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Monitoring technologies in the neonatal intensive care unit: implications for the detection of necrotizing enterocolitis

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Necrotizing enterocolitis is the most common and fulminant gastrointestinal disease affecting neonates. Its pathogenesis is heterogeneous and not clearly understood. Early detection could prevent some of the devastating consequences of this disease, but currently there is no noninvasive method of reliable early-stage detection. Here, we review various noninvasive monitoring technologies that have already been employed or show promise for early detection. Each method may have an important role after its technical difficulties are resolved. These are discussed in detail as they relate to various aspects of the putative pathophysiology of this devastating disease.

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Introduction

In the neonatal intensive care unit (ICU), necrotizing enterocolitis (NEC) is the most severe and prevalent bowel disease primarily affecting premature infants. Currently, 7 to 10% of the premature infants whose birth weight is less than 1500 g are affected.[1] The current mortality rate for patients with NEC is 15 to 25%. Surgery is required for roughly one out of three patients, and the postoperative mortality rate increases to about 40%.[2] There has not been a significant decrease of these rates despite decades of research.[3] Because the survival rates of very-low-birth-weight infants are increasing from improved obstetrical and neonatal care, the number of patients with NEC or at risk for NEC is also bound to increase.

Owing to the fulminant nature of NEC, any delay in intervention from diagnosis later in the course can lead to rapid deterioration of the infant, hence worsened prognosis. Timely decision making regarding intervention, based on early detection, may aid in decreasing the overall morbidity and associated mortality, as well as hospital expenses.[4] In most institutions, the diagnosis of NEC is largely based on the use of the modified Bell's criteria.[5] Many of the signs and symptoms in these staging criteria are not specifically ascribed to NEC. Signs of early-stage NEC ('stage 1') are even less specific, making the detection and proper diagnosis much more difficult. Thus, there is an unquestioned need for a new detection method that is safe, specific and sensitive to early changes related to NEC onset. A continuous bedside monitoring capability would be an additional benefit, especially because the infants with NEC can become severely ill almost immediately after the symptoms begin to appear. In this review, we present various noninvasive modalities that have potentials for early detection by meeting the above requirements. Clinical adaptation of these technologies for the investigation of NEC will provide valuable insights into the unknown areas of this disease, which may provide clues to early NEC detection.

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NEC pathophysiology

There are many risk factors associated with the development of NEC. Although the precise etiology is not known, the known common predisposing risk factor for NEC in premature infants is intestinal immaturity. Immaturity of the intestines can be characterized in terms of intestinal motility and absorption, intestinal barrier function, immune response and circulatory regulation.[6] Other risk factors such as genetic susceptibility, abnormal intestinal microbiota, feeding insult and compromised blood flow also seem to have a role in NEC development.[7] When these factors interact and combine with other aspects of the early perinatal period, an inflammatory cascade leading to bowel tissue necrosis can be triggered. If this inflammatory cascade is left unchecked, the tissue necrosis may progress rapidly. In the most severe cases of NEC, intestinal perforation, sepsis and death may result. Figure 1 illustrates the pathophysiology of NEC based on the risk factors stated above.

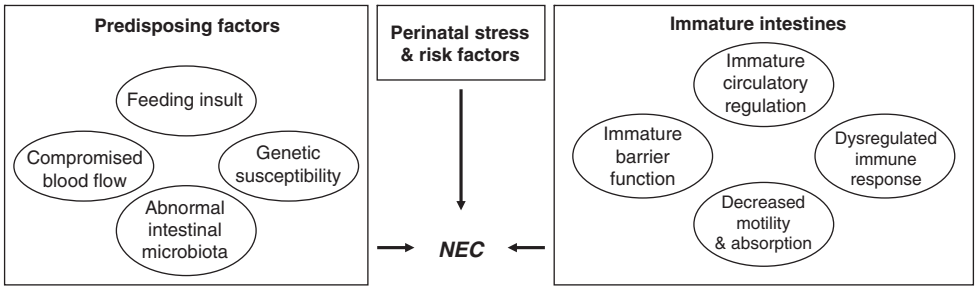

Figure 1 Pathophysiology of necrotizing enterocolitis (NEC).

