

# Incidence and cost of stress ulcer prophylaxis after discharge from the intensive care unit: a retrospective study

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There is increasing recognition that “unnecessary” or “low-value” treatments are provided in medicine.<sup>1,2</sup> In critical illness, physiological stress can lead to disruption of gastrointestinal mucosal defences and the development of stress ulcers.<sup>3,4</sup> The use of stress ulcer prophylaxis (SUP) in selected patients admitted to the intensive care unit to reduce the development of stress ulcers is supported by historical evidence and international guidelines.<sup>3-5</sup> SUP refers to the use of acid suppression therapy such as proton pump inhibitors (PPIs) or histamine receptor blockers to prevent the development of stress ulcers (distinct from the use of acid suppression therapy for gastro-oesophageal reflux disease or for gastric ulcer disease).

The optimal agent for maximal efficacy and minimal complications is still unclear (and is currently the subject of the Peptic study, endorsed by the Australian and New Zealand Intensive Care Society), but the rationale that empirical SUP in the ICU may be harmful or represent an unnecessary or low-value treatment is several-fold. First, early studies found a high incidence of gastrointestinal bleeding associated with stress ulceration in the ICU, but this risk has decreased substantially, independent of the use of SUP over subsequent decades.<sup>4,6</sup> Second, SUP is increasingly initiated outside evidence-based indications in critical care and inpatient settings and continued without a clear indication for ongoing use.<sup>7-10</sup> Finally, PPIs, a commonly used SUP therapy, have been associated with an increased risk of adverse effects including pneumonia, infection with *Clostridium difficile* and, more recently, myocardial infarction and dementia.<sup>3,6,11-13</sup>

We hypothesised that ICU admission continues to result in significant prescriptions for SUP therapy and continuation without an evidence-based indication. The aim of our study was to describe current patterns of initiation and cessation of SUP across WA ICUs, and to assess the added costs associated with inappropriate SUP therapy.<sup>14</sup> Previous studies have recognised this as a problem, and we provide data from multiple sites and explore the economic impact with a cost analysis.<sup>9,14,15</sup>

## Methods

Our study took place at five adult ICUs in WA: two tertiary, two metropolitan and one regional. Together, these units represent most of the public ICUs in WA at the time of the

## ABSTRACT

**Objective:** To describe current patterns in initiation and cessation of proton pump inhibitors (PPIs) for stress ulcer prophylaxis (SUP) in intensive care units, and to assess the costs associated with inappropriate (non-evidence-based) SUP.

**Design, setting and participants:** Retrospective observational study in five ICUs in Western Australia. We assessed the medical records of consecutive patients admitted to the ICUs between September 2013 and January 2015. Patients aged < 18 years were excluded.

**Results:** We included 531 patients in the study. Of the 184 patients in whom PPIs were initiated for SUP in the ICU, 90 (48.9%) were still taking the therapy at the time of discharge from hospital. A documented indication for ongoing therapy was present in only nine patients (10%). We assumed a 10-year life expectancy after ICU discharge and that most patients continued taking a PPI, and calculated an additional cost of \$180.20 per patient admitted to the ICU. This was based only on unnecessary PPI costs (ignoring costs of managing additional adverse events). The direct cumulative annual cost to the WA health system of PPIs continued unnecessarily for patients at discharge from hospital is estimated to be \$250 800 for each year they continue to receive them.

**Conclusion:** A substantial proportion of patients prescribed SUP in the ICU continue receiving this therapy at hospital discharge despite no clear indication. In addition to potential adverse clinical effects, this is associated with major direct and indirect cost implications.

Crit Care Resusc 2016; 18: 270-274

study. None of the units had a protocol or guideline directed specifically at the initiation and cessation of SUP at the time of the study. All units used paper-based records and did not have electronic prescribing or decision support.

Data were collected retrospectively using a standardised data extraction form for consecutive patients admitted to the ICU. This occurred at the first site in September 2013, as part of a quality improvement project, and was expanded to other sites in the subsequent year between October 2014 and January 2015. We collected data at each site, reviewing

inpatient medical records and discharge summaries, until a target number was reached. Patients younger than 18 years were excluded.

Data collected included patient demographic information, lengths of stay, pre-hospital use of acid suppressive therapy, prescribing patterns, enteral feeding, mortality, complications of significant upper gastrointestinal bleeding (requiring blood transfusion or gastroscopy), pneumonia (defined by initiation of antibiotics for pneumonia after > 48 hours in hospital), and infection with *C. difficile* (confirmed by toxin polymerase chain reaction test or positive stool culture).

