

# Gastro-oesophageal reflux disease in children with neurological impairment: a retrospective cohort study

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## ABSTRACT

**Objectives** To determine the incidence and prevalence of gastro-oesophageal reflux disease (GERD) diagnosis and treatment in children with neurological impairment (NI) along with relationship to key variables.

**Design** This is a population-based retrospective cohort study.

**Setting** This study takes place in Alberta, Canada.

**Patients** Children with NI were identified by hospital-based International Classification of Diseases (ICD) codes from 2006 to 2018.

**Main outcome measures** Incidence and prevalence of a GERD diagnosis identified by: (1) hospital-based ICD-10 codes; (2) specialist claims; (3) dispensation of acid-suppressing medication (ASM). Age, gender, complex chronic conditions (CCC) and technology assistance were covariates.

**Results** Among 10 309 children with NI, 2772 (26.9%) met the GERD definition. The unadjusted incidence rate was 52.1 per 1000 person-years (50.2–54.1). Increasing numbers of CCCs were associated with a higher risk of GERD. The HR for GERD associated with a gastrostomy tube was 4.56 (95% CI 4.15 to 5.00). Overall, 2486 (24.1%) of the children were treated with ASMs of which 1535 (61.7%) met no other GERD criteria. The incidence rate was 16.9 dispensations per year (95% CI 16.73 to 17.07). The prevalence of gastrojejunostomy tubes was 1.1% (n=121), surgical jejunostomy tubes was 0.7% (n=79) and fundoplication was 3.4% (n=351).

**Conclusions** The incidence of GERD in children with NI greatly exceeds that of the general paediatric population. Similarly, incidence rate of medication dispensations was closer to the rates seen in adults particularly in children with multiple CCCs and gastrostomy tubes. Further research is needed to determine the appropriate use of ASMs balancing the potential for adverse effects in this population.

## INTRODUCTION

Gastro-oesophageal reflux disease (GERD) can result in distressing symptoms and serious complications.<sup>1</sup> GERD diagnosis is increasingly common in children, accompanied by increased prescribing of acid suppressing medications (ASMs) including proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H<sub>2</sub>RA).<sup>2</sup> There has been a 2–8 fold increase in PPI prescriptions to children

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gastro-oesophageal reflux disease (GERD) is increasingly being diagnosed and treated in children. Neurological impairment (NI) is a known risk factor for GERD but existing evidence applies only to specific subpopulations such as those with severe NI.

## WHAT THIS STUDY ADDS

⇒ The prevalence and incidence of GERD diagnosis in children with NI is significantly higher than in the general paediatric population.  
⇒ Children with NI are more likely to be treated with acid-suppressing medications and treatment tends to be prolonged.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights the need for further investigation into GERD diagnostic criteria and prescribing patterns for children with NI to facilitate clearer guidance on the appropriate use of acid-suppressing medications.

in the past decade.<sup>3 4</sup> This trend continues in spite of mounting evidence of adverse effects with ASMs.<sup>5–7</sup> Clinical practice guidelines exist to guide management but do not address all clinically important scenarios.<sup>8 9</sup>

Children with neurological impairment (NI) have increased risk of GERD.<sup>10–14</sup> To date, studies are limited by selection bias towards participants with gastrointestinal symptoms or living under institutional care.<sup>11–14</sup> In these studies, diagnosis was based on invasive tests such as pH probes, oesophageal manometry and endoscopy, which can be challenging to interpret in paediatrics.<sup>12 15</sup> All prior studies are more than two decades old and may not represent current practice.

