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BRIEF REPORT

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Evaluating the use of Drotrecogin alfa (activated) in adult severe sepsis: a Canadian multicenter observational study

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Abstract *Background:* The purpose of this study was to characterize the usage patterns and clinical outcomes of DAA in Ontario and Quebec over a 1-year period. *Methods:* All hospitals with DAA on formulary in Ontario and Quebec were invited to participate. Consecutive patients who received DAA from 1 March 2003 to 29 February 2004 were identified retrospectively. Demographic, treatment, and outcome variables were collected via chart review. Descriptive statistics on relevant variables were performed, along with logistic regression to determine relevant risk factors for survival and bleeding. *Results:* Thirty-seven sites participated with a total of 261 courses of DAA administered. The overall mortality rate was 45%; age (> 65 years), multiple organ system failure (> 3), and nosocomial source of sepsis were predictors of mortality, whereas early DAA administration (< 12 h) was associated with lower mortality. Serious bleeding events occurred in 10% of the patients. Only 1 case (0.4%) of fatal intracranial bleed was observed. Multiple organ system failure (≥ 4)and relative contraindications to DAA were predictors of bleeding events. *Interpretation:* Mortality and bleeding complications associated with the use of DAA were higher than that reported in randomized trials but similar to other usage database. This may be due to the higher severity of illness seen in this cohort of patients. Modifiable risks associated with mortality and bleeding, such as time to treatment, and knowledge of relative contraindications should be targets of further research and future educational efforts in order to optimize the risk-to-benefit ratio of DAA.

Keywords Drotrecogin alfa (activated) · Sepsis · Severe sepsis · Post-marketing surveillance · Drug utilization evaluation

Introduction

Sepsis syndromes are common among critically ill patients, are associated with significant morbidity and mortality, and represent significant cost to the health care system [1, 2]. Recombinant human activated protein C [drotrecogin alfa (activated), Xigris, DAA] is the first immune modifying agent shown to be effective in interrupting the sepsis cascade and reducing mortality when compared with placebo [3, 4]. Although the

therapeutic benefits of DAA were well described in the PROWESS trial, it is associated with a substantial acquisition cost and an associated risk of bleeding. Most Canadian institutions that have DAA on formulary have developed standardized protocols for use generally based on the inclusion/exclusion criteria from the PROWESS trial, the product monograph, and Canadian consensus guidelines [5].

Many Canadian institutions have mandated that drug-use evaluations of DAA be conducted to confirm appropriateness of utilization and safety; however, there are limitations to the generalizations that can be made regarding the safety and efficacy of this drug from single institutions. The purpose of this multi-center retrospective observational study was to describe the prescribing practices and clinical outcomes associated with DAA therapy across Ontario and Quebec in the first year following DAA availability in Canada.

Methods

Site participation

Sixty-nine acute care hospitals were identified as having DAA on formulary during the study period in Ontario and Quebec for adult patients with severe sepsis. The ICU pharmacists or pharmacy directors from each hospital were invited to participate. Of the 26 and 43 hospitals in Quebec and Ontario, respectively, 17 and 20 of them agreed to participate (Appendix I). Approval for the study was obtained from the local Research and Ethics Boards of each participating site.

Patient selection/data collection

Consecutive patients who received any duration of DAA during the first year of availability (1 March 2003 to 29 February 2004) were identified from pharmacy records by each site investigator. Medical records were reviewed for all patients identified and data collected pertained to patient demographics, treatment indications, severity of illness, contraindications to treatment, adjunctive sepsis modifying therapies, adverse events related to DAA therapy, outcomes, and disposition. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were only collected if originally calculated for consideration of DAA eligibility as per local protocol. Infections were considered community acquired unless the patient was admitted to a hospital for ≥ 72 h prior to developing signs of infection. Organ failures were limited to renal, cardiovascular, hematological, respiratory, and metabolic failures, and were defined as per the PROWESS trial [3]. Absolute and relative contraindications were consistent with the Canadian product monograph. Data were collected for concomitant sepsis therapies including low-dose corticosteroid replacement, antimicrobial therapy, glycemic control, and pharmacological thromboembolism prophylaxis. Appropriateness of antimicrobial therapy was assessed for patients with positive cultures and was considered appropriate if the offending organism was sensitive to the initial antimicrobial regimen and was administered within 24 h of diagnosis of severe sepsis (as defined by the onset of organ failure). A serious bleeding event was defined as intracranial hemorrhage, any bleeding event classified as serious by the primary treating physician (per progress notes), or any bleeding event requiring 3 units of packed red blood cells for 2 consecutive days (as per the PROWESS trial) [3].

