Crying and spilling—time to stop the overmedicalisation of normal infant behaviour

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Abstract

Many infants have periods of unsettledness, or irritability, over the first months of life. Spilling (or possetting) due to reflux of gastric contents is also seen very frequently. Almost universally, these are normal patterns of infancy (the first 12 months of life) that resolve with the passage of time. In recent years, these normal developmental processes have increasingly been ascribed to pathology and treated with medical therapies, including acid suppressants. There is clear evidence, however, that acid suppression has no role in the management of these behaviours. In addition, recent data illustrate increased risk of adverse effects of these drugs in infants.

Crying and spilling are very common behaviours in the first 6 months of life. The extent of these normal patterns varies widely, as does the extent to which parents seek help with them. As both occur commonly, health professionals may attribute persistent crying and irritability to gastro-oesophageal reflux. However, whilst both may occur simultaneously, they are not necessarily related. Over recent years, the tendency has been to label these behaviours as pathologic and to treat with various medical therapies, including acid suppressive drugs.

Many infants have periods of irritability, unsettledness or unexplained crying typically starting in the first weeks of life, peaking around 3–4 months and then resolving spontaneously by 6 months of age. Infants in this age group may cry for up to 5–6 hours each day, with unsettledness typically worse in the late afternoon or early evening.

Up to 20% of parents report a problem with crying or irritability in the first 3 months. These patterns have been observed in infants in both Western and hunter-gatherer cultures. These behaviours are also well-described in historical accounts. For instance, the “all the world’s a stage” monologue in Shakespeare’s “As You Like It” describes the first of the seven ages of life thus: “And one man in his time "plays many parts, His acts being seven ages. As, first the infant, Mewling and puking in the nurse’s arms”.

Over time, these patterns have been labelled in various ways, including the term “colic”. Various management techniques have been suggested and different therapies have been utilised. Although the cause of these behaviours has not been fully defined, they are most likely related to difficulties in the infant changing from one state of awareness to another as part of a normal maturational phase. This likely reflects a normal neurodevelopmental stage for infants.

Regurgitation, spilling and possetting are also commonly seen in otherwise healthy infants, consequent to the regurgitation of buffered gastric contents. This
developmentally normal process, termed physiological gastro-oesophageal reflux (GOR), is due to the immaturity of the upper gut in infancy. The infant oesophagus is relatively short with less intra-abdominal length. In addition, the lower gastro-oesophageal sphincter is immature, with increased transient relaxations leading to reduced patency. These anatomical features evolve over the first months of life, leading to self-resolution of physiological reflux by 12–15 months in almost all infants.

Up to 5% of infants with excessive crying or unsettled behaviours will have an underlying organic problem. Similarly, only a very small number of infants with reflux will have gastro-oesophageal reflux disease (GORD), which can be defined as upper gut symptoms present in association with complications (such as failure to thrive or haematemesis).

If these behaviours are sufficiently concerning, parents may seek medical attention or ask the advice of allied health professionals. Australian data show that parental concern about infant crying is the most common reason for general practitioner (GP) consultation in the first months of life.

Parental responses to crying and unsettled behaviours in their infants are likely reflective of their social supports and experience. Mothers with their first child are more likely to consult their GP about these concerns. In addition, higher levels of parental concern about infant unsettledness are linked with increased use of multiple health services in the first months of life.

More and more commonly, these behaviours have been erroneously seen as pathologic events or diseases and treated with a medical model of care. This may reflect societal expectations for a disease to be the cause of these behaviours, or perhaps an increasing parental expectation for an instant cure. As both physiological reflux and developmental irritability temporally coincide, it is perhaps not surprising that the former has been assigned a causative role for the latter.

The existence of (albeit rare) GORD and its association with acid damage appears then to have given both the physiological reflux, together with the coincidental irritability, status as an illness which in turn has provided a rationale for the decision to treat both medically, using drug therapies such as those that neutralise or suppress gastric acid.

Despite being unlicensed for use in infancy, there have been dramatic increases in prescribing of proton pump inhibitors (PPI) in infants over recent years. In Partnership Health Primary Health Organisation (PHO), Canterbury, 15% of infants (<1 year) received a prescription for the PPI omeprazole in 2010 (Personal communication, P Bridgford, Pegasus Health 2011). Five years earlier in 2005, only 4% of children in this age group were prescribed this drug (Figure 1).
Similar to the events in Canterbury, prescriptions of omeprazole in under-1 year olds across New Zealand also increased between 2006 and 2010. Over this period the greatest increase was in those aged 0–3 months amongst whom the number of prescriptions more than doubled. Data from the United States also show increasing rates from late last century, with one assessment demonstrating an 11-fold increase in PPI prescriptions for infants between 2002 and 2009.