Table 1 Comparison of current noninvasive technologies for the detection of NEC

Method/measurement variable	*Advantages*	*Limitations*
Radiographic imaging/X-ray mass attenuation coefficient	Current standard for NEC detection	Late findings, images are not produced instantaneously or frequently enough
Ultrasonography/tissue echogenicity	Blood flow monitoring in superior mesenteric artery, useful for gasless abdomen	Comet-tail image artifact due to the presence of air
MRI/spin density of hydrogen molecules	Capable of imaging various tissue characteristics, image contrast is high for soft tissues	Risky for highly unstable infants owing to required transportation to the MR unit
Gastric tonometry[a,b]/intramucosal pH	Measurement indicates gastric mucosal tissue perfusion, monitoring is possible on alternate sites for easier access (that is, sublingual tonometry)	Measurement is spatially variable and sensitive to other factors, gastric tube insertion is required, long calibration time
Breath hydrogen monitor[a]/ concentration of hydrogen or methane gas in a breath sample	Measurement is related with intestinal circumstances (that is, abnormal growth of intestinal bacteria and malabsorption)	Technical difficulty in obtaining good quality samples
Computerized auscultation[a,b]/bowel sound intensity	Monitoring of gastric emptying and bowel motility, continuous monitoring is possible	Complexity of the bowel sound signal
Pulse oximetry[a,b]/light absorbance of arterial hemoglobin	Continuous monitoring of arterial oxygen saturation and peripheral tissue perfusion	Not specific to NEC or changes in the bowel
NIR spectroscopy and imaging[a,b]/ light absorbance of microvascular hemoglobin	Continuous monitoring of splanchnic or mesenteric tissue perfusion	Measurement is low in resolution, intraluminal contents (that is, feeding and air) interfere the measurement

Abbreviations: MRI, magnetic resonance imaging; NEC, necrotizing enterocolitis; NIR, near-infrared.
[a]Bedside monitoring.
[b]Continuous monitoring.

Technologies for NEC detection

There are available technologies that can be considered as a potential method to monitor and detect certain stages of NEC. In Table 1, comparisons are made between measuring variables, advantages and limitations of each technology. Safe diagnostic imaging modalities without capabilities as a bedside monitor are also mentioned in our review. The ionizing radiation of nuclear imaging methods is potentially hazardous to premature infants, microscopic imaging methods typically do not provide penetration depth required for producing noninvasive images of the intestines and in endoscopy and colonoscopy, there is a risk of injuring the vulnerable premature intestines. Thus, these methods are excluded from our review owing to safety concerns or their inefficiency for use in premature infants. Wireless capsule endoscopy is a recent advancement that may resolve these problems, but such a device has yet to be designed for the use in premature infants and tested for safety.

Radiographic imaging

Currently, the diagnosis of NEC relies heavily on radiographic findings, and the method of interpreting the images is well established. For a patient with suspected NEC, abdominal radiographic images are obtained using either a vertical or horizontal beam when the patient is lying in the supine or decubitus position. Images are examined for signatures of dilated bowel loops, pneumatosis intestinalis and pneumoperitoneum.

The diagnosis of NEC based on radiographic examination relies on destruction of the air/fluid and soft tissue interface in intestines due to bacterial translocation or bowel tissue necrosis. Radiographically detected pneumatosis intestinalis and pneumoperitoneum are rather specific pathognomonic indicators of the need for medical and surgical interventions. Pneumatosis intestinalis is characterized as gas in the bowel wall and often appears as bubbly patterns or duplicated intestinal wall linings in radiographic images. In some cases, portal venous gas can also be found, which represents air entering the small portal vein tributaries in the intestinal wall and traveling to the liver. These are indicated by white and black arrows respectively in Figure 2a. Pneumoperitoneum develops when air leaks out of the intestines after perforation, which is indicated by arrows in Figure 2b.

