(TITLE PAGE)

Title:

Non-indicated acid-suppression prescribing in a tertiary paediatric hospital: an audit and costing study.

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(MAIN TEXT)

ABSTRACT

Aims: To quantify: (i) indicated versus non-indicated prescribing of acid-suppression therapies (AST) in a tertiary paediatric hospital; (ii) patient, provider and hospital factors associated with non-indicated prescribing; and (iii) medication costs.

Methods: Prospective, electronic medical audit conducted at The Royal Children's Hospital Melbourne, August-September 2016. Proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H_2RA) prescriptions were extracted, with relevant patient, provider and hospital data. Logistic regression analysis of variables associated with indicated and non-indicated

prescribing was undertaken. Costs of indicated and non-indicated prescriptions were estimated, with annual costs projected.

Results: There was more non-indicated than indicated prescribing across inpatient, outpatient and emergency department settings. Of the total 303 prescriptions analysed, 238 (78.5%) were non-indicated. Gastrostomy presence (OR 5.51 [1.96 – 15.46], $p = 0.001$), consultant providers (OR 2.69 [1.23 -5.87], $p = 0.01$) and inpatient setting (OR 2.35 [1.16 – 4.77], $p = 0.02$) were all associated with a higher likelihood of non-indicated prescribing. The child having a predisposing diagnosis was significantly associated with indicated prescribing (OR 0.41, [0.21- 0.80], $p = 0.009$). Seventy-five percent of hospital and patient spending was for non-indicated prescriptions. Annual costs of non-indicated AST for Melbourne's Royal Children's Hospital were projected to be $15,493.

Conclusion: Non-indicated acid-suppression prescribing is common in a tertiary paediatric hospital and associated with gastrostomy presence, consultant providers and inpatient status. Future research should employ qualitative methods to understand clinician and patient drivers of prescribing and use this information to develop and test targeted solutions to reduce non-indicated AST prescribing.

KEY WORDS: Low-value care/prescribing; paediatric hospitals; gastro-oesophageal reflux; proton pump inhibitors; histamine H2 antagonists

WHAT IS ALREADY KNOWN ON THIS TOPIC:

- Prescribing of AST amongst infants and children has increased worldwide in recent decades.
- Infants who present with unsettled behavior, feeding difficulty or frequent regurgitation, but are otherwise healthy and thriving, should not routinely be prescribed AST.
- Inappropriate use of AST may lead to unwarranted side effects and healthcare costs.

WHAT THIS PAPER ADDS:

- Non-indicated prescribing of AST is common in a tertiary paediatric hospital.
- Factors associated with higher odds of non-indicated prescribing included gastrostomies, inpatient setting and prescribing by consultants.
- Non-indicated prescriptions accounted for 75% of total spending on AST during the study period.

INTRODUCTION

Most low-value health care research has focused on adults rather than children.[1] Recently however, the Australian CareTrack Kids study demonstrated substantial variation in care across 17 important child health conditions, with overall adherence to quality indicators being 59.8%.[2] Internationally, endeavours such as Choosing Wisely seek to measure low-value, unnecessary care across all ages and specialties.[3] Paediatric low-value health practices are currently a focus of national initiatives, including the CareTrack Kids study and Royal Australasian College of Physicians' EVOLVE recommendations.[4-6] Such initiatives consistently advise that acid-suppression therapy (AST) is ineffective for treating infants with non-specific symptoms, like 'spitting up' or unsettled behavior.[7,8]

Based on The Global Consensus Definition, gastro-oesophageal reflux disease (GORD) occurs when persistent reflux of gastric contents causes 'sufficiently troublesome' symptoms and/or complications.[9] Defining troublesome symptoms is complex in infants and children. Features consistently concerning for GORD include haematemesis, anaemia, failure to thrive and dysphagia, as well as persistent vomiting with respiratory complications (Appendix A).[9-11] GORD and its direct complications (e.g. reflux oesophagitis, Barrett's oesophagus) are the only evidence-based indications for AST. Distinguishing simple, physiological reflux from GORD can be difficult, but is critical to avoiding unnecessary interventions.[9]

The problem of 'unsettled infants' further complicates matters. Infant 'colic' and regurgitation, both common, are susceptible to conflation as 'reflux disease', though no causal relationship is known.[12,13] Food refusal, back arching and sleep disturbance are not significantly associated with pathological GORD.[11,12] Crying, feeding difficulties or unsettled behavior do not correlate with objective reflux on pH-monitoring.[7,8,10]

