Cerebral and splanchnic oxygenation and necrotizing enterocolitis in preterm infants

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DOI: 10.1016/j.earlhumdev.2014.04.008

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Document Version
Publisher's PDF, also known as Version of record

Publication date: 2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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CHAPTER 7

GENERAL DISCUSSION
AND FUTURE PERSPECTIVES

Trijntje E. Schat
Despite extensive research in the past few decades, predictive and preventive strategies for necrotizing enterocolitis (NEC) are lacking. It is believed that early detection of and intervention in NEC might result in a reduction of short- and long-term complications. The ideal method to predict NEC would be non-invasive, portable, accurate, easy to use, cost-effective, and would have a high sensitivity and specificity for predicting NEC and its complications. Currently, no apparatus meets these criteria. Near-infrared spectroscopy (NIRS), however, is non-invasive, portable, and easy to use. This tool provides insight in cerebral and splanchnic perfusion by measuring regional tissue oxygen saturation. Since it has been hypothesized that impaired intestinal perfusion is a critical step in the development of NEC, NIRS might prove to be a valuable tool to predict this disease. The main aim of this thesis was therefore to investigate whether monitoring cerebral, liver, and intestinal oxygenation could be useful in infants who develop NEC. To this end, we formulated the following research questions:

1. Is it feasible to study splanchnic oxygenation simultaneously in two abdominal regions in infants with suspected and definite NEC? Can liver and infrabumilcal oxygen saturation values \( r_{\text{liv}} \text{SO}_2 \) and \( r_{\text{int}} \text{SO}_2 \), respectively) substitute each other for the purpose of assessing splanchnic oxygenation? (Chapter 2)

2. Can cerebral and splanchnic fractional tissue oxygen extraction (FTOE) values be used as markers for intestinal damage in infants with NEC? (Chapter 3)

3. Do preterm infants with NEC show impaired cerebrovascular autoregulation (CAR) more often than infants without NEC? (Chapter 4)

4. Can we differentiate high-risk infants who develop NEC from those who do not by monitoring cerebral and intestinal oxygenation as early as in the first days after birth? (Chapter 5)

5. Can we, in an early stage of the disease, differentiate infants with definite NEC from infants with suspected NEC, and infants with complicated NEC from infants with uncomplicated NEC by monitoring cerebral, liver, and intestinal oxygenation? (Chapter 6)

**MAIN FINDINGS**

Is it feasible to study splanchnic oxygenation simultaneously in two abdominal regions in infants with NEC? Can \( r_{\text{liv}} \text{SO}_2 \) and \( r_{\text{int}} \text{SO}_2 \) values substitute each other for the purpose of assessing splanchnic oxygenation?

To address this question, we monitored \( r_{\text{liv}} \text{SO}_2 \) and \( r_{\text{int}} \text{SO}_2 \) simultaneously for 48 consecutive hours in preterm infants with suspected and definite NEC. We found that it was possible to monitor \( r_{\text{liv}} \text{SO}_2 \) and \( r_{\text{int}} \text{SO}_2 \) simultaneously 67% of the time. We did not encounter adverse skin effects or hindrance of routine clinical care. Additionally, we found a weak association between \( r_{\text{liv}} \text{SO}_2 \) and \( r_{\text{int}} \text{SO}_2 \) values and poor agreement between these values as assessed by a Bland-Altman plot.
Can cerebral and splanchnic FTOE values be used as markers for intestinal damage in infants with NEC?

To answer this question, we associated cerebral and splanchnic FTOE values with a marker for intestinal damage: intestinal fatty acid-binding protein in plasma (I-FABPp). I-FABP is primarily located in enterocytes of the small bowel and is secreted after compromised cell membrane integrity, such as occurs in intestinal ischemia and inflammation, including NEC. During the first 16 hours after NEC onset, we found strong associations between cerebral and splanchnic FTOE values and I-FABPp levels in infants with NEC. From 16 hours after NEC onset, infants who developed complications as a result of NEC had both decreasing splanchnic FTOE values and I-FABPp levels, whilst infants with uncomplicated NEC showed increasing splanchnic FTOE values concurrent with decreasing I-FABPp levels.

Do preterm infants with NEC show impaired CAR more often than infants without NEC?

