Epidemiology and outcomes of advanced necrotising enterocolitis

Background: A life-threatening gastrointestinal emergency, necrotising enterocolitis (NEC) presents commonly in neonates. It may be medically or surgically managed. The demographics of NEC patients in the University Hospital of Wales (UHW) and their long-term outcomes are largely unknown.

Aims: To investigate factors associated with NEC, including methods of management, and correlate these with outcomes (mortality/discharge).

Methods: A retrospective service evaluation comparing inborn and outborn infants diagnosed with NEC during a 5-year period, who were admitted to the Neonatal Intensive Care Unit (NICU), UHW. The Vermont-Oxford Network (VON) criteria determined the confirmed cases and the data was collected from the ‘BadgerNet’ database and IMPAX image viewer.

Results: All infants with poor outcomes (mortality) were preterm. Most were born by emergency caesarean, had low APGAR scores and birth weights <1kg. There was a significant difference in the volume of feeds at diagnosis between the inborn and outborn cohort (p<0.01) and between those who died and those with better outcomes (p<0.05).

Discussion: Most infants in UHW with NEC require surgical input, but surgery alone does not correlate directly with higher mortality. Low gestation/birthweight and larger volume of feeds at diagnosis are high contributors. Further research will expand the database and permit follow-up of the cohort post-discharge.
BACKGROUND

Necrotizing enterocolitis (NEC) is one of the most common and serious gastrointestinal emergencies of the newborn, especially the premature. Pathologically, it involves ischaemic necrosis of the bowel mucosa, inflammation, invasion of bacteria and perforation.

Figure 1- Pathophysiology of NEC

A premature bowel (with its increased permeability and immature host defences) predisposes an infant to NEC. Milk stagnation and hypoxic insults pre and/or perinatally are also thought to contribute. (2)

The disease occurs in around 1 in 1000 live births. (3) Incidence decreases with increasing gestational age and birth weight, affecting near 10% of very low birth weight infants i.e. those <1500g. (4–6) There is currently little data regarding the incidence of NEC in Wales.

Also associated with an increased risk of NEC are low APGAR scores. Created by the anaesthetist Virginia Apgar, the one minute APGAR score was used to quickly determine whether an infant required resuscitation at birth. Years later, a five-minute score was added to assess subsequent response to interventions. (7)

The score assesses heart rate, respiratory effort, tone, irritability and colour, each of which is scored from 0–2. A score of 7 or more is considered reassuring.

Despite advances regarding early recognition and aggressive treatment, NEC still has poor outcomes. (8) Mortality has been quoted around 15–30%. (9)

On average, NEC presents in the first few weeks of life, with the later diagnoses occurring most commonly in the premature, after the commencement of first feeds. (10) There are many management options available, depending on the individual and surgical preference, but little agreement between paediatric surgeons as to the best approach. (11) Surgical management is usually reserved for the most serious cases (unless the patient is unstable) and is imperative in NEC-related bowel perforation. Bowel resections with the creation of a stoma are commonly performed, but the extent of resection and reversibility of stoma varies between patients.

There is no doubt, however, that NEC requires significant medical and surgical input and can lead to long-term morbidity including, strictures, short-bowel syndrome, and neurodevelopmental delay. (12–15)

It is important that information about the outcomes of NEC is gathered so that improvements in the current follow-up of these patients are made and effective counselling can be offered to parents. Investigating how these patients are managed in UHW allows for future comparison with the methods in recent surgical studies and the UK Neonatal Collaborative Necrotising Enterocolitis (UKNC-NEC) Study which includes only data from England. (16,17)
METHODOLOGY

See Figure 2 for a diagrammatic representation of the methodology.

Figure 2- Step-by-step methodology

Research was primarily carried out using ‘BadgerNet’, the electronic neonatal medical records database established in 2011 and IMPAX, the digital radiology imaging system. It did not require ethical approval. The Vermont-Oxford Network (VON) criteria determined the confirmed cases.

