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Testing a new NIRS method to measure regional mesenteric tissue oxygen saturation in preterm infants that compensates for meconium and transitional stool interference

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Abstract. *Objective*: Simultaneous monitoring of cerebral and mesenteric tissue saturations were recorded in preterm neonates using near infrared spectroscopy (NIRS) to evaluate if NIRS method can be improved to compensate for the optical absorption properties of stool interference, particularly meconium and transitional stools, in order to reliably measure gastrointestinal (GI) tissue oxygen saturation.

Study design: With parental agreement, we used a 4-wavelength cerebral & tissue oximeter (FORE-SIGHT®, CAS Medical Systems, Branford, CT USA) to monitor premature neonates. The NIRS sensors were placed in the right lower quadrant of the abdomen and the forehead, with continuous data collection every 2 seconds for 72 hours. Simultaneously, continuous peripheral pulse oximetry (SpO_2) was recorded. Feeding regimens, stooling patterns and clinical outcomes were recorded. Raw data from FORE-SIGHT were recorded and analyzed using a prototype neonatal stool compensation algorithm.

Results: Twenty-three preterm neonates with adjusted gestational ages of 26–34 weeks, weighing 740–1930 grams were studied. NIRS stool interference level was determined for all subjects, and found to be extremely variable. High and Very High stool interference occurred for subjects passing meconium. Moderate and High stool interference resulted in erroneously computed very low GI StO_2 using traditional NIRS methods. Stool compensated GI StO_2 measurements showed a higher correlation to cerebral $SctO_2$ and pulse oximetry SpO_2 in subjects with healthy bowel.

Conclusion: Measurement of mesenteric saturations via NIRS proves to be a useful tool in neonates. A NIRS algorithm that compensates for interference caused by meconium and transitional stools shows promising results to measure GI StO_2 accurately.

Keywords: NIRS, mesenteric saturation, meconium, NEC

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Abbreviations

NIRS	near infrared spectroscopy
GI StO_2	gastrointestinal tissue oxygen saturation
$SctO_2$	cerebral Tissue Oxygen Saturation
SpO_2	pulse oximeter arterial oxygen saturation
SaO_2	arterial oxygen saturation
NEC	necrotizing enterocolitis

1. Introduction

Premature infants with immature organ systems are predisposed to a number of comorbidities in the neonatal intensive care unit (NICU). Among these, is the development of necrotizing enterocolitis (NEC) and/or intestinal perforation. Currently, 7 to 10% of premature infants born 1500 grams or less develop NEC associated with significant morbidity and mortality in the NICU [1].

The exact pathogenesis of NEC remains largely unknown. It appears to be multifactorial, and may be related to relative bowel ischemia, enteric feeding regimens, alterations in the normal bacterial colonization of the gastrointestinal (GI) tract, bacterial translocation and activation of the cytokine cascade, decreased epidermal growth factor, increased levels of platelet activating factor, and mucosal damage from free radical production [2]. Currently the diagnosis of NEC is largely based on clinical, laboratory and radiologic findings. These findings may or may not be all present, making diagnosis difficult at times.

Non-invasive continuous monitoring is used in the intensive care unit, and is helpful in determining changes in an infant's clinical status. Most commonly seen is continuous cardiorespiratory and pulse oximetry monitoring, allowing detection of heart rate, respiratory rate and arterial oxygen saturation. The use of near infrared spectroscopy (NIRS) has also become popular over recent years. While several studies have validated the use of a NIRS monitor to measure cerebral saturations [3–5], few data is available regarding oxygenation of mesenteric tissue. The use of NIRS technology to monitor GI oxygenation is increasing, and may prove to be a useful tool in detecting the presence of bowel ischemia. However, its use may be limited if an infant is still passing meconium, which can cause interference with NIRS measurements, often resulting in artificially low tissue saturation readings [6]. Studies using NIRS monitors to test the interference effects of meconium spread on a forearm revealed a significant drop in tissue oxygen saturation measurements (StO_2) to either very low or undetectable, as a function of meconium film thickness [6]. Meconium also interferes with pulse oximetry measurements if smeared on the skin [7]. The aim of this study was to evaluate the NIRS limitation in measuring GI tissue saturation due to neonatal stool interference using a conventional algorithm designed for cerebral tissue saturation and compare to a prototype GI NIRS algorithm that compensates for the optical absorption properties of neonatal stools as a first step in order to be able to reliably measure GI tissue oxygen saturation.