Nine infants with definite NEC (9/15, 60%) and five infant without NEC (5/13, 38%) had a statistically significant negative correlation between mean arterial blood pressure and cerebral FTOE, suggesting impaired CAR. The difference in prevalence of impaired CAR between these two groups was not statistically significant. Compared with the prevalence of impaired CAR in our control group (38%) and with the reported prevalence in infants without NEC in literature (40%), infants with NEC in our study population had a high prevalence of impaired CAR.

Can we differentiate high-risk infants who develop NEC from those who do not by monitoring cerebral and intestinal oxygenation as early as in the first days after birth?

Infants with cerebral oxygen saturation ($r_cSO_2$) values < 70% (< 25th percentile) in the first two days after birth had a nine-fold higher risk of developing radiologically confirmed NEC than infants with $r_cSO_2$ values ≥ 70% (≥ 25th percentile). Intestinal oxygenation values obtained in the first days after birth were not predictive for NEC development. Two days prior to NEC development, we did find, however, higher intestinal FTOE values in infants who developed NEC compared with infants who did not develop NEC. Variability of $r_cSO_2$ and $r_{int}SO_2$ values in the first days after birth was not of additive value in predicting the onset of NEC.

Can we, in an early stage of the disease, differentiate infants with definite NEC from infants with suspected NEC, and infants with complicated NEC from infants with uncomplicated NEC by monitoring cerebral, liver, and intestinal oxygenation?

NIRS monitoring during the first 24 hours after onset of NEC symptoms in the cerebral as well as the splanchnic region did not distinguish infants with definite NEC from infants with suspected NEC. We did find, however, that liver $rSO_2$ values ≤ 59% in the first 8 hours after NEC onset predicted the development of complicated NEC in infants with definite NEC with a sensitivity and specificity of 1.00. Also, cerebral $rSO_2$ values ≤ 71% in the first 8 hours after NEC onset predicted complicated NEC with a sensitivity of 1.00 and a specificity of 0.80.
Variability of $r_{SO_2}$, $r_{livSO_2}$, and $r_{intSO_2}$ values had no additive predictive value for differentiating infants with definite NEC from infants with suspected NEC or for differentiating infants with complicated NEC from infants with uncomplicated NEC.

**GENERAL DISCUSSION**

*Feasibility of measuring splanchnic oxygenation*

Our first question was whether it was feasible to study splanchnic oxygenation in two abdominal regions simultaneously in preterm infants with NEC. For this purpose, we measured $r_{LivSO_2}$ and $r_{IntSO_2}$ values concurrently for 48 consecutive hours in infants with suspected and definite NEC (Chapter 2). Median gestational age of the included infants was 28 weeks and median postnatal day of the first NIRS measurement was 9 days. We did not observe any problems concerning safety, such as adverse skin effects. Liver and intestinal rSO$_2$ could be measured simultaneously for 67% of the time; in five infants we were unable to monitor $r_{LivSO_2}$ and $r_{IntSO_2}$ at the same time. In four infants this was due to shortage of equipment. In one infant, $r_{IntSO_2}$ monitoring was not performed due to the lack of space for the sensor because of an umbilical venous catheter taped to the infraumbilical skin.

In contrast, we encountered more practical difficulties concerning intestinal oxygenation monitoring in the first two days after birth (Chapter 5). We measured $r_{IntSO_2}$ in preterm infants at high risk of NEC who had a median gestational age of 28 weeks and a median birth weight of 955 grams. Intestinal oxygenation monitoring was possible in only seven out of the thirty infants (23%) in the first days after birth. In the remaining 23 infants adequate sensor placement was not possible due to the presence of an umbilicus venous catheter or lack of space in very low birth weight infants and infants small for gestational age. Theoretically, the placement of the umbilicus catheter could be easily adjusted. However, obviously, lack of space due to a very low birth weight or small for gestational age cannot be altered. Three other studies also measured intestinal oxygenation by means of NIRS in the infraumbilical region in the first days after birth.$^{10-12}$ McNeill et al. and Cortez et al. did not report practical difficulties.$^{10,11}$ However, compared with our study population, they included preterm infants with higher birth weights of median 1138 grams and mean 1640 grams.$^{10,11}$ Mintzer et al. included infants with a very low birth weight more similar to the birth weight of our population; they reported a median birth weight of 988 grams.$^{12}$ They also found that lack of space hindered adequate sensor placement. In these instances, they placed the sensor obliquely from the subumbilical region toward the left flank.$^{12}$ We did not replace the sensor, since we established that splanchnic oxygenation values differ when obtained in different abdominal regions (Chapter 2).

