Stress ulcer prophylaxis in critical illness: a Canadian survey

Traitement prophylactique de l'ulcère de stress en cas de maladie grave: un sondage canadien

Melissa Shears, BSc · Waleed Alhazzani, MBBS · John C. Marshall, MD · John Muscedere, MD · Richard Hall, MD · Shane W. English, MD · Peter M. Dodek, MD · François Lauzier, MD · Salmaan Kanji, BSc, PharmD · Mark Duffett, MSc, RPh · Jeffrey Barletta, PharmD · Mohammed Alshahrani, MD · Yaseen Arabi, MD · Adam Deane, MBBS, PhD · Deborah J. Cook, MD

Received: 14 January 2016 / Revised: 18 January 2016 / Accepted: 4 February 2016 / Published online: 24 February 2016
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Abstract

Purpose Stress ulcer prophylaxis (SUP) using histamine-2-receptor antagonists has been a standard of care in intensive care units (ICUs) for four decades. Proton pump inhibitors (PPIs) are increasingly used despite apparently lower background rates of gastrointestinal bleeding and growing concerns about PPI-associated complications. Our objective was to understand the views and prescribing habits amongst Canadian physicians regarding SUP in the ICU and to gauge interest in a future randomized-controlled trial (RCT).

Methods We created a short self-administered survey about SUP for critically ill adults, evaluated its clinical

sensibility, and pilot tested the instrument. We surveyed all physician members of the Canadian Critical Care Trials Group (CCCTG) by e-mail and sent reminders three and five weeks later.

Results We received 94 of 111 (85%) surveys from the validated respondent pool between May and June, 2015. Respondents reported use of SUP most commonly in patients 1) receiving invasive mechanical ventilation (62, 66%), 2) expected to be ventilated for $\geq$ two days (25, 27%), or 3) receiving mechanical ventilation but nil per os (NPO) (20, 21%). Stress ulcer prophylaxis is discontinued when patients no longer receive mechanical ventilation (75%), no longer are NPO (22%), or are discharged from the ICU (19%). Stress ulcer prophylaxis involves PPIs in 68% of centres. Most respondents endorsed the need for a large rigorous RCT of PPI vs placebo to understand the risks and benefits of this practice.

For the Canadian Critical Care Trials Group.

Electronic supplementary material The online version of this article (doi:10.1007/s12630-016-0612-3) contains supplementary material, which is available to authorized users.

M. Shears, BSc
Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada

W. Alhazzani, MBBS
Departments of Medicine, Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, ON, Canada

J. C. Marshall, MD
Department of Surgery, Interdepartmental Division of Critical Care, University of Toronto, Toronto, ON, Canada

J. Muscedere, MD
Department of Critical Care Medicine, Queen's University, Kingston, ON, Canada

R. Hall, MD
Departments of Anesthesia and Critical Care Medicine, Dalhousie University, Halifax, NS, Canada

S. W. English, MD
Department of Medicine, University of Ottawa, Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

P. M. Dodek, MD
Division of Critical Care Medicine and Center for Health Evaluation and Outcome Sciences, St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada

F. Lauzier, MD
Departments of Medicine, Anesthesiology & Critical Care, Population Health and Optimal Health Practice Research Unit, CHU de Québec Research Center, Université Laval, Quebec City, QC, Canada

S. Kanji, BSc, PharmD
Department of Pharmacy, The Ottawa Hospital, Ottawa, ON, Canada

Conclusions *Stress ulcer prophylaxis is reportedly used primarily for the duration of mechanical ventilation. The CCCTG physicians believe that a placebo-controlled RCT is needed to evaluate the effectiveness and safety of contemporary SUP with PPIs.*

Résumé

Objectif *Depuis quarante ans, les antagonistes des récepteurs 2 de l'histamine constituent la norme de soins dans les unités de soins intensifs (USI) pour le traitement prophylactique de l'ulcère de stress. Les inhibiteurs de la pompe à protons (IPP) sont de plus en plus employés malgré des taux naturels apparemment plus bas de saignements gastro-intestinaux et des inquiétudes croissantes quant aux complications associées aux IPP. Notre objectif était de comprendre les opinions et les habitudes de prescription des médecins canadiens concernant le traitement prophylactique de l'ulcère de stress à l'USI et de sonder leur intérêt pour une étude randomisée contrôlée (ERC) future.*