1.1. NIRS background

Near-infrared spectroscopy (NIRS) measures light in the wavelength range of 650–950 nm. With its ability to penetrate biologic tissues in this range, NIRS offers the ability to measure regional tissue oxygenation noninvasively by measuring chromophores in the body such as hemoglobin, myoglobin, and cytochrome aa3. Regional tissue oxygenation can be measured with the use of somatic or cerebral oximeters, in which the light absorption of oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb) are measured by an NIRS sensor placed on the skin containing a light source and detector. The FORE-SIGHT cerebral oximeter measures cerebral tissue oxygen saturation ($SctO_2$) as an absolute value, which does not require a baseline measurement like trending cerebral oximeters [8–10]. Because the blood in the cerebral tissue microvasculature is a mix of arterioles, venuoles, and capillaries, the FORE-SIGHT monitor uses an algorithm that approximates the contribution of venous blood to arterial blood of 70–30% ratio in the tissue microvasculature [4, 8, 11]. This leads $SctO_2$ measurements to be less than pulse oximetry measurements (SpO_2), less than arterial oxygen saturation (SaO_2), but higher than brain venous oxygen saturation $SjvO_2$ (i.e., blood measured from a cephalad catheter of a VV ECMO patient) by approximately 10% [4, 9].

2. Methods

Approval was obtained from the hospital's Institutional Review Board (IRB). This study did not require an informed written consent. After parental verbal agreement for voluntary participation, subjects were

recruited from the 54-bed Neonatal Intensive Care Unit (NICU) at Children's National Medical Center. Twenty three preterm infants born between 24 and 33 weeks gestation were enrolled in this study between June 2009 and October 2010. Subjects with perinatal asphyxia, intracranial pathology (including intraventricular hemorrhage grade III–IV), bleeding disorders, congenital cardiac disorders, including hemodynamically significant patent ductus arteriosus, known chromosomal abnormalities, and history of surgical NEC were excluded from the study.

2.1. Study procedures

We used a 4-wavelength cerebral and tissue oximeter (FORE-SIGHT®, CAS Medical Systems, Branford, CT USA) to monitor premature neonates for 72 hours. The NIRS sensors (FORE-SIGHT Small sensors with 25 mm optode separation) were placed on the forehead of the neonate, just below the hairline to measure cerebral saturations ($SctO_2$), and on the anterior abdominal wall, just inferior and lateral to the umbilicus in the right lower abdominal quarter, for measurement of mesenteric saturations (GI StO_2). Data was collected continuously every 2 seconds for 72 hours. Continuous peripheral pulse oximetry (SpO_2) was simultaneously recorded using a pulse oximeter (Radical, Masimo Corp. Irvine, CA). Demographic data including gestational age, birth weight, corrected gestational age during study, current weight during study, gender, medications, and primary diagnoses, were collected. In addition, feeding regimen and stooling patterns were recorded, as well as clinical outcomes including feeding intolerance and development of NEC.

2.2. NIRS methodology

The FORE-SIGHT algorithm to measure cerebral tissue oxygen saturation $SctO_2$ has been described elsewhere (11). Briefly, the cerebral $SctO_2$ algorithm was developed to measure the concentrations of deoxy-hemoglobin (Hb) and oxy-hemoglobin (HbO_2) in order to obtain $SctO_2$ from the ratio of $HbO_2/(HbO_2 + Hb)$. This same cerebral algorithm was applied to NIRS sensor data collected from the GI tract in order to calculate an *Uncompensated GI* StO_2 value. Then we tested a new NIRS "prototype" algorithm that includes a third variable (MEC), an unknown chromophore in neonatal stools that seems to have the highest concentration in meconium. Optical characteristics of neonatal stools obtained from spectrometer data of a meconium sample [6] were incorporated in the prototype algorithm to calculate a relative MEC concentration. The MEC value was used as an indication of the presence of the undetermined chromophore in meconium and transitional stools, which in effect indicates the degree of interference due to the presence of stools interrogated by the NIRS sensor while measuring regional mesenteric tissue oxygen saturation. Therefore the value range of MEC was quantified broadly into reportable categories of *low*, *moderate, high, and very high* stool interference. The MEC value was also used in the prototype NIRS algorithm to correct for errors in calculating Hb and HbO_2 in order to calculate a *Stool compensated GI* StO_2 value.