In conclusion, monitoring intestinal oxygenation at the infraumbilical region is feasible if enough space is available for adequate sensor placement. Since we did not apply a sensor in the liver region during the first days after birth, further studies are needed to determine the feasibility of monitoring the liver region during these first days.
Validity of measuring splanchnic oxygenation in infants with NEC

To investigate whether splanchnic oxygenation values can be used to assess intestinal damage in NEC, we associated liver and intestinal FTOE values with I-FABPp levels (Chapter 3). I-FABP is a protein that resides in epithelium cells of predominantly the small bowel. In case of intestinal injury due to, amongst others, inflammation and ischemia, I-FABP is rapidly released into the circulation. It was found that I-FABPp levels were associated with the development and severity of NEC.

We found strong associations between liver and intestinal FTOE values on the one hand and I-FABPp levels on the other hand in preterm infants with NEC, suggesting that splanchnic FTOE values do indeed provide information about the degree of intestinal damage during NEC.

However, since we found poor agreement between $r_{liverSO_2}$ and $r_{intSO_2}$ values measured in infants with suspected and definite NEC (Chapter 2), we believe that site-specific factors might influence $rSO_2$ values. These site-specific factors may include, amongst others, differences in local intestinal and/or hepatic blood flow, interference by enteric contents, bowel movements within the abdominal cavity, and peristalsis. These need particular attention in infants with NEC, since intestinal blood flow might be altered locally due to intestinal injury. Indeed, Zabaneh et al. found reduced cerebro-splanchnic oxygenation ratio (CSOR) values in certain, but not all, areas around the umbilicus in an infant with NEC. They reported that the area in which they measured reduced CSOR values corresponded to the area of ischemic bowel, active inflammation, and adhesions as seen during surgery. These results suggest that impaired oxygenation values due to NEC may only be detected when a NIRS sensor is applied to skin exactly overlapping intestinal injury. It would therefore be more informative to gather NIRS measurements of multiple abdominal regions (> 2) simultaneously. Currently, this has not yet been investigated. We speculate that measuring three or more abdominal locations at the same time in preterm infants might prove to be difficult for several reasons. First, as described previously, infants with a very low birth weight and infants small for gestational age might not have enough space on the abdominal wall to apply multiple sensors. Second, applying sensors in close proximity to each other might cause signal interference of the different sensors. The distance between light emitter and receivers of the neonatal SomaSensor is 40 mm at most. To avoid signal interference, the minimal distance between sensors should therefore be 40 mm. This undoubtedly limits the number of sensors that can be applied to the abdominal skin to monitor splanchnic oxygen saturation of different areas simultaneously. However, the fact that FTOE values obtained in the liver and intestinal region independently were strongly associated with I-FABPp levels still suggests that one location might be sufficient to assess the presence of intestinal damage in preterm infants with NEC. Further research is necessary to investigate the feasibility and necessity of monitoring splanchnic oxygen saturation of multiple abdominal locations simultaneously in infants with NEC.
Cerebral and splanchnic oxygenation and NEC

Table 1 summarizes our main findings. In the first two days after birth, we were able to differentiate high-risk infants who developed NEC from infants who did not using $r_{cO_2} < 70\%$. In the week prior to NEC onset, intestinal FTOE values were significantly higher in infants who developed NEC compared with infants who did not (median 0.65 versus 0.44). Finally, in the first 8 hours after NEC onset, $r_{cSO_2} \leq 71\%$ and $r_{livSO_2} \leq 59\%$ predicted the development of complicated NEC in infants with established NEC with a sensitivity of 1.00 and a specificity of 0.80 and a sensitivity and specificity of 1.00, respectively.