Analysis

Patient demographics, treatment characteristics, and outcomes were described using measures of central tendency or proportions with measures of variance as appropriate. Demographic and treatment variables were compared between survivors and non-survivors and between those who experienced a major bleeding event and those who did not using a Student's *t*-test or Mann–Whitney U-test for continuous variables and chi-square tests for ordinal data. Variables found to be significantly different ($\alpha = 0.05$) were then modeled using forward multivariate logistic regression to determine predictors of mortality and major bleeding.

Results

The 37 participating hospitals represent 54% of eligible institutions and account for 727 ICU beds and 47,234 yearly ICU admissions (Table 1). Twenty-three (63%)

Table 1 Hospital demographics

Hospital participation (%)	Hospitals ($n = 37$)
Ontario	20 (54)
Quebec	17 (46)
Teaching hospital	23 (63)
Community hospital	14 (38)
Total ICU beds (%)	727
ICU admissions/year	47,234
Institutional guidelines present (%)	37 (100)
Pre-printed order	33 (89)
DAA allowed outside of ICU	6 (16)
DAA eligibility	
Organ failure	26 (70)
APACHE II score	3 (8)
Both	8 (22)
Prescribers	
ICU only	30 (81)
ICU and Emergency Department	3 (8)
ICU and Infectious Disease Department	4 (11)

of these hospitals are teaching institutions. Two hundred sixty-one patients received DAA during the study period (5.5 cases/1,000 ICU admissions). Between the provinces, the incidence was 8.7 and 3.3 cases/1,000 ICU admissions for Ontario and Quebec, respectively. The incidence by type of hospital was 5.0 and 7.1 cases/1,000 ICU admissions for teaching and community hospitals, respectively.

Most patients were admitted to the ICU with diagnoses of sepsis syndrome (53%) or respiratory failure (23%; Table 2). Respiratory and intra-abdominal infections were the most common sources of sepsis, with 72% being community acquired. The offending organisms were Gram-positive, Gram-negative, anaerobic, or fungal in 27, 21, 4, and 5% of cases, respectively, when single organisms were identified. In 8% of cases multiple organisms were identified, whereas 37% of infections were culture negative. The distribution of organ failure is described in Table 3. Most patients were admitted to the

Table 2 Patient demographics

Province (%)	All patients ($n = 261$)
Ontario	168 (64)
Quebec	93 (36)
Teaching hospital	186 (72)
Community hospital	75 (29)
Sex (% male)	133 (51)
Age (years)	56 ± 17
Weight (kg)	79 ± 23
Reason for ICU admission (%)	
Severe sepsis/septic shock	138 (53)
Respiratory failure/pneumonia	60 (23)
Thoracic or abdominal surgery	25 (10)
Acute abdomen	10 (4)
Cardiac surgery	6 (2)
Trauma	6 (2)
Meningitis	4 (2)
Other	12 (5)

Table 3 Infection characteristics and illness severity. *IQR* interquartile range

Source of sepsis (%)	All patients ($n = 261$)
Respiratory	106 (41)
Intra-abdominal	69 (26)
Genitourinary	27 (10)
Wound/soft tissue	22 (8)
Other	25 (10)
Source unknown	12 (5)
Source of infection (%)	
Community	187 (72)
Hospital	71 (27)
Missing	3 (1)
SIRS criteria (mean)	3.5 ± 0.5
APACHE ($n = 98$) (median, IQR)	31 (26,36)
Organ failure (mean)	3.4 ± 0.9
One organ failure	2 (1)
Two organ failures	51 (20)
Three organ failures	89 (35)
Four organ failures	90 (34)
Five organ failures	29 (11)
CVS failure	246 (94)
Renal failure	166 (64)
Respiratory failure	217 (83)
Hematological failure	92 (35)
Metabolic failure	159 (61)

Table 4 The DAA treatment characteristics and concomitant therapies. *LMWH* low molecular weight heparin

