Clinical Investigation

Current Opinions on Stress-Related Mucosal Disease Prevention in Canadian Pediatric Intensive Care Units

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OBJECTIVE: To describe current opinions about stress-related mucosal disease (SRMD) prevention in Canadian pediatric intensive care units (PICUs).

METHODS: A 22-question survey covering several aspects of SRMD was sent to all identified PICU attendings in Canada.

RESULTS: Sixty-eight percent of identified attendings completed the questionnaire. Thirty-eight percent were based in Quebec, 31% in Alberta, and 31% from other provinces. Most attendings (78%) had worked in a PICU for 6 years or more. When asked about risk factors for prescribing SRMD prevention drugs (more than 1 answer was accepted), the most popular answers were prior history of gastric ulceration/bleeding (33 respondents), coagulopathy (28 respondents), and major neurologic insult (18 respondents). Almost half of the attendings (48%) mentioned that they prescribe SRMD prophylaxis directly upon PICU admission to more than 25% of their patients. Forty-nine percent of respondents subjectively estimated that clinically significant upper gastrointestinal bleeding (UGIB; defined as UGIB associated with either hypotension, transfusion within 24 hours of the event, or death) occurred in less than 1% of their patients. Fifty-seven respondents (93%) used ranitidine as first-line therapy (average dose: 4.1 mg/kg/day, mainly intravenously). As second-line therapy, 32 attendings (52%) used pantoprazole and 13 (21%) used omeprazole.

CONCLUSIONS: Despite the paucity of guidelines on SRMD prevention and the low reported incidence of clinically significant UGIB, SRMD prevention is frequently used in Canadian PICUs. Ranitidine is the first-line drug used by most attendings.

INDEX TERMS: gastrointestinal agents, pediatric intensive care units, pediatrics, prevention, ulcer

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INTRODUCTION

Stress-related mucosal disease (SRMD) is a comorbidity often seen in pediatric intensive care units (PICUs). Depending on the definition used, its prevalence in critically ill children ranges from 6% to 10%, with nearly 1% of cases being referred to as clinically significant upper gastrointestinal bleeding (UGIB), defined as UGIB associated with hypotension, need for transfusion in the first 24 hours after diagnosis, or death.[1-3] Mortality in critically ill adult patients with SRMD has been reported to be 5 times higher than for those without it. Stress-related mucosal disease is known to have significant clinical and economic impacts. Gauvin et al[4] found that SRMD in pediatric patients is associated with lower hemoglobin concentration, a higher rate of blood transfusions, prolonged mechanical ventilation, and prolonged PICU hospitalization, the latter factors known to be positively correlated with increased morbidity and mortality. They also showed that hospitalization fees were approximately 4 times higher for these patients.

Multiple aspects of SRMD have been addressed, albeit more so in adult than pediatric literature. Risk factors (respiratory failure, coagulopathy, and fasting, among others) have been studied in both populations.[2,5] Different prophylactic medications have also been studied. Surface agents, H2-receptor antagonists, and proton pump inhibitors (PPIs) are among the most studied.[6] While there are no widely accepted clinical guidelines currently available to help

clinicians with SRMD prevention in children, there are meta-analyses and guidelines addressing adult prophylaxis.[5,7–11] The majority of these documents recommend that H2-receptor antagonists be used to prevent stress ulcer in vulnerable adult ICU patients. Despite these guidelines, SRMD prophylaxis is not uniformly prescribed in adult ICUs. Daley et al[12] studied SRMD prevention among American intensivists working in adult ICUs. Most participants believed that SRMD prevention was necessary for their patients, even though clinically significant UGIB was infrequent. The choice of intervention was diverse among these respondents. Most (64%) preferred H2-receptor antagonists but there was an increasing trend of PPI use despite evidence suggesting a relationship between PPI use and nosocomial ventilator-associated pneumonia.[13] Currently, there are no data on the pediatric use of SRMD prevention in Canada. The purpose of this study was to assess current opinions among Canadian PICU attendings regarding SRMD prevention, risk factor assessment, and drug prescription.

MATERIALS AND METHODS

The Centre Hospitalier Universitaire de Québec Ethics Board (C11-02-160) approved this descriptive study on SRMD prevention in Canadian PICUs. The study population was staff physicians working in 1 of the 16 Canadian PICUs. To identify our population, an email was sent to each Department of Pediatrics and PICU director in Canada, requesting contact information for their current staff. Available PICU Web sites were also browsed for similar information. The sole exclusion criterion was being already involved in the current study as a co-investigator.

