
**EBM PEARL: RECEIVER OPERATING CHARACTERISTIC CURVES (ROC):** The true positive rate (sensitivity) of a test measured against its false positive rate (1-specificity), on the x-axis and y-axis, respectively, generates an ROC. ROC analysis was first developed during World War II to measure radar’s ability to detect objects on the battlefield. Each point along the ROC curve represents diagnostic test cut-offs, unique true and false positive values. The curve is concave in the upper left-hand corner of a graph (Figure). The closer the curve approaches the upper left-hand corner, the more accurate the test. The diagonal line from 0,0 to 100,100 represents the true positive and false positive rates when the test cannot determine diseased from well patients (the likelihood ratio = 1). A common way to express test accuracy is to measure the area under the ROC curve (AUC). The higher the AUC, the more accurate is the test (ie, higher sensitivity and specificity). An example of the use of ROC and AUC may be noted in the De Martino et al paper in this issue of Current Best Evidence.

**CRITICAL STATISTICAL DISTINCTION PEARL: 95% CONFIDENCE INTERVAL (CI) VERSUS THE P VALUE:** Both the 95% CI and *P* value may be used to determine statistical significance. The *P* value is a single value expressing the likelihood that the difference between 2 or more populations responding to 2 or more interventions (eg, new drug and placebo) is due to random variation within the populations and not due to the interventions. By convention, a *P* value < .05 represents statistical significance. This means that there is less than a 5% chance that the difference between the 2 populations is due to chance. The 95% CI gives a range of values where, if the study were repeated 100 times, 95 out of 100 times the true effect would be found within the CI (this is a “working” definition, not strictly accurate). A 95% CI is statistically significant if the range from the lowest to highest values of the 95% CI cross the point of equivalence for the specific statistical parameter employed. For example, if the parameter is a relative risk which is a proportion (X/Y), when X = Y, the point of equivalence is 1; absolute risk reduction is expressed as the solution to X-Y, where the point of equivalence is 0. The 95% CI [0.3, 6] is not statistically significant for a relative risk but is statistically significant for an absolute risk reduction. The 95% CI also gives more information than a *P* value, as one can get a sense of whether the limits of the 95% CI exceed what one may consider a clinically significant value. Thus, even if the 95% CI is statistically significant, it may cross a *clinically* significant value, rendering the study’s results not clinically useful (significant).

—Jordan Hupert, MD

**Figure.** Example of an ROC curve. Reprinted with permission from MedCalc Software (https://www.medcalc.org/manual/roc-curves.php).
Lung ultrasound may allow for timelier surfactant administration and reduce radiograph use


**Question** Among extremely premature infants with respiratory distress syndrome (RDS), what is the diagnostic accuracy of neonatal lung ultrasound (LUS) as measured by receiver operating characteristic curves (ROC), compared with fraction of inspired oxygen (FiO2) threshold levels, in predicting the need for surfactant treatment and re-treatment?

**Design** Prospective cohort diagnostic accuracy study.

**Setting** Academic tertiary-care referral neonatal intensive care unit (NICU) in France.

**Participants** Neonates ≤30 weeks of gestational age with RDS and on continuous positive airway pressure (CPAP).

**Intervention** LUS on admission to NICU (and always before surfactant administration) compared with FiO2 thresholds.

**Outcomes** LUS diagnostic accuracy as determined by area under the curve (AUC).

**Main Results** ROC analysis predicted surfactant treatment, AUC, 0.94 (95% CI, 0.90-0.98) and retreatment AUC, 0.80 (95% CI, 0.72-0.89), \( P < .001 \) for both.

**Conclusions** LUS satisfactorily predicts need for surfactant, possibly allowing for earlier surfactant treatment than using current FiO2 protocols and reducing radiograph use.

**Commentary** The mainstay of lung assessment and clinical decision making in the NICU for the past many decades has been the chest radiograph. The procedure, however, is not without theoretical risk, especially when numerous radiographs are performed. A better approach is needed, and the use of lung ultrasound (LUS) to assess lung pathology in adults may finally lead the way. In the study by De Martino et al, the LUS technique previously published by their group is extended to the extremely premature infant. Premature infants ≤30 weeks of gestational age and who required CPAP were managed according to a standardized respiratory protocol that included radiographs. The LUS was not used in determining the need for dosing surfactant and was performed by the neonatology team as a “point-of-care” procedure prior to surfactant administration with a score assigned based upon aeration in the chest. Interestingly, not only was LUS predictive of need for surfactant treatment, but also it was most effective in the younger gestational age infants. The authors attribute this enhanced success to the homogeneity of lung pathology in prematurity. Although additional studies will undoubtedly follow to optimize the procedure and choice of probe, make no mistake about it, the era of point-of-care ultrasound has arrived for the NICU.