Pathophysiology of NEC

The occurrence of bowel ischemia is hypothesized to play a crucial role in the development of NEC. The timing of this ischemic insult, however, remains unclear: it may be a primary inciting factor or it may be a secondary development as a result of intestinal injury and inflammation. Several studies found indications of impaired splanchnic perfusion in the first days after birth in infants who developed NEC later on. We therefore measured intestinal oxygenation in the first days after birth in high-risk preterm infants and assessed whether intestinal oxygenation values could enable us to discriminate between infants who developed NEC from infants who did not (Chapter 5). We also measured $r_{SO_2}$ values since impaired intestinal perfusion might be the result of a compromised systemic circulation. We matched two control infants to each NEC case using the following criteria: gestational age, birth weight, and the presence of a hemodynamically significant patent ductus arteriosus. In the first two days after birth, we did not find differences in intestinal oxygenation values between infants who went on to develop NEC and infants who did not. However, infants who developed NEC had lower $r_{cSO_2}$ values compared with infants who did not develop NEC. These findings suggest that, in those infants, the systemic circulation is compromised during the first two days after birth.

Numerous prenatal and postnatal factors have been associated with the development of NEC, including but not limited to maternal infections, placental insufficiency resulting in growth-restricted newborns, resuscitation at birth, mechanical ventilation in the first days of life, and a hemodynamically significant patent ductus arteriosus. Associations were found between lower $r_{cSO_2}$ values and ascending intrauterine infection, resuscitation at birth, and hemodynamically significant patent ductus arteriosus. One or more of the aforementioned factors might have contributed to the lower cerebral oxygenation values we found in preterm infants who developed NEC.

Decreased blood flow to cerebral tissue almost always occurs when compensatory flow redistribution away from the less essential organs, such as the splanchnic tissue, has failed. We therefore speculate that splanchnic perfusion is also affected at birth. In the first two days after birth, we found a median $r_{intSO_2}$ of 44\% in infants who went on to develop NEC compared with 50\% in infants who did not develop NEC; this difference was not statistically significant. Our small sample size might have hindered us from finding significant differences
Table 1. Key Findings.

<table>
<thead>
<tr>
<th></th>
<th>First two days after birth</th>
<th>One week before NEC onset</th>
<th>First eight hours after NEC onset</th>
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</thead>
<tbody>
<tr>
<td>NEC versus no NEC in high-risk infants (Chapter 5)</td>
<td>Infants with ( r_{SO_2} &lt; 70% ) developed NEC 9 times more often than infants with ( r_{SO_2} \geq 70% )</td>
<td>Not significant</td>
<td>NA</td>
</tr>
<tr>
<td>Liver</td>
<td>NI</td>
<td>NI</td>
<td>NA</td>
</tr>
<tr>
<td>Intestinal</td>
<td>Not significant</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>intFTOE was significantly higher in infants who developed NEC compared with infants who did not (median 0.65 versus 0.44).</td>
<td></td>
<td>NA</td>
</tr>
</tbody>
</table>

| Complicated NEC versus uncomplicated NEC in high-risk infants | Cerebral | Not significant | Not significant | NA                               |
|                                                               | Liver    | NI              | NI              | NA                               |
|                                                               | Intestinal | Not significant | Not significant | NA                               |

| Definite NEC versus suspected NEC in infants with abdominal symptoms (Chapter 6) | Cerebral | NA              | NA              | Not significant |
|                                                               | Liver    | NA              | NA              | Not significant |
|                                                               | Intestinal | NA              | NA              | Not significant |

| Complicated NEC versus uncomplicated NEC in infants with established NEC (Chapter 6) | Cerebral | NA              | NA              | \( r_{SO_2} \leq 71\% \) predicted complicated NEC with a sensitivity of 1.00 and a specificity of 0.80. |
|                                                               | Liver    | NA              | NA              | \( r_{SO_2} \leq 59\% \) detected the presence of complicated NEC with a sensitivity of 1.00 and a specificity of 1.00. |
|                                                               | Intestinal | NA              | NA              | Not significant |

intFTOE - intestinal fractional tissue oxygen extraction; NEC - necrotizing enterocolitis; NA - not applicable; NI - not investigated; \( r_{SO_2} \) - cerebral oxygen saturation; \( r_{liv}SO_2 \) - liver oxygen saturation.
in intestinal oxygenation values between infants who developed NEC and infants who did not. In line of the proposed hypothesis, it could be suggested that the first insult to intestinal tissue can already occur before or shortly after birth, predisposing an infant to developing NEC later on.

