Intensive Care Med (2017) 43:1132–1134
DOI 10.1007/s00134-017-4733-0

WHAT'S NEW IN INTENSIVE CARE

What's new with stress ulcer prophylaxis in the ICU?

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What is known?

Critically ill patients are at risk of stress-related mucosal erosions [1]. These are typically superficial and asymptomatic but may progress to ulceration and overt and clinically important gastrointestinal (GI) bleeding, a serious condition associated with increased morbidity and mortality [2]. The reported incidence of GI bleeding varies between 2 and 5% [3, 4], probably because of heterogeneous populations, varying definitions of GI bleeding, and difficulties in diagnosing stress ulcers [3, 4]. Importantly, stress ulcerations have been identified as the sole source of GI bleeding by endoscopy in fewer than 50% of patients with GI bleeding [5]. A number of risk factors for stress ulcer-related bleedings have been suggested, including mechanical ventilation, coagulopathy, acute kidney injury, hepatic failure, and disease severity [2–4, 6]. A protective effect of enteral nutrition has been proposed [1], however this has not been confirmed in subsequent studies [6].

In critically ill patients with risk of GI bleeding, use of stress ulcer prophylaxis (SUP) is recommended [7]. Accordingly, SUP is widely used in intensive care units (ICU) [3]. The most frequently prescribed SUP agents are proton-pump inhibitors (PPIs) and histamine-2-receptor antagonists (H2RAs) [3]. It seems that PPIs are preferred and more efficient in preventing GI bleeding events than H2RAs [8]. However, in the latest systematic review comparing SUP with placebo or no treatment in general ICU patients, the quantity and quality of evidence supporting use of SUP was low, with no firm evidence for benefit or harm [6].

Importantly, accumulating evidence suggests that use of PPIs may increase the risk of nosocomial pneumonia, *Clostridium difficile* infections (CDIs) and cardiovascular events [4, 9]. Consequently, the current situation is one of clinical equipoise—the balance between benefits and harms of SUP is unknown [6].

What is new?

Recent observational studies have added to the knowledge about the potential harms of SUP. A retrospective American observational study ($n = 18{,}134$) reported an 1.5% incidence of CDI in general ICU patients with an ICU stay of more than 3 days, with no greater risk in PPI users than in non-PPI users [10]. Concordantly, a systematic review found a 2% incidence of CDI in the ICU [11]. Importantly, CDI was associated with increased mortality and prolonged length of stay [11].

The potential harm of PPI has also received attention outside the ICU. A Danish nationwide cohort study of 244,679 individuals undergoing gastroscopy found increased risk of first-time stroke in PPI users, compared with non-users [12]. As acid suppressants are inappropriately continued in a large proportion of patients after ICU discharge and even after hospital discharge [13], the potential risks and costs associated with SUP may not be confined to the ICU.

A recent exploratory randomized clinical trial (RCT) on PPI vs. placebo—the POP-UP trial—assessed the feasibility of conducting a large RCT on intravenous PPI vs. placebo in mechanically ventilated critically ill patients anticipated to receive enteral nutrition. No episodes of clinically important GI bleeding were identified among the 214 patients included, and the rates of hospital-acquired pneumonia and CDI were comparable between the treatment and placebo groups. Because this was a feasibility trial, no firm evidence on the balance between patient-important benefits and harms of prophylactic pantoprazole administration could be inferred [14]. The authors concluded that it was possible to administer SUP

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promptly after commencing mechanical ventilation, and that a large multicenter trial assessing the safety of SUP is needed [14]. A small Taiwanese single-center RCT assessed oral daily lansoprazole (via nasogastric tube) vs. no prophylaxis in 120 patients being weaned from the ventilator. No statistically significant differences in the reported outcome measures were found [15]. Limitations of this trial include lack of blinding, use of oral PPI with unknown absorption, the single-center design, and the high risk of type 1 and 2 errors due to the very limited sample size.

The recently published Surviving Sepsis Campaign 2016 guideline issues a strong recommendation—based on low-quality evidence—in favor of use of SUP in high-risk ICU patients [7]. This is surprising and unexpected, first due to the lack of firm evidence for benefit or harm of SUP (clinical equipoise), and second because a strong recommendation implies that "the desirable effects of an intervention clearly outweigh the undesirable effects", whereas low quality of evidence implies that "further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate" [16].

What is coming?