An English survey was adapted from a previously published questionnaire.[12] It was reviewed and critiqued by 2 pediatric intensive care fellows who were not otherwise involved in this study. Twenty-two questions were included in the final version. Twenty of them were multiple-choice questions. The questionnaire took about 10 minutes to complete. The addressed topics were the definition of SRMD, risk factors for SRMD prophylaxis, and choice of therapeutic intervention. Anonymous demographic data were also included (primary workplace, PICU characteristics, professional experience, and training). The questionnaire is available in the Appendix.

As per recommendations to increase survey participation,[14] the questionnaire, along with information about the study, was sent to the 90 identified attendings twice within a 1-month interval (April 29, 2011, and May 30, 2011). Respondents received questionnaires via both electronic and conventional mailing systems. The electronic version of the questionnaire could be completed and submitted via a Web browser. A blinded third person collated and anonymized the data before sending it to the investigators. After receiving completed questionnaires, data were compiled by using Excel 2007 (Microsoft, Redmond, WA). Confidentiality was ensured during the entire process by using non-identified mailing material.

RESULTS

Demographic Data

Of the 90 identified attendings eligible for our survey, 61 (68%) answered the questionnaire, 8 (13%) responding electronically. Demographic data are shown in Table 1. Forty-eight respondents (78%) had worked in PICU for 6 years or more. Most of the surveyed attendings had been trained and were working in Quebec or Ontario. Respondents represented 14 different institutions spread throughout Canada. The institution with the greatest number of respondents represented 20% of the overall providers surveyed.

SRMD Definition and Epidemiology

Forty-nine percent of respondents subjectively estimated that clinically significant UGIB (defined in the questionnaire as UGIB associated with either hypotension, transfusion within 24 hours of the event, or death) occurred in less than 1% of their patients (Table 2). Respondents most frequently defined failure of their SRMD prevention as blood in gastric aspirate/nasogastric tube (34%), spontaneously externalized visible bleeding (28%), and documented ulcers or gastritis per esophagogastroduodenoscopy (21%).

SRMD Prevention

Respondents were questioned regarding their SRMD prophylaxis assessment. As one of the main goals of this study, respondents were asked about the risk factors used to influence their decision on whether or not to prescribe SRMD

Table 1. Demographic Data of the Respondents

Demographic Question	No. of Respondents (%)*
Residency training (number of attendings)	
Atlantic provinces (4)	2 (3%)
Quebec (24)	16 (26%)
Ontario (27)	12 (20%)
Prairie provinces (29)	12 (20%)
British Columbia (6)	2 (3%)
Others	16 (26%)
PICU training (number of attendings)	
Atlantic provinces (4)	0 (0%)
Quebec (24)	18 (30%)
Ontario (27)	22 (36%)
Prairie provinces (29)	5 (8%)
British Columbia (6)	1 (2%)
Others	15 (25%)
Workplace (number of attendings)	
Atlantic provinces (4)	2 (3%)
Quebec (24)	23 (38%)
Ontario (27)	13 (21%)
Prairie provinces (29)	19 (31%)
British Columbia (6)	4 (7%)
PICU experience	
<3 yr	10 (16%)
3-5 yr	3 (5%)
6-12 yr	16 (26%)
>12 yr	32 (52%)
Characteristics of PICU	
Neonatal intensive care unit within PICU	19 (31%)
Medical/surgical excluding postoperative care of cardiac surgery	25 (41%)
Medical/surgical including postoperative care of cardiac surgery	36 (59%)
Postoperative care of cardiac surgery alone	0 (0%)

PICU, pediatric intensive care unit

* Percentage data based on total number of respondents (n=61).

prophylaxis. To this end, they could choose up to 3 of 15 risk factors commonly described in the literature, including "other." Thirty-three respondents (54%) chose prior history of gastric ulceration/bleeding; 28 (46%), coagulopathy; and 18 (30%), major neurologic insults (Figure 1). Almost half of the attendings (48%) prescribed SRMD prophylaxis directly on PICU admission to more than 25% of their patients. The main reasons for discontinuing SRMD prevention were tolerating enteral feedings for 66% of attendings, resolution of all risk factors for 13%, and clinically improved status for 11% (Figure 2). Twenty-one percent of respondents monitored SRMD prevention efficacy, mostly with gastric pH measurement.