1. The search began with the following parameters:
   a. Date of birth: Jan 1st 2011-Dec 31st 2015
   b. Care location: UHW
   c. Recorded NEC episodes: suspected, confirmed and perforated

   This produced a list of 213 infants whom had recorded episodes of NEC. Using Microsoft Excel, the following information was collated for each patient:
   a. Hospital identification number
   b. Initials
   c. Gender
   d. Date of birth
   e. Date of admission
   f. Gestation
   g. Birth weight
   h. Inborn (UHW) / Outborn (other hospital)

2. A definite diagnosis of NEC was required to be made, therefore ‘suspected only’ NEC cases were excluded. For the remaining infants, further parameters were investigated:
   i. Admitting hospital
   j. Date and time of discharge
   k. Place to be discharged to
   l. Outcome (home, hospital, died)
   m. Place of birth (hospital, home, non-NHS location)
   n. Birth location (labour ward, obstetric theatre, main theatre, home, birth center, ambulance, unknown)
   o. Onset of labour (none, induced, spontaneous, unknown)
   p. Method of delivery (elective caesarean section, emergency caesarean section (not) in labour, vaginal spontaneous, vaginal forceps assisted, unknown)
   q. Single or multiple pregnancy (single, multiple)
   r. Prenatal concerns (e.g. pregnancy-induced hypertension (PET), premature/prolonged rupture of...
and admitting hospital. There were 21 infants with NEC born in UHW, 46 born in another hospital and 3 home births. For this list of 70, parameters were then investigated including:

a. Date of 1st episode
b. Age at diagnosis (days since birth)
c. Gestational age
d. Birth Weight
e. Intrauterine growth restriction (IUGR) (Y, N)
f. Prenatal IUGR/ PET/Doppler concerns (IUGR, PET, absent end diastolic flow (AEDF), reversed end diastolic flow (REDF), atrio-ventricular septal defect (AVSD))
g. Maternal steroids (Y, N)
h. Feed start date
i. Date full feeds achieved
j. Type of feed up until diagnosis (expressed breast milk (EBM), formula, EBM + formula, unknown, other, nil)
k. All feeds
l. TPN start date
m. Blood transfusions (up to 1 week prior to diagnosis) (Y, N, unknown)

Note that medical management includes supportive care (cardio-respiratory support, discontinuation of enteral feeds, decompression, total parenteral nutrition, fluids etc.), antibiotic therapy and close laboratory/radiological monitoring.

The data was obtained from discharge letters, summaries and the daily care charts.

3. After duplicates were removed from the 2 patient lists, 123 infants remained. They were all first presentations. (Figure 2).

4. As the nature of the patient’s NEC diagnosis was at the discretion of the inputting doctors, a further method was required to determine true cases of NEC. Therefore, the universally accepted Vermont-Oxford Network definition of NEC was used (Table 1). (18)

<table>
<thead>
<tr>
<th>CLINICAL</th>
<th>RADIOLOGICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Bilious gastric aspirate or emesis</td>
<td>4. Pneumatosis intestinalis</td>
</tr>
<tr>
<td>2. Abdominal distension</td>
<td>5. Hepatobiliary gas</td>
</tr>
<tr>
<td>3. Blood in stool (no fissure)</td>
<td>6. Pneumoperitoneum</td>
</tr>
</tbody>
</table>

Table 1- VON criteria (1 of clinical plus 1 of radiological)

From discharge letters and summaries, a list of 28 Vermont-Oxford Network (VON) classification confirmed cases and 90 still querying confirmation was obtained.

5. 5 infants were also removed from the list. These were inputted onto the system as being confirmed or perforated but their discharge letters denied this. They may have been inputted as such by mistake. The VON classification requires specific plain radiograph details. As these are not always commented on in the patient notes, it was necessary for them to be accessed manually, via the IMPAX radiology database. Any available abdominal and/or chest radiograph was screened.

6. A further 42 infants to the initial 28 were added via this method. (Total: 70 infants).

It was important that the outcomes of the inborn and outborn infants could be compared. Therefore, the list of true cases was correlated with the initial information regarding place of birth and admitting hospital.
flagged up as non-NEC or spontaneous perforation (non-NEC). (Total: 63 infants, Figure 3).

The data was then analysed. Most comparisons were to be made between two separate groups displaying Gaussian distributions e.g. inborn vs outborn, died vs survived, medical vs surgical management etc. Therefore, a two-sample non-paired t test (using GraphPad Prism 7) was applied to identify p values and statistical significance. For the analysis of contingency tables, a Chi-squared test was used.