Limitations of radiography are also relatively well-understood along with the importance of its current role in the diagnosis of NEC. Currently, radiography is only a snapshot of a single point in time and does not allow instantaneous or continuous evaluation. Thus, some intestinal necrosis or perforation in evolution may go undetected in the images. In addition, diagnosis supported by these findings is based on the changes of intestinal structure, which may occur too late to be clinically useful. Finally, radiographic images are two-dimensional projection images. When three-dimensional images are needed, computed tomography is an option. However, its frequent use in the neonatal patients should not be encouraged, because associated dose of ionizing radiation is high. Premature infants may be at an increased risk of radiation-related cancer mortality because of their younger age and potentially larger cumulative dose. Considering above limitations, there is little expectation of advancement in the use of radiographic imaging for NEC detection. In this review, we will see how the current limitations of detection could be extended by using other technologies.

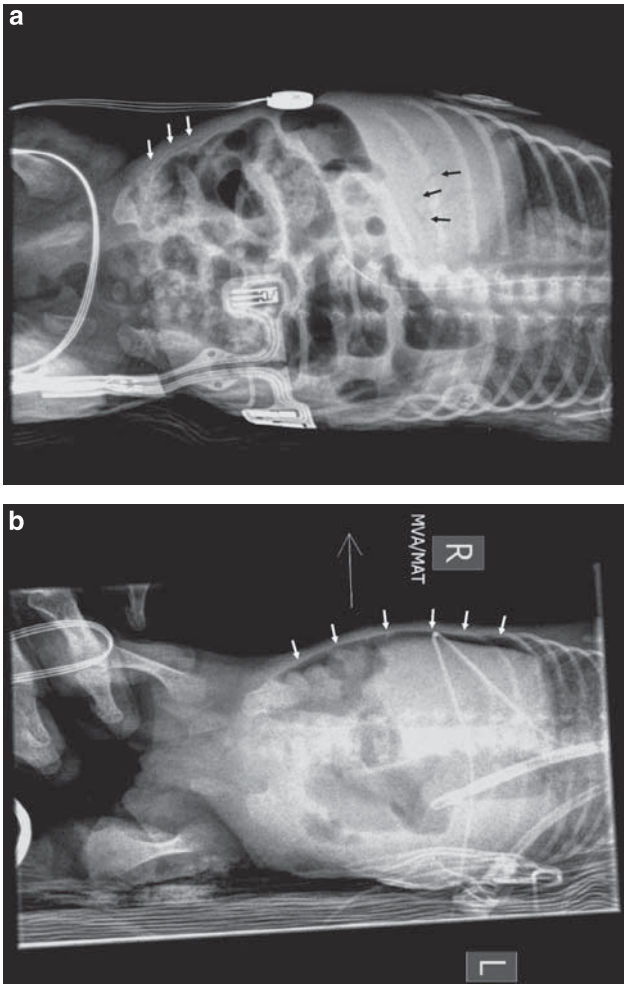

Figure 2 Abdominal X-ray image showing signs of necrotizing enterocolitis. (**a**) Pneumatosis intestinalis and portal venous gas and (**b**) pneumoperitoneum.

Ultrasonography

Intestinal perforation in NEC may develop without any radiographic evidence of free air, presenting a diagnostic dilemma. An abdomen with paucity or absence of gas is such a case in which ultrasonography (U/S) may be useful as an early detection modality.[8–10] When there were clinical symptoms, but no radiographic evidence, of NEC in neonates with gasless distended abdomen, U/S findings of ascites and intraperitoneal fluid–debris levels were regarded to be suggestive of intestinal perforation.[9] For clinically deteriorating patients with no definitive radiographic evidence of NEC due to paucity of abdominal gas, U/S findings of ascites and hyperemia of the bowel loops was used to support the decision of surgical treatment of NEC.[10] In a retrospective investigation of the U/S parameters related with NEC,[11] clinical outcome for the patients with free air and focal fluid collection[3] was comparatively poor.