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**References**


**Association of bacterial coinfections in febrile infants with viral infections**


**Question** What is the association of serious bacterial infection (SBI) among febrile infants <60 days of age with, versus without, an identified viral infection?

**Design** Secondary analyses of a prospective cohort study.

**Setting** Twenty-six emergency departments across the US.

**Participants** Febrile infants <60 days of age without clinical signs of sepsis.

**Intervention** Testing for SBI (urinary tract infection [UTI], bacteremia, meningitis).

**Outcomes** Detection of SBI among infants tested for viral infection.

**Main Results** Among 2495 infants tested, 3.7% with a viral infection (95% CI, 2.7%-4.9%) versus 12.7% without a viral infection (95% CI, 11.2%-14.4%) had an SBI-rate ratio 3.5 (95% CI, 2.5-4.8). UTI and bacteremia were statistically significantly lower among those infants with, versus without, viral coinfection, 2.8% vs 10.7% and 0.8% vs 2.9%, respectively. There was no statistically significant difference between the 2 groups among infants with meningitis.

**Conclusions** Viral infection in febrile infants <60 days of age is associated with a decreased, but not negligible (30% relative) SBI risk, compared with non-viral-infected febrile infants.

**Commentary** Appropriate, targeted, and cost-effective management of the febrile infant has vexed clinicians for many years. Can detection of viral infection help us stratify well-appearing infants into those more or less likely to have bacterial infection? The study by Mahajan et al extends previous studies with the power of large numbers, multiple institutions and varied practice patterns. Their study confirms that 1) documented viral infection decreases the risk of SBI, 2) young infants with viral infection continue to have a non-negligible risk of SBI, and 3) it is difficult if not impossible to know which infants absolutely need a lumbar puncture. It points to ways we can move forward, possibly with comprehensive viral testing for all admitted infants, such as is performed at our own institution with demonstrable savings in cost and length of stay.
know that some viruses are likely to decrease risk more than others,2 but even large studies such as this one with thousands of infants have not been adequately powered to answer our questions virus by virus.3 A key take away, particularly in the era of rapid, multiplex panels is that febrile infants in whom comprehensive testing is negative for viral pathogens are at increased risk of bacterial infection and a thorough work up should be strongly considered.

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References

Maternal prenatal Tdap not associated with autism development in the child

Question What is the magnitude of association of autism spectrum disorder (ASD) among children born to mothers who received prenatal tetanus, diphtheria, acellular pertussis (Tdap) vaccine, compared with mothers who did not receive Tdap?

Design Retrospective, Mother-Baby cohort.

Setting Kaiser Permanente Southern California hospitals.

Participants Mother-child pairs.

Intervention Prenatal Tdap vaccination or not.

Outcomes ASD, diagnosed by the Autism Diagnostic Observation Schedule (ADOS) instrument.

Main Results The unadjusted ASD incidence rate was 3.78 per 1000 person years in the Tdap exposed and 4.05 per 1000 person years in the unexposed group, hazard ratio, 0.98 (95% CI, 0.88-1.09). Adjustment for a variety of potential confounding variables confirmed statistical non-significance.

Conclusions Prenatal Tdap vaccination is not associated with ASD.

Commentary One in 57 children in the United States receives an ASD diagnosis by the age of 8 years.1 Although genetic lesions are described, the majority of ASD cases are unexplained. Despite strong evidence to the contrary, a persistent belief that vaccines can cause ASD has resulted in reduced uptake of vaccines and the resurgence of measles and pertussis.2 Epidemiological studies and research in animal models suggest that gestational infection or maternal innate immune responses may trigger disease.3 This in turn has raised new concerns about the safety of maternal vaccination during pregnancy. Here, Becerra-Culqui et al demonstrate that immunization with Tdap vaccine during the second trimester is not associated with increased risk of ASD. These findings support the gestational use of Tdap vaccine and may have implications for the use of other vaccines during pregnancy to reduce morbidity and mortality due to infections with other agents including influenza viruses and group B Streptococci.

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References

Early onset and hospital acquired neonatal sepsis associated with high mortality

Question Among bacteremic infants, what is the epidemiology of early-onset sepsis (EOS) versus hospital acquired (HA) and community acquired (CA) late-onset sepsis (LOS)?

Design Prospective cohort.

Setting Swiss neonatal intensive care units (NICU).

Participants All bacteremic infants >37 weeks of gestation with sepsis onset <28 days or <37 weeks of gestation with sepsis onset <44 weeks corrected gestational age admitted between September 2011 and December 2015.

Intervention EOS (<3 days after birth) versus LOS (>3 days after birth), HA and CA.

Outcomes Incidence of sepsis and mortality.