Regurgitation, irritability and vomiting lack sensitivity and specificity to distinguish physiologic infant reflux versus GORD.[9,10] Symptom overlap has led to a negative

definitional approach: 'healthy infants and children with reflux symptoms that are *not* troublesome and are *without* complications should *not* be diagnosed with GORD'.[9]

Acid-suppression therapies are ineffective in reducing symptoms purported to be GORD in infants (i.e. crying, 'spitting up'), with proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs) showing no greater effect than placebo.[7,8,10,14,15] Efficacy in children remains uncertain, with insufficient high quality data.[8] In the minority with chronic GORD, AST improves symptoms and signs seen at endoscopy.[10]

Increasingly, ASTs are recognized to have potential harms, especially when taken long-term. Cohort studies demonstrate higher rates of gastroenteritis (e.g. 47% vs. 20%, p = 0.001, OR 3.58) and community-acquired pneumonia (e.g. 12% vs. 2%, $p < 0.05$, OR 6.39) in children taking either PPIs or H_2RAs, versus healthy controls.[8,16,17] Micronutrient deficiencies, particularly B12, have also been associated with these therapies.[18,19] Fracture rates appear significantly greater (increased risk 22% for PPIs, 31% combined PPI - H_2RA use) and median age to first fracture younger (3.9 vs. 4.5 years, $p < 0.05$) in children receiving AST as infants.[20,21] Longer treatment, dual therapy and commencement under six months' age are associated with higher fracture rates.[21]

Despite growing concerns surrounding efficacy and safety, paediatric use of PPIs and H_2RAs is increasing.[22,23] Large studies across the USA and Europe indicate AST prescriptions for infants and children rose seven-fold from the late 1990s to mid-late 2000s.[24,25] These observational studies often rely on retrospective analyses of pharmacy charges and do not typically capture where prescriptions were written, by whom and why. [20,24]. Only one Australian study has examined hospital-based AST use and was limited to infants and PPI prescribing alone.[26] Inter-country variation in AST prescribing is likely. For example, evidence suggests the USA experiences greater low-value health care.[27] Local data on prescribing practices is required to inform appropriate interventions.

This study aimed to determine prevalence, factors and financial costs of non-indicated AST prescribing within a tertiary, paediatric hospital.

We hypothesized that non-indicated prescriptions would be more common than indicated and would occur disproportionately amongst infants. We also predicted that children with a 'predisposing condition' for GORD would have relatively more indicated prescriptions.

METHODS

Design

A prospective, single-centre audit study was conducted at the Royal Children's Hospital (RCH) in Melbourne, a tertiary paediatric hospital, from 1 August – 30 September 2016. Data for PPI and H_2RA prescriptions during this period were extracted from the hospital electronic medical record (EMR) 'EPIC' using a report designed with the EMR-research team. The RCH Human Research Ethics Committee approved this study (HREC 36088A).

Study population

PPI and H_2RA prescriptions for patients aged 0 – 18 years were assessed. Only enteral medication forms – administered orally, via naso-gastric (NG), naso-jejunal (NJ), percutaneous endoscopic gastrostomy (PEG) or jejunostomy (PEJ) – were included. Duplicate orders (e.g. identical, repeat orders within an encounter) and those outside inpatient, outpatient or emergency department (ED) settings (e.g. 'documentation' or 'telephone' encounters) were removed. Neonatal and Paediatric Intensive Care Unit patients were omitted, as were oncology, metabolic and nephrotic syndrome patients, who are managed as per protocols that include AST. Following removal of all exclusion groups, 303 prescriptions (232 unique patients) remained for analysis (Figure 1).

Factors associated with prescribing

For each prescription, additional data regarding patient demographics (age, gender and postcode), prescribing provider (seniority, specialty background), hospital setting (inpatient, outpatient or ED) and clinical presentation (presenting and secondary diagnoses) were extracted. Family postcode was used to generate variables for remoteness and Socio-

Economic Indexes for Areas (SEIFA) rank. We reported the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) SEIFA, ranking postcodes from most disadvantaged '1' to advantaged '10', based on five-yearly Census.[28]

We developed a list of 'indicators' for prescribing AST (Table 1), informed by international guidelines (published 2009) and updated literature.[9,10] When newer evidence contradicted international guidelines, we removed the earlier symptom or sign (e.g. irritability in infants). Non-specific symptoms (e.g. sleep disturbance, abdominal pain) were omitted to more accurately identify patients with GORD. We also developed a list of 'predisposing conditions' for GORD using international guidelines. From documented diagnoses, prescriptions were categorised as 'indicated' or 'non-indicated', as was the presence of a 'predisposing condition'.