Choice of Medication

Ninety-three percent of respondents used ranitidine as first-line therapy (26% because of efficacy, 23% because of cost, and 16% because of ease of administration). As second-line therapy,

Table 2. Estimated Epidemiology of Clinically Significant UGIB in Canadian PICU

Proportion of Patients	Estimated Occurrence
Less than 1%	49%
1%-3%	38%
4%-7%	7%
More than 7%	7%

UGIB, upper gastrointestinal bleeding; PICU, pediatric intensive care unit

PPIs were the most commonly used drugs; 52% of attendings used pantoprazole and 21%, omeprazole. First-line therapy was prescribed via intravenous route for 48 respondents (79%), with 5 using a continuous infusion. Mean administered dose of ranitidine was 4.1 mg/kg/day (ranging from 1 to 7 mg/kg/day). Ranitidine was mostly prescribed by using intermittent dosing: 5 respondents (9%) in 2 divided doses, 34 (60%) in 3 divided doses, and 9 (16%) in 4 divided doses. Seven percent of respondents reportedly had an SRMD prevention protocol in their PICU.

DISCUSSION

To our knowledge, this is the first study describing SRMD prevention among PICU attendings. Results from this study suggest that although SRMD prophylaxis is not prescribed to every patient in Canadian PICUs, it is a relatively common practice. These PICU attendings use several different factors to assess at-risk patients. Ranitidine was by far the most commonly prescribed drug; however, we believe there were no inciting factors favoring ranitidine over other H2-receptor antagonists, since there is no specific formulary for its use in Canada and SRMD prevention protocols were uncommonly used.

Canadian PICU attendings identified prior history of gastric ulceration/bleeding, coagulopathy, and major neurologic insult as major risk factors requiring SRMD prophylaxis. Previously, Lacroix et al[1] prospectively studied patients admitted in a Canadian PICU in order to determine the frequency of UGIB (defined as an episode of hematemesis or if any amount of blood was seen in drainage from a nasogastric

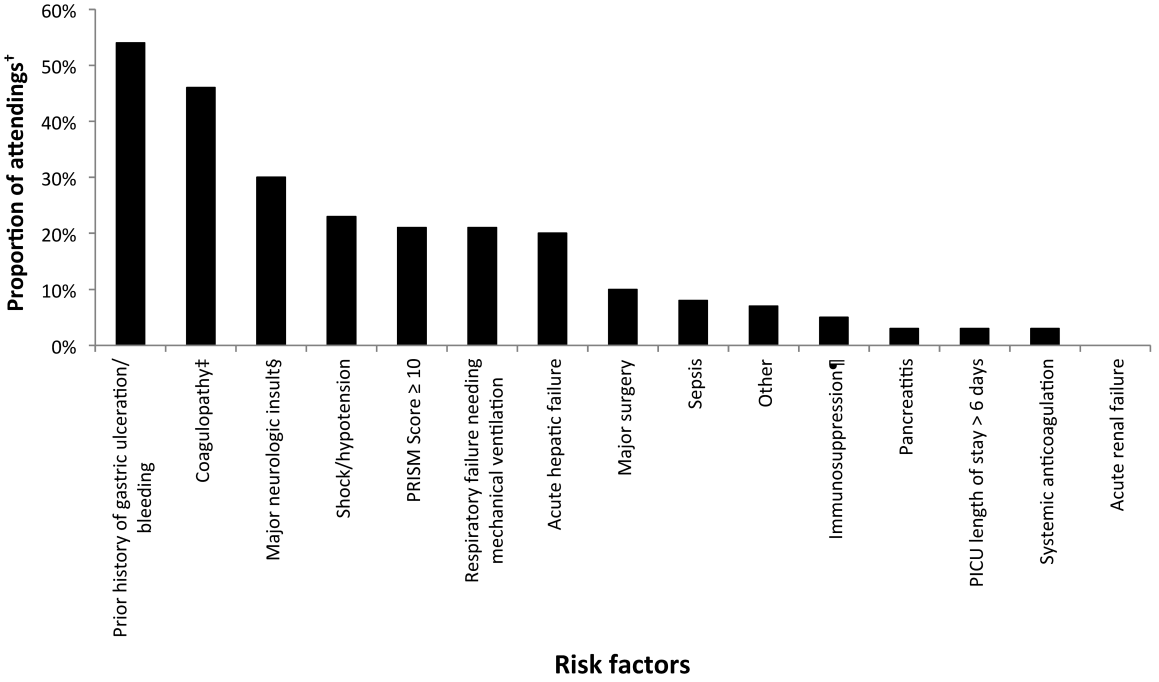

Figure 1. Risk factors* used to prescribe stress-related mucosal disease prevention in pediatric intensive care units.
* Respondents could choose 3 different answers among the list provided in the questionnaire.
† Percentage data based on total number of respondents (n=61).
‡ Platelet count <50,000/mm^3 and/or international normalized ratio >1.5 and/or partial thromboplastin time >2 times normal.
§ Glasgow Coma Score <8.
¶ Congenital or acquired (including secondary to medication such as corticosteroids).