Time to treatment with DAA	All patients ($n = 261$)
< 12 h	93 (36)
12–24 h	104 (40)
24–48 h	41 (16)
> 48 h	21 (8)
Missing	2 (1)
Duration of infusion	
< 24 h	42 (16)
24–72 h	51 (20)
72–96 h	167 (64)
Missing	1 (0.4)
Low-dose steroid therapy	177 (68)
Appropriate antibiotic therapy	242 (93)
Glycemic control	
Insulin infusion	146 (56)
Subcutaneous insulin	27 (10)
None	88 (34)
DVT prophylaxis	
Unfractionated heparin	121 (46)
LMWH	1 (0.4)
No pharmacological prophylaxis	139 (53)
Need for dialysis (intermittent or continuous)	52 (20)

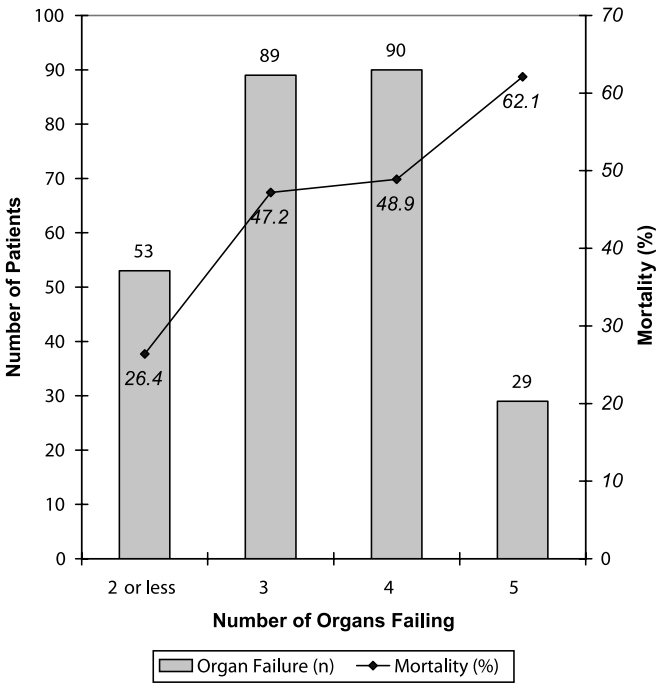

Fig. 1 Hospital mortality stratified by organ failure. Of those patients with ≤ 2 organ failures, two had single organ failure (both of whom survived) and 51 had two organs failing

Table 5 Mortality, morbidity and safety. *LOS* length of stay, *IQR* interquartile range

	All patients ($n = 261$)
ICU LOS (median, interquartile range)	11 (5, 20)
Hospital LOS (median, interquartile range)	19 (9, 37)
Disposition	
Died in hospital/ICU	118 (45)
Survived to hospital discharge	113 (44)
Transferred to other institution or long-term care	29 (11)
Missing	1 (0.4)
Vasopressor days (median, IQR)	3 (2, 7)
Ventilator days (median, IQR)	7 (3, 14)
Absolute contraindications	4 (2)
Relative contraindications	52 (20)
Therapeutic anticoagulation	7
Platelets < 30	6
INR > 3	5
Recent GI bleeding	4
Trauma	1
Recent thrombolytics	1
Recent oral anticoagulants	15
Recent ischemic stroke	1
Bleeding diathesis	1
Severe hepatic disease	3
Significant bleeding hazard	7
Pregnant	1
Severe bleeding	25 (10)
Bleeding during infusion	19
Bleeding after infusion	5
Missing	1

ICU from the Emergency Department (45%), whereas the rest came from the ward (30%) or a peripheral hospital (22%; 3%missing). The DAA treatment characteristics and concomitant sepsis therapies are described in Table 4.

The overall mortality rate was 45% (Fig. 1; Tables 5, 6) Logistic regression analysis revealed that age greater than 65 (OR = 3.4, 95% CI = 1.9–6.0, $p < 0.001$), having three or more organs failing (OR = 3.3, 95% CI = 1.6–7.0, $p = 0.002$) and having a nosocomial source of sepsis (OR = 2.2, 95% CI = 1.2–4.0, $p = 0.013$) were predictive of mortality and that early treatment with DAA within 12 h of diagnosis of severe sepsis (OR = 0.51, 95% CI = 0.28–0.92, $p = 0.024$) was associated with decreased mortality.