The variable 'possible steroids' was created from diagnosis data to reflect frequent prescribing of AST alongside high-dose corticosteroids in specific conditions. Routine steroid use for these conditions in our cohort (e.g. acute transverse myelitis, juvenile idiopathic arthritis etc.) was then corroborated against hospital guidelines.

Statistical analysis

SR conducted data validation by reviewing the charts of 12 randomly selected prescriptions. There was complete correlation between chart review and electronic data extracted. If diagnoses fell outside the predetermined 'indicators' and there was uncertainty regarding appropriate prescribing, SR conducted an additional literature search and discussed the case with the supervising researcher (HH). If doubt remained, a relevant specialist was consulted to obtain consensus on whether or not prescribing of an AST was indicated.

We calculated the number and proportion of non-indicated prescriptions by setting and age. Within each setting, we conducted bivariate analyses between patient, provider, clinical characteristics and prescribing. Pearson's chi-squared and t-tests were used to compare proportions and means, respectively. Logistic regression was performed to determine factors

associated with non-indicated prescriptions, adjusting for all characteristics associated at the bivariate level with $p < 0.1$. Statistical analyses were conducted using STATA version 14.2 and R version 3.4.0.

Cost analysis

Total spending on AST during the study period, including hospital and patient costs, was estimated for indicated and non-indicated prescriptions. Inpatient medication costs were calculated using inpatient prescriptions multiplied by the hospital formulary's medication cost. For Outpatient and ED prescriptions, 2016 Pharmaceutical Benefits Scheme (PBS) prices were applied. For non-PBS medications, mean costs were estimated from information provided by five community pharmacies across Melbourne (medication prices documented in Appendix B). Estimated costs were then extrapolated to predict annual RCH expenditure for indicated and non-indicated AST prescriptions.

RESULTS

Of the 303 prescriptions analysed, esomeprazole was the most common AST (64%) followed by ranitidine (24%) (Table 2). Non-indicated AST prescriptions were more common than indicated across all three settings: ED (n = 21, 62%), inpatients (n = 157, 83%) and outpatients (n = 60, 75%). This difference reached statistical significance across inpatient and outpatient settings (both $p < 0.001$). Table 3 lists the top ten diagnoses per setting for non-indicated prescriptions.

Factors associated with non-indicated AST (n = 238) at the bivariate level differed by setting (Table 4). In the ED, no factors were associated with non-indicated prescriptions, though this may reflect fewer total ED prescriptions and hence reduced power to detect significant differences. Within inpatient and outpatient settings, 'possible steroids' and PEG/PEJ were associated with greater non-indicated prescribing (all p d 0.01). Notably, no patients receiving indicated prescriptions (n = 65) were possibly taking steroids. For outpatients only, consultant providers were associated with more non-indicated prescriptions (n = 52, 86.7%, p = 0.01). 'Predisposing conditions' were associated with indicated

prescriptions amongst inpatients and outpatients ($p < 0.001$ and $p = 0.04$, respectively). Age < 1 year was not associated with higher rates of non-indicated prescribing.

Table 5 depicts adjusted logistic regression outputs, in which non-indicated prescriptions were significantly associated with PEG/PEJ presence (OR 5.51 [1.96 – 15.46], $p = 0.001$), consultant providers (OR 2.69 [1.23 -5.87, $p = 0.01$) and inpatient setting (OR 2.35 [1.16 – 4.77], $p = 0.02$). Having a 'predisposing condition' was associated with indicated prescribing (OR 0.41 [0.21 – 0.80], $p = 0.009$). The relationship between 'possible steroids' and non-indicated AST was attenuated in regression analysis.

Seventy-five percent of spending ($2,582 of $3,447) during the study was for non-indicated prescriptions. Outpatient non-indicated AST prescribing generated the highest cost ($1834), followed by ED ($417) and inpatients ($331). Estimated national annual expenditure for non-indicated AST within The Royal Children's Hospital, Melbourne was $15,493 (Table 6).

DISCUSSION

To our knowledge, this is the first study to examine factors associated with non-indicated AST in a tertiary paediatric hospital. Overall, non-indicated prescriptions were greater than indicated across hospital settings. Factors associated with non-indicated AST prescribing included gastrostomy presence, consultant providers and inpatient setting, while child age was not associated with any prescribing pattern. Unsurprisingly, a predisposing condition was associated with indicated prescribing. Overall, 75% of total spending on AST was for non-indicated prescriptions.