The frequency of GERD in the broad population of children with NI will help define the scope of this condition and identify targets for further study and guideline development. The aim of this study was to determine the incidence and prevalence of a diagnosis of GERD in children with NI. In addition,

**Table 1** Cohort characteristics

	NI cohort	NI, no GERD	NI+GERD	P value
n (%)	10309	7537	2772	
Age at NI (mean (SD))	4.15 (5.82)	4.65 (6.07)	2.79 (4.84)	<0.001
Gender (F)	4738 (46.0)	3483 (46.2)	1255 (45.3)	0.578
<b>CCC</b>				
Cardiovascular	1589 (15.4)	951 (12.6)	638 (23.0)	<0.001
Metabolic	743 (7.2)	429 (5.7)	314 (11.3)	<0.001
Renal/urologic	665 (6.5)	398 (5.3)	267 (9.6)	<0.001
Genetic/congenital	2656 (25.8)	1787 (23.7)	869 (31.3)	<0.001
Neonatal	1678 (16.3)	1200 (15.9)	478 (17.2)	0.114
Gastrointestinal	663 (6.4)	381 (5.1)	282 (10.2)	<0.001
Haemat/immunol	444 (4.3)	226 (3.0)	218 (7.9)	<0.001
Respiratory	485 (4.7)	182 (2.4)	303 (10.9)	<0.001
Malignancy	603 (5.8)	391 (5.2)	212 (7.6)	<0.001
No of CCC				<0.001
0	4323 (41.9)	3488 (46.3)	835 (30.1)	
1	3651 (35.4)	2697 (35.8)	954 (34.4)	
2	1509 (14.6)	957 (12.7)	552 (19.9)	
3	547 (5.3)	279 (3.7)	268 (9.7)	
4+	279 (2.7)	116 (1.5)	163 (5.9)	
<b>Technology</b>				
Tracheostomy	75 (0.7)	28 (0.4)	47 (1.7)	<0.001
Evacuation tube	467 (4.5)	325 (4.3)	142 (5.1)	0.089
Gastrostomy	1359 (13.2)	406 (5.4)	953 (34.3)	<0.001
Renal support	203 (2.0)	140 (1.9)	63 (2.3)	0.206
No of technology				<0.001
0	8160 (79.2)	6528 (86.6)	1632 (58.9)	
1	1965 (19.1)	952 (12.6)	1013 (36.5)	
2+	184 (1.8)	57 (0.8)	127 (4.6)	

CCC, complex, chronic conditions; GERD, gastro-oesophageal reflux disease; NI, neurological impairment.

relationships between GERD diagnosis/treatment and demographic characteristics, complex, chronic conditions (CCCs) and need for medical technology assistance (TA) were examined.

## METHODS

### Study design and data source

This population-based retrospective cohort study used administrative data from the province of Alberta (population 4.4 million) including demographic information, hospitalisation data (Hospital Discharge Abstract Database), physician outpatient billings (Alberta Health Care Insurance Plan), emergency department visits (National Ambulatory Care Reporting System) and pharmaceutical data (Pharmaceutical Information Network) (online supplemental information 1). The Strengthening the Reporting of Observational Studies

in Epidemiology guideline for reporting observational studies was followed.<sup>16</sup>

### Study population

We first identified all children (less than age 18) who had a hospital discharge between 1 April 2006 and 31 March 2018 with a diagnostic code indicating NI based on an established list of International Classification of Diseases, 10th Revision (ICD) codes (online supplemental information 2).<sup>17–19</sup>

The case definition for GERD was designed to achieve reasonable accuracy and specificity, given that GERD is likely overdiagnosed in paediatrics.<sup>20,21</sup> Each case had to meet at least one of the following criteria:

1. An ICD-10 code indicating GERD from a hospitalisation or emergency visit.
2. At least two paediatric specialist claims within 2 years with an ICD-9 code indicating GERD. This aligns with

**Table 2** Source of GERD diagnosis

	n (%)
n	2772
PIN	1935 (69.8)
DAD	598 (21.6)
NACRS	66 (2.4)
Physician claims	134 (4.8)
Multiple criteria met on same day	39 (1.4)

DAD, discharge abstract database; GERD, gastro-oesophageal reflux disease; NACRS, National Ambulatory Care Reporting System; PIN, Pharmaceutical Information Network.

current recommendations that GERD should be diagnosed by a specialist.<sup>9</sup>

### 3. At least one dispensation of an ASM.

Children entered the cohort on the date of their first NI diagnosis (on or after 1 April 2006). GERD diagnoses that occurred simultaneously or shortly after the NI diagnosis were included.

