously compromises its reliability as a predictive measure.

The recommendation to treat infants exposed to chorioamnionitis was largely based on the belief that chorioamnionitis was a factor in nearly 90% of the instances in which intrapartum antibiotics had failed to prevent EOS.[41] More recent data suggest that fewer instances of "failed" intrapartum prophylaxis are associated with chorioamnionitis (<50%[42]). Only one study published before the year 2000 provided data for calculation of an overall (all birth weights) OR for EOS associated with chorioamnionitis (aOR 4.4, 95% CI 1.2-16.1).[43] More recent reports indicate that the risk of EOS in infants born to women with chorioamnionitis is strongly dependent on gestational age. In 3 reports including 1892 infants born at ≥35 weeks' gestation to mothers with clinical chorioamnionitis, the rates of EOS (positive blood culture at ≤72 hours of age) were only 0.47%,[44] 1.24%,[29] and 0.72%[30] (NNT to prevent one infection 80-210). In contrast, 4.8%-16.9%[45-49] of preterm infants exposed to chorioamnionitis develop EOS (NNT 6-21). None of these studies stratified risk according to presence or absence of clinical signs of illness, so the proportion of affected infants who would have been treated on that basis cannot be estimated. Among preterm infants, that proportion is likely to have been substantial, so the utility of chorioamnionitis as a screening tool in that population is uncertain. Nonetheless, treatment for chorioamnionitis-exposed preterm infants, based on the high attack rates and low NNT in that group, remains justified.

Among asymptomatic late-preterm and term infants with risk factors as defined by the CDC[8] (including but not limited to clinical chorioamnionitis), the risk of EOS is extremely low. Hashavya et al[33] found no cases of early-onset GBS sepsis among 1413 clinically well infants. Flidel-Rimon et al[34] reported a single instance of a positive blood culture (in a preterm infant) among 1662 at-risk infants. Ottolini et al[32] and Buckler et al[50] reported no EOS cases among 1665 and 242 at-risk infants ≥35 weeks' or >37 weeks' gestation, respectively. Predictive utility is not enhanced by use of the more objective diagnosis of histopathologic chorioamnionitis (HCA). Cuna et al[51] observed no cases of clinical or culture-proven sepsis among 284 newborn infants who had HCA but neither risk factors for nor clinical signs of infection. Among infants admitted to the neonatal intensive care unit because of risk factors or clinical signs, there was no difference in the prevalence of EOS between those with (1 of 105) or without HCA (2 of 283). The authors concluded that histopathologic examination of the placenta adds little to conventional testing in guiding decisions about discontinuation of treatment. These data make it apparent that it is time to abandon the policy of treating well-appearing infants ≥34 weeks' gestation because of chorioamnionitis alone.

Investigators in Boston and Northern California have taken the lead in implementing a change in practice. Recognizing the potential inconsistency in making the diagnosis of chorioamnionitis, they have chosen to rely upon maternal fever alone as a surrogate for the risk associated with chorioamnionitis.[19] Using data from more than 600 000 infants ≥34 weeks' gestation at birth, they developed a model for EOS risk prediction based on maternal factors (gestational age, GBS colonization, duration of ruptured membranes, greatest intrapartum temperature, and nature and duration of intrapartum antibiotics),[52] and then combined that model with findings from examination of the infants[28] to stratify subgroups according to EOS attack rates (**Table I**).[53] Sequential selection of subgroups for empiric treatment, in order of increasing NNT (**Table II**), demonstrates a trade-off between the proportion of cases included in the treatment group and the overall NNT, implying that the practitioner must either treat a very large proportion of the population (large NNT) or fail to achieve early treatment of a large fraction of the cases (high false-negative rate). In the latter case, close clinical monitoring will be necessary to identify untreated infants who develop clinical signs of sepsis. The observation that even such optimal utilization of information about maternal risk factors fails to yield an efficient and highly effective ascertainment strategy[28] should prompt consideration of alternative approaches.

Reports of reliance on serial examination rather than risk factors or screening laboratory tests are emerging from the

Table I. Risk stratification based on maternal risk factors and newborn examination[28]

	Sepsis risk at birth (cases per 1000 births)*			
	<0.65	0.65-1.54	≥1.54	All
Proportion of cases, %				
Well-appearing	15.6	8.8	7.7	32.0
Equivocal findings	14.4	10.9		25.3
Clinical illness	24.5	18.2		42.7
Total	54.5	45.5		100.0
Proportion of cohort, %				
Well-appearing	84.7	4.7	0.7	90.1
Equivocal findings	6.4	0.6		7.0
Clinical illness	2.6	0.4		2.9
Total	93.7	6.3		100.0
Attack rates (per 1000 births)				
Well-appearing	0.11	1.08	6.74	0.21
Equivocal findings	1.31	11.07		2.11
Clinical illness	5.57	27.10		8.43
Total	0.34	4.18		0.58
NNT				
Well-appearing	9370	923	148	4845
Equivocal findings	763	90		474
Clinical illness	180	37		119
Total	2961	239		1722

*Data for infants with previous probabilities of 0.65-1.54 or ≥1.54 are pooled for those with equivocal findings or clinical illness, due to small sample sizes in the corresponding cells. Values calculated from data of Escobar et al[28] in Supplemental Figure 8 and published erratum.[53]

Table II. Case capture and NNT for sequential inclusion of groups based on risk stratification model[28]

Group (exam findings and prior probability)	Cumulative % of cases	Cumulative % of population	Cumulative NNT
Ill ≥0.65	18	0.4	37
+ Equivocal ≥0.65	29	1.0	57
+ Well ≥1.54	37	1.6	76
+ Ill <0.65	61	4.2	117
+ Equivocal <0.65	76	10.6	241
+ Well 0.65-1.54	84	15.3	312
+ Well <0.65	100	100.0	1722