Main Results Among 429 infants with 444 cases of sepsis, 20% were EOS, 62% HA-LOS, and 18% CA-LOS. Incidence of EOS, HA-LOS, and CA-LOS was 0.28 (95% CI, 0.23-0.35), 0.86 (95% CI, 0.76-0.97), and 0.28 (95% CI, 0.23-0.34) per 1000 livebirths, with 18%, 12%, and 0% mortality in EOS, HA-LOS, and CA-LOS, respectively. Preterms and those with comorbidities fared worse.
Conclusions These data demonstrate a significant burden of sepsis among neonates and associated with significant mortality.

Commentary Giannoni et al present prospectively-collected data that is current, nearly comprehensive (~90% of sepsis cases in the country), and includes descriptions of cases in 3 categories of neonatal sepsis (EOS, HA-LOS, CA-LOS). All neonates had bacteremia. Evidence of a systemic inflammatory response demonstrated by adjusted pediatric consensus sepsis definition criteria was also required, although these criteria have limitations in this population. In addition to an assessment of the primary source of infection (clinical localizing signs of infection, eg, pneumonia or meningitis), as well as organ dysfunction (need for inotropes or ventilation), they uniquely segregated LOS into HA and CA groups. HA-LOS cases were predominantly preterm infants, whereas CA-LOS were predominantly term infants discharged home after uncomplicated birth who returned with bacteremia but also included preterm infants admitted after NICU discharge and before 44 weeks post-conceptual age. They demonstrated neonatal sepsis has at least 3 “flavors,” each with a differential clinical phenotype, common bacterial pathogens, primary infection sites, and outcomes. Organ dysfunction in the setting of infection portends mortality, not simply the presence of bacteremia alone. Despite bacteremia, infants with CA-LOS had less organ dysfunction (cardiovascular and respiratory) and mortality than infants with EOS or HA-LOS. Consistent with our report on progression of organ failure with lethal LOS, they also found a strong correlation between death and a requirement for mechanical ventilation or inotropes. The variability in disease presentation and outcomes highlighted by Giannoni et al reiterates the unmet critical need for a consensus definition for neonatal sepsis (organ dysfunction in the setting of infection that increases the risk of mortality) to improve diagnostic testing and outcomes for this vulnerable population with a high disease burden.

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References


Intravenous immunoglobulin use in children with ITP does not affect development of chronic disease


Question Among children with immune thrombocytopenia (ITP), what is the therapeutic benefit of intravenous immunoglobulin (IVIG), compared with no IVIG, in preventing development of chronic ITP?

Design Randomized, multicenter, stratified, open, parallel-group study.

Setting Sixty hospitals in The Netherlands, 7 pediatric hospitals and 53 general hospitals.

Participants Two hundred six patients age 3 months to 16 years with newly diagnosed ITP and mild to moderate bleeding.

Intervention Single dose IVIG or none.

Outcomes Development of chronic ITP (defined as persistent platelet count <150x10^9/L at 6 months after diagnosis); secondary outcome of platelet count <100x10^9/L at 1 year after diagnosis (current definition of chronic ITP).

Main Results There was no significant difference in development of chronic ITP at 6 months or 12 months with an overall low rate of development of chronic ITP (<100 x 10^9/L) in the treatment and observation arms of 10% and 12%, respectively.

Conclusions Observation offers a safe alternative to treatment with IVIG. Treatment with IVIG was required in 100 patients to prevent 8 significant bleeding episodes and resulted in 5 hospital admissions due to adverse effects of IVIG.

Commentary The positives of this large pediatric, multicenter trial are randomization of many children to treatment versus observation and inclusion of children with moderate bleeding in that randomization. However, because the rate of chronic ITP development was lower than they anticipated (11% vs 28%), the study may not have had the power to actually demonstrate a difference in rate of chronic ITP development. Nonetheless, some interesting information is learned from this study. As a result of inclusion of children with moderate bleeding in the observation as well as the treatment arms, there was an increased incidence of significant (grade 4/5) bleeding (9% vs 1%, respectively). Most of the bleeding occurred within the first month of diagnosis, and all patients responded well to intervention. This study therefore highlights the key to a safe observation strategy: prompt evaluation and intervention for changes in symptoms. This study also demonstrates that although IVIG safely increases platelet counts, there are side effects associated with treatment and these can be significant and severe. Fourteen patients reported significant but milder adverse effects (AEs) including headache, nausea, fever, malaise, and skin rash and 5 additional patients had severe AEs requiring admission to the hospital. Overall, this study provides important information in making treatment decisions and providing counseling to families: those patients with grade 1 and 2 bleeding did well without treatment and patients with more significant bleeding are at increased risk especially during the first month and may benefit from treatment, but that treatment is unlikely to alter the overall course of disease.

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