In their review of North American healthcare databases, Barron et al suggest that few of the infants receiving PPI had acid-related disease. Although the local data on the indication for acid suppression are not available, it is likely that prescribing in NZ is similar.

Despite these changing patterns of prescription, there is little evidence that acid plays any role in patterns of unsettledness and irritability in infancy. Furthermore, there is evidence that acid suppression does nothing to improve these distressing behaviours and that PPI therapies are associated with important adverse effects.

Over the last decade, a small number of studies have assessed the role of acid suppressant therapy in the management of unsettled infants and those with reflux (physiological or pathological). None of these studies support the use of acid suppressants for these indications in infants.

A group of Australian investigators prospectively studied the impact of anti-reflux therapy in a group of infants with persistent crying. The 103 infants in this study were randomised to receive one of three interventions: anti-reflux therapy or placebo or an infant maternal health consultation. The anti-reflux intervention involved acid
suppression with a histamine antagonist (ranitidine) and a prokinetic (cisapride) in standard doses. All infants had reduction in crying duration over the four week study regardless of their intervention with no particular advantage seen for anti-reflux therapy.

Four separate studies have examined the efficacy of proton pump inhibition to reduce gastric acid in infants with GORD. A placebo-controlled cross-over study conducted in Adelaide, Australia, randomised 30 infants to two treatment periods: omeprazole followed by identical placebo or placebo followed by omeprazole. The infants, with median age of 4.8 months, were shown to have increased oesophageal acid exposure (as indicated on 24 hour oesophageal pH studies) or histological evidence of oesophagitis. Oesophageal pH monitoring was repeated at the end of the first treatment period and parents kept cry/fuss diaries and visual analogue scales (VAS) of their infants’ irritability.

Infants receiving omeprazole had a significant reduction in their oesophageal acid exposure compared to placebo (-8.9% ± 5.6% vs -1.9% ± 2.0%; p<0.001), demonstrating that this drug reduced oesophageal acid exposure. However, despite this there was no difference in parent-recorded symptoms between the two groups of infants. Furthermore, symptoms significantly improved with time compared to baseline during treatment with both placebo and omeprazole. Infants who began the study with greater oesophageal acid exposure or abnormal oesophageal biopsy were no more likely to respond to omeprazole than those without these findings. Baseline scores for crying/fussing and VAS were not significantly different between infants with and without abnormal oesophageal biopsy or greater oesophageal acid exposure.

Similar findings were demonstrated by the same group in a small study of omeprazole in preterm infants. Ten preterm infants with features of GORD and evidence of pathological acid exposure were enrolled in this randomised double-blind placebo-controlled cross-over study of 1 week of omeprazole or placebo followed by one week of the other treatment. Oesophageal pH measurement was repeated at the end of the first and second weeks and a reflux symptom chart was completed by nursery staff. Although treatment with omeprazole significantly reduced gastric acidity and oesophageal acid exposure, this was not associated with any change in symptom scores.

Other PPI agents were evaluated in two studies based in North America. A multi-centre randomised placebo-controlled trial of lansoprazole enrolled 162 infants (median age 16 weeks, range 4–51 weeks) with GORD symptoms persisting despite one week of conservative measures. Infants were randomised to receive 4 weeks of lansoprazole or placebo. Symptoms were recorded using parent questionnaires. After 4 weeks of treatment, an equal proportion (54%) of infants in both arms responded to treatment and there was no significant difference between the groups for either parental or physician’s global severity assessment. Adverse outcomes occurred more frequently in infants taking lansoprazole than those receiving placebo (12% vs 2%; p=0.032).

A more recent study evaluated another PPI (pantoprazole) in a randomised placebo-controlled withdrawal study of 106 infants (mean age 5.1 months) with clinically diagnosed GORD and whose symptoms had improved during 4 weeks of open-label pantoprazole. Infants were randomised to continue pantoprazole or receive placebo
and were followed for 4 weeks. There was no significant difference between the two
groups in the primary endpoint - withdrawal due to lack of efficacy.