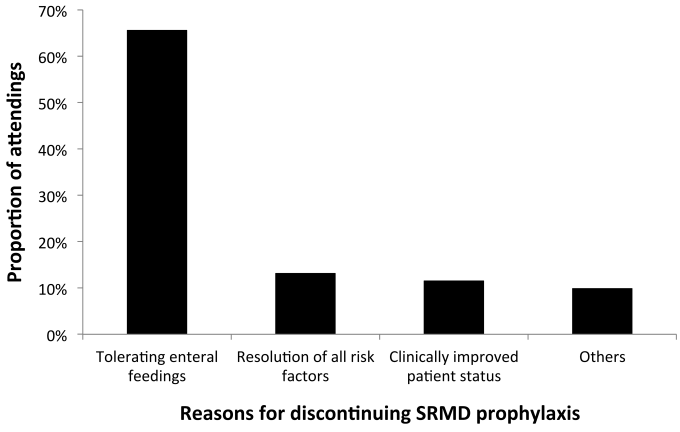

Figure 2. Reasons for discontinuing SRMD prophylaxis.
SMRD, stress-related mucosal disease.

tube). They found 4 major risk factors for UGIB in critically ill pediatric patients: high Pediatric Risk of Mortality (PRISM) score,[15] pneumonia, coagulopathy, and multiple trauma (including severe head trauma). PRISM is a scoring system used to predict survival in ICU patients, using neurologic findings, vital signs, and laboratory results collected during the first 24 hours after ICU admission. In another survey study,[12] risk factors identified by ICU attendings were respiratory failure (69%), shock/hypotension (49%), and sepsis (39%). In a mixed medical/surgical PICU population, Gauvin et al[4] identified that clinically significant UGIBs were more associated with coagulopathy, use of mechanical ventilation, and PRISM score ≥ 10. Factors considered for SRMD prophylaxis by Canadian PICU attendings in our study differ slightly from those reported risk factors, most likely because of the absence of clear guidelines about SRMD prevention in children, and the extrapolation of adult data. Because of the low incidence of this condition, studies addressing that aspect would be difficult to conduct.

Daley et al[12] surveyed a group of American intensive care attendings working with adult patients. Several differences between their results and those of the present study are of interest. Respondents of the study tended to initiate SRMD prevention therapy upon admission to a larger group of patients (94% of respondents initiated SRMD prevention therapy to at least 25% of their patients), compared with our respondents (48%). Guideline availability, increased data in adult patients, and differences in pathologies cared for could possibly explain this difference. In addition, American ICU attendings prescribed ranitidine to adults less often than the respondents of our study who care for children (22.7% vs. 93%). H2-receptor antagonists were also their most popular choice of drug (63.9%). Cost and ease of use of ranitidine could explain, at least in part, its popularity over PPI and surface agents in Canadian PICUs, as stated by our respondents.

Economic aspects of SRMD prophylaxis have to be considered. Gauvin et al[4] showed that hospitalization costs for pediatric patients with SRMD are significantly higher (about 4 times) than for those without this condition. In addition, in an adult care setting, a reported 3- to 4-fold increase in total hospitalization costs was described for 6 patients who had clinically significant bleeding (hemodynamic compromise or transfusion),[16] though those 6 patients were already receiving ranitidine prophylaxis. The mean medication cost for SRMD prevention in this study was US $24 to US $36 per patient per stay. The authors concluded that SRMD prophylaxis needs to be rationalized to limit expenses. The relatively low occurrence of SRMD in children, the ever-increasing medication and hospitalization costs for critical care patients, and the lack of centralized statistics about PICU hospitalizations in Canada make financial comparisons even more complex. We believe that cost-effectiveness analysis would be useful in determining the need for pediatric SRMD prevention guidelines.

