

Citation	Sample size & Inclusion criteria	Country of origin	Conclusions
2023 Christensen RD, Bahr TM, Pakeeto S, Supapannachart S, Zhang, HY. <i>Current Ped. Reviews</i> 2023, 19, 376-387		USA, Thailand, China	<ul style="list-style-type: none"> Established normal reference intervals for ETCO in various perinatal populations can be used to (1) identify patients with hemolytic disorders from any cause, (2) characterize the severity of hemolysis in each patient, and (3) predict and prevent co-morbidities, and thereby improving outcomes. Reports and theories support the use of ETCO methodology to diagnose and quantify hemolytic disorder in term and premature neonates, anemic pregnant women, and fetuses in utero.
2023 Yang G, Deng L, Zhang K, Yuan Y, Zhang H. Pediatric Academic Societies (PAS) Presentation, April 2023	n=2500 <35 wks, TB >40th percentile	China	<ul style="list-style-type: none"> The use of ETCOc with TCB can decrease the rate of first phototherapy within 7 days of life (DOL) by 23% and it is associated with early identification of infants who needed phototherapy. The intervention group received risk assessment based on ETCOc <1.5 ppm indicates low risk, >1.5 ppm indicates increased risk for hemolysis. The intervention group started phototherapy earlier with higher ETCOc level but similar TCB/TSB.
2023 Du L. Pediatric Academic Societies (PAS) Presentation, April 2023	Review of studies		<ul style="list-style-type: none"> The predominant cause of elevated TSB is an increase in bilirubin production primarily due to ongoing hemolysis. The diagnosis of ABO hemolytic disease of the newborn (HDN) and optimal management can be improved by ETCOc technology. ETCOc, in combination with TSB/TcB, can be used to identify and predict hemolytic hyperbilirubinemia requiring phototherapy or readmission in the early postnatal period (late-first week of life).
2023 Christensen RD, Bahr TM, Wong RJ, Vreman HJ, Bhutani VK, Stevenson DK. <i>J Perinatol.</i> 2023 Jul 19.	Clinically available tests for hemolysis	USA	<ul style="list-style-type: none"> ETCOc measurement is the "Gold Standard" to diagnose hemolysis in a neonate and infant and best fulfills the AAP 2022 recommendation to "identify neonates with hemolysis from any cause." ETCOc is reproducible, have few false positives and false negatives, and is as sensitive and specific as is carboxyhemoglobin quantification. The test is easy to perform, rapid (one to two minutes), and noninvasive. Making a confident diagnosis of hemolysis can identify neonates that need: (1) vigilant monitoring of bilirubin and hemoglobin levels; (2) phototherapy; (3) post-phototherapy bilirubin monitoring; and (4) outpatient follow-up and neurodevelopmental assessment.
2023 Ruparel JN, Madani A, Escovedo C, Henry A, Nadar K, Rabizadeh S, Bhutani V, Berger G, Reanton G, and Mirocha J. American Academy of Pediatrics (AAP) Presentation, Oct 2023	122+600 <35 wks, TB>75th percentile, 122 intervention, 600 control	USA	ETCOc enhances routine management of neonatal HB in well-baby nursery by decreasing the number of lab tests ordered and potentially reducing cost and blood testing burden.
2023 Bahr TM, Christensen TR, Cheatham LS, Page JM, and Christensen RD <i>J Perinatol.</i> 2023	5 mothers ≥ 32 weeks gestation with a pregnancy complicated by hemolytic disease	USA	Measuring maternal ETCOc during the third trimester when a woman was carrying a fetus with a hemolytic condition is feasible.