Our study detected similar proportions of non-indicated prescribing – 61% (ED) to 83% (inpatients) – to those reported in adults.[29] Our findings occur in the context of international data demonstrating increasing AST use across ages and support existing concerns regarding low-value practices in this area. [22,24,30,31]

Significant study findings align with a recent review of variation in paediatric practice, where greater disease severity was associated with greater practice variation, correlating with our inpatient setting being associated with non-indicated prescribing.[32] This may partly be due to insufficient evidence for best practice in sicker children.[32] Most variation in inpatient care involves 'over-management', including over-prescription of inappropriate treatments.[32]

Consultant status was associated with non-indicated prescribing, consistent with the review finding that consultants were less likely to use effective care.[32] Less experienced doctors may follow clinical practice guidelines more, whilst consultants employ previous experience, which may not keep pace with emerging evidence regarding AST efficacy and safety.

This is the first paediatric study to identify gastrostomy as a factor associated with non-indicated AST. No causal association between gastrostomies and increased GORD has been demonstrated, with vomiting generally improving after PEG insertion.[33] Confirmed reflux rates remain similar pre- (22.1%) and post- (25%) PEG, with children requiring further GORD management usually having abnormal pH-monitoring prior to gastrostomy.[34,35] Notwithstanding this evidence, many children with PEG/PEJs, remain on AST indefinitely. Similarly, despite being 'at risk' of GORD, routine AST in children with neurodisability is not indicated.[10] Safety concerns regarding increased pneumonia, C.difficile gastroenteritis and fracture rates are particularly pertinent to this population.[16,20,36,37]

'Possible steroid' use was associated with non-indicated AST prescribing within inpatient and outpatient bivariate analyses. The relationship between corticosteroids and gastro-intestinal complications is controversial. There is no consistent evidence, however, that steroids directly cause GORD and paediatric data is currently insufficient to support routine AST use alongside corticosteroids.[38] In our study, children receiving AST without primary indication whilst also potentially on steroids may have been placed on acid-suppression prophylactically. High rates of inappropriate prophylactic acid-suppression, mainly in

adults, have been found across Malaysia, Europe and the U.S.[39-42] Data suggest that routine acid-suppression 'prophylaxis' for corticosteroids alone, particularly amongst outpatients, is unnecessary.[38,41] More paediatric data are required to understand the relative risks to these patients.

Costs of AST prescribing

Seventy-five percent of total AST spending at RCH was for non-indicated prescriptions. Adult U.S. research has shown approximately 70% of inpatients commencing PPIs continue these at discharge, despite no apparent need.[40] Paediatric data regarding AST continuation post hospital instigation are lacking, but some children likely continue these unnecessarily. Complete costing should additionally account for post discharge prescribing, as well as patient 'costs' of inappropriate prescribing – i.e. repeat doctor visits. Our findings likely represent 'the tip of the iceberg' of a greater problem.

Market factors influence low-value health practices. In Australia, PPI use substantially increased after 2001, prior to which endoscopy diagnosis of ulcerating oesophagitis was required for prescribing.[31] Free samples of PPIs have demonstrably increased use, ultimately reducing cost per prescription.[43] Specific to infants and children, availability of liquid formulations may contribute to prescribing.[25,44]

Strengths and limitations

This is the first paediatric study to link diagnoses to AST prescriptions and assess treatment appropriateness alongside associated factors. National all-ages and international paediatric studies have relied on large databases to appraise prescribing, with limited details regarding indication.[24,31]

Use of a sophisticated EMR permitted highly accurate data collection. The 'a priori' determination of clear, specific 'indicators', drawn from international guidelines and recent literature, is another strength. Finally, our costing study includes state, federal and private prescription costs.

Limitations include single-site design and relatively small sample size. Tertiary and teaching hospitals generally achieve better compliance with practice guidelines,[32] and RCH guidelines specifically recommend against AST for infant 'colic'.[45,46] This may have influenced results and limits generalisability including cost-extrapolation to other settings, where low-value practices are likely higher.[32] As with all EMR studies, data quality depended on accuracy of data entered.

Implications and future research

Despite evidence-based guidelines for AST use in infants and children, non-indicated prescribing still appears common. To improve implementation, barriers and enablers to best practice should be investigated through qualitative research considering clinician and patient drivers of prescribing.

Appropriate trials to ascertain first efficacy, then specific indications, for AST in children with gastrostomies or taking steroids are necessary. Future research should study use post hospital initiation, to better understand the magnitude of this issue and potential intervention points.