Méthode *Nous avons créé un bref questionnaire auto-administré concernant le traitement prophylactique de l'ulcère de stress chez l'adulte gravement malade, évalué sa sensibilité clinique et effectué un test pilote de notre instrument. Nous avons envoyé le sondage par courriel à tous les médecins membres du Groupe canadien de recherche en soins intensifs (CCCTG), puis avons renvoyé des rappels trois et cinq semaines plus tard.*

Résultats *Entre mai et juin 2015, nous avons reçu 94 des 111 (85 %) questionnaires du groupe de répondants validé en retour. Les répondants ont rapporté avoir recours au traitement prophylactique de l'ulcère de stress le plus fréquemment chez les patients suivants : 1) ceux recevant une ventilation mécanique effractive (62, 66 %); 2) ceux dont la ventilation devait durer $\geq$ deux jours (25, 27 %); ou 3) ceux recevant une ventilation mécanique mais rien*

par voie orale (nil per os – NPO) (20, 21 %). Les médecins interrompent le traitement prophylactique de l'ulcère de stress lorsque les patients ne reçoivent plus de ventilation mécanique (75%), ne sont plus NPO (22%), ou reçoivent leur congé de l'USI (19%). Le traitement prophylactique de l'ulcère de stress comporte des IPP dans 68 % des centres. La plupart des répondants sont d'accord avec la nécessité d'une ERC d'envergure et rigoureuse examinant les IPP vs un placebo pour comprendre les risques et les avantages de cette pratique.

Conclusion *Selon nos sources, le traitement prophylactique de l'ulcère de stress est principalement utilisé pour la durée de la ventilation mécanique. Les médecins du CCCTG estiment qu'une ERC contrôlée par placebo est nécessaire pour évaluer l'efficacité et l'innocuité du traitement prophylactique de l'ulcère de stress par des IPP.*

Stress ulcer-related gastrointestinal (GI) bleeding results from superficial ulcers in the stomach or duodenum in critically ill patients. Stress ulcer prophylaxis (SUP) to prevent upper GI bleeding has been a standard of care in the intensive care unit (ICU) for almost four decades.¹

In a 1999 survey of physician members of the Society of Critical Care Medicine (SCCM), most commonly perceived risk factors for SUP were burns (91%), shock (90%), and sepsis (88%).² In a 1999 survey of the Pharmacy and Pharmacology Section of the SCCM, respondents stated that medications for SUP are used in > 90% of patients admitted to the ICU.³ A subsequent survey of members of the SCCM in 2004 indicated that 29% of physicians initiate SUP in all ICU patients regardless of bleeding risk.⁴ Respiratory failure was stated as the most frequent reason to use SUP (69%), followed by shock/hypotension (50%), sepsis (39%), and head injury/neurological insult (35%).

S. Kanji, BSc, PharmD
Department of Clinical Epidemiology, The Ottawa Hospital
Research Institute, Ottawa, ON, Canada

M. Duffett, MSc, RPh
Department of Pediatrics, McMaster University, Hamilton, ON,
Canada

J. Barletta, PharmD
Department of Pharmacy Practice, Midwestern University,
College of Pharmacy-Glendale, Glendale, AZ, USA

M. Alshahrani, MD
Department of Emergency and Critical Care, King Fahad
Hospital of the University of Dammam, Khobar, Saudi Arabia

Y. Arabi, MD
Department of Intensive Care, King Saud bin Abdulaziz
University for Health Sciences, Riyadh, Saudi Arabia

A. Deane, MBBS, PhD
Department of Intensive Care, University of Adelaide, Adelaide,
Australia

D. J. Cook, MD (✉)
Departments of Medicine, Clinical Epidemiology &
Biostatistics, McMaster University, Health Sciences Center,
Room 2C11, 1200 Main Street West, Hamilton, ON L8N 3Z5,
Canada
e-mail: debcook@mcmaster.ca

Previous self-administered surveys suggested that histamine-2-receptor antagonists (H2RAs) were the most commonly prescribed agents.²⁻⁴ In 1999, Lam *et al.* conducted a survey in which respondents specified H2RAs as the dominant drug class (67%).² In 1999, Erstad reported that 77% of respondents cited H2RAs as the preferred medication for SUP.³ Similarly, in 2004, Daley reported H2RAs to be the first-line SUP agents (64%).⁴ In a self-administered survey conducted in the UK in 2007, 90% of respondents reported having an SUP protocol in their institution, and 81% of respondents stated that SUP was considered in all patients who were admitted to their ICU.⁵ For standard SUP, H2RAs were used most frequently, whereas use of proton pump inhibitors (PPIs) was more common in higher risk patients.