Doppler U/S measures the relative velocity of blood flow, which can be useful in evaluating mesenteric blood flow. Blood flow velocity in the superior mesenteric artery, measured using Doppler ultrasound in 478 very-low-birth-weight neonates (<1500 g), was predictive of subsequent intestinal dysmotility and correlated with the quantity of tolerated enteral feeding.[12] In this case, the pulsatility index showed 95% sensitivity and 82% specificity in predicting intestinal dysmotility. Color Doppler U/S may be useful in determining bowel viability, which can be characterized by bowel wall thickness and perfusion.[13,14] Determining the viability by differentiating ischemic from necrotic bowel is not possible using the current radiographic method. Color Doppler detection of absent blood flow showed 100% sensitivity, which is far greater than that of radiographic detection of peritoneal free air (40%) as a positive sign for severe NEC with necrotic bowel ($P = 0.3$).[14] In NEC, inflammation causes initial hyperemia in the bowel wall, which is followed by ischemia and bowel wall thinning. This progression of NEC, which was confirmed by color Doppler U/S evidence,[13] is illustrated in Figure 3.

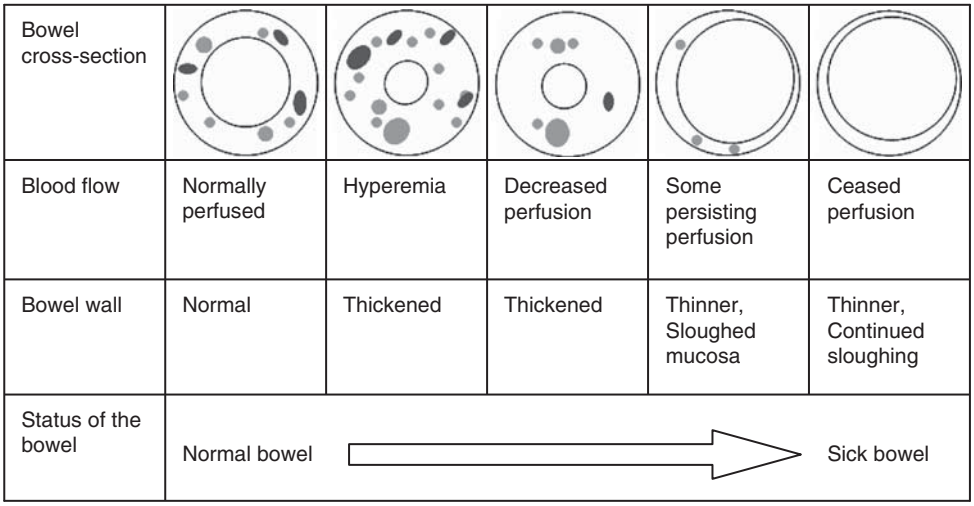

Figure 3 Perfusion and thickness changes of intestinal wall in necrotizing enterocolitis.

An important limitation with the use of U/S is related to the presence of intraluminal air, causing comet-tail image artifacts. Unfortunately, many cases of NEC are characterized by the presence of intraluminal or intraperitoneal air, making U/S assessment of bowel viability effective only for cases of gasless abdomen.

Magnetic resonance imaging

A clinical magnetic resonance imaging (MRI) study was performed in preterm infants with NEC, in which pneumatosis intestinalis could be identified in MR images.[15] In the MR images, ischemic changes as an early sign of NEC could not be identified. Because signs of pneumatosis intestinalis are more readily detectable in routine abdominal radiography, the ability of MRI to diagnose NEC earlier has not yet been clearly shown.

Mesenteric ischemia caused by compromised blood flow is a risk factor for the development of NEC.[16] This situation is most commonly shown in infants with cardiac disease, resulting in low flow states to the intestine. It is difficult, however, to discern when ischemia occurs. Recent advancements in MRI technology and contrast agents allow real-time imaging of the small bowel with improved image contrast. Using a combined method of MRI and oral caloric stimulation, six healthy adults and six adult patients with mesenteric ischemia could be differentiated.[17] The greatest differences were identified between 35 and 75 s after the oral intake ($P = 0.002$), suggesting the feasibility of the method for detecting mesenteric ischemia. This type of MRI may be useful for NEC evaluation, but the clinical safety of these contrast agents in premature infants remains untested.