Two days prior to NEC onset on median postnatal day eight, we found significantly higher intestinal FTOE values in preterm infants who developed NEC compared with infants who did not develop NEC (Chapter 5). This finding suggests that impaired splanchnic perfusion is present before the clinical onset of NEC. Postnatal factors that might have negatively influenced splanchnic perfusion are anemia, feeding practices, especially during red blood cell transfusion, and a hemodynamically significant patent ductus arteriosus. These factors have also been found to increase the risk of developing NEC. We speculate that a combination of multiple prenatal and/or postnatal factors eventually contribute to intestinal ischemia and injury and the subsequent development of NEC.

Once NEC had developed, we clearly observed distinct courses of simultaneously measured I-FABP levels in plasma and splanchnic FTOE values for infants with complicated NEC compared with infants with uncomplicated NEC in the first 48 hours after NEC onset (Chapter 3). Infants with an uncomplicated and complicated course showed decreasing I-FABP levels during the development of NEC. This might be the result of either recovery of intestinal tissue or extension of intestinal injury. Based on the course of splanchnic FTOE values we ventured to discriminate between these two hypothesized mechanisms. Infants with complicated NEC showed high splanchnic FTOE values in the first 16 hours after NEC onset that gradually decreased in the 32 hours that followed. We speculate that intestinal perfusion is compromised in infants with complicated NEC as a result of decreased splanchnic metabolism due to the presence of necrotic bowel. In infants with uncomplicated NEC splanchnic FTOE values were low in the first 16 hours after NEC onset and gradually increased afterwards. Possibly, hyperemia is present which allows the intestinal tissue to recover. Impaired splanchnic perfusion seems, therefore, to be a major determinant in the development of complications once NEC has been clinically diagnosed.

In conclusion, our results suggest that the first insult or first ‘hit’ on intestinal tissue that predisposes an infant to NEC development might occur as early as before birth. One or multiple insults afterwards, for example due to anemia and/or the presence of a hemodynamically significant patent ductus arteriosus might eventually contribute to impaired intestinal perfusion and the subsequent development of NEC. The responsible factors might differ between individual patients. After NEC has developed, sustained intestinal hypoperfusion induces the development of complications, i.e. bowel perforation or death. Based on our results, impaired intestinal perfusion might be both an inciting factor as well as a secondary event in NEC development.
**Prognostic value of cerebral and splanchnic NIRS monitoring in predicting and diagnosing NEC**

It was suggested that values of CSOR might be more helpful than splanchnic oxygenation monitoring alone in predicting and diagnosing bowel ischemia. However, to be able to use CSOR, cerebral perfusion must be maintained during periods of splanchnic hypoperfusion due to the presence of CAR. We established that CAR was not present in a considerable proportion (60%) of infants with NEC. Using cerebral oxygenation as reference for splanchnic oxygenation therefore seems unreliable. We therefore investigated whether both cerebral and splanchnic oxygenation monitoring could independently enable us to predict and diagnose NEC and its complications timely.

Due to a possible link between intestinal perfusion and NEC, studies have focused on determining the usefulness of splanchnic oxygenation values, specifically values obtained in the infraumbilical region, for predicting and detecting NEC early on. Our results, however, suggest that rSO\(_2\) values obtained in the liver region might be more appropriate for this purpose. In contrast to the non-significant findings for r\(_{\text{int}}\)SO\(_2\) values, all infants with definite NEC who had r\(_{\text{liv}}\)SO\(_2\) values ≤ 59% in the first 8 hours after NEC, developed complicated NEC. Monitoring the liver region for the purpose of predicting and diagnosing NEC might have some benefits over monitoring the infraumbilical region. First of all, as opposed to intestinal tissue, the liver is a solid and non-moving organ; it was found that the precision of NIRS depends on tissue homogeneity. Second, applying the infraumbilical sensor is associated with practical difficulties, especially in the first days after birth. We do not expect these difficulties to be present when monitoring the liver region: there is usually enough space, also during the first days after birth, and no catheters are taped to the skin just below the right costal margin. Larger patient studies are warranted to examine the additive value of monitoring r\(_{\text{liv}}\)SO\(_2\) in the first days after birth and whether liver oxygenation values might be more suitable than intestinal oxygenation values for the purpose of predicting and diagnosing NEC and its complications timely.