2022 Pakdeeto S, Christensen TR, Bahr TM, Gerday E, Sheffield MJ, Christensen KS, et al. <i>J Perinatol.</i> 2022;42:116–20.	71 28 - 34 wks	USA, Thailand	<ul style="list-style-type: none"> Established reference intervals for end-tidal carbon monoxide (ETCOc) levels of neonates 28 0/7 to 34 6/7 weeks gestation to assess hemolytic rate. During the entire 28 days, the ETCOc upper reference intervals (>95th percentile) from babies in Bangkok were higher than those in Utah. No differences were found due to sex, or earliest vs. latest gestation at birth. View Chart
2022 Bao Y, Zhu J, Ma L, Zhang H, Sun L, Xu C, et al. <i>J Pediatr.</i> 2022;250:16–21.e3.	455 35-42 wks, 2500g, 12-120 HOL	China	<ul style="list-style-type: none"> Establish a reference nomogram for end-tidal CO corrected for ambient CO (ETCOc) levels in term and late-preterm newborns and its efficacy to identify hemolytic HB. For predicting HB requiring predischarge phototherapy in the early postnatal period, the combination of ETCOc ≥75th percentile and TSB/TcB ≥75th percentile had the best sensitivity (92.1%). The combination of ETCOc ≥95th percentile and TSB/TcB ≥75th percentile yielded the best specificity (97.8%). For predicting readmission for HB, ETCOc > 1.7 ppm in the late postnatal period had the highest AUC (0.82), the combination of ETCOc ≥95th percentile and TSB/TcB ≥75th percentile had a specificity of 98.4%, 90.5% readmitted infants had predischarge ETCOc ≥75th percentile. View Chart
2021 Du L, Ma X, Shen X, Bao Y, Chen L, Bhutani VK. <i>Semin Perinatol.</i> 2021;45:151351.	750+51 750 healthy control infants and 51 with severe HB	China USA	<ul style="list-style-type: none"> ETCOc can be used as a direct indicator of ongoing hemolysis. During early postnatal life, an infant's hepatic conjugation for bilirubin is very limited, mainly due to a low expression of the bilirubin-conjugating enzyme (UGT1A1), in the newborn liver (about 1% of adult levels). Because all infants have a reduced capacity to conjugate bilirubin, increased bilirubin production rates primarily drives TB levels. Evidence have shown that hemolysis is a major cause of bilirubin encephalopathy or kernicterus.

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2021 Bahr TM, Shakib JH, Stipelman CH, Kawamoto K, Lauer S, Christensen RD. <i>J Pediatr.</i> 2021 Nov;238:168-173.e2.	170 Infants receiving phototherapy	USA	<ul style="list-style-type: none"> Higher ETCOc values were associated with earlier treatment and with and longer duration of phototherapy, and ETCOc has predictive value to prevent readmission. There is no associations between ETCOc and birth weight, gestational age, maximum total serum bilirubin (TSB) during hospitalization, positive direct Coombs test, age at maximum TSB, or length of hospital stay. However, there is an association between ETCOc (considered as either a continuous or categorical variable) with the age of initiation of phototherapy. ETCOc measurement will be increasingly important to both avoid the risks of phototherapy for infants who do not require it, and to ensure increased vigilance of those with high ETCOc who are at risk of bilirubin neurotoxicity. For every 1ppm increase, phototherapy needs to start 9.1 hours early or extend 9.3 hours. DAT is an unreliable marker of clinically relevant hemolysis. Dropping DAT from their protocol will save the hospital approximately \$200,000/year.
2020 Blumovich A, Mangel L, Yochpaz S, Mandel D, Marom R. <i>BMC Pediatr.</i> 2020 May 26;20(1):248.	200 100 readmission, 100 non-readmission	Israel	<ul style="list-style-type: none"> None of the neonates in the readmission group had major risk factors for developing HB and were in the low-risk zone according to the AAP guidelines and discharged early. The AAP guidelines are appropriate for the management of high-risk neonates presenting with jaundice, less suitable to low-risk neonates presenting with physiological jaundice. The risk of readmission decreased by 48% with every day added to the original hospitalization stay, and by 71% if phototherapy had been administered during postnatal hospitalization.
2020 Bhatia A, Chua MC, Dela Puerta R, Rajadurai VS. <i>Neonatology.</i> 2020;117:612-8.	50 <35 wks	Singapore	<ul style="list-style-type: none"> Neonates with an elevated ETCOc level of >1.8 ppm had higher serum bilirubin levels needed increased surveillance, close monitoring, early treatment, and a longer duration of phototherapy. ETCOc measurement at 24 h or earlier may be a more precise predictor of later development of HB. Higher ETCOc values may also be taken as a high-risk criterion to start phototherapy at a corresponding lower threshold. In infants with ABO incompatibility, lower ETCOc values may be reassuring and obviate the need for unnecessary phototherapy by using the normal-risk category instead of the high-risk category.