### Comorbidities and technology

Age and gender were collected. All ICD-10 codes were collected from hospitalisation data (up to 25) to describe CCC and TA. NI, CCC and TA have all been used to categorise children with medical complexity.<sup>17</sup> CCCs refer to any chronic medical condition that involves either several organ systems or severe disease in one system.<sup>22</sup> TA can include any device that is required to maintain the child's health status.<sup>17</sup> We used previously developed categorisations of ICD-10 codes for this purpose (online supplemental information 2).<sup>17 19 22</sup>

### Acid-suppressing medications

Data were abstracted from the Pharmaceutical Information Network using two Anatomical Therapeutic Chemical codes, A02BA for H2RA and A02BC for PPI. The number of dispensations was obtained for each individual for their entire period in the study cohort.

**Table 3** Association between demographics, CCC/TA and diagnosis of GERD

Variable	HR (95% CI)	P value
Gender (M)	1.07 (0.98 to 1.16)	0.118
Age at NI	0.97 (0.96 to 0.97)	<0.001
1 CCC	1.20 (1.09 to 1.33)	<0.001
2 CCC	1.74 (1.55 to 1.96)	<0.001
3 CCC	2.05 (1.75 to 2.39)	<0.001
4+CCC	2.37 (1.95 to 2.87)	<0.001
1 TA	3.23 (2.96 to 3.52)	<0.001
2+TA	3.56 (2.92 to 4.34)	<0.001

CCC, complex, chronic conditions; NI, neurological impairment; TA, technology assistance.

### Antireflux surgeries and procedures

Antireflux procedures were abstracted using Canadian Classification of Health Interventions codes from the Discharge Abstract Database. These procedures were gastrojejunostomy tubes, surgical jejunostomy tubes and fundoplication (online supplemental information 2). The first occurrence of each procedure was used to calculate incidence rates.

### Statistical analysis

Measured variables were reported with the mean and SD. Categorical variables were reported as counts and proportions. Comparisons were made using t-tests and  $\chi^2$  tests, respectively. Univariable incidence rates with 95% CIs were calculated. Multivariable Cox proportional hazards models were used to calculate hazard ratios for the occurrence of GERD. Multivariable negative binomial models were used to calculate incidence rate ratios for the prescription of additional ASMs. Models were adjusted for age, gender and number of technologies used. The right-censor date for patients without the outcome of interest was calculated as the earlier of either the patient's 18th birthday, the date of death or the end date of data collection, which was 31 March 2018.

## RESULTS

### Incidence and prevalence of GERD

Of the cohort of 10 309 unique children with NI, 2772 met the case definition of GERD. This corresponds to an overall period prevalence of 26.9%. The unadjusted incidence rate of GERD was 52.1 per 1000 person-years (95% CI 50.2 to 54.1). When the ASM criteria were removed from the case definition, the incidence rate was 46.7 per 1000 person-years (95% CI 44.9 to 48.4). The mean age at GERD diagnosis was 5.04 years (95% CI 4.84 to 5.24) and the mean age at NI diagnosis was 4.15 years (95% CI 4.04 to 4.26).

A full description of the cohort of individuals with NI and the breakdown of characteristics in the subgroups with and without GERD can be found in [table 1](#). A breakdown of the source of GERD diagnosis (based on first criterion met) can be found in [table 2](#) (online only).

### Comorbidities and technology

There were numerous relevant associations between clinical characteristics and a diagnosis of GERD. In particular, subgroups with increasing numbers of CCCs and forms of TA independently predicted a diagnosis of GERD ([table 3](#)). Children with four or more CCC's had twice the chance of being diagnosed with GERD (HR 2.37, 95% CI 1.95 to 2.87,  $p<0.001$ ) compared with those without CCC, adjusted for gender, age and number of technology devices. Similarly, children with multiple forms of TA were at significantly greater risk of developing GERD (HR 3.56, 95% CI 2.92 to 4.34,  $p<0.001$ ) than subgroups without technology.