Recent studies have suggested a growing use of PPIs for SUP. In 2014, a survey of prescriber perceptions in the United States showed that PPIs and H2RAs were the most frequently chosen SUP agents (40% and 50% of prescribers, respectively).⁶ In a survey of Australian and New Zealand intensivists in 2014, respondents found that 84% of patients with and 53% of patients without mechanical ventilation received SUP during their ICU admission.⁷ Half of the respondents indicated that they preferred PPIs to H2RAs. Observational studies also show increasing use of PPIs. In 2014, Barletta *et al.* conducted a point prevalence study involving 58 ICUs in the United States and Canada which documented that PPIs were the most commonly used agents (70%).⁸ MacLaren *et al.* recently performed a retrospective observational study of 35,512 adult patients who received mechanical ventilation for ≥ 24 hr and were administered SUP. Their study results showed that 62% of patients received PPIs and 38% received H2RAs.⁹ In a recent international survey, PPIs were identified as the most common agent (66%) for SUP.¹⁰

Despite their widespread use, questions are emerging about whether SUP is still indicated. These questions are based on whether SUP is effective and whether it increases the risk of other complications in the ICU setting. Surveys of Canadian practices are lacking on this topic. The objective of this survey (SURMISE: Survey of Medications for the Inhibition of Stress Erosions) was to understand the views and prescribing habits amongst Canadian intensivists regarding SUP in the ICU and to gauge their interest in a future randomized-controlled trial (RCT) on this topic.

Methods

Ethics

The Hamilton Integrated Research Ethics Board approved the study. Survey responses were de-identified by the

McMaster University Methods Centre, thus anonymizing the data.

Instrument development

We generated a short survey instrument using rigorous survey development and testing methods.¹¹ Items were chosen based on literature review, e-mail, and telephone correspondence among investigators representing physicians and pharmacists from four countries, as well as consensus discussion. Our overall goals for survey composition were simplicity and brevity. The self-administered instrument (Appendix, available as Electronic Supplementary Material) consisted of 15 items that focused on four domains: respondent and ICU characteristics, current stated SUP practice, views about the risk of current medications used for SUP, and interest in a future trial. Questions were configured as yes/no, “select all that apply”, and free text.

Instrument testing

We conducted both pilot testing and clinical sensibility assessments of the survey. For the clinical sensibility assessment, we invited 15 colleagues with methodologic and clinical expertise to evaluate the comprehensiveness, clarity, and face validity of our instrument on a scale of 1-5.. Results of the clinical sensibility testing using mean scores on the five-point scale suggested that the instrument had content validity (4.9), face validity (4.7), discriminability (4.3), and clarity (4.8). In addition, the instrument was evaluated as having minimal omissions (4.6) and redundancies (4.9). Subsequently, a convenience sample of five members of the Canadian Critical Care Trials Group (CCCTG) pilot tested the instrument, and minor modifications were then made to the text.

Instrument administration

Following CCCTG approval, we directed this survey to all currently practicing physician members who care for critically ill adult patients. In May 2015, we sent an e-mail with an embedded link to the web-based survey on SurveyGizmo (Boulder, CO, USA) along with instructions for completing the survey. No incentives were offered. Two standardized reminders followed at three and five weeks, respectively. The link to the questionnaire was closed three weeks after the final reminder e-mail.

Statistical analysis

We used descriptive statistics for reporting. Data are presented as mean [standard deviation (SD)]. Absolute

counts and proportions are also presented as appropriate. We report results by individual response and, for some responses, by centre.

Results

Thirty-one of 142 initial contacts were no longer CCCTG members, no longer practiced, or the initial e-mail address was incorrect and an alternate could not be found. From the 111-person validated respondent pool, we received 94 completed surveys (85% response rate) from 25 academic centres in six provinces across Canada. Physicians were in practice for a mean (SD) of 15 (9) yr (Table 1). Forty-six percent of respondents stated that their ICU collects information on SUP for purposes of quality improvement and tracking the use of a bundle for prevention of ventilator-associated pneumonia (VAP).