RESULTS

For the following data analyses, the 3 home births were excluded to diminish confounding factors (n=60).

Outcomes (Mortality)

There were significantly more surgical patients than medical in both inborn and outborn groups (Table 2). Out of the surgically managed infants, there was 19.6% mortality (Table 3). This was not statistically different from the mortality of the medical group (p = 0.478, 95% CI [-15.80, 40.30]).

Of the infants whom had recorded bowel resections, death during stay at UHW was low in only 3 infants out of 26.

This suggests that there are factors which have a greater effect on mortality than surgical procedure alone.

Prenatal Parameters

Interestingly, all of the infants who died were born preterm. (Table 4) 4 were very preterm (<28 weeks) and 9 extremely preterm (<28 weeks). (19) In addition, nearly 80% had birth weights under 1kg (Table 5). (20,21)

The majority of infants had abnormally low APGAR scores at 1 minute, (7) and 31% of infants who died still had at low scores at 5 minutes, a proven association with increased risk of NEC. (22)

By far the most common delivery for the infants who died was an emergency caesarean (not in labour). For all other infants there was an equal number of vaginal and caesarean births. There were also 13% more prenatal concerns in the group who died; 38.5% (died) vs 25.5% (survived).

Table 2- Outcomes of all medical and surgical patients

<table>
<thead>
<tr>
<th></th>
<th>Inborn</th>
<th>Outborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Survived</td>
<td>37</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 3- Surgical vs Medical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Surgical</th>
<th>Medical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Survived</td>
<td>37</td>
<td>10</td>
<td>47</td>
</tr>
<tr>
<td>Total</td>
<td>46</td>
<td>14</td>
<td>60</td>
</tr>
</tbody>
</table>

Postnatal Parameters

A significant factor in the development of NEC is the volume and type of feeds at the time of NEC diagnosis. (23)

The mean volume of feeds was 79.1ml for inborns and 173.2 ml for outborns (Figure 4, Table 6). This difference was statistically significant (P<0.01, 95% CI [16.975 to 185.633]).

The inborn infants who were exclusively breast fed up until their diagnosis also did better as 7/9 of them were discharged home.
There was also a statistically significant difference in feed volume between the outcome groups \((p<0.05, 95\% \text{ CI} \ [15.492 \text{ to } 198.706])\). The mean volume of feeds at diagnosis in the infants who died was 200.6ml; 107.1 more than the infants with better outcomes.

The mean age of surgery for all infants (and also for the group with poorer outcomes) was 36 days (Table 6). The most common surgical procedure overall was bowel resection with ileostomy and mucus fistula formation. There was no significant difference in outcomes between the ileocaecal valve resection and non-resection groups \((p=0.913, 95\% \text{ CI} \ [-46.492 \text{ to } 26.730])\).

The infants who died were diagnosed on average at 33 days, significantly different \((p<0.05, 95\% \text{ CI} \ [1.69 \text{ TO } 32.65])\) from the infants who went home (diagnosis around 16 days). This poor outcome may be attributable to a larger volume of feeds achieved in these infants.

**DISCUSSION**

**Summary of findings**

It appears that a low gestation and low birthweight are both contributors to mortality (Table 4). In fact, when evaluating the whole cohort of infants, over a quarter of infants with birth weights under 1000g died. These findings correlate with current literature.

One of the most important factors contributing to outcome was volume of feeds. There was a significant difference in the inborn and outborn cohort, the inborn cohort being given smaller amounts. In addition, exclusive breast feeding seems to correlate with a better outcome.

Due to the grossly higher volume of feeds in the group who died, it can be concluded that those who received larger volume of feeds developed more serious NEC. These findings emulate the current literature, which identifies duration and advancement of feeds as risk factors and recognises that cases of NEC are often found to be fully fed significantly earlier than non-NEC controls. (23) However, delaying feeds soon after birth may actually be counterproductive as enteral feeding is necessary for gastrointestinal tract maturation. (24) There are few randomised control trials that discuss the optimum rate of feed advancement. (25) Although the correct amount of feeds varies on a case-by-case basis, many have called for standardised feeding regimens to minimize cases of NEC. (26)

In terms of management, the majority of patients who died had had some surgical input (70%), but surgical technique does not directly correlate with a high mortality. There are many factors that could have influenced mortality, including a pre-existing morbid state.