Twenty percent of treated patients had relative contraindications and 2% had absolute contraindications (therapeutic futility in all cases as identified by the site investigator based on retrospective review of chart documentation). Twenty-five patients (10%) experienced a serious adverse bleeding event, the majority of which (76%) occurred during the infusion (Tables 5, 7). Of these 25 bleeding episodes, 9 were gastrointestinal or intra-abdominal, 3 were intra-thoracic, one was intracranial, 2 were skin or soft tissue, 3 were genitourinary, 2 were "other," and 5 had no identified source. One patient died of an intra-cranial hemorrhage during the infusion. Logistic regression analysis demonstrated that having four or more failing organs (OR = 3.1, 95% CI = 1.2–7.8, $p = 0.016$) and having a relative contraindication to DAA therapy (OR = 2.7, 95% CI = 1.1–6.5, $p = 0.028$) were predictive of a serious adverse bleeding event.

Discussion

The ability to extrapolate the benefits of treatment from the clinical trial setting to the "real-life" setting is often logistically difficult. It appears that within the restrictions of the PROWESS trial the benefits of DAA outweighed the potential risks; however, given the extensive inclusion and exclusion criteria of the trial, one must assume that to achieve the same ratio in real life the same patient selection criteria must be applied. Strategies such as national consensus statements and institutional guidelines are useful in providing guidance to the ICU practitioner but cannot ensure that predictable efficacy and safety outcomes are realized through stringent patient selection; thus, post-marketing surveillance in the form of drug use evaluations is essential to periodically evaluate real-life outcomes and adherence to clinical practice guidelines for new therapies with potential for harm.

Table 6 Univariate analysis of mortality

Variable	Survivors ($n = 143$)	Non-survivors ($n = 118$)	p-value
Age ≥ 65 years[a]	33 of 143 (23)	57/118 (48)	< 0.001
No. of organs failing	3.2 ± 1	3.6 ± 0.9	0.001
≥ 3 organ failures[a]	104 of 143 (73)	104 of 118 (88)	0.002
Renal failure[a]	81 of 143 (57)	85 of 118 (72)	0.010
Serious bleeding[a]	8 of 143 (6)	17 of 118 (14)	0.015
Admit from ward[a]	32 of 143 (22)	47 of 118 (40)	0.002
Admit from ER[a]	76 of 143 (53)	41 of 118 (35)	0.003
Nosocomial infection[a]	26 of 141 (18)	45 of 117 (38)	< 0.001
Treatment within 12 h[a]	62 of 143 (43)	31 of 118 (26)	0.004
Treatment within 24 h[a]	115 of 143 (80)	82 of 118 (69)	0.041

Numbers in parentheses are percentages; [a] Variables selected for the multivariate logistic regression analysis

Table 7 Univariate analysis of severe bleeding

Variable	Major bleeding ($n = 25$)	No bleeding ($n = 235$)	p-value
No. of organs failing	3.9 ± 0.8	3.3 ± 0.9	0.002
≥ 3 organ failures	24 of 25 (96)	183 of 235 (78)	0.035
≥ 4 organ failures[a]	18 of 25 (72)	101 of 235 (43)	0.006
Metabolic failure	22 of 25 (88)	137 of 235 (58)	0.004
Relative contraindication[a]	10 of 25 (40)	42 of 235 (18)	0.009
CRRT	11 of 25 (44)	41 of 235 (17)	0.002

Numbers in parentheses are percentages; [a] Variables selected for the multivariate logistic regression analysis; CRRT = continuous renal replacement therapy

This multi-center, observational study evaluates DAA utilization in Ontario and Quebec and describes outcomes among treated patients. More than half of the target population was represented in this study from which 261 patients were identified as having received DAA during the 1-year study period, equating to 5.5 cases/1,000 ICU admissions. The drug acquisition cost alone represents more than $2,250,000 CAN during the study period taking into consideration that many patients did not complete the full 96-h course of treatment. All institutions had some form of institutional guidelines for prescription developed from either the Canadian consensus statement or the recommendations from the product monograph. Interestingly, only three hospitals used APACHE-II scoring as their sole severity of illness scoring tool to identify eligible candidates for DAA therapy.