2020 Elsaie AL, Taleb M, Nicosia A, Zangaladze A, Pease ME, Newton K, Schutzman DL. <i>J Perinatol.</i> 2020 Oct;40(10):1513-1517.	191 <35 wks, ETCOc and DAT positive	USA	<ul style="list-style-type: none"> Only 27.2% of 191 DAT(+) infants were hemolyzing based on ETCOc, while 29.1% of DAT (-) infants were hemolyzing based on ETCOc. Applying the AAP criteria for initiating phototherapy, the researchers found that the management of 9.4% of the infants would have been different had ETCOc been used as an indicator of significant hemolysis as opposed to DAT(+). 13 of 18 infants would have avoided phototherapy. TSB screening results do not have a turnaround time that is rapid enough to be useful for the clinical management of HB. Thus, the use of ETCOc should be valuable for identifying those infants who are at increased risk of BIND. ETCOc is a more accurate determinant of hemolysis in the newborn, and its use can lead to less phototherapy.
2018 Bhutani VK, Maisels MJ, Schutzman DL, Castillo Cuadrado ME, Aby JL, Bogen DL, Christensen RD, Watchko JF, Wong RJ, Stevenson DK. <i>Acta Paediatr.</i> 2018 Aug;107(8):1350-1356.	283 <35 wks, 2000g, 6-60 HOL	USA	<ul style="list-style-type: none"> Hemolysis increases bilirubin production of unconjugated (unbound) bilirubin that can lead to hemolytic jaundice and bilirubin neurotoxicity. ETCOc measurement is the best method available to identify increased heme turnover and bilirubin production. ETCOc together with TB/TcB percentiles and measurements of TB/TcB provide additional diagnostic accuracy. TB/TcB levels in infants differed significantly from one facility to another, while no differences in ETCOc levels were found.
2018 Olusanya BO, Kaplan M, Hansen TWR. <i>Lancet Child Adolesc Health.</i> 2018 Aug;2(8):610-620.	Review of studies	Nigeria, Israel, Norway	<ul style="list-style-type: none"> Uncontrolled or rapidly rising unconjugated (indirect) HB attributable to a metabolic imbalance favoring bilirubin production over hepatic-enteric bilirubin clearance can reach neurotoxic levels with potentially lethal consequences. TSB is a poor predictor of neurotoxicity compared to unconjugated (unbound) bilirubin.
2017 Wong RJ, Bhutani VK, Stevenson DK. <i>Curr Pediatr Rev.</i> 2017;13(3):193-198.		USA	The determination of a newborn's bilirubin production rate is critical to the assessment of a newborn's risk for developing unpredictable extreme HB and preventing BIND.
2016 Christensen RD, Mallese DT, Lambert DK, Baer VL, Prchal JT, Denson LE, et al. <i>Neonatology.</i> 2016;109(1):1-5.	100 <38 wks, TB>75th percentile	USA	Zero readmission in the ETCOc group vs 2.99% in the TB >75th percentile group. Hospital readmission for jaundice treatment and the risk of neonatal bilirubin neurotoxicity support the need for ETCOc determination.

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2016 Bhutani VK, Srinivas S, Castillo Cuadrado ME, Aby JL, Wong RJ, Stevenson DK. <i>Acta Paediatr.</i> 2016 May;105(5):e189-94.	79 <35 wks, 2000g, 6-144 HOL	USA	<ul style="list-style-type: none"> Near-simultaneous ETCOc and TB measurements in infants with TB >75th percentile accurately identify hemolytic HB. Hour-specific bilirubin load, consequent to bilirubin production, coupled with knowledge about bilirubin elimination disorders, can help predict an infant's post-discharge TB risk zone. In addition, identification of hemolytic disorders can help guide clinicians in their treatment of HB to deduce when patients lack adequate bilirubin elimination mechanisms. An elevated ETCOc level (>1.5 ppm) and/or an excessive rate of TB rise may identify those infants who are most at risk and should be aggressively treated with phototherapy. In the absence of clinical risk factors, these at-risk newborns could be observed and provided lactation support to enhance enteral milk intake such that phototherapy could be deferred.