Risk factors for stress ulcer bleeding were classified according to current literature, with the major risk factors being mechanical ventilation > 48 hours, coagulopathy (defined as international normalised ratio > 1.5 or platelet count < 50 000/ $\mu$ L), head injury (defined as Glasgow coma scale score < 11), spinal injury, severe burns (defined as burns to > 30% of the skin), or gastrointestinal bleeding within the past 12 months. Minor risk factors were liver failure (defined as two or more of: bilirubin level > 150 IU/L, aspartate transaminase level > 500 IU/L or encephalopathy), renal failure (defined as creatinine level > 250  $\mu$ mol/L or oliguria < 500 mL/24 hours), solid organ transplant (heart, lung, liver or kidney), septic shock (defined as hypotension despite fluid resuscitation) and high-dose steroids (defined as > 200 mg hydrocortisone/day or > 50 mg prednisolone/day).<sup>4</sup>

If a patient was discharged from hospital with new acid suppressive therapy, we recorded the indication (upper gastrointestinal bleed, steroid use or other documented indication) as documented in inpatient notes or discharge summaries. For the purposes of our study, chronic PPI use was considered an acceptable indication for ongoing acid suppressive therapy. All study sites prescribed the PPI pantoprazole for SUP.

Our cost calculations for the total financial implications of SUP overuse across WA were based on estimations from Australia-wide data from 2013–14, which suggested that there were 124 290 ICU patients over the year. We assumed this was evenly distributed over the population, and that there were about 13 912 patients in WA.<sup>16</sup> Using our data and the previously described New Zealand data (in which 71% of ICU patients kept taking PPIs long term), we estimated the number of patients receiving PPIs after discharge (and not discontinuing them in the immediate subsequent period).<sup>17</sup>

As the sites all used pantoprazole, we assumed that it was the most likely PPI used in this patient group. The Dispensed Price for Maximum Quantity (DPMQ) for pantoprazole was \$13.91, covering 30 days of treatment. This was the price

for dispensing the maximum quantity of a product under a given prescribing rule, and reflected the actual cost of the medicine (including patient cost and government subsidy).

We calculated the financial implications of patients being discharged with an inappropriate PPI prescription, based on the estimated number of patients and the DPMQ. We then calculated the cumulative costs, based on the life expectancy of the patients. Using the work of Williams and colleagues, we assumed a conservative mean life expectancy of 10 years.<sup>18</sup> We then extrapolated these data across Australia to calculate the financial implications of unnecessary PPI usage in a year.

We obtained ethics or quality improvement approval for all study sites.

We performed descriptive statistical analyses and characterise raw data as means or medians with interquartile ranges (IQRs). We compiled data in Excel 2013 (Microsoft) and analysed it using Stata, version 12 (StataCorp).

## Results

We analysed a total of 531 patients across all the sites. Figure 1 shows the flow of patients through the study. Of patients prescribed a PPI for SUP in the ICU (after excluding inpatient deaths), 48.9% (90/184) continued taking this medication on discharge from hospital, with 90% (81/90) of them having no documented indication for continued SUP. Of patients prescribed SUP, 25.9% (54/212) had no clear indication for it, with no major risk factors for developing gastrointestinal bleeding.

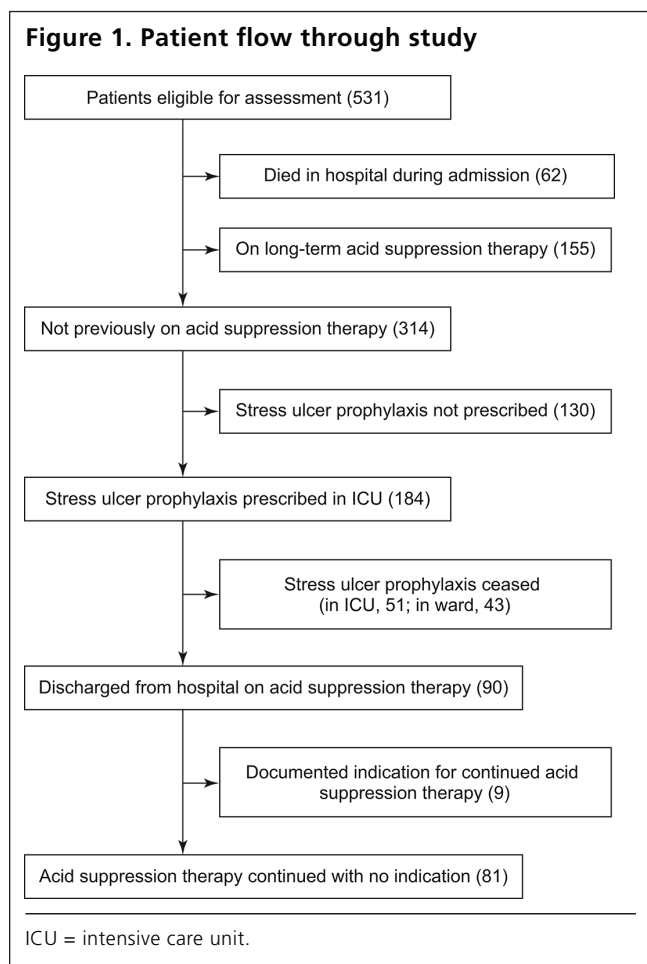
Table 1 shows the pattern of SUP prescribing, by risk factors, admission types and sites. Most patients with risk factors for stress ulcers were appropriately prescribed SUP (77% of patients with one or more major risk factors).