The mortality rate in our study was higher that that described in both the PROWESS trial and the global Extended Evaluation of Recombinant Human Activated Protein C (ENHANCE) trial [3, 6]. A probable explanation for this observation is that our cohort had a greater severity of illness than those patients enrolled in either the PROWESS or ENHANCE studies based on the prevalence of organ failure at DAA initiation (Fig. 2) [3, 6]. Our results have been more consistent with other retrospective observational studies of DAA use. Preliminary results from the MERCURY study describe a hospital mortality rate of 42.3% from 287 patients treated with DAA over a 13.5-month period after FDA approval in five American academic centers where 67.1% of patients had three or more organs failing [7].

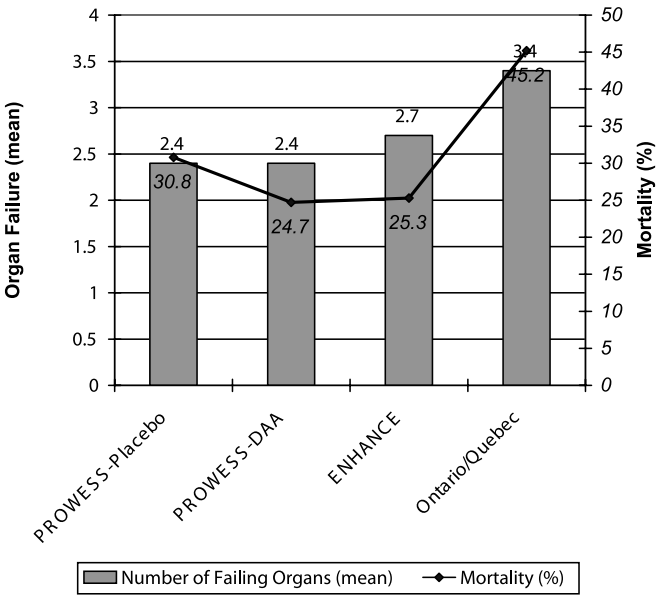

Fig. 2 Severity of illness and mortality compared between the present study, ENHANCE, and PROWESS. *DAA* Drotrecogin alfa (activated)

The multivariate analysis of mortality identified delays in treatment with DAA as a potentially modifiable predictor of mortality. Since the PROWESS study protocol required that patients enrolled have infusions of DAA or placebo initiated within 48 hours of meeting the diagnostic criteria for severe sepsis, all institutional guidelines from participating centers in this study allow a 48 hour window from diagnosis to treatment; however, a sub-group analysis of the ENHANCE study suggests that the magnitude of the absolute mortality benefit associated with DAA may be significantly greater if the infusion is started within 24 hours rather than after 24 hours (22.9 vs 27.4% absolute mortality, respectively; $p = 0.01$) [6]. A similar observation was noted in our study. In this case treatment within 12 hours was found to be an independent predictor of survival, further suggesting that earlier disease recognition and assessment for treatment eligibility may be important in maximizing the outcome benefit of DAA; however, transfer of patients from other institutions, which accounts for 22% of patients treated with DAA, is responsible for significant delays in recognition and assessment.

In this study 7.3% of patients had a serious bleeding event during the infusion of DAA and 1 patient (0.4%) died of an intracranial hemorrhage which was higher that that reported in the ENHANCE, PROWESS, and MERCURY studies (Fig. 3) [3, 6, 8]. The two independent predictors of having a severe adverse event related to bleeding identified in this study were severity of illness as measured by having four or more organs failing and having a relative contraindication. The high rate of bleeding observed in this study may be explained by the fact that 44% of patients had four or more organ failures and 20% of patients

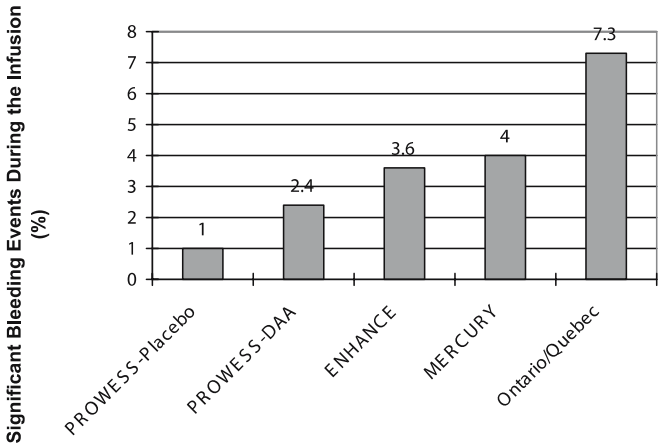

Fig. 3 Significant adverse bleeding events during the infusion: a comparison of PROWESS, ENHANCE, and this study. *DAA* Drotrecogin alfa (activated)

having a relative contraindication to DAA therapy, the latter being the obvious modifiable risk factor. Despite the level of participation in this study, it is still underpowered to adequately assess the risk benefit ratio for DAA therapy given these "real-life" estimates of benefit and risk; however, since the mortality rate among patients with serious adverse bleeding events was lower (32%) than the mean mortality rate of the entire group it is unlikely that adverse events contributed to the high mortality rate observed.