2.3. Data analysis

The type of stool (meconium or transitional) was recorded from each subject and correlated to the average value of meconium interference over the monitoring period to determine if *very high*, *high*, *moderate*, or *low* interference is present. The percentage of *very high* stool interference over the monitoring period was calculated for each subject as well. Maximum and minimum range of values for cerebral $SctO_2$, Stool compensated GI StO_2, uncompensated GI StO_2, and SpO_2 from the pulse oximeter was recorded for comparison. Then, using linear regression, Stool compensated GI StO_2 and uncompensated GI StO_2 was correlated to cerebral StO_2 and pulse oximetry SpO_2 to determine a correlation coefficient "*r*" to compare any correlation differences.

3. Results

3.1. Population demographics

Twenty-three preterm neonates, with corrected gestational ages of 26 to 34 weeks, and a study weight of 740–1930 grams were studied. All patients had a primary diagnosis of prematurity and respiratory distress syndrome. Patients' demographic data is provided in Table 1.

3.2. NIRS interference analysis

The detected stool interference level, as determined from calculating MEC, tended to be very variable,

Table 1
Subjects demographic information

Subject number	Birth weight (Kg)	Birth GA (weeks)	Study weight (Kg)	Study age (days)	Outcome post study
1	0.89	27	1.06	13	Subglottic stenosis
2	1.02	29	1.49	22	Discharged
3	1.21	29	1.35	13	NEC (pneumatosis) +35 days after study
4	1.10	29	1.30	11	Discharged
5	1.01	28	1.65	31	Discharged
6	1.09	28	1.61	34	Discharged
7	1.13	30	1.33	7	Discharged
8	0.87	26	1.57	38	UTI
9	1.38	33	1.49	10	Discharged
10	1.56	32	1.80	12	Discharged
11	0.88	26	1.53	37	NEC (pneumatosis) +1 day after study, feeding intolerance, pulmonary hypertension
12	0.62	25	1.24	54	Discharged
13	1.23	28	1.39	22	Discharged
14	0.93	27	1.01	10	Discharged
15	0.97	27	1.24	23	Sepsis (during study), NEC +27 days after study
16	1.43	28	1.24	10	Discharged
17	1.21	28	1.35	14	PVL
18	1.28	28	1.34	10	Discharged
19	0.83	26	1.00	19	Meningitis
20	0.90	26	1.13	30	NEC +17 days after study, sepsis
21	1.73	32	1.61	15	Discharged
22	0.73	24	0.74	15	Sepsis, meningitis, hydrocephalus, seizures
23	1.62	30	1.93	13	Discharged

Abbreviations: GA, gestational age; Kg, kilogram; NEC, necrotizing enterocolitis.

likely due to the passage of stools and movement of the intestines under the NIRS sensor. NIRS average stool interference level and percentage of *very high* stool interference to overall monitor time was determined for all subjects as shown in Table 2. Subjects still passing meconium tended to have a greater frequency of *high* and *moderate* stool interference compared to those with transitional stool, but in some occasions, transitional stool subjects also exhibited *high* stool interference. Likewise, meconium stool subjects had a higher percentage of *very high* stool interference when compared to transitional stool subjects, 26.4% vs. 4.3% ($p = 0.016$) respectively. Of importance is to note the range of stool compensated GI StO_2 and uncompensated GI StO_2 values in relation to cerebral $SctO_2$ and pulse oximetry SpO_2 values. For all meconium subjects, uncompensated GI StO_2 values were 0% at some time during the measurement, which is likely an erroneous result when considering the general health of the subject. For most transitional stool subjects, uncompensated GI StO_2 values were also 0% at some time during the measurement. In two subjects, uncompensated GI StO_2 values were always 0%. Subjects that did not have an episode of uncompensated GI StO_2 of 0% exhibited *low* or *moderate* stool interference levels.