Radiographic imaging and U/S devices that are used in the neonatal ICU are designed to be portable for common clinical use. On the contrary, an important limitation of MRI is the real risk associated with transporting neonatal patients, who are already highly unstable, to an MRI unit usually located remote from the neonatal ICU owing to its size.[18] Therefore, the routine clinical use of MRI to evaluate NEC is not yet convincing.

Gastric tonometry

In gastric tonometry, gastric mucosal oxygenation is estimated as intramucosal pH by means of intraluminal P_{CO2}, which is measured using a balloon-tipped catheter inserted into the stomach. The intramucosal pH has been shown to be a valuable indicator of gut ischemia,[19] early hypovolemia,[20] mortality and sepsis.[21] Gastric tonometry has been applied to two term infants with hypoplastic left heart syndrome, which is generally regarded to be a risk factor for NEC.[22] The patient with a significant decrease in gastric intramucosal pH (<7.32) was diagnosed with NEC by radiography, which was confirmed at post-mortem examination.

To improve accuracy or to gain easier access, several studies tested measurements from alternate sites such as small intestine,[19] rectum[23] and sublingual.[24] In detecting the onset of anaerobic metabolism caused by hemorrhagic shock in 10 anesthetized and mechanically ventilated pigs, small bowel P_{CO2} was more accurate with less noise compared with gastric P_{CO2}, showing significant correlation with superior mesenteric vein P_{CO2} ($r^2 = 0.81$, $P<0.001$).[19] In premature neonates, the small intestine is difficult to access, but the rectum could be a more accessible and less fragile alternate location. Rectal tonometry was shown to be poorly correlated with gastric measurement in a study of 26 adult cardiac surgery patients in the perioperative period (elective coronary artery bypass grafting with cardiopulmonary bypass) and 4 h post-surgery.[23] In hemodynamically unstable ICU patients, sublingual tonometric measurements were correlated with gastric measurements.[24] Alternate site tonometry methods have mainly been studied as an indicator of impending global hypoperfusion, as

in septic or hemorrhagic shock, and has not yet been evaluated for association with intestinal tissue perfusion or NEC.

There are several challenges in tonometric methods that remain unresolved. Tonometry is intrinsically sensitive to factors such as gastric acid, enteral feeding, duodenal reflux and global acid–base abnormalities. The long equilibrium time (30 to 90 min) of this method can be a disadvantage when instantaneous reading is desired. Lastly, measurements may vary depending on the location of a catheter. These technical problems must be investigated and resolved before this modality can be adapted for use in early NEC detection.

Breath hydrogen monitoring

In human breath, various gases are present such as carbon dioxide, carbon monoxide, hydrogen and nitric oxide. Analytic tests of breath samples are accurate, reproducible and inexpensive. For this reason, breath analysis has been investigated as a potential diagnostic technique for multiple disease states. Mucosal stress is likely a factor in the development of inflammatory bowel disease, and breath analysis can be used to assess stress levels in the gastrointestinal mucosa.[25] Hydrogen, a bacterial metabolite of carbohydrates in the gastrointestinal system and exhaled in the breath, seems to have potential as a diagnostic tool. Increased concentrations of hydrogen in an exhaled breath sample indicate bacterial metabolization of luminal substrates, because there is no other bodily source of hydrogen production. Breath hydrogen is currently being investigated in the areas of small intestinal bacterial overgrowth and lactose/fructose malabsorption.[26,27]

Bacterial overgrowth in the intestines of neonates is a risk factor for the development of NEC. A significant increase in breath hydrogen concentration derived from these bacteria was found in the infants who were later confirmed to have developed NEC.[28] This increase occurred before clinical signs, showing potential application of this test for early NEC detection. In a study of hydrogen excretion in 103 neonates for the purpose of NEC screening, it was found that factors such as gestational age, caloric intake and antibiotic usage increased the measurement (H_2/CO_2 concentration ratio), whereas frequency of feeding did not.[29]

In analyzing gases in a breath sample, calibration is a confounder. Once a gas collection method is chosen, patient's breathing during the gas collection has to be carefully controlled. Interference can be introduced with changes in tidal volume, respiratory rate, breath holding, collection site (mouth or nose) and the patient's cardiopulmonary status. The collection site is required to be sealed tightly to prevent ambient air or humidity from corrupting the measurement. In addition, adaptation of this method for mechanically ventilated infants, who are also having frequent alterations in feeding volumes, will be a significant challenge. In a recent review of biomarkers for infants at risk of NEC, the authors showed concerns about the technical difficulties and low positive predictive value related with this method.[30] Further study is necessary to overcome these technical difficulties and to establish the complicated link between inflammatory bowel disease, small intestinal bacterial overgrowth and NEC.