Retrospective studies such as this are not without limitations. The quality and completeness of data collected are dependent on the accuracy and comprehensiveness of documentation. We have attempted to address this issue by using standardized data collection tools and quantifying missing data, which represents $< 1\%$ of all data collected. Although this study represents more than half of the target population in Ontario and Quebec, it is still underpowered to adequately evaluate risk factors for adverse outcomes; therefore, only two variables identified in the univariate analysis of bleeding were included in the multivariable model. Finally, this study was not designed to evaluate the efficacy of DAA in the treatment of severe sepsis. Although outcomes are described and qualitatively compared with other published estimates, conclusions about efficacy cannot be drawn from quantitative comparisons between studies, as the populations studied are clearly different. There is, however, an opportunity to compare patient populations and hypothesize as to why outcome rates appear different.

This study describes the utilization of DAA for the treatment of severe sepsis in the first year of availability in Ontario and Quebec. Mortality rates and the incidence of serious adverse bleeding events were higher than expected from literature estimates. In light of more plausible reasons for the high mortality rate (i. e., patients with greater severity of illness) this study provides no reason to believe that the risks associated with DAA therapy outweigh the benefits although efforts aimed at earlier disease recognition, earlier assessment of treatment eligibility, and greater awareness of relative contraindications may still make the risk/benefit ratio more appealing.

Appendix 1: Participating hospitals and site investigators

Ontario:

G. Bunston, St. Mary's General Hospital, Kitchener; L. Burry, Mt. Sinai Hospital, Toronto; C. Cameron, Grand River Hospital, Kitchener-Waterloo; C. Chant, St. Michael's Hosptial, Toronto; H. Chase, Guelph General Hospital, Guelph; M. Duffet, Hamilton Health Sciences Corporation, Hamilton General Division, Henderson Hospital, Hamilton; N. Giovinazzo, Joseph Brant Memorial Hospital, Burlington; P. Grayhurst, Lakeridge Health Center, Oshawa; J. Kim, The Ottawa Hospital, General and Civic Campus', Ottawa; A. Kwan, The Scarborough Hospital, General Division and Grace Site, Scarborough; A. McMann, Sault Area Hospital, Sault Ste Marie; A. Mills, Trillium Health Center, Mississauga; P. Newman, Kingston General Hospital, Kingston; M. Schnalzer, South Lake Regional Hospital, Newmarket; C. Stumpo, Toronto East General Hospital, Toronto; S. Yamashita, Sunnybrook and Women's College Health Sciences Center, Toronto.

Quebec:

D-K. Awissi, Hôpital Maisonneuve-Rosemount, Montreal; S. Caron, Cité de la Santé de Laval, Laval; A. Dumas, Hôpital Laval, Sainte-Foy; C. Gravel, Centre Hospitalier Régional de Lanaudière, Joliette; F. Giguère, Réseau Santé Richelieu Yamaska, Saint-Hyacinthe; C. Manoukian, The Sir M.B. Davis-Jewish General Hospital, Montreal; G. Morneau, Centre Hospitalier d'Université du Québec, CHUL, l'Hôtel-Dieu de Québec and Hôpital Saint-François d'Assise, Sainte Foy and Quebec; M. Perreault, Royal Victoria Hospital and Montréal General Hospital of McGill University Health Center, Montreal; A. Rioux, Pavillon de l'Enfant Jésus-Centre Hospitalier Affilié Universitaire de Québec, Quebec; F. Tétrault, Centre Hospitalier de l'Université de Montréal (CHUM) – Hôpital Notre-Dame, Hôtel-Dieu de Montréal and Hôpital Sant-Luc, Montreal; V. Uon, Hôpital Charles LeMoyne, Greenfield Park; D. Williamson, Hôpital Sacré-Coeur de Montréal, Montreal.

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