**Table 4** Association between individual CCCs, TAs and GERD

	HR (95% CI)	P value
Technology		
Tracheostomy	0.97 (0.69 to 1.35)	0.851
Evacuation tube	0.94 (0.76 to 1.17)	0.589
Gastrostomy	4.56 (4.15 to 5.00)	<0.001
Renal support	1.00 (0.75 to 1.32)	0.980
CCC		
Cardiovascular	1.25 (1.12 to 1.39)	<0.001
Metabolic	1.25 (1.09 to 1.42)	0.001
Neonatal	1.14 (1.03 to 1.29)	0.017
Gastrointestinal	1.23 (1.04 to 1.44)	0.013
Haemat/immunol	1.37 (1.17 to 1.62)	<0.001
Respiratory	1.45 (1.25 to 1.68)	<0.001
Malignancy	1.35 (1.14 to 1.59)	<0.002
Renal/urologic	1.12 (0.96 to 1.30)	0.147
Genetic/congenital	1.07 (0.98 to 1.18)	0.149

CCC, complex, chronic conditions; GERD, gastro-oesophageal reflux disease; TA, technology assistance.

Multivariable Cox proportional-hazards analysis showed that cardiovascular, metabolic, neonatal, gastrointestinal, haematologic, respiratory and malignancy CCCs imparted a higher risk of GERD diagnosis. Presence of a gastrostomy tube, but not other forms of TA, was also significantly associated with GERD (HR 4.56, 95% CI 4.15 to 5.00) (table 4).

### Treatment with ASM

In this cohort, 2486 individuals (24.1%) were treated with ASMs during the study period. Of these, 1535 (61.7%) had no evidence of a GERD diagnosis based on other criteria. A total of 457 (18.4%) individuals had dispensed both types of medications (H2RAs and PPIs) in the study period.

For those individuals who had at least one ASM dispensed, the incidence rate for number of dispensations was 16.9 per year (95% CI 16.73 to 17.07). The incidence rate of H2RA dispensing, for those who received at least one, was 3.72 per year (95% CI 3.66 to 3.78). The incidence rate of PPI dispensing was 11.66 per year (95% CI 11.59 to 11.73).

There were certain comorbidities that were associated with a higher rate of dispensations for ASMs (table 5). Having a gastrostomy tube was associated with twice the rate of treatment with ASMs (IRR 2.28, 95% CI 1.80 to 2.91). Tracheostomy was associated with a significantly decreased rate of ASM dispensing (IRR 0.29, 95% CI 0.11 to 0.75). In the categories of CCCs, neonatal and genetic/congenital were associated with higher rates of ASM dispensing whereas those with metabolic and malignancy conditions had decreased rates. Notably, there was no significant association with gastrointestinal or respiratory CCCs.

### Treatment with antireflux surgical procedures

The period prevalence of gastrojejunostomy tubes was 121 individuals out of the 10309 (1.1%) and the incidence rate was 1.78 per 1000 person-years (95% CI 1.49 to 2.13). A further 79 children had surgical jejunostomy tube placement corresponding to a period prevalence