Multi-component interventions are more effective than singular, across adult and paediatric literature.[47-49] Additional strategies – auditing and feedback, electronic prescribing prompts and in-built EMR clinical practice protocols – may help reduce variation in AST use.

CONCLUSION

Non-indicated AST prescribing is common in a tertiary paediatric hospital and associated with gastrostomy presence, consultant prescribers and inpatient status. Future research should employ qualitative methods to understand clinician and patient perspectives regarding non-indicated AST prescribing, which can then inform development and evaluation of interventions designed to reduce non-indicated prescribing. Finally, robust

trials are required to determine whether routine AST in children taking steroids is necessary, given growing evidence around these medications' potential harm.

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(APPENDICES)

Appendix A: International Guidelines for symptoms, signs and other associations of GORD

Guideline	Symptoms, signs and other associations
Vandenplas et al, 2009 North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and European Society for Gastroenterology, Hepatology and Nutrition (ESPGHAN) Guidelines based on international consensus, 600 articles reviewed, expert panel. Age range covered: infants to adolescents	Symptoms • Recurrent regurgitation with/without vomiting • Weight loss or poor weight gain * • Irritability in infants • Rumination behavior • Heartburn or chest pain * • Hematemesis * • Dysphagia, odynophagia * • Wheezing * • Stridor ** • Cough ** • Hoarseness ** Signs • Reflux Oesophagitis * (also diagnosis) • Oesophageal stricture * (also diagnosis) • Barrett oesophagus * (also diagnosis) • Laryngeal/pharyngeal inflammation • Recurrent pneumonia ** • Anemia * • Dental erosion • Feeding refusal • Dystonic neck posturing (Sandifer syndrome) * • Apnoea spell * • Apparent life-threatening events *
Sherman et al, 2009 A Global, Evidence-Based Consensus on the Definition of Gastroesophageal Reflux Disease in the Paediatric Population Guideline inspired by Montreal Definition working group for adult GORD, based on international consensus, statements by international panel of 8 paediatric gastroenterologists and a modified Delphi technique. Age range covered: 0 to 18 years	Symptoms • Excessive regurgitation • Heartburn in retrosternal area * • Epigastric pain • Sleep disturbance • Haemorrhage * • Feeding refusal/anorexia • Unexplained crying • Choking/gagging/coughing • Abdominal pain Signs *Syndromes with oesophageal injury* • Reflux Oesophagitis *

	• Barrett's oesophagus * • Stricture * • Adenocarcinoma *Definite associations* • Sandifer's syndrome * • Dental erosion Possible extra-oesophageal associations • Apnoea * • Bradycardia • Asthma • Chronic cough ** • Chronic laryngitis • Hoarseness ** • Pharyngitis • Pulmonary Fibrosis • Bronchopulmonary dysplasia • Sinusitis • Serous otitis media

* Denotes signs, symptoms and other associations we have included as an indicator
** 'With vomiting' in study Indicator Table, see Methodology

Appendix B: Cost prices used for Costing Study

			Price		
Medication	**Dose**	**Form**	**RCH unit cost**	**PBS cost**	**Non-PBS price**
cimetidine	200 mg	tablet	Not on RCH formulary	60 x 400mg tab = $19.56 †	
esomeprazole	10 mg	sachet	30 x 10 mg sachet = $ 26.00	Not on PBS	30 x 10mg sachets = $41.70 ‡
	20 mg	tablet	30 x 20mg tabs = $5.94	30 x 20mg EC tab = $21.54 §	
	40 mg	tablet	30 x 40mg tabs = $9.55	30 x 40mg EC tab = $29.18 k	
omeprazole	20 mg	enteric coated capsule	30 x 20mg EC caps = $4.20	30 x 20mg EC tab = $14.99	
pantoprazole	20 mg	enteric coated tablet	30 x 20 mg EC tab = $1.00	30 x 20mg EC tab = $ 12.04	
	40 mg	enteric coated tablet	Not on RCH formulary	30 x 40mg EC tab = $13.60	
ranitidine	15 mg/mL	solution	300mL bottle = $ 7.65	2 x 300mL bottle = $26.30	
	150 mg	effervescent tablet	30 x 150mg Eff tab = $2.75	60 x 150mg Eff tab = $15.62	
	150 mg	tablet	60 x 150mg tab = $1.91	60 x 150mg tab = $14.02	

Footnotes and assumptions:

† Assumed that 200mg is likely half of 400mg tablet, given 200mg tablets not PBS listed.