Together the available evidence of acid suppressive therapy in infants does not
support the use of PPIs in unsettled infants or those with clinically-diagnosed GORD.
Furthermore, the results arising from the two studies that included endoscopy and
oesophageal pH monitoring,\textsuperscript{16,17} clearly also question the central role that has been
ascribed to gastric acid in the causation of these infants’ symptoms.

In these studies, although oesophageal acid exposure was reduced with the drug
therapy, this was not associated with any symptomatic benefit. In addition, infants
with more severe baseline measures of oesophageal acid exposure and histological
changes neither displayed more severe symptoms nor responded more favourably to
acid suppression than those infants without these findings.

Another important finding of these studies is that symptoms tend to improve over the
study period in infants receiving active drug or placebo treatments. This is consistent
with the observation that the patterns of infant irritability and reflux resolve
spontaneously with time. This is likely to be an important confounding factor in non-
controlled trials or in empirical trials of treatment for individual patients.

Over recent years, it has become clear that the spectrum of adverse effects of PPI
drugs is broader than first envisaged. The use of PPIs in adults is now associated with
problems such as increased risk of community acquired pneumonia, \textit{Clostridium
difficile} infection, fractures, vitamin B12 deficiency and acute interstitial nephritis.\textsuperscript{20–24}

Although adverse effects in infants are less well studied, recent data raise significant
concerns. For example, one prospective cohort study followed 91 infants and children
prescribed acid suppressants (histamine antagonists or PPIs) for GORD and a
matched group of 95 healthy children who were neither diagnosed with GORD nor
prescribed acid suppressing medication.\textsuperscript{25} The median age of the subjects was 10
months and follow up was for 4 months. The infants and children prescribed an acid
suppressant had significantly higher incidence of pneumonia (12% vs 2%; \textit{p}=0.003)
and gastroenteritis (47% vs 20%, \textit{p}=0.001) over the period of observation than the
control group.

Although it may be argued that, because the study was observational rather than
experimental, the higher rates of gastroenteritis and pneumonia could be due to the
presence of GORD rather than the acid-suppressing medication, it is notable that in
the 4 months preceding the initiation of acid suppression, the incidence of
gastroenteritis and pneumonia was not significantly different between the two groups.

Further evidence of adverse effects from these drugs in infants comes from the above-
mentioned randomised controlled trial of lansoprazole, in which serious adverse
events occurred six times more frequently in the group receiving PPI than placebo
(\textit{p}=0.032).\textsuperscript{18} The most common serious adverse events in the infants receiving PPI
were lower respiratory tract infections.

In view of the available data regarding the balance between benefit and harm of PPIs
in infancy, there is increasing recognition that these drugs are not indicated,
particularly in infants with excessive crying or physiological reflux who are otherwise
healthy. Indeed, a recently published clinical guideline for the management of reflux in children concluded that PPI therapy was not indicated as empiric therapy for infant irritability or GOR and that these drugs have little role in the management of most infants with GORD.\textsuperscript{8} A recent systematic review reached similar conclusions.\textsuperscript{26}

In the light of the currently available evidence, it is clear that the management of infants with irritability or spilling should focus on supporting the parents, not on drugs. In the vast majority of cases reassurance and support is all that is required. Acid suppression is not indicated without histologically-proven oesophagitis. Warning signs indicative of possible serious conditions include haematemesis, bilious vomiting, melaena, poor weight gain, altered development or apnoeas. Infants with one or more of these features may require specific investigations and paediatric consultation.

In contrast, infants lacking these warning signs (the majority) should be managed conservatively with an expectation of spontaneous improvement. This approach should be multidisciplinary and encompass education, support, and appropriate resources. Parental mental health assessment, support and intervention may be required.

Persistent crying has been implicated as a trigger for children being harmed by their care-givers.\textsuperscript{27,28} Hence as part of a holistic approach, practitioners should discuss with caregivers strategies for managing the stress involved in caring for an unsettled infant and involve social service agencies as needed.

In summary, crying and spilling are common, unlinked and normal behavioural patterns in early infancy. Almost all infants with excessive crying or irritability are healthy without any underlying disease. Spilling on the basis of physiological reflux is also common, and is infrequently complicated as GORD. Both crying and spilling behaviours are expected to resolve spontaneously with the passage of time. Medical therapies for these patterns are unnecessary, non-efficacious and potentially harmful.

In conclusion, it is now time for us to move from thinking of irritable but healthy infants as having underlying treatable pathology, to approaching this as a normal (albeit sometimes difficult) period of infant development to be managed with multidisciplinary education, support and reassurance.

**Competing interests:** None.

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