Although this study has multiple strengths (e.g., the high response rate and the possibility to compare results with previously reported data), it also has its limitations. For instance, the Canadian perspective may not be applied to all settings, considering the intercountry variability in health care systems. The study design could also have introduced unintentional biases. Because of the survey format, respondents could have been influenced by answer lists or the multiple-choice format, which limits the number of possible answers for some questions. Because we mostly derived our answer choices from adult literature, it may not fully represent pediatric practice and may influence results. Recall bias is another potential confounder and our study was not designed to compare stated to actual

prescribing habits. Also, despite the minimal presence of formal SRMD prevention protocols within PICUs (7% of respondents), it is possible that local practice patterns within physician groups influence prescription habits. We were, however, statistically underpowered to examine that possible influence. Finally, we did not study SRMD prevention by PICU residents and fellows. Knowing that these workers are often involved in admission and follow-up prescriptions, it would have been interesting to investigate their knowledge and practice. Interestingly, previous studies[17] have shown that residents' prescriptions are often inaccurate for SRMD prophylaxis.

We conclude that it is a common practice and that ranitidine is the first-line drug used by most attendings despite the lack of clinical guidelines. Our study shows that the most important risk factors considered by our respondents before prescribing SRMD prevention are prior history of gastric ulceration/bleeding, coagulopathy, and major neurologic insult. Given the low occurrence of clinically significant UGIB in Canadian PICUs and the consensus toward ranitidine use among attendings, we suspect that further studies comparing H2-receptor antagonists with PPI in this population would be unlikely to yield clinically relevant results outside of the context of a randomized clinical trial.

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Abbreviations ICU, intensive care unit; PICU, pediatric intensive care unit; PPI, proton pump inhibitor; PRISM, Pediatric Risk of Mortality; SRMD, stress-related mucosal disease; UGIB, upper gastrointestinal bleeding

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SECTION 1 – SRMD PROPHYLAXIS

1.1 Which risk factors are most important to you when deciding to prescribe UGIB prophylaxis in the PICU (choose 1 to 3 different items)?

☐ Acute hepatic failure ☐ Acute renal failure ☐ Coagulopathy[a] ☐ Immunosuppression[b]
☐ Major neurologic insult[c] ☐ Major surgery ☐ Pancreatitis ☐ PICU length of stay > 6 days
☐ Prior history of gastric ulceration/bleeding ☐ PRISM Score ≥ 10
☐ Respiratory failure needing mechanical ventilation ☐ Sepsis ☐ Shock/hypotension
☐ Systemic anticoagulation ☐ Other

[a] platelet count <50,000/mm^{3}and/or international normalized ratio >1.5 and/or partial thromboplastin time >2 times normal; [b]congenital or acquired (including secondary to medication like corticosteroids); [c]Glasgow Coma Score <8

1.2 Approximately to what percentage of patients do you prescribe SRMD prophylaxis upon PICU admission?

☐ 0% ☐ 1-24% ☐ 25-50% ☐ 51-75% ☐ 76-99% ☐ 100%

1.3 What is your principal reason to discontinue SRMD prophylaxis?

☐ Tolerating enteral feedings ☐ Clinically improved patient status
☐ Transfer to a non-PICU setting ☐ Extubation ☐ Resolution of all risk factors
☐ Medication is not discontinued during the hospitalization ☐ Other

1.4 Do you monitor the efficacy of your SRMD's prophylaxis?

☐ Yes ☐ No

Appendix. Questionnaire.

1.4.1 If you answered yes to question 1.4, what kind of monitoring do you principally prescribe?

☐ Gastric pH measurement ☐ Blood search on NG aspirate and/or stool
☐ EGD ☐ CBC parameters ☐ Gastric tonometry ☐ Other

1.5 Is there a SMRD prophylaxis protocol in your PICU?

☐ Yes ☐ No

1.5.1 If you answered yes to question 1.5, since when is this protocol in place?

1.5.2 If you answered yes to question 1.5, which type of medication is included in the protocol?

☐ PPI ☐ H_2RA ☐ Gastric coating agent
☐ Combination of two or more molecules ☐ Other

SECTION 2 – MEDICATION

2.1 Which of these agents represent your choice for first-line therapy for SRMD prophylaxis in the PICU?

☐ Lansoprazole (Prevacid©) ☐ Omeprazole (Losec©) ☐ Pantoprazole (Pantoloc©)
☐ Ranitidine (Zantac©) ☐ Sucralfate (Sulcrate©) ☐ Other

2.2 What are the dosage, number of daily doses and administration route that you use principally for your first-line therapy medication?