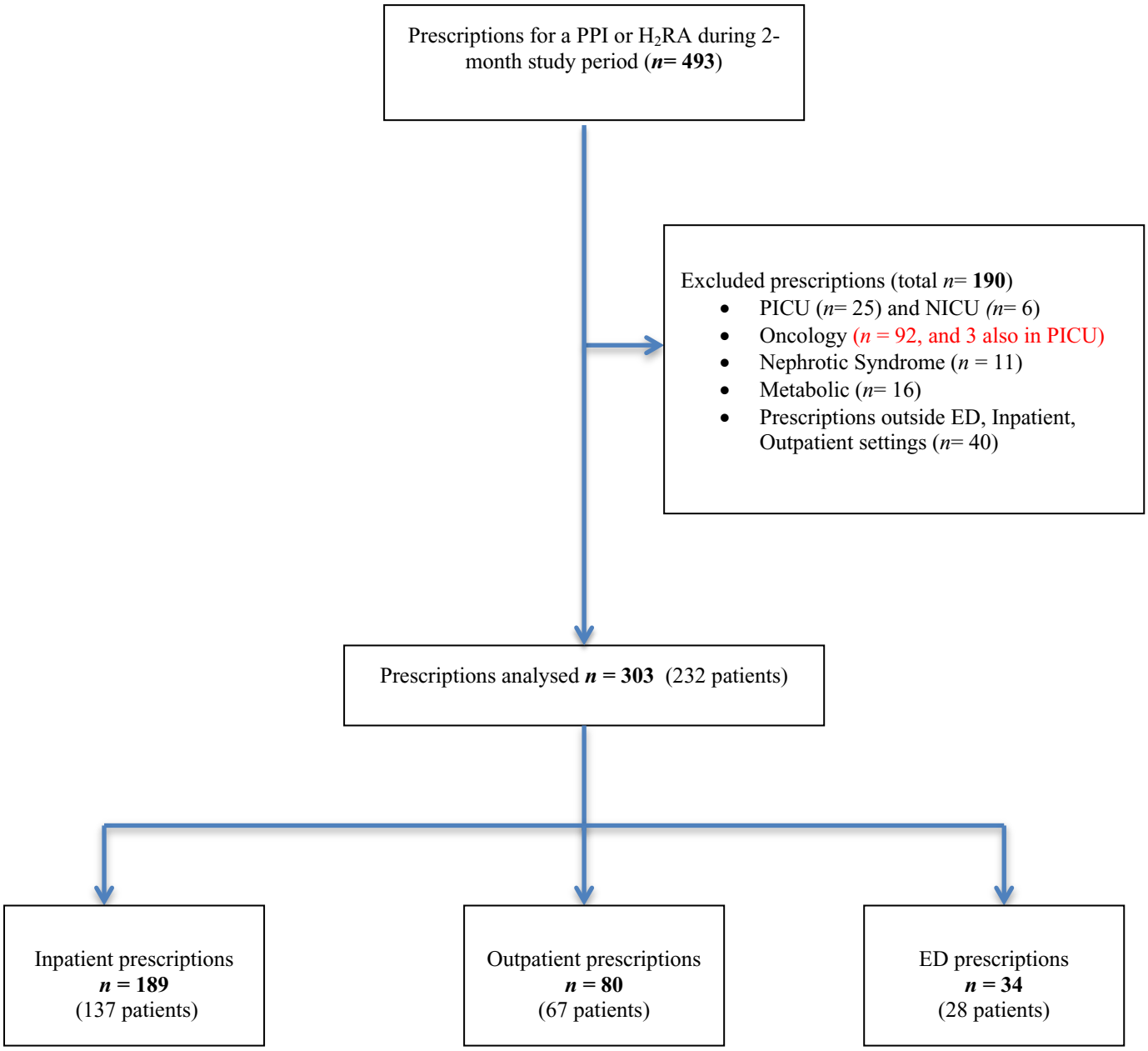
‡ Non-PBS price calculated by averaging 5 chemists from varied suburbs in Melbourne.

§ Presumed to be enteric-coated tablets, though not specified, as only 20mg and 40mg enteric coated tablets available on PBS.

The RCH 'unit' cost was applied for inpatient scripts, multiplied by the actual dose prescribed. All ED and Outpatient scripts were costed using PBS prices. Exceptions to the above rules included: (i) 4 prescriptions for ranitidine liquid within the ED, where it was clear from the order that the medication was administered within the department and hence the RCH unit price was applied (ii) scripts documented as 'SENT' for inpatients, indicating a script written for discharge, where the PBS cost was applied (iii) esomeprazole sachets which are not covered by the PBS and require private payment.
Any PBS price below the co-payment of $38.30 is paid out of pocket by the patient or family.