Survey respondents reported using SUP most commonly in patients 1) receiving invasive mechanical ventilation (62, 66%), 2) expecting to receive invasive mechanical ventilation for $\geq$ two days (25, 27%), or 3) receiving invasive mechanical ventilation for any duration in conjunction with *nil per os* (NPO) (20, 21%) (not mutually exclusive categories; Fig. 1). When asked about agents used in clinical practice, 79 (84%) respondents reported prescribing H2RAs and 75 (83%) respondents reported prescribing PPIs (Table 2). The most common H2RA used was ranitidine (66, 83%), and the most common PPI used was pantoprazole (38, 51%). Respondents most frequently used the nasogastric or oral route for H2RAs (51, 65%) and PPIs (55, 73%). In 20 (80%) centres, stress ulcer prophylaxis was most commonly prescribed using a standardized order set.

Table 1 Characteristics of physician survey respondents

Years in critical care practice, mean (SD)	14.6 (8.8)
Number of beds in the ICUs of respondents, mean (SD)	25.2 (10.1)
ICU patients cared for by respondents, <i>n</i> (%) [*]	
Medical	90 (95.7)
Surgical	90 (95.7)
Neurological	62 (66.0)
Trauma	54 (57.5)
Cardiac surgery	34 (36.2)
Burns	31 (33.0)
Other	7 (7.5)

This table shows the practice profiles of 94 physician survey respondents

^{*} Categories are not mutually exclusive. ICU = intensive care unit

When aggregating responses from the 25 centres regarding use of SUP agents, PPIs are used in 5 (20%) centres and H2RAs are used in 8 (32%) centres. Both PPIs and H2RAs are used in almost half of the centres represented in this survey (12, 48%). Therefore, when analyzing results by centre rather than by respondent, 17 (68%) centres incorporate PPIs into current SUP practice.

Individuals reported that, when used, SUP was discontinued most frequently when mechanically ventilation is withdrawn (71, 76%) or NPO is no longer needed (21, 22%) (Table 3). Some respondents reported maintaining SUP until a patient is discharged from the ICU (18, 19%).

In planning a future RCT comparing PPI with placebo, physicians were asked if certain populations should not receive a placebo. Respondents expressed the most concern about administering a placebo to patients receiving a H2RA or PPI at home for clear medical indications (60, 64%), and those with a severe coagulopathy (43, 46%), severe thrombocytopenia (35, 37%), burns (33, 35%), or some other conditions (Fig. 2). Physicians estimated that the rate of clinically important upper GI bleeding is currently 3% in patients who receive invasive mechanical ventilation for at least 48 hr.

Overall, 79 (85%) CCCTG physicians endorsed the need for a large rigorous RCT of PPI vs placebo to inform practice. Reasons stated for a trial of this design included uncertainty whether SUP confers the same benefit today as was apparent in the past, acknowledgement that bleeding rates seem lower now than in the past, and the potential for increased harm from SUP agents, including VAP and *Clostridium difficile* infection.

Discussion

In this national survey, we found that physicians from 80% of participating ICUs prescribe SUP. Respondents confirmed the widespread use of SUP in all patients receiving invasive mechanical ventilation in the ICU. Eighty-five percent of physicians endorsed the need to revisit SUP in a new RCT.

In prior surveys, the agent of choice for SUP was a H2RA, ranging from 64–77%.^{2–4,8} In our survey, 64% of physicians stated that they prescribe either H2RAs or PPIs for SUP, while 20% prescribe only H2RAs and 16% prescribe only PPIs. When responses were aggregated by centre, almost half of ICUs used either a H2RA or PPI for SUP. These results show a growing use of PPIs in Canadian critical care practice, and they reflect prescribing trends documented elsewhere. Other recent research shows a growing use of PPIs as the primary SUP agent, ranging from 39–70%.^{6,9,10,12} This may reflect

Fig. 1 Respondents' reported indications for stress ulcer prophylaxis. This figure shows the clinical indications for SUP as reported by respondents. Totals exceed 100% as participants could select more

than one indication. ICU = intensive care unit; IMV = invasive mechanical ventilation; NIMV = noninvasive mechanical ventilation; NPO = *nil per os*; SUP = stress ulcer prophylaxis