_____ mg/kg/day divided in _____ doses using the ☐ IV or ☐ PO route

2.3 What is the main reason for your choice of first-line medication?

☐ Efficacy ☐ Side effects profile ☐ Ease of administration ☐ Cost
☐ Interaction profile ☐ Availability inside your hospital ☐ Protocol in the hospital ☐ Other

2.4 Which of these agents represent your choice for second-line (back-up) therapy for SRMD prophylaxis in the PICU (you can choose the same item as question 2.1)?

☐ Lansoprazole (Prevacid©) ☐ Omeprazole (Losec©) ☐ Pantoprazole (Pantoloc©)
☐ Ranitidine (Zantac©) ☐ Sucralfate (Sulcrate©) ☐ Other

Appendix. Questionnaire *(cont.)*.

2.5 What are the dosage, number of daily doses and administration route that you use principally for your second-line therapy medication?

_____ mg/kg/day divided in _____ doses using the ☐ IV or ☐ PO route

2.6 What is the main reason for your choice of second-line medication?

☐ Efficacy ☐ Side effects profile ☐ Ease of administration ☐ Cost
☐ Interaction profile ☐ Availability inside your hospital ☐ Protocol in the hospital ☐ Other

SECTION 3 – STRESS-RELATED MUCOSAL DISEASE

3.1 When do you consider SRMD prophylaxis has failed (choose one answer)?

☐ Blood in gastric aspirate/NG tube
☐ Documented ulcers or gastritis per EGD
☐ Spontaneously exteriorized visible bleeding (hematemesis, hematochezia, melena, rectorrhagia)
☐ Alteration of objective hemodynamic parameters (Hb/Hct, blood pressure, heart rate)
☐ Need for blood transfusion ☐ Other

3.2 What is the incidence of clinically significant UGIB[a] in your PICU (according to your impression)?

☐ <1% ☐ 1-3% ☐ 4-7% ☐ 8-10% ☐ >10% ☐ Unknown
[a]UGIB associated to hypotension, death or need for transfusion within 24 hours after an UGIB (Lacroix et al, 1992)

SECTION 4 – IDENTIFICATION

4.1 Which of these hospitals is your primary workplace?

☐ Alberta Children's Hospital ☐ B.C. Children's Hospital
☐ Children's Hospital, London Health Sciences Centre ☐ Children's Hospital of Eastern Ontario
☐ CHU Sainte-Justine ☐ CHUS ☐ CME-CHUL ☐ Hospital for Sick Children
☐ IWK Health Centre, Children's Site ☐ Janeway Children's Health & Rehabilitation Centre
☐ Kingston General Hospital ☐ McMaster Children's Hospital ☐ Montreal Children's Hospital
☐ Royal University Hospital ☐ Stollery Children's Hospital
☐ Thunder Bay Regional Health Sciences Centre ☐ Winnipeg Health Sciences Centre

Appendix. Questionnaire *(cont.)*.

4.2 Which of these answers best represents the type of patient in your PICU?

☐ Medical/chirurgical EXCLUDING post-operative care of cardiac surgery
☐ Post-operative care of cardiac surgery ALONE
☐ Medical/chirurgical INCLUDING post-operative care of cardiac surgery
☐ Other

4.3 Is there neonatal intensive care in the PICU you work in?

☐ Yes ☐ No

4.4 Where did you pursue your paediatrics residency program (select the location where you spent most of the time)?

☐ Alberta ☐ British Columbia ☐ Manitoba ☐ New Brunswick
☐ Newfoundland and Labrador ☐ Nova Scotia ☐ Ontario ☐ Prince Edward Island
☐ Quebec ☐ Saskatchewan ☐ United States of America ☐ Other

4.5 Where did you pursue your intensive care fellowship program (select the location where you spent most of the time)?

☐ Alberta ☐ British Columbia ☐ Manitoba ☐ New Brunswick
☐ Newfoundland and Labrador ☐ Nova Scotia ☐ Ontario ☐ Prince Edward Island
☐ Quebec ☐ Saskatchewan ☐ United States of America ☐ Other

4.6 How many years have you been working as an attending paediatric intensive care specialist?

☐ <3 ☐ 3-5 ☐ 6-12 ☐ >12

Appendix. Questionnaire *(cont.)*.