(FIGURE)

Figure 1. Process of data cleaning and application of exclusion criteria for PPI and H_2RA prescriptions



(TABLES)

Table 1: Indicators for acid-suppression therapy by age < 1 year and e 1 year of age

INDICATORS < 1 year of age

• **Non-indicated Care Measures** †
Infant with reflux who is healthy and thriving with:‡ • Irritability or unexplained crying • Feeding refusal • Frequent regurgitation
Indicated Care Measures
Weight loss or FTT §
• Haematemesis §
Vomiting with: § • Wheezing § • Stridor § • Cough § • Hoarseness § • Recurrent pneumonia §
Apnoea spells §
Apparent Life-Threatening Event §
Anaemia §
Sandifer syndrome (dystonic neck posturing) §
Reflux Oesophagitis §
Oesophageal stricture §

INDICATORS e 1 year of age

Indicated Care Measures
• Heartburn ‡ §
Weight loss or FTT §
Haematemesis §
Vomiting with: § • Wheezing § • Stridor § • Cough § • Hoarseness § • Recurrent pneumonia §
Dysphagia §
Odynophagia §
Sandifer syndrome (dystonic neck posturing) §
Anaemia §
Reflux Oesophagitis §
Oesophageal stricture §
Barrett's Oesophagus ‡ §

† For infants < 1 year, three recently developed CareTrack Kids indicators were included. These together state that infants with reflux who are healthy and thriving, with *irritability* or *unexplained crying*, *feeding refusal* or *frequent regurgitations*, should not be prescribed these medications at first presentation. Although CTK specify *at the first presentation,* we removed this caveat as the literature suggests that infants who remain thriving and well, should not have their non-specific symptoms labeled GORD, particularly given the natural history of physiological reflux to self-resolve.

‡ Indicator from Care Track Kids – GORD indicators

§ Indicators based on International guidelines and literature review

Table 2. Acid-suppression therapy prescriptions, ranked by frequency

Medications prescribed	Frequency (n)	Percentage (%)
Esomeprazole	194	64.03
Ranitidine	72	23.76
Omeprazole	31	10.23
Pantoprazole	5	1.65
Cimetidine	1	0.33
Total	303	100

Table 3: Primary diagnoses for non-indicated AST prescriptions, ranked by frequency and setting

	Emergency (n = 21) [††]		Inpatient (n= 157) [‡‡]		Outpatient (n = 60) [§§]	
Rank	**Diagnosis**	**Frequency (%)**	**Diagnosis**	**Frequency (%)**	**Diagnosis**	**Frequency (%)**
1	Abdominal pain – unknown aetiology or acute LUQ	9 (42.9)	LRTI	13 (8.3)	Cerebral Palsy	10 (16.7)
2	Vomiting	3 (14.3)	Hypoglycaemia	11 (7)	IBD	6 (10)
3	Chronic constipation	1 (4.8)	Vomiting	9 (5.7)	PEG/feeding tube related	6 (10)
4	Back pain	1 (4.8)	PEG/feeding tube related	8 (5.1)	Abdominal pain – nonspecific	3 (5)
5	Dermatological diagnosis	1 (4.8)	Congenital heart disease	7 (4.5)	Behavioural issue	3 (5)
6	Fever	1 (4.8)	OSA	6 (3.8)	Congenital syndrome	3 (5)
7	Headache	1 (4.8)	Viral illness/URTI	6 (3.8)	Seizure disorder	3 (5)
8	IBD	1 (4.8)	Encephalitis, myelitis and encephalopathy	5 (3.2)	Chronic kidney disease	2 (3.3)
9	Mental health	1 (4.8)	Fever	5 (3.2)	Congenital heart disease	2 (3.3)
10	Viral illness/URTI	1 (4.8)	Seizure disorder	5 (3.2)	Dermatological diagnosis	2 (3.3)

[††] Emergency: one further diagnosis at a frequency of 1 occurred

[‡‡] Inpatients: a further 13 more diagnoses occurred at a frequency of 2 – 4, a further 45 more diagnoses occurred at a frequency of 1, and there were 7 prescriptions with no data for diagnosis

[§§] Outpatients: a further 4 diagnoses occurred at a frequency of 2, a further 11 diagnoses occurred at a frequency of 1, and 1 prescription had no data for diagnosis

Table 4: Bivariate associations between number of indicated and non-indicated AST prescriptions, across hospital settings