2015 Christensen RD, Lambert DK, Henry E, Yaish HM, Prchal JT. <i>Blood Cells Mol Dis.</i> 2015;54:292-6.	74 <35 wks	USA	ETCO is an indicator of hemolytic rate. ETCO reference intervals in healthy neonates during the first three days after birth (5th to 95th percentile reference range are 1.4 to 1.7 ppm). Pathological hemolytic conditions such as hereditary spherocytosis, G6PD deficiency, or ABO hemolytic disease can be recognized by an ETCO above the reference range.
2015 Lal A, Patterson L, Goldrich A, Marsh A. <i>Pediatr Blood Cancer.</i> 2015 May;62(5):912-4.	33 Infants w Sickle Cell Anemia	USA	ETCO reflects severity of hemolysis in SCA patients. ETCO values 5-fold higher in SCA subjects than controls and the ETCO values correlated with reticulocytes and bilirubin.
2015 Castillo Cuadrado ME, Bhutani VK, Aby JL, Vreman HJ, Wong RJ, Stevenson DK. <i>Acta Paediatr.</i> 2015;104:e279-82.	83 <30 wks, 1500g, 5mg/dL, >5 days	USA	Strong linear correlation between CoSense ETCO and Carboxyhemoglobin (COHb) indicates accurate detection of hemolysis by CoSense.
2015 Bhutani VK, Wong RJ, Vreman HJ, Stevenson DK. <i>J Perinatol.</i> 2015 Sep;35(9):735-8.	641 <35 wks	USA	<ul style="list-style-type: none"> Increased bilirubin production (hour-specific ETCOc > 1.7 ppm at age 30±6 h) was noted in ~80%, 42% and 32% of infants in the high-, intermediate- and low-risk TB zones, respectively. Infants in the high-risk quartile of the hour-specific bilirubin nomogram have a higher mean bilirubin production. Infants with TB levels > 95th percentile without increased bilirubin production have impaired bilirubin elimination.
2015 Wusthoff CJ, Loe IM <i>Semin Fetal Neonat M.</i> Feb. 2015. Volume 20, Issue 1, P52-57.		USA	<ul style="list-style-type: none"> The overall TB level may not be as important in determining neurotoxicity as is the free or unbound bilirubin level, or the bilirubin-albumin binding capacity. AAP Subcommittee on HB, "the use of a single total serum bilirubin level to predict long-term outcomes is inadequate and will lead to conflicting results."
2015 Wong RJ, Stevenson DK. <i>Semin Fetal Neonat M.</i> 2015;20(1):26-30.		USA	<ul style="list-style-type: none"> Infants with hemolytic disease are at greater risk of developing bilirubin-induced neurotoxicity and BIND. The hyperbilirubinemia requiring treatment in newborn infants is associated with increased bilirubin production.
2014 Christensen RD, Nussenzveig RH, Yaish HM, Henry E, Eggert LD, Agarwal AM. <i>J Perinatol.</i> 2014 Aug;34(8):616-9.	12 TSB>25mg/dL	USA	<ul style="list-style-type: none"> Extreme HB have an underlying basis involving hemolysis. Inherited conditions such as hereditary spherocytosis and G6PD deficiency can be missed in neonates.
2014 Du L, Zou P, Chen L, Bhutani V. American Academy of Pediatrics (AAP) Presentation, May 2014.	56 TSB>75th percentile	China	CoSense provided similar information as invasive blood tests (DAT, retic count, hematocrit, and bilirubin), confirming feasibility of detecting hemolysis using a simple breath test.
2011 Blok CA, Krediet TG, Kavelaars A, Koopman-Esseboom C, Vreman HJ, Van Bel F. <i>Dev Med Child Neurol.</i> 2011 Dec;53(12):1113-8.	105 < 32 wks		<ul style="list-style-type: none"> ETCO <2.0 ppm in the first 24 hours of life is highly predictive of a favorable neurodevelopmental outcome at 3.5 years. Majority of children with an ETCO >2.0 ppm in the first 24 hours of life had adverse neurodevelopmental outcomes.
2009 Kuzniewicz M, Newman TB. <i>Pediatrics.</i> 2009 Mar;123(3):1045-50.	54795 >36 wks, DAT+	USA	There is an association between TSB levels >25 mg/dL, a positive DAT, and lower IQ scores.
2006 Maisels MJ and Kring E. <i>Pediatrics.</i> 2006;118(1):276-279.	272 108 < 75th percentile, 164 healthy control	USA	Hemolysis is an important mechanism responsible for HB in the first 4 days of life.