3.3. Mesenteric versus cerebral NIRS measurements

Figures 1 and 2 are examples of data collected from one transitional stool subject over several hours that exhibited variations in cerebral StO_2, and demonstrates that in general, Stool compensated GI StO_2 correlates better to cerebral $SctO_2$ than uncompensated GI StO_2. Since the subjects enrolled in the study had respiratory distress syndrome (RDS) and mostly healthy GI tracts, it was expected that GI StO_2 would correlate to some degree with cerebral $SctO_2$ and pulse oximetry SpO_2. For the next part of the analysis, linear regression was used to determine the correlation of Stool compensated GI StO_2 and uncompensated GI StO_2 to cerebral StO_2 and pulse oximetry SpO_2 to determine a correlation coefficient "*r*". Mean and range of *R* values were reported in Table 3. The mean "*r*" values were higher for the stool compensated GI StO_2 in each comparison. In some subjects, the variation of cerebral StO_2 and pulse oximetry SpO_2 was not as great to effectively evaluate correlation relationships, which resulted in lower "*r*" values for all comparisons.

4. Discussion

The results of our study demonstrate that NIRS algorithms designed to measure cerebral tissue oxygen saturation may not perform well when applied to mesenteric tissue saturation measurements. The interfering effect of an unknown chromophore in neonatal stools, particularly high in concentration in meconium, needs to be addressed for accurate GI StO_2 measurements. We demonstrate the potential for a neonatal stool compensation NIRS algorithm to overcome this issue. The next step will be to validate the algorithm.

Table 2
Range of SpO_2, cerebral $SctO_2$, and GI StO_2 (Stool compensated & uncompensated) for subjects with meconium & transitional stool

Subject	Range SpO_2	Range cerebral $SctO_2$	Range stool compensated GI StO_2	Range uncompensated GI StO_2	Average stool interference Level	Percent time of very high stool interference%
Meconium subjects (9)						
1	66–100	45–85	39–76	0–73	Moderate	1.2
3	75–100	64–78	66–81	0–99	High	53.4
4	77–100	68–84	62–80	0–95	High	56.9
7	88–100	66–79	64–84	0–99	Moderate	8.7
17	81–100	53–90	58–87	0–0	High	25.1
18	76–100	58–89	45–74	0–70	High	40.9
19	50–100	44–79	21–83	0–89	High	38.0
20	55–100	10–74	29–85	0–99	Moderate	1.3
21	65–100	60–87	46–88	0–99	High	12.1
Transitional stool subjects (14)						
2	61–100	50–80	41–76	0–85	Moderate	0.0
5	73–100	54–84	55–78	0–78	Moderate	0.2
6	65–100	51–77	46–77	0–75	Moderate	0.7
8	69–100	58–81	50–83	30–88	Moderate	0.0
9	65–100	65–93	69–95	66–95	Low	0.1
10	77–100	62–79	52–90	0–99	High	15.0
11	62–100	52–81	53–89	40–93	Low	0.2
12	66–100	48–84	52–82	0–99	Moderate	0.2
13	85–100	66–82	54–94	0–96	Moderate	0.1
14	72–100	55–81	26–70	0–0	High	39.1
15	32–100	37–85	62–95	0–99	Moderate	0.6
16	74–100	63–88	50–91	32–99	Moderate	0.9
22	56–100	45–82	38–80	0–99	High	1.7
23	66–100	59–81	59–88	35–96	Moderate	1.3

Abbreviations: SpO_2, pulse oximetry oxygen saturation; $SctO_2$, cerebral tissue oxygen saturation; GI StO_2, gastrointestinal.