Table 2 Reported use of SUP medications in practice

SUP drug class, <i>n</i> (%)	
H2RA	19 (20)
PPI	15 (16)
Either	60 (64)
H2RA agents (<i>n</i> =79)	
Ranitidine	66 (84)
Famotidine	13 (17)
H2RA route of administration (<i>n</i> =78)	
<i>iv</i>	27 (35)
NG/PO	51 (65)
PPI agents (<i>n</i> =75)	
Pantoprazole	38 (51)
Lansoprazole	25 (33)
Esomeprazole	10 (13)
Omeprazole	2 (3)
PPI route of administration (<i>n</i> =75)	
<i>iv</i>	20 (27)
NG/PO	55 (73)

This table shows the agents that physicians reported for SUP. Respondents were requested to "choose all that apply" for SUP agent type and to "choose one of the above" for route of administration. H2RA = histamine-2-receptor antagonists; NG = nasogastric; PO = *per os*; PPI = proton pump inhibitors; SUP = stress ulcer prophylaxis

perceived superiority of PPIs as indicated in a recent systematic review and meta-analysis. The study at issue showed that PPIs were associated with a 60% relative risk reduction in clinically important stress ulcer-related GI bleeding when compared with H2RAs.¹³

In this survey, the agents of choice for SUP were ranitidine in the H2RA class and pantoprazole in the PPI class. Regardless of the agent used, the respondents cited enteral as the preferred method of administration, which is similar to survey findings among Australian prescribers.⁶ In contrast, results of the observational study in Canada and the United States by Barletta *et al.* revealed that many

Table 3 Respondents' reported usual reasons for discontinuing SUP

SUP discontinued, <i>n</i> (%)*	
No longer receives mechanical ventilation	71 (76)
No longer NPO	21 (22)
Discharged from ICU	18 (19)
Not stopped at ICU discharge	0 (0)
Other (variable practice, decreased risk factors for bleeding)	15 (16)

This table shows when physicians reported discontinuing SUP. Respondents were requested to "choose all that apply"

* Categories are not mutually exclusive. ICU = intensive care unit; NPO = *nil per os*; SUP = stress ulcer prophylaxis

patients received intravenous therapy despite having enteral access or receiving other enteral medications.¹²

The guidelines of the Surviving Sepsis Campaign recommend SUP for patients with severe sepsis who have bleeding risk factors as well as a periodic evaluation to determine the continued need for prophylaxis.¹⁴ Our survey respondents reported administering SUP primarily until patients no longer received mechanical ventilation, no longer required *nil per os*, or were discharged from the ICU. In practice, prior multicentre observational studies have shown that most critically ill patients routinely receive SUP while receiving mechanical ventilation, and in many cases, SUP is discontinued upon tracheal extubation.¹⁵ That being said, almost 20% of survey respondents indicated that they do not discontinue SUP until a patient is discharged from the ICU. Documentation of an Australian chart review revealed that, among 190 patients prescribed SUP in the ICU, 63% of patients continued receiving their SUP on the ward without any obvious indication, and 39% of patients' SUP medications were inappropriately continued on discharge from hospital.¹⁶ These findings are congruent with those of the recent survey by Krag *et al.* in which 22% of respondents

Fig. 2 Contraindications to patients receiving placebo in a randomized-controlled trial. This figure shows perceived contraindications to patients receiving placebo in a future randomized-controlled trial to evaluate SUP. The totals exceed

100% as respondents could select more than one indication. NPO = *nil per os*; H2RA = histamine-2-receptor antagonist; PPI = proton pump inhibitor; SUP = stress ulcer prophylaxis

discontinue SUP upon discharge from the ICU, and only 13% discontinue SUP after tracheal extubation.¹⁰

The prevailing impression of many physicians is that the clinically important GI bleeding rate has decreased over time in the ICU, whether due to prevalent acid suppression in the community and in the hospital setting or improvements in resuscitation and the use of enteral nutrition. Over 20 years ago, only 2% of critically ill patients had clinically important bleeding while receiving SUP.¹⁵ In our survey, we asked respondents to estimate the current rate of clinically important upper GI bleeding in patients receiving invasive mechanical ventilation for at least 48 hr, and they predicted a rate of approximately 3%. A recent international study published after the conduct of this survey documented a major bleeding rate of 2.6%.¹⁷