Computerized auscultation

Peristalsis (bowel motility) is present in both fed and unfed states creating audible sound. Immature intestines may show decreased motility, which is thought to predispose the infants to developing NEC. Auscultation is an assessment method frequently used in the clinical setting that can provide an important indicator of bowel motility.

Although the traditional auscultation is available for qualitative analysis of bowel sound, quantitative analysis is also possible by computerized pattern analysis of recorded sound signal. An efficient bowel sound monitor may potentially describe bowel sounds quantitatively and help clinicians make diagnosis more objectively. In an investigation of irritable bowel syndrome using computerized auscultation, the irritable bowel syndrome patient group could be differentiated from the control group with 89% sensitivity and 100% specificity using the fasting sound-to-sound interval (time interval between bowel sounds: cutoff at 640 ms).[31] In a study of infants with hypertrophic pyloric stenosis, the sound index (amplitude sum of the sound signal) of the patient group was significantly smaller before pyloromyotomy than that of the healthy control group.[32] At 12 h after surgery, the sound index increased significantly with significant correlation with gastric emptying, which was measured immediately before sound recording using a marker dilution double sample method. The authors concluded that the sound index is a useful indicator of gastric emptying and bowel motility after pyloromyotomy. In 10 diabetes mellitus patients with delayed gastric emptying, the sound index of the gastroduodenal sound was significantly lower after the intake of a liquid meal compared with that of 20 healthy adults.[33] The authors characterized bowel sounds to be gastroduodenal, if they occurred with the activities of the stomach and duodenal wall (determined by U/S), or as intestinal, if occurring with no stomach and duodenal activity.

A pattern analysis of bowel sounds was performed with the aim of developing a long-term unsupervised expert bowel sound monitoring system.[34] The system showed promising overall recognition accuracy (94.84%), with only a small level of interfering noise (2.19%). Current sound sensors are not customized for use on the abdomen of premature infants. To be clinically applicable, the sensors should be small and light weight with a long-term recording capability.[35] Using the expert monitoring system and the custom sensors, peristaltic movements of premature infant intestines could be characterized, which may help in the early detection of decreased bowel motility and add to the current understanding of NEC pathogenesis.

Pulse oximetry

In pulse oximetry, light is transmitted through a body part to measure oxygen saturation in the arterial blood continuously and in real time. For abdominal measurements, a reflectance oximeter sensor probe could be placed on the flat abdominal surface, which will be more adequate than the commonly used transmission probes. There are previous investigations that applied pulse oximetry to the abdomen, such as for the detection of bowel ischemia. Using pulse oximetry, intestinal viability could be assessed in dogs,[36] and bowel segments were intraoperatively identified so as to preserve dubious but viable parts.[37,38] However, an important limitation of pulse oximetry for NEC detection is lack of specificity. Tissue oxygenation in splanchnic/mesenteric microcirculation can be compromised in NEC of the preterm infants without any disturbances in systemic hemodynamics or arterial oxygen saturation (S_pO_2). Thus, the efficacy of pulse oximetry is limited to the detection of ischemic NEC, in which S_pO_2 may actually affect intestinal tissue oxygenation.