US,[32] Israel,[33,34] and Italy[35,54] (Table III), showing that: (1) the risk of EOS is very small in well-appearing, late-preterm and term infants (the sole asymptomatic infant with sepsis in these reports was a preterm infant exposed to chorioamnionitis[34]); and (2) in well-appearing infants identified as "at-risk" based on maternal findings, laboratory screening tests have poor specificity, a low positive predictive value, and add very little diagnostic information. Reliance on serial examinations did not increase the interval between onset of clinical signs and initiation of treatment.[35] The low case-mortality rate (1.1%) reported by Escobar et al,[28] despite the large proportion of cases that were recognized only after development of clinical signs, suggests that diagnosis based on clinical findings does not markedly increase mortality risk. Notably, only 3 of 55 infants with EOS who were assigned to the observational protocol in that experience presented with sudden collapse; it is not apparent whether more frequent examinations might have averted those more severe findings, but it is clear that risk factors failed to identify infants with EOS. These experiences cast substantial doubt on the utility of risk factors and laboratory testing for ascertainment of EOS in late-preterm and term infants and indicate that reliance on serial examinations alone may be safe and effective. Furthermore, simple serial examinations can be performed by bedside nursing staff, with physician notification should signs of illness develop.[35,54] Adoption of such approaches will require strong assurance that frequent examinations actually are performed, particularly over the first 24 hours. Early hospital discharge practices therefore may be a substantial impediment to implementation.

Conclusions

The changing environment and new data require reappraisal of traditional approaches to management of infants at risk for sepsis, with willingness to question and abandon, if necessary, long-held assumptions. Neither identification of maternal risk factors nor screening using laboratory testing is an effective strategy for the ascertainment of infants with EOS in the current era. Recommendation of such approaches in current CDC and AAP recommendations should not prohibit development and adoption of alternative approaches that are better suited to current knowledge and conditions. On the contrary, such innovation should be strongly encouraged, and should be informed by the following principles:

1. Obstetric interventions to prevent EOS are effective and should be continued.
2. Infants who exhibit persistent, progressive, or moderately severe to severe clinical signs consistent with EOS should receive empiric antibiotic therapy after cultures are obtained. Infants with mild-to-moderate respiratory findings (flaring, grunting, retractions, or tachypnea) immediately after birth may be monitored closely for resolution of transitional behaviors, without initiation of antibiotic treatment unless signs worsen or persist for more than 6 hours.
3. A rapid diagnostic test with a high sensitivity and negative predictive value early in the course of suspected illness offers the best opportunity for reduction of unnecessary treatment of symptomatic infants who are at low risk for EOS. Efforts to develop such tests should be sustained.
4. Preterm infants (<34 weeks' gestation or <1500 g) are at significantly increased risk for EOS. Additional data are needed to ascertain the independent roles of maternal risk factors (including chorioamnionitis), clinical signs of illness, and laboratory findings in guiding empiric antibiotic therapy. Until such data are available, it is reasonable to continue to stratify risk based on those traditional risk factors. Because

Table III. Clinical signs and laboratory screening in ascertainment of EOS in late-preterm and term infants

				Symptomatic infants			Well-appearing infants		Laboratory screening*	
Source	Era	Gestation, wk	Births, n	n	Cases of EOS†	NNT	N	Cases of EOS†	n	Cases of EOS identified‡
Ottolini 2003[32]	1996-1999	≥35	19 320	300	8	38	19 020	0	1665	0
Cantoni 2013[35]	2005-2006	≥37	7611	44	2	22	7567	0	-	-
Flidel-Rimon 2012[34]	2005-2008	All	22 215	434§	20	22	1661§	1	2058	1
Hashavya 2011[33]	2005-2009	All	53 788	N.S.	11¶	-	N.S.	0¶	1413	0§
Berardi 2014[54]	2009-2011	≥35	19 504	80	16	5	N.S.	N.S.	44§	2

N.S., not specified.
*Screening tests performed in at-risk infants.
†Culture-proven cases only.
‡Cases identified by before appearance of clinical signs.
§"At-risk" infants only.
¶Cases with GBS only.

most preterm infants have clinical signs of illness, most will qualify for empiric treatment. Preterm infants who appear well and have minimal or no risk factors (eg, no chorioamnionitis, preterm premature rupture of membranes, or GBS colonization with inadequate intrapartum prophylaxis) may be candidates for close monitoring and serial laboratory evaluation.

5. Well-appearing late-preterm and term infants should be managed with close clinical observation, because of the low sensitivity of risk factors in ascertainment of EOS in this group. Efforts to improve ascertainment of EOS cases in this population are commendable, but should not obscure the limited utility of the strategies attempted to date.
6. Even with selective treatment strategies, most treated infants will not have bacterial infection. In treated infants, serial normal diagnostic tests, such as blood counts or C-reactive protein levels, are highly predictive of the absence of infection and should be relied upon (in addition to culture results) to minimize the duration antibiotic exposure. However, isolated abnormal hematological or acute-phase-reactant measurements should not justify continuation of empiric antibiotics for more than 48 hours in well-appearing infants with negative culture results.
7. Implementation of novel strategies for ascertainment and treatment of EOS in late preterm and term infants should be incremental and accompanied by close surveillance for both safety and efficacy.
8. Prospective capture of detailed information regarding risk factors, clinical signs, and laboratory findings in newborn infants, as now enabled by electronic medical records, should be an operational priority. Correlation of these data with outcomes attributable to bacterial sepsis, especially among preterm infants, will allow further refinement of ascertainment and treatment strategies. ■

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