**Table 5** Association between CCC and TA and incidence rate of treatment with ASMs

Category	Variable	Beta	SE	IRR (95% CI)*	P value
TA					
	Tracheostomy	-1.25	0.49	0.29 (0.11 to 0.75)	0.011
	Evacuation tube	0.87	0.34	2.39 (1.22 to 4.67)	0.011
	Gastrostomy	0.83	0.12	2.28 (1.80 to 2.91)	<0.001
	Renal support	0.18	0.34	1.20 (0.62 to 2.33)	0.596
CCC					
	Cardiovascular	-0.11	0.15	0.90 (0.66 to 1.21)	0.467
	Metabolic	-0.62	0.18	0.54 (0.38 to 0.76)	<0.001
	Neonatal	0.67	0.16	1.95 (1.42 to 2.68)	<0.001
	Gastrointestinal	-0.25	0.22	0.78 (0.50 to 1.20)	0.255
	Haemat/immunol	0.15	0.21	1.16 (0.77 to 1.74)	0.472
	Respiratory	0.27	0.20	1.31 (0.89 to 1.92)	0.172
	Malignancy	-1.06	0.22	0.35 (0.23 to 0.53)	<0.001
	Renal/urologic	0.01	0.22	1.01 (0.66 to 1.54)	0.981
	Genetic/congenital	0.58	0.14	1.78 (1.37 to 2.33)	<0.001

\*Adjusted for age and gender.

ASM, acid-suppressing medication; CCC, complex, chronic conditions; IRR, incidence rate ratio; TA, technology assistance.



of 0.7% and an incidence rate of 1.16 per 1000 person-years (95% CI 0.93 to 1.44). Finally, fundoplication was performed in 351 individuals with a period prevalence of 3.4% and an incidence rate of 5.29 per 1000 person-years (95% CI 4.76 to 5.87). The mean age at first fundoplication was 2.43 years (95% CI 2.05 to 2.81).

## DISCUSSION

In this population-based cohort of over 10 000 children, just over one-quarter of them had been diagnosed or treated for GERD. Multiple CCCs and presence of a gastrostomy tube were associated with a higher incidence of GERD.

This incidence and prevalence of GERD in children with NI is significantly higher than in the general paediatric population. Population-based paediatric studies from the primary care setting in the UK found an incidence of 0.84 per 1000 person-years and a period prevalence of 1.25% in a 5-year study period.<sup>23</sup> An American study reported an annual prevalence of GERD in 12.3% of infants and 1.26% of adolescents.<sup>2</sup> Our case definition has important differences that must be noted. Prior studies included diagnoses by family physicians whereas our study was limited to paediatric specialists. Our study also included ASM prescriptions as a criterion for GERD. Even with these methodological differences, it is evident that our incidence rate of 52 per 1000 person-years may be up to 60-fold higher than the general paediatric population.

Previous studies included only individuals with severe NI and/or symptoms of GERD. The largest case series enrolled 435 institutionalised individuals with intellectual disability (only 48 children). In this group, 186 (42.8%) had an abnormal pH probe and, of those, 129 (69.4%) had oesophagitis on endoscopy.<sup>12</sup> Other studies enrolled small numbers of children with NI presenting with symptoms finding a prevalence as high as 70%.<sup>11 13</sup> The prevalence of 26.9% in this study is lower than previous reports, but reflects a wider range of children with NI.

The association between a GERD diagnosis and multiple CCCs may relate to the severity of NI, which is correlated with both an increased risk of GERD and a higher number of comorbidities.<sup>12 14 24–26</sup> Similarly, a gastrostomy tube may simply indicate more severe NI. Alternatively, this relationship could reflect imprecise diagnoses due to the overlapping symptom profiles of GERD and dysphagia.<sup>27</sup> The possibility of increased risk of GERD following G tube insertion has also been suggested by some studies but refuted by others.<sup>28–31</sup>

Of even greater clinical significance is the use of ASMs in children with NI. The period prevalence of treatment with ASMs that we found is dramatically higher than the general paediatric population (23.7% vs 0.3%–1.3%) and more comparable to that of adult populations (15%–33%).<sup>3 32–36</sup> We also found evidence of prolonged or recurrent treatment courses. An incidence rate of more than one ASM dispensed per month suggests that

children may be on long-term treatment and/or are on combined treatments. Data were not available on the amount of medication prescribed so some prescriptions could have been shorter courses (<30 days). Those with neonatal CCCs were an important subgroup associated with higher rates of ASM dispensing which fits with the greater prevalence of GERD in the first year of life.<sup>37</sup>

These results raise concerns about potential over-prescribing of ASMs in children with NI. Existing guidelines, including those for children with NI, recommend short therapeutic trials of ASM for GERD.<sup>8 9</sup> Regular assessment of the ongoing need for acid suppression is recommended including an attempted wean at 8 weeks.<sup>8 9</sup> Adult guidelines suggest intermittent therapy, but there is no current data to guide this practice in paediatrics.<sup>38</sup> Many patients in this cohort received ASM without a GERD diagnosis by a specialist in contravention to current guidelines. It is possible that some children were treated for other conditions, such as eosinophilic oesophagitis, although these are rare. Some children could have received a diagnosis of GERD prior to the study period.