Near-infrared spectroscopy and imaging

In near-infrared spectroscopy (NIRS), concentrations of bodily chromophores can be measured noninvasively. Similar to pulse oximetry, relative light absorption by hemoglobin can be measured. The difference is that NIRS measurements are derived from smaller blood vessels (that is, arteriole, capillary and venule), from which the level of tissue oxygenation is estimated (Figure 4). Principles in NIRS allow measurement of multiple wavelengths (750 to 1100 nm) and good penetration depth up to several centimeters. Measurements of various quantities, such as concentrations of water, bulk lipid, oxyhemoglobin, deoxyhemoglobin and cytochrome *c* oxidase can potentially be produced. Additional indirect parameters, such as total hemoglobin, blood flow and blood volume, can also be obtained.[39] Clinical applications of NIRS exist in many areas including neurological investigation, peripheral vascular disease, muscle/exercise physiology and fetal/neonatal monitoring.[40] Currently, NIRS exists as a bedside device in many operating rooms and ICUs for real-time monitoring of cerebral oxygenation. It is also feasible to apply NIRS to monitor organ or muscle tissue perfusion, such as in the cases of septic shock, trauma, organ failure and ischemia.

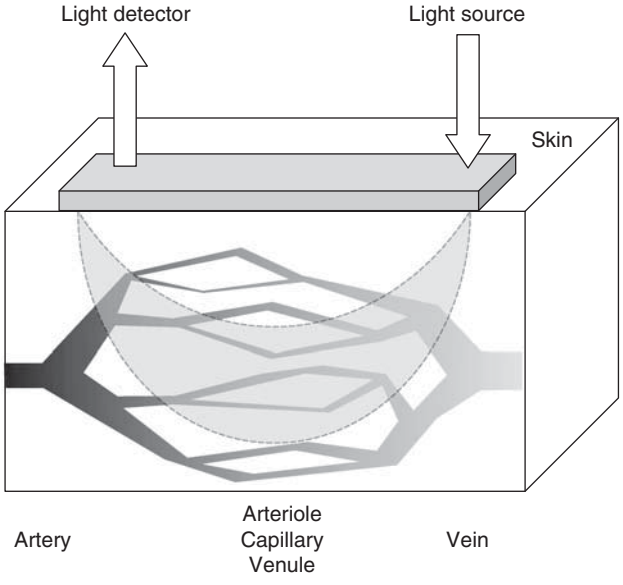

Figure 4 Near-infrared spectroscopy measurement of tissue oxygen status.

Several studies have applied NIRS to the abdomen to investigate postprandial changes, bowel ischemia and NEC. In three neonatal patients with apneic episodes and peripheral desaturation, changes in oxyhemoglobin concentration were coincident with changes of peripheral saturation.[41] In these patients, apnea was associated with consequent NEC, gastroesophageal reflux and aspiration or enteral feeding. In another study, tissue oxygenation index was postulated to change below the normal range in the vascular beds when blood flow decreases in ill and hypotensive infants.[42] Cerebral and splanchnic tissue oxygenation index ratio showed 90% sensitivity in predicting splanchnic ischemia. In a case study about an infant with congenital heart disease and NEC, it was hypothesized that impaired tissues extract more oxygen, making the venous oxygen saturation decrease for a constant oxygen delivery. The authors showed that the patient's mesenteric oxygen saturation as well as clinical status improved with antibiotic treatment and bowel rest.[43] Questions about postprandial changes in tissue perfusion can be answered using NIRS. In stable preterm infants who tolerated full orogastric feeds, there was an increase in splanchnic oxygenation relative to cerebral oxygenation, both measured using NIRS 1 h after feeding.[44] Further validation is necessary, however, to determine applicability of the NIRS technology to studies involving NEC associated with enteral feeding and feeding intolerance.

Currently, NIRS is generally regarded to be a trend monitoring method, because its measurement is low in resolution. A multisite measurement may provide more accurate information about regional tissue perfusion.[45] The problem associated with low resolution may be resolved as the technology evolves.[46] Improved algorithms, such as time-resolved spectroscopy, allow calculation of the absolute values of oxygen saturation. An optimal selection of the optical path length and instrument parameters is important for enhancing accuracy.[47] Technically, an adequate penetration depth should be determined and followed by the optimal location of detection. Uncertainties exist about the movement or geometrical changes of the intestines due to motility or distension from the intraluminal air. Pneumoperitoneum can also cause artifacts by pushing down the intestines, thus changing the optical path. Characteristics of the artifacts caused by these types of uncertainties should be investigated. One may measure at the liver to avoid these