Enteral feeding occurred in 80.2% of patients. There was no difference in SUP prescription in patients receiving enteral feeding ( $P = 0.79$ ).

## Complications associated with SUP

Presumed new upper gastrointestinal bleeding occurred in two patients (excluding admissions for gastrointestinal bleeding) who both started receiving SUP with a PPI on admission. Both patients had a blood transfusion, receiving two units of packed red blood cells each. Neither patient underwent gastroscopy.

Of the potential complications from SUP, *C. difficile*-related disease occurred in 10 patients, all of whom received SUP (three were taking acid suppression therapy before admission), and hospital-acquired pneumonia occurred in 15 patients, 12 of whom received SUP (two were taking acid suppression therapy before admission).



### Costs

The ICU patient data we reported suggest that PPI use at discharge is about 15%, meaning an estimated 2087 patients across WA are discharged with PPIs each year. After accounting for patients who may have discontinued using PPIs, this means that 1482 patients continued to receive PPIs after discharge (2087 patients  $\times$  0.71 [71% of ICU patients kept taking PPIs long term]).

We estimate the cost of these 1482 patients continuing to receive PPIs at about \$250 811 (1482  $\times$  \$13.91  $\times$  365/30) for each year that they continue to receive them. The cumulative cost is \$250 811 multiplied by the number of previous cohorts still receiving SUP. If we assume that these patients receive PPIs for 10 years (which is conservative, based on current knowledge of life expectancy after ICU discharge), the cost is \$250 811 multiplied by each of the previous cohorts that are less than 10 years post-discharge. This amounts to \$2.508 million, and equates to an additional \$180.20 per patient admitted to the ICU. Extrapolating these data across Australia, using the 124 290 ICU admissions in the 2013–14 reporting period, the cost of unnecessary PPI use is estimated as \$22.4 million/year (124 290  $\times$  0.15  $\times$  0.71  $\times$  \$13.91  $\times$  365/30  $\times$  10).

**Table 1. Stress ulcer prophylaxis (SUP) prescribing and patient demographic data**

Prescribing variable	Not receiving SUP at admission		Receiving long-term SUP (n = 170)
	Received SUP (n = 212)	Did not receive SUP (n = 149)	
Major risk factors, n (%)			
$\geq 2$	26 (12.3%)	4 (2.7%)	19 (11.2%)
1	143 (67.4%)	42 (28.2%)	80 (47.1%)
Minor risk factors, n (%)			
$\geq 2$	4 (1.9%)	0	10 (5.9%)
1	44 (20.8%)	26 (17.4%)	54 (31.8%)
No risk factors, n (%)	43 (20.3%)	67 (45.0%)	61 (35.9%)
Admission type, n (%)			
Medical	120 (56.6%)	102 (68.5%)	104 (61.2%)
Surgical (emergency)	41 (19.3%)	20 (13.4%)	24 (14.1%)
Surgical (elective)	30 (14.2%)	26 (17.4%)	29 (17.1%)
Cardiothoracic	21 (9.9%)	1 (0.7%)	13 (7.6%)
ICU site, n (%)			
Tertiary	136 (64.2%)	26 (17.4%)	91 (53.5%)
Metropolitan	57 (26.9%)	73 (49.0%)	69 (40.6%)
Regional	19 (9.0%)	50 (33.6%)	10 (5.9%)
Demographic variable			
Median age, years (IQR)	60 (42–71)	–	–
Men, n (%)	301 (56.7%)	–	–

ICU = intensive care unit. IQR = interquartile range.