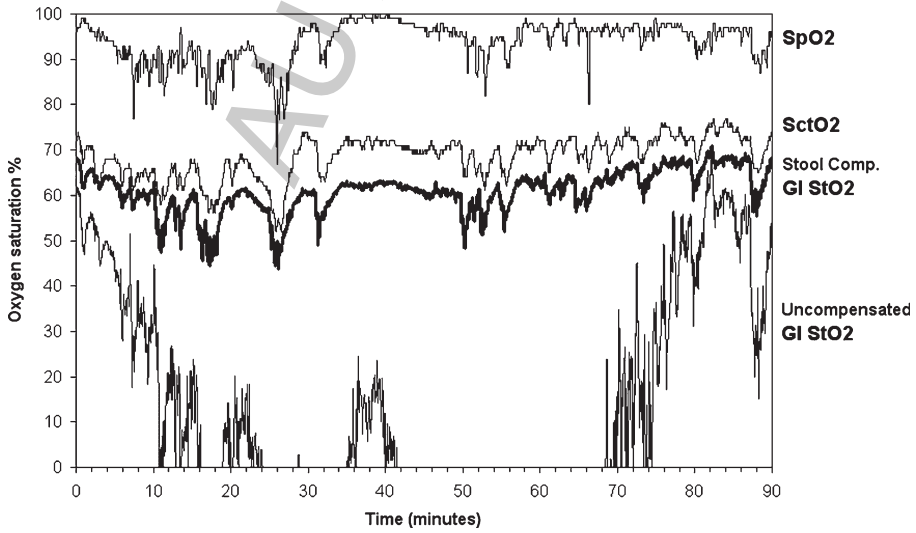

Fig. 1. 90 minute recording of NIRS GI StO_2 (Stool compensated & uncompensated) with NIRS cerebral $SctO_2$ and pulse oximetry SpO_2.

The interfering effect of neonatal stools on NIRS monitors diminishes with subject age and weight, with complete disappearance for infants ≥2 months old and >4 kg (unpublished data). The precise time when stool interference is no longer an issue for NIRS monitoring is not known.

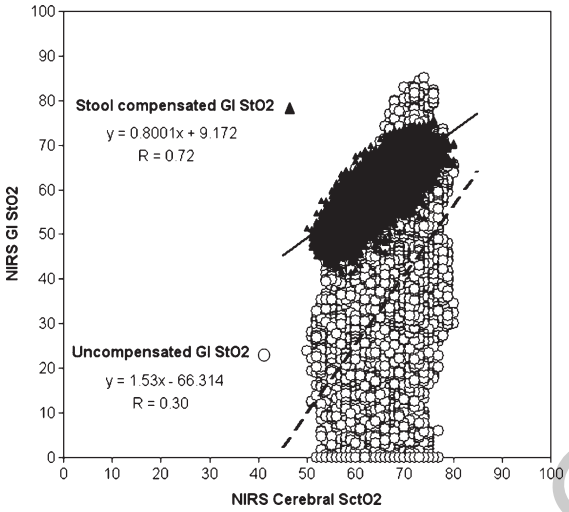

Fig. 2. NIRS GI StO_2 (Stool compensated & uncompensated) vs. NIRS cerebral $SctO_2$ scatter plot.

During the start of the study, we also made spot check measurements with the NIRS sensor over the liver and flank areas of the subject. The stool interference measurement values over these non-intestinal areas typically were lower than that of the intestines, but not absent, especially for lower weight neonates. This is perhaps because the light path of the NIRS sensor used also interrogated a portion of the intestine either by the sensor being too big or slightly off target as for the liver, or the interrogation depth of the sensor passed through the skeletal muscle layers of the flank and interrogated some intestine tissue and stools very deep. This issue would likely increase with larger 40 mm optode separation NIRS sensors with higher interrogation depth that are commonly used over the liver or flank on neonates.

The use of NIRS in the neonate is increasing, as it has proven to be a useful tool in the non-invasive monitoring of cerebral tissue saturations. The same principal can be applied to various other organ systems; however, limited validation studies for this purpose have been completed. There is little known about normative baseline values for somatic organ systems, such as the liver, kidney, and or gastrointestinal system. Studies have been conducted to determine normal baseline trends in regional tissue oxygenation in preterm infants. McNeill et al. sought to determine normal baseline trends in premature neonates. Using the INOVS 5100C (Somanetics, Troy, MI USA), they observed a high degree of variability in the measurement of abdominal saturations, which decreased over time. They also observed regional abdominal saturations as low as 15% (the lowest displayed by INVOS measurement, not zero) for a period of hours, with good sensor pickup and no signs of feeding intolerance [12]. This concurs with our observation of a high degree of variability and much lower mesenteric saturation measurement as compared with cerebral saturation measurement. Figure 1 shows a 90 minute snapshot recording of GI StO_2, with uncompensated and compensated tracings for stool interference, as well as cerebral $SctO_2$ and pulse oximetry SpO_2 for a 21 days old subject, already passing transitional stools, with an uncomplicated hospital course. As seen in the figure, uncompensated GI StO_2 values are extremely variable and often are zero. This high degree of variability and interference is likely due to passage of stool underneath the sensor, thereby giving erroneously low values. Using a prototype NIRS algorithm, which modifies the traditional NIRS algorithm to account for the