There is increasing evidence of potential adverse effects with ASMs that are concerning in the context of high treatment rates.<sup>7 39</sup> There are significant associations between ASMs and respiratory infections, asthma, allergic diseases, inflammatory bowel disease and fractures in paediatric populations.<sup>5 6 40–42</sup> ASMs impact the gut microbiome which could have undetermined downstream effects.<sup>43 44</sup> Adult studies have also found associations between PPIs and cardiovascular and renal morbidity.<sup>45 46</sup> Although many of these pathological mechanisms have yet to be elucidated, there is a building burden of evidence for possible harms.

Although children with NI do have higher risk of GERD, they may also be at higher risk of significant complications from ASMs. A retrospective cohort study in paediatrics showed a nearly twofold increase in hospitalisations for children with dysphagia who were treated with a PPI compared with untreated children.<sup>47</sup> A large population-based cohort study demonstrated a twofold increased risk of community-acquired pneumonia in children treated with PPIs compared with controls with an even greater risk in children with disability.<sup>5</sup> Further, children with NI have increased baseline risk of low bone mineral density and fractures as well as alterations in gut flora if they are enterally fed.<sup>48–50</sup>

A major strength of our study is the use of a population-based sample of children with NI to describe GERD and ASM use. However, the reliance on retrospective administrative data introduces a number of limitations. Only children with NI who had a hospital-based encounter were included in the cohort. This may result in an over-representation of children with more severe NI. The diagnosis of GERD is complicated by the lack of a gold standard diagnostic tool and cannot be verified or confirmed using administrative data.<sup>9</sup> The primary aim for this study was to determine how frequently GERD was

diagnosed and treated, as opposed to assessing the accuracy of the diagnosis. The case definition for this study was created to be moderately restrictive, to align with published guidelines and to provide a reasonable estimate of GERD prevalence and incidence. Finally, as this was a provincial population study, these results may not be generalisable to other jurisdictions.

This study demonstrates that GERD is an important clinical issue among children with NI. For accurate GERD cases, further guidance is needed on the most judicious use of ASMs balancing the risk of adverse effects in this population. We also suspect that some cases are inaccurately diagnosed and may be inappropriately treated with ASMs. Communication impairments limiting self-report, non-specific symptoms and frequent comorbidities make the diagnosis of GERD particularly challenging. Future research is required to better delineate prescribing patterns for ASM in children with NI as well as better characterise their risk of adverse events. This could lead to more specific recommendations to guide diagnosis, follow-up and pharmacological management of GERD.

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**Contributors** TD is the guarantor for this study and, as such, accepts full responsibility for the finished work, conduct of the study, data access and publication decisions. TD also conceptualised the study, led the design of the study, contributed to data analysis and interpretation and wrote the initial draft of the manuscript. DWJ guided the design of the study as senior author, contributed to data analysis and interpretation and edited the final manuscript. JT contributed to the design of the study, data analysis and interpretation and edited the final manuscript. BCL contributed to the design of the study, led the data analysis and edited the final manuscript. Jenna Dobry provided study coordination and research support.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by University of Calgary Conjoint Health Research Ethics Board (REB20-0062) and the University of Alberta Health Research Ethics Board (Pro00111982). This study used administrative data and was approved, with a waiver of consent, from the Research Ethics Board and the data custodian (Alberta Health Services).

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**Data availability statement** Data are available on reasonable request. Requests for data can be directed to TD.

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