### Discussion

For patients who survived to hospital discharge, 44% of those who started taking SUP were discharged from hospital with a PPI with no documented indication. This is consistent with local and international data showing a high frequency of inappropriate continuation of acid-suppressing medications.<sup>9,10,14</sup> Recent Australian and New Zealand data from a survey and a registry-based feasibility study showed high prescribing rates overall, with a trend toward routine prescribing and some variability in the choice of agent. This reflects the current uncertainty about risks and benefits of SUP.<sup>19,20</sup> It is likely that a significant proportion of these patients would remain taking a PPI long term, as shown by a study from Grant and colleagues that found that 71% of patients deemed inappropriately discharged with a PPI prescription were still receiving the PPI at 6 months after discharge.<sup>14,17,21</sup> The opportunity to wean off or discontinue medications at discharge from the ICU, and then from hospital, is often not taken.<sup>9,10,22,23</sup>

Our study also reflects the wider problem of inappropriate PPI use across different patient populations. Our results show a high frequency of SUP use within the ICUs we audited. Although 77% had an appropriate indication for prescribing, this meant that almost one-quarter did not. This is consistent with international and Australian data which show an increasing use of SUP in the ICU.<sup>14,15</sup>

The ubiquitous use of PPIs in hospital and in the community for indications that are not evidence-based may perpetuate unnecessary continuation of PPIs after ICU discharge. Prescribers may presume that subsequent appropriate cessation of the SUP will occur, or they may under-recognise the well established risks from PPIs because of their limited immediate side effects, widespread use and high prescribing rates.<sup>7,24</sup> In Australia, the use of PPIs has increased substantially since their introduction. In 2014, the PPI esomeprazole was the second most prescribed drug (7 134 970 prescriptions) and the third most costly (at more than \$250 million).<sup>25</sup> This is shown by the high numbers of patients already receiving PPIs before their admission to the ICU (32%).

Our cost estimations are likely to be conservative, for several reasons. First, the price of the PPI is based on the DPMQ for pantoprazole, which is the cheapest commonly used alternative for patients in this setting. Second, our estimate does not account for costs accrued to the patient and the Medicare Benefits Schedule for extra visits to their primary care practitioner for ongoing prescriptions. Third, in addition to the cost of the PPI itself, there is also the economic cost of side effects and adverse events such as pneumonia and *C. difficile* disease. The importance of appreciating the cost of these adverse events was highlighted in a recent review of SUP economics. Costs of adverse events must be kept in mind, particularly when prescribing for patients at low risk of stress ulcers.<sup>26</sup>

Our study has several limitations. The first is that it reflects the practice of WA ICUs, but other units may use a different agent for SUP or may have stronger enforcement of an SUP policy. Nonetheless, the sites involved represented most of the ICU beds in the state and included different sized ICUs. Second, we had data from two different time frames, but there were no changes to unit policies or prescribing methods over our data collection period. Third, we conducted our analysis on a limited number of patients, and by sampling consecutive patients we may have inadvertently captured a non-standard patient population. Also, our cost analysis was limited by our need to make an assumption about the duration of PPI use after ICU discharge. Finally, we assumed that most patients (71%) continued using a PPI for 10 years, but we note that individual durations of use can be very different.

Our results have implications in and out of the ICU setting. Despite evidence to the contrary, ICU clinicians currently continue to prescribe SUP to patients in the ICU

who are low risk and unlikely to benefit. This has negative clinical and economic sequelae, particularly if the SUP is inadvertently continued.<sup>26-28</sup> The high level of inappropriate continuation of SUP makes a case for measures to improve prescribing and discontinuation of SUP. For example, patients who reach goal enteral feeding may be suitable for earlier discontinuation of SUP.<sup>20</sup> Other measures could include prescribing guidelines and education, or the use of an ICU pharmacist to stop prophylactic medications at discharge from the ICU. This has been shown to improve the appropriateness of SUP use in inpatients and to decrease inappropriate prescribing of SUP on discharge.<sup>29-34</sup>

Looked at outside the ICU setting, our results highlight a mechanism and a contributing factor to increasing medication burden, costs and polypharmacy. Improved awareness and understanding of this may help ameliorate the perpetuation of inappropriate medication use in inpatients and outpatients and support the trend towards reducing prescribing.<sup>35</sup>

## Conclusion

A substantial proportion of patients prescribed SUP in the ICU continue taking this therapy at hospital discharge, despite no clear indication. This has potential adverse clinical effects and cost implications.

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## Competing interests

None declared.

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