Table 3
Mean and range of linear regression correlations (R) of GI StO_2 (Stool compensated & uncompensated) vs. cerebral $SctO_2$ and pulse oximetry SpO_2

	Meconium subjects (9)		Transitional stool subjects (14)	
Linear regression variables	Mean R	Range	Mean R	Range
Stool compensated GI StO_2 vs. cerebral StO_2	0.32	0.08–0.69	0.56	0.09–0.80
Uncompensated GI StO2 vs. cerebral $SctO_2$	0.12	0.00–0.47	0.32	0.00–0.75
Stool compensated GI StO_2 vs. SpO_2	0.29	0.02–0.69	0.44	0.05–0.74
Uncompensated GI StO_2 vs. SpO_2	0.10	0.00–0.47	0.24	0.00–0.55
Cerebral $SctO_2$ vs. SpO_2	0.56	0.27–0.92	0.68	0.33–0.89
Percent time of very high stool interference	26.4%	1.2–56.9%	4.3%	0.0–39.1%

Abbreviations: R, correlation coefficient; GI, gastrointestinal; StO_2, tissue oxygen saturation; $SctO_2$, cerebral tissue oxygen saturation; SpO_2, pulse oximetry oxygen saturation.

chromophoric properties of oxy-hemoglobin and deoxy-hemoglobin, as well as the chromophoric properties of newborn stool, allows for stool compensated GI StO_2 value to be computed. As seen in Fig. 1, stool compensated GI StO_2 values have much less variability and correlate much better with cerebral $SctO_2$ values. Table 2 describes the degree of interference measured by the prototype NIRS algorithm to stratify subjects into categories of low, medium and high NIRS interference. Those subjects still passing meconium had a large percentage of time with either moderate or high interference. However, more than 50% of subjects passing transitional stools also exhibited moderate or high interference.

Generally, those subjects born at a lower gestational age tended to have a larger percentage of time with high interference, which may speak to overall lower bowel motility and more immature function. For example, Subject 3 (Tables 1 and 2), had an extremely high degree of NIRS interference, with 53.4% of total time monitored, recorded as *very high* interference. This patient's primary diagnosis was meconium ileus, and then went on to develop necrotizing enterocolitis 12 days after monitoring was completed. The primary diagnosis of meconium ileus is usually consistent with poor GI motility, which may be related to the large amount of time that meconium was detected underneath the sensor.

Several other studies have used NIRS as a tool to potentially detect bowel ischemia and NEC, one of which showed that tissue oxygenation index (another NIRS methodology) fell below normal ranges when blood flow decreased in ill or hypotensive patients [13, 14]. In an infant with congenital heart disease and necrotizing enterocolitis, NIRS was used to show mesenteric perfusion improved with antibiotics and bowel rest [15]. Not only has NIRS been shown to be a promising adjunct tool at the bedside for monitoring critically ill infants in the intensive care unit, it has been shown to be safe in neonates [12, 16].

As the use of NIRS continues to grow, there is emerging evidence that new algorithms and advances in technology can allow for more precise measurement of tissue oxygenation. As our results demonstrate, the presence of meconium and transitional stools causes variable interference in the measurement of mesenteric tissue oxygenation, which required changes in the NIRS algorithm in order to measure GI tissue oxygen saturation accurately. The new algorithm requires that the NIRS system have at least 3 wavelengths, as the chromophore(s) contained in newborn stools become the third unknown to be calculated, along with oxy- and deoxy-hemoglobin, which is used to calculate StO_2. This will allow for the ability to produce a more precise StO_2 value and give a better reflection of true GI tissue oxygenation.

5. Conclusion

The use of NIRS technology has already proved to be a reliable, noninvasive tool to measure regional tissue saturation of the brain. Measurement of mesenteric saturations via NIRS may prove to be a useful tool in neonates, particularly in premature infants at risk for complications including feeding intolerance and the development of NEC. The establishment of normal range of GI tissue saturation in healthy neonates, and examining changes in bowel saturations during periods of enteral feeds may help to determine whether the bowel is in fact healthy enough to tolerate feeds, or whether the infant may be at higher risk for developing NEC. A new prototype NIRS algorithm that compensates for interference caused by meconium and transitional stools shows promise to measure GI StO_2 accurately. Further studies are needed to validate the new prototype NIRS algorithm.

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