Most randomized-controlled trials evaluating SUP were conducted many years ago, rendering the state of knowledge on this topic outdated. Nevertheless, SUP is a common practice, as supported by several randomized trials and the guidelines of the Surviving Sepsis Campaign, although SUP does not appear to influence the risk of death in ICU patients.^{13,14,18} Regarding interest in re-evaluating SUP in a RCT comparing placebo with PPI, 85% of physicians agreed that a trial is necessary due to their concerns about lack of benefit and possible harmful effects of acid suppression. In Australia, the pilot randomized POPUP (Pantoprazole Or Placebo for Stress Ulcer Prophylaxis) trial of 214 patients was recently completed on this topic (trial registration no., ACTRN126130 00807752).¹⁹ The Scandinavian Critical Care Trials Group is also conducting a large randomized trial on this topic evaluating the effect of PPI on mortality (trial registration no., NCT02467621).²⁰

The Canadian Critical Care Trials Group is undertaking a small pilot trial called REVISE (REVisiting the Inhibition of Stress Erosions) (trial registration no., NCT02290327).²¹ In this trial, patients receiving a PPI or H2RA at home are eligible for randomization unless they have a clear indication to continue (e.g., recent GI bleed). Randomization is stratified based on pre-ICU PPI or H2RA exposure so the consent rate and effects of PPIs can be evaluated in those with and without prior acid suppression.

In this survey, we asked respondents about their concern for sub-populations of ICU patients who may not receive SUP. Respondents were most concerned about patients receiving a PPI or H2RA at home “if it was medically indicated” (64% of physicians). A few of our survey respondents were concerned about patients receiving a PPI or H2RA “regardless of the reason” (11% of physicians), which reflects the view that many patients in the community are receiving these drugs for an unclear and potentially unsuitable reason. Based on observational studies and pilot trial data,^{12,17,19} we estimate that approximately 40% of patients eligible for the REVISE Pilot will have been taking a PPI or H2RA at home. If the REVISE Pilot Trial suggests that bedside clinicians and substitute decision makers are uncomfortable randomizing such patients, this may be considered in the design of a future large RCT.

Strengths of this study include the 85% response rate, which was higher than many of the previous self-administered questionnaires.²⁻⁶ This is a novel survey of stated SUP practices and prescribing habits in Canada. The protocol and analysis underwent peer review and pilot and clinical sensibility testing. The limitations of our study reflect how surveys record perceived prescribing and do not evaluate actual prescribing. These results reflect the views and practice of physician members of the CCCTG who work largely in academic institutions and whose views about the state of the science and interest in research participation may differ from other physicians.

Conclusions

In summary, in this national survey of physicians, we found that most ICUs prescribe SUP primarily for patients receiving invasive mechanical ventilation and use standardized physician order sets for efficiency. Concerns remain about whether SUP is still effective and whether SUP confers increased risk of infectious complications. Most centres use PPIs as one of their SUP agents. Canadian physicians agree with the call for a trial to evaluate the

impact of PPIs vs no SUP on clinically important outcomes in today's critical care practice. The trial would require patients receiving as well as not receiving these drugs as outpatients or inpatients.²²

Author contributions: *Deborah J. Cook* devised the study and led its development and testing. *Waleed Alhazzani* helped devise the study and participated in its design. *Melissa Shears* designed the survey, led its administration, performed the statistical analysis, and drafted the manuscript. *John C. Marshall, John Muscedere, Richard Hall, Shane W. English, Peter M. Dodek, François Lauzier, Salmaan Kanji, Mark Duffett, Jeffrey Barletta, Mohammed Alshahrani, and Yaseen Arabi* helped develop the survey. *Mark Duffett, Waleed Alhazzani, and Deborah J. Cook* helped draft the manuscript. *Melissa Shears, Mark Duffett, Waleed Alhazzani, and Deborah J. Cook* interpreted the survey results. *Mark Duffett* helped with the survey testing and set up the database. *John C. Marshall, John Muscedere, Richard Hall, Shane W. English, Peter M. Dodek, François Lauzier, Salmaan Kanji, Mark Duffett, Jeffrey Barletta, Mohammed Alshahrani, Yaseen Arabi, and Adam Deane* helped interpret the survey results and critique the manuscript.

Acknowledgements We thank the CCCTG members for their help with piloting the survey instrument and McMaster University's ACCADEMY (Academy of Critical Care: Development, Evaluation, and Methodology) members for their help with the clinical sensibility testing. We appreciate the contributions from all the physicians of the CCCTG who responded to this survey.

Conflicts of interest None declared.

Disclosures François Lauzier is a recipient of a Research Career Award from the Fonds de recherche du Québec-Santé. Deborah Cook holds a Chair of the Canadian Institutes of Health Research.

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