Reported mortality figures from NEC vary in the literature but, in line with this study’s findings, current research suggests a mortality in the region of 15–30%. (27) The mortality of the low birth weight infants (<1500g) in this cohort was 26% (13/50). This is slightly lower than the UK Neonatal Collaborative Necrotising Enterocolitis Study, which quotes a mortality of around 30–50% in low birth weight infants. (17)

**Limitations**

Due to the nature of data collection, the list of confirmed cases is by no means exhaustive. The use of the VON classification was imperative in ensuring that all patients were subjected to the same inclusion criteria. It is a well-tested classification system but, by its nature, is more likely to identify the more advanced and/or severe NEC cases. (18) Clinical notes prior to UHW admission for the outborn babies were scarce, another reason for limited data. Given the small sample size of this study the results have limited reliability. Studies identified in systematic reviews involve numbers of participants ranging from a few hundred to around 2000, with the very low birth weight infants making up the smallest proportion of participants. (26) However, the findings mirror those of larger studies; the importance of standardised feeding regimes and the protective use of breast milk are documented in Cochrane reviews. (28–29) Additionally, there are no current Cochrane reviews that appear to support any surgical intervention over another.

One important distinction to be made is between spontaneous and NEC-related intestinal perforation. (26) Clinical judgement was used to exclude the spontaneous cases, a method with limited reliability.
Finally, the exclusively medically managed cohort should be interpreted with caution as some babies may have had too advanced disease to be considered for surgical procedures.

Data collection presented unforeseen challenges; differing and/or unidentifiable hospital numbers and surname changes were frequent. All documentation was therefore cross-referenced, a time-consuming process. In addition, many infants had numerous admissions, so care was taken to ensure only first presentations were recorded.

**Significance and generalisability**

Although a small set of data, the data collected will be useful for the creation of a UHW NEC database. It will enable the unit to more accurately assess the management of their patients and most importantly, improve long term outcomes.

It is reassuring to see that the protective use of exclusive breast milk in small quantities has already been adopted in UHW, more so than perhaps other hospitals.

**CONCLUSION**

In conclusion, there are many factors involved in the outcome of NEC. Surgery is not a curative step and medical treatment is the mainstay. It is therefore of paramount importance that both surgical and medical parameters are investigated in future studies, as in this. The project has highlighted a difference in feeding regimes between local centres as well as strengthened the evidence of a link between low gestation and birthweight and mortality. It has also revealed previously unknown demographical information, including the fact that all babies to be treated for NEC were premature.

Future goals are to continue to expand and spread awareness of the database. In addition, to assess long term outcomes, the surviving NEC patients may be followed up with parental questionnaires and/or clinic visits.

**REFERENCES**

https://doi.org/10.1016/S0031-3955(05)70413-2


https://doi.org/10.1046/j.1365-3016.2002.00445.x PMid:12445151

https://doi.org/10.1097/00005176-200410000-00012 PMid:15448426


https://doi.org/10.1542/peds.2006-0325 PMid:16585348


https://doi.org/10.3345/kjp.2011.54.9.368 PMid:22232629 PMCid:PMC3250602

https://doi.org/10.1542/peds.2011-2022 PMid:22271701

https://doi.org/10.1053/j.sempedsurg.2013.01.009 PMid:23611616


https://doi.org/10.1136/adc.2004.051862
PMid:15724040 PMCid:PMC1721850


https://doi.org/10.1038/sj.jp.7210892
Table 4- Prenatal Parameters Inborn vs Outborn deaths