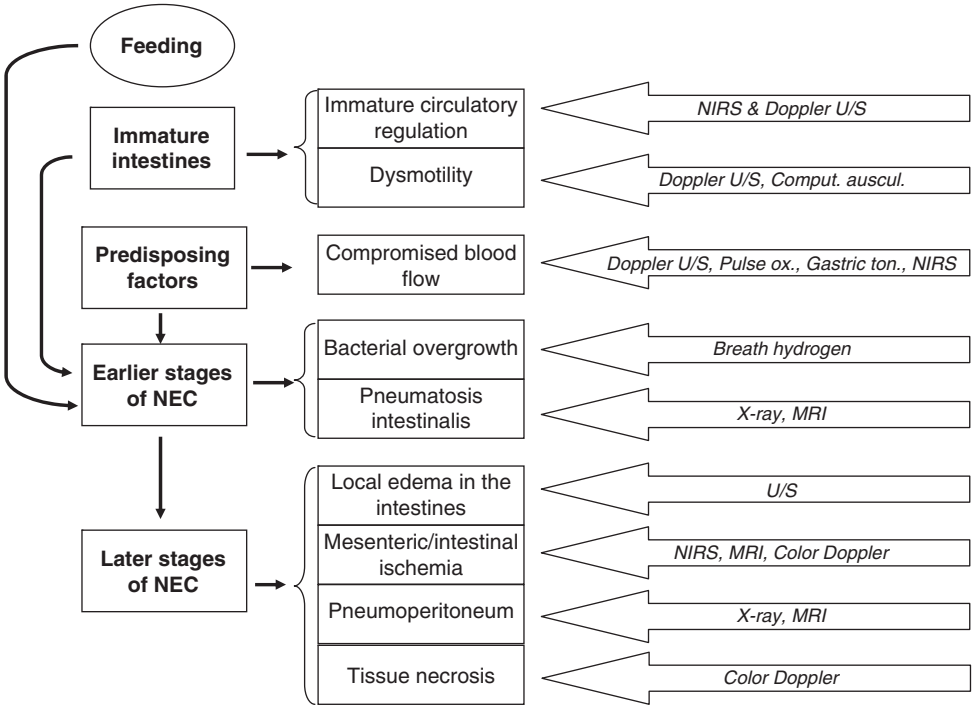

Figure 5 Noninvasive technologies for detection of stages of necrotizing enterocolitis (NEC). NIRS, near-infrared spectroscopy; U/S, ultrasonography; MRI, magnetic resonance imaging

issues arising from intestinal shape changes, but liver measurement will reflect splanchnic circulation rather than mesenteric circulation.

The motivation for multisite measurement naturally leads to the idea of imaging. NIR spectroscopic and imaging methods have been applied to assess hemodynamic changes in the early post-burn period.[48] The authors identified differential changes in tissue oxygenation, blood volume and tissue water content after a thermal injury in adult pigs. Diffusion optical tomography (DOT) is one example of the NIR imaging modalities. In DOT, cross-sectional images of light absorption, light scattering and concentrations of chromophores are reconstructed by solving model equations (that is, photodiffusion equations) from the measured reflected light for an assumed object of geometry and light absorption characteristics. Thus, functional imaging of biological tissues and organs is feasible using DOT. This method holds promise as a clinical application in other areas including brain function monitoring, detection of breast cancer, rheumatoid arthritis and osteoporosis.[49] Images produced in DOT have low resolution, and it is unlikely that DOT will be considered for anatomical imaging. Still, its capability of producing images continuously at the bedside makes this method attractive. In a study of cerebral hemodynamics, DOT showed spatial accuracy in quantifying simulated focal changes of chromophore concentrations.[50] This result suggests that a future application of DOT may become possible in visualizing local changes of intestinal tissue perfusion.

Conclusion

Detection of NEC in its early stages remains a major challenge, but is clearly necessary if we are to prevent this devastating disease. Here, we have provided an overview of several emerging noninvasive technologies (Figure 5), which clearly show promise for the early detection of NEC and will require further adaptation and customized development.

Conflict of interest

The authors declare no conflict of interest.

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