A number of large phase-III trials are under way [17, 18]. The ongoing European "Stress Ulcer Prophylaxis in the Intensive Care Unit" (SUP-ICU) trial is an international blinded, multicenter, investigator-initiated RCT of PPI (pantoprazole) versus placebo in acutely admitted ICU patients with risk factors for GI bleeding ($n = 3350$) [17]. This trial has just passed the half-way mark and is expected to complete inclusion late in 2017.

The ongoing "Proton pump inhibitors vs. histamine-2 rEceptor blockers for ulcer Prophylaxis Therapy in the Intensive Care unit" (PEPTIC) trial in New Zealand and Australia is a cluster-randomized cross-over trial comparing PPI to H2RA in around 40,000 patients using hospital-registry-based data [Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG): study number 1415-01]. A subsequent RCT comparing either PPI or H2RA to placebo is planned Table 1.

The Canadian "Re-Evaluating the Inhibition of Stress Erosions: Gastrointestinal Bleeding in ICU" (REVISE) trial, a feasibility trial assessing the efficacy and safety of pantoprazole vs. placebo in mechanically ventilated patients in the ICU, has been completed but not yet published [18].

The results of these three RCTs and subsequently updated meta-analyses are expected to provide important data on the balance between benefits and harms of SUP in ICU patients.

What is needed?

The balance between benefits and harms of SUP is unknown. On the one hand it may very well be that SUP reduces the risk of GI bleeding; on the other hand, however, SUP may increase the risk of nosocomial infections and other serious adverse events.

Table 1 Recent clinical trials on use of stress ulcer prophylaxis in the intensive care unit

Trial acronym	Trial number	Country	Estimated Sample size	Design	Population	Intervention	Comparator	Primary outcome(s)	Status
PEPTIC	1415-01 (ANZICS CTG study number)	Australia New Zealand	40,000	Cluster-randomized cross-over trial	Adults	PPI	H2RA	Stress-related upper GI bleeding, CDI, and episodes of mechanical ventilation lasting more than 10 days	Ongoing
PIC-UP	NCT02929563	Canada	120	RCT (feasibility)	Children	PPI	Placebo	Feasibility outcomes[a]	Ongoing
REVISE [18]	NCT02290327	Canada Australia Saudi Arabia	91	RCT (feasibility)	Adults	PPI	Placebo	Feasibility outcomes[b]	Completed
SUP-ICU [17]	NCT02467621	Europe	3350	RCT	Adults	PPI	Placebo	90-day mortality	Ongoing

Sources: clinicaltrials.gov (advanced search: "ulcer prophylaxis + intensive care," design: interventional), accessed January 26, 2017 and http://www.anzics.com.au/pages/CTG/current-research.aspx, accessed January 30, 2017

SUP-ICU Stress Ulcer Prophylaxis in the Intensive Care Unit, *REVISE* Re-Evaluating the Inhibition of Stress Erosions: Gastrointestinal Bleeding in ICU, *PEPTIC* Proton pump inhibitors vs. histamine-2 rEceptor blockers for ulcer Prophylaxis Therapy in the Intensive Care unit, *PIC-UP* Pediatric Intensive Care Ulcer Prophylaxis pilot trial, *RCT* Randomised clinical trial, *PPI* Proton pump inhibitor, *H2RA* Histamine-2-receptor antagonist, *ANZICS CTG*: Australian and New Zealand Intensive Care Society Clinical Trials Group

[a] Effective screening, timely enrollment, participant accrual, and protocol adherence

[b] Consent rate, recruitment rate, and protocol adherence

While awaiting the results of the ongoing phase-III RCTs, we need to consider whether additional large, methodologically sound RCTs and systematic reviews of SUP are warranted. If SUP proves to be superior to placebo (net benefit), the preferred SUP agent also needs to be established.

As critical illness is not limited to ICU patients, assessment of the benefits and harms of SUP in a wider perspective than exclusively the ICU setting is needed.

Conclusion

Given the widespread use of SUP and the lack of firm evidence for benefit or harm, we believe it is essential to re-assess the use of SUP in ICU patients. Ongoing and future research on SUP is expected to provide important data on the balance between benefits and harms of SUP in the ICU population. Routine administration of SUP to ICU patients is not justified by current evidence.

Compliance with ethical standards

Conflicts of interest

The authors are members of the Steering Committee of the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) trial. The authors declare no other conflicts of interest.

Received: 3 February 2017 Accepted: 16 February 2017
Published online: 25 February 2017

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