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<tr>
<th></th>
<th>Sex</th>
<th>Gestational Age (weeks)</th>
<th>Birth Weight (g)</th>
<th>IUGR</th>
<th>Prenatal Concerns?</th>
<th>Maternal Steroids?</th>
<th>Details of delivery</th>
<th>APGAR score at 1 min</th>
<th>APGAR score at 5 mins</th>
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<tr>
<td>Inborn</td>
<td>1</td>
<td>M</td>
<td>27</td>
<td>790</td>
<td>Y</td>
<td>PET</td>
<td>Y</td>
<td>Emergency caesarean- not in labour</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>M</td>
<td>31</td>
<td>1040</td>
<td>Y</td>
<td>AVSD</td>
<td>Y</td>
<td>Emergency caesarean- not in labour</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>M</td>
<td>26</td>
<td>940</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Vaginal- spontaneous</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>M</td>
<td>25</td>
<td>610</td>
<td>N</td>
<td>PET</td>
<td>Y</td>
<td>Emergency caesarean- not in labour</td>
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</tr>
<tr>
<td></td>
<td>5</td>
<td>M</td>
<td>31</td>
<td>1240</td>
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<td>N</td>
<td>Y</td>
<td>Emergency caesarean- in labour (Twin 1)</td>
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<tr>
<td>Outborn</td>
<td>1</td>
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<td>590</td>
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<td>N</td>
<td>Y</td>
<td>Emergency caesarean- not in labour</td>
<td>3</td>
</tr>
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<td></td>
<td>2</td>
<td>F</td>
<td>25</td>
<td>650</td>
<td>N</td>
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<td>N</td>
<td>Vaginal- spontaneous</td>
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</tr>
<tr>
<td></td>
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<td>F</td>
<td>26</td>
<td>700</td>
<td>T-T</td>
<td>REDF</td>
<td>Y</td>
<td>Emergency caesarean- not in labour (Twin 2)</td>
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<td>780</td>
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<td>Y</td>
<td>Emergency caesarean- in labour</td>
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<td>F</td>
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<td>750</td>
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<td>Vaginal- spontaneous</td>
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<tr>
<td></td>
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<td>F</td>
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<td>1260</td>
<td>Y</td>
<td>IUGR</td>
<td>Y</td>
<td>Unknown</td>
<td>8</td>
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</table>

T-T- Twin-to-twin transfusion, PET- Pre-eclamptic Toxaemia (Hypertension), AVSD- Atrioventricular Septal Defect, REDF- Reversed End Diastolic Flow, IUGR- Intrauterine Growth Restriction
### Table 6 – Postnatal Parameters Inborn Vs Outborn Deaths

<table>
<thead>
<tr>
<th>Age at diagnosis (days)</th>
<th>Age at Surgery (days since birth)</th>
<th>Volume of feeds at NEC (ml)</th>
<th>Blood transfusions (&lt;1 week prior to NEC)?</th>
<th>PDA treatment?</th>
<th>Probiotics?</th>
<th>Details</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inborn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34</td>
<td>N/A</td>
<td>128</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Medical</td>
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<tr>
<td>2</td>
<td>35</td>
<td>N/A</td>
<td>11</td>
<td>Y</td>
<td>Hy</td>
<td>N</td>
<td>Surgical (Duodenoduodenostomy)</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>38</td>
<td>216</td>
<td>Y</td>
<td>Hy</td>
<td>N</td>
<td>Surgical (Laparotomy, resection Inc. ileocaecal valve, colostomy, drain)</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>62</td>
<td>240</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Necrotic bowel, adhesions</td>
</tr>
<tr>
<td>Outborn</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>17 (drain)</td>
<td>198</td>
<td>Y</td>
<td>Hy</td>
<td>Y</td>
<td>Perforation</td>
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<tr>
<td>1</td>
<td>103</td>
<td>N/A</td>
<td>420</td>
<td>N</td>
<td>N</td>
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<tr>
<td>2</td>
<td>11</td>
<td>11 (drain)</td>
<td>0</td>
<td>N</td>
<td>Ib+ Hy</td>
<td>N</td>
<td>Surgical (Drain)</td>
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<tr>
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<td>31</td>
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<td>unknown</td>
<td>N</td>
<td>Hy</td>
<td>N</td>
<td>Surgical (Laparotomy, appendicostomy, cecostomy, herniotomy, right hemicolecotomy, Bishop Koup anastomosis)</td>
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<tr>
<td>4</td>
<td>31</td>
<td>32</td>
<td>100</td>
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<td>N</td>
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<td>102</td>
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<td>N</td>
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<td>Perforation</td>
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</table>

Hy-Hydrocortisone Ib-Ibuprofen
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