The findings of this thesis suggest that cerebral oxygenation monitoring might also be of additive value in predicting and diagnosing NEC. We found that infants with r\(_{\text{c}}\)SO\(_2\) values < 70% in the first days after birth developed NEC nine times more often later on than infants with r\(_{\text{c}}\)SO\(_2\) values ≥ 70%. Moreover, we found that all infants who would develop complicated NEC had r\(_{\text{c}}\)SO\(_2\) values ≤ 71% in the first 8 hours after clinical NEC onset, compared with 20% of infants who would not develop complicated NEC. Monitoring cerebral rSO\(_2\) values offers several important benefits over monitoring splanchnic rSO\(_2\) values. First of all, cerebral oxygenation values are more robust with little variability compared with splanchnic rSO\(_2\) values which are more inconsistent, possibly due to the influence of enteric contents, peristalsis, and movements of intestinal tissue within the abdominal cavity. Second, cerebral NIRS monitoring is already used in clinical practice as a monitoring device and a large multicenter randomized trial is currently investigating whether cerebral oxygenation values can be implemented in treatment guidelines.
other hand is presently used for research purposes only. Finally, we found that monitoring the infraumbilical region is associated with practical difficulties in the first days after birth, thereby limiting the application in clinical practice. Based on the findings presented in this thesis, we cannot draw a definite conclusion concerning the superiority of cerebral or splanchnic NIRS monitoring in infants at risk of NEC or infants with NEC. It is to be determined whether cerebral and/or splanchnic NIRS monitoring is preferred for this purpose.

Cortez et al. suggested that variability measurements of splanchnic rSO$_2$ values might contribute to predict the onset of NEC.$^{11}$ They described the course of intestinal rSO$_2$ values in two infants who developed NEC. One infant had extremely low r$_{int}$SO$_2$ values with loss of variability followed by very high r$_{int}$SO$_2$ values, whilst the other infant illustrated the opposite: very high r$_{int}$SO$_2$ values followed by extremely low r$_{int}$SO$_2$ values with loss of variability.$^{11}$ We calculated variability measurements based on the definition set by McNeill et al.$^{10}$ We did not find variability measurements of cerebral and splanchnic rSO$_2$ values to be of additive value in predicting and diagnosing NEC and its complications. Interpretation of individual courses of oxygenation values will possibly be more informative than the use of median or mean values of group of infants. Further research is necessary to confirm this hypothesis.

**FUTURE PERSPECTIVES**

To date, no tool or test is available that can accurately predict the onset and development of NEC and its complications. In our opinion, the results of this thesis suggest that cerebral and splanchnic NIRS monitoring are of additive value for this purpose. It is, however, yet to be determined whether both the cerebral and splanchnic region need to be monitored by NIRS or if one of these locations suffices. Moreover, since our results suggest that splanchnic oxygenation values differ when obtained in different abdominal regions, further research should also focus on investigating the predictive value of monitoring one or multiple abdominal regions in infants at high risk of developing NEC or in infants with established NEC.

Since the cut-off values we presented in this thesis are based on rather small sample sizes, larger multicenter trials are needed to provide more definite cut-off values. Additionally, the clinical relevance of these cut-off values is yet to be determined. With the current knowledge and available treatment options, we suggest that infants with low cerebral and/or splanchnic rSO$_2$ values in the first days after birth and in the first 8 hours after NEC onset should be monitored more intensively. Deterioration might thus be noticed earlier, which may lead to a more timely intervention. Moreover, further research is warranted to investigate treatment options that can improve intestinal perfusion, since impaired splanchnic perfusion seems to play an important role in the development of NEC and complicated NEC. Several studies found increased intestinal blood flow after administration of potential therapeutic targets in animal models.$^{46-49}$ These possible therapeutic options should be studied further.

Finally, the use of cerebral and splanchnic NIRS monitoring in infants with NEC should not be limited to predict NEC and complicated NEC. NIRS might have an additional application
in helping determine readiness to accept full feeds after NEC treatment and the effect of surgery on CAR in infants with NEC. These possible applications should be studied as well to improve neonatal and neurological outcome.
REFERENCES