	Hospital Setting								
	ED			Inpatient			Outpatient		
	Indicated	Non-indicated	*p*-value	Indicated	Non-indicated	*p*-value	Indicated	Non-indicated	*p*-value
Number of scripts, n	13	21	0.17	32	157	<0.001	20	60	<0.001
Number of children, n	12	16	0.45	26	111	<0.001	18	49	<0.001
Child characteristics									
Male, n (%)	4 (30.8)	9 (42.9)	0.17	16 (50)	92 (58.6)	< 0.001	12 (60)	27 (45)	0.02
Age in years, mean (*SD*)	11 (2.9)	11 (4.7)	0.98	8 (6.9)	6 (6.3)	0.18	9 (5.8)	9 (5.4)	0.53
Age < 1 year, n (%)	0	0		7 (21.9)	32 (20.3)	<0.001	2 (10)	4 (6.7)	0.41
Possible steroids - Yes, n (%)	0	0		0	12 (7.6)	<0.001	0	4 (6.7)	0.01
PEG/PEJ – Yes, n (%)	0	3 (14.3)	0.08	4 (12.5)	55 (35)	<0.001	1 (5)	9 (15)	0.01
Team			1.00			0.09			0.34
Medical, n (%)	-	-		7 (21.9)	40 (25.5)		0	4 (6.7)	
Surgical, n (%)	-	-		2 (6.3)	27 (17.2)		1 (5)	1 (1.7)	
Specialty, n (%)	-	-		22 (68.8)	90 (57.3)		9 (95)	55 (91.7)	
Emergency, n (%)	13 (100)	21 (100)		-	-		-	-	
Medical Imaging, n (%)	-	-		1 (3.1)	0		0	0	
Predisposing diagnosis, n (%)	0	1 (4.8)	0.31	12 (37.5)	40 (25.4)	<0.001	11 (55)	23 (38.3)	0.04
Family/caregiver characteristics									
SEIFA*** (IRSAD), mean (SD)	6 (2)	5 (3)	0.73	6 (3)	6 (3)	0.68	6 (3)	6 (3)	0.97
Remoteness			0.51			0.38			0.07
Regional, n (%)	0	2 (9.5)		11 (34.4)	39 (24.8)		7 (35)	8 (13.3)	
Major city, n (%)	13 (100)	18 (85.7)		21 (65.6)	117 (74.5)		13 (65)	52 (86.7)	
Prescriber characteristics			1.00			0.76			0.01
Junior Medical Staff, n (%)	12 (92.3)	19 (90.5)		28 (87.5)	140 (89.2)		9 (45)	8 (13.3)	
Consultant, n (%)	1 (7.7)	2 (9.5)		4 (12.5)	17 (10.8)		11 (55)	52 (86.7)	
Diagnoses			1.00			0.14			
1 diagnosis, n (%)	13 (100)	21 (100)		18 (56.3)	89 (56.7)		10 (50)	35 (58.3)	0.64
2 diagnoses, n (%)				5 (15.6)	39 (24.8)		6 (20)	12 (20)	
3 or more diagnoses, n (%)				9 (28.1)	22 (14)		6 (30)	12 (20)	

*** SEIFA Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) reported - ranks postcodes 1 to 10, from most disadvantaged to most advantaged

Table 5: Adjusted logistic regression of variables associated with non-indicated AST prescriptions [***]

Independent variable	Adjusted OR (95% C.I.)	*p*-value
Consultant	2.69 (1.23 – 5.87)	0.01
Major city	1.56 (0.78 – 3.11)	0.20
Predisposing condition	0.41 (0.21 – 0.80)	0.009
Male	1.00 (0.55 – 1.82)	0.99
Age > 1 year	0.67 (0.27 – 1.63)	0.38
PEG/PEJ present	5.51 (1.96 – 15.46)	0.001
Inpatient setting	2.35 (1.16 – 4.77)	0.02

[***] Adjusted for all variables listed in the table

Table 6: Calculated costs of indicated and non-indicated AST prescriptions and projected annual expenditures for the Royal Children's Hospital

	Indicated (n = 65)	Non-indicated (n = 238)	Total (n = 303)
2-month	$865	$2,582	$3,447
Relative % of total	25%	75%	100%
Annual †††	$5,188	$15,493	$20,681

††† 2-month cost multiplied by a factor of six to reflect annual hospital expenditure

(TITLE PAGE)

Title:

Non-indicated acid-suppression prescribing in a tertiary paediatric hospital: an audit and costing study.

Manuscript: Original article

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study and can take responsibility for the integrity of the data and the accuracy of the data analysis. HH is the guarantor.

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