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EVALUATING THE EFFICACY AND SAFETY OF UNFRACTIONATED HEPARIN IN PATIENTS DIAGNOSED WITH SEPSIS

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in Partial fulfillment of the requirements for the Masters of Science degree in Epidemiology

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ABSTRACT

Statement of the Problem: Unfractionated heparin (UFH) is an anticoagulant with anti-inflammatory properties. The efficacy and safety of UFH in severe sepsis or septic shock has yet to be evaluated in clinical trials.

Methods of Investigation: We performed a systematic review to evaluate the current evidence regarding the use of heparin in patients with sepsis. We then conducted a cross-sectional survey to evaluate the perceived utility and current use of anticoagulants in sepsis, to assess the degree of certainty regarding clinical benefits and harms of heparin, and to assess the willingness of physicians to consider future clinical trials of heparin.

Results: The pooled OR for mortality in 7 trials comparing heparin to any other intervention was 0.88 (95%CI 0.74 to 1.05, I^2 0%, n=2473). A large observational cohort study also showed a similar reduction in death associated with heparin (HR 0.85, 95%CI 0.73 to 1.00, n=1390). Data from the national survey indicate that 89% (n=279) of critical care physicians believe that anticoagulant therapies used to modulate host inflammation in patients with severe sepsis or septic shock are clinically important, but not routinely used. Respondents were uncertain if UFH or LWMH are beneficial (67%, n=211), or harmful (61%, n=189) when used in this context, and 90% (n=281) believe that further clinical trials or UFH or LMWH are warranted.

Conclusion: Limited evidence to date suggests UFH may be beneficial when administered to patients with severe sepsis or septic shock. Future clinical trials are warranted and supported by a medical community that believes this avenue of research is clinically important and who is genuinely uncertain regarding the potential therapeutic benefits or harms of heparin in this patient population.

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Finally, I would like to dedicate my thesis to my son Alexei John Kirby Zarychanski born on May 17, 2010, who while in his cradle, watched his father hard at work. It is my hope that, through observation and practice, he too will learn the value of hard work and perseverance.

Few things are impossible to diligence and skill. Great works are performed not by strength, but perseverance (Samuel Johnson (1709 – 1784)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 INTRODUCTION

1.1 Overall Objective

The overall objective of this thesis is to construct the evidence based-framework to justify prospective clinical trials of unfractionated heparin in patients with severe sepsis and septic shock. This objective will be met by conducting a systematic review of the literature, and a national cross-sectional survey.

1.2 Sepsis defined

The word *sepsis* is based on the Greek language word *pepsis*. Pepsis was the word to describe the natural process of metabolism and fermentation. Sepsis, on the other hand, was synonymous with putrefaction and malodour(1). Millennia later, Louis Pasteur conclusively linked putrefaction to a bacterial cause. Although the accepted definition of sepsis continues to be revised over time, it essentially describes the host response to an invading pathogen.

Since 1992, at a conference of key stakeholders charged with improving patient care and standardizing research protocols, a uniform definition of sepsis was agreed upon whereby categories of 'sepsis' were defined by a hierarchical spectrum of disease severity(2). The *sepsis syndrome* was defined as a suspected or documented infection plus two of the following four systemic inflammatory response (SIRSs) elements: a) temperature >38°C or <36°C; b) heart rate >90 beats/min; c) respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg; d) white blood cell count >12 000 cells/mm^3, <4 000 cells/mm^3 or >10% immature (band) forms. *Severe sepsis* was defined as sepsis *plus* new organ dysfunction, while *septic shock* was said to occur in patients with sepsis who

have persistent arterial hypotension despite adequate fluid resuscitation (mean arterial pressure <65 mmHg for >2 hrs). These definitions continue to be used in the practice of medicine, but efforts to revise and improve them based on our evolving knowledge in this field are underway(3).

1.3 Epidemiology of sepsis and septic shock

In 2000, the incidence of sepsis in the United States was estimated to 240.4 per 100,000 people, and appears to be increasing at an annualized rate of 8.7%(4). Sepsis and septic shock account for approximately 5-15% of all intensive care unit (ICU) admissions and constitute the second most frequent cause of death in the ICU after primary cardiovascular diseases(4-6). Data from several large clinical trials in severe sepsis (i.e. sepsis with new onset organ failure) indicate that the incidence of septic shock approaches 435 000 cases annually(7;8), but this exceeds estimates from previously published observational studies(6;9). The mortality rate associated with severe sepsis is approximately 25% to 50%, while mortality in septic shock ranges between 40% and 75%(5-8;10).

The average age of patients diagnosed with sepsis and admitted to a hospital in the U.S. is approximately 60.8 (±13.7) years, new diagnoses are made in males and females with similar frequency, and the average length of hospital stay is 11.8 (±2.6) days(4). In 2001 the annual national hospital cost associated with the care of patients diagnosed with sepsis in the United States of America was estimated to be US$16 billion(5). This estimate is likely to be a serious underestimate of the true cost given that it did not include post-hospital based post-discharge costs or absence from work, and did

not account for the annualised increase in the incidence of sepsis currently observed in North America(4).

1.4 Inflammation and coagulation in sepsis

The pathogenesis of sepsis involves a systemic inflammatory response (SIRs) secondary to an invading pathogen. While the initial and intended purpose of the host inflammatory response is likely adaptive, the intensity of the host inflammatory response can be maladaptive(11). Systemic inflammation leads to the activation of blood coagulation, resulting in systemic micro-thrombosis and multi-organ dysfunction(12). The 'cytokine storm' that characterizes SIRs and the activation of coagulation following microbial invasion are now recognised as leading causes of organ failure and death in sepsis(13). Disseminated intravascular coagulation, a state of systemic activation of coagulation accompanied by widespread thrombosis and simultaneous bleeding secondary to clotting factor consumption, is known to occur in severe sepsis and septic shock. Sepsis is the principal cause of disseminated intravascular coagulation(14).

1.5 Statement of the problem and a possible role for heparin

The mainstay of treatment for sepsis is prompt antimicrobial therapy and source control (e.g. abscess drainage, tissue debridement). Despite adequate therapy, approximately 30% of patients with sepsis will die(15), and the mortality associated with septic shock ranges between 40% and 75%(5-8;10). Though patients generally present with 'infection' or bateraemia (i.e. bacteria in the blood), it is not the invading pathogen that is responsible for death, rather it is the host response to infection, or the 'sepsis' as defined

in section 1.2. The host response to infection is to elicit an inflammatory response that includes activation of coagulation. Though initially adaptive and intended evolutionarily to eradicate invading pathogens, if sufficiently intense, this response can become maladaptive and results in multiorgan failure and death.

Given the recognised link between coagulation and inflammation, several anticoagulant compounds have been evaluated for efficacy in clinical trials. Among several agents that have progressed to phase III trials, only human recombinant activated protein C (APC) has been shown to reduce mortality in severe sepsis and septic shock in a single multicentre randomised controlled trial (The PROWESS trial)(7). Uptake of this therapy has been slow for several reasons, one of which may relate to the cost of this agent. A 4 day course of APC costs approximately CDN $10,000 per patient, which renders the compound inaccessible to most global health care systems. Even in North America, use of this drug is restricted to the *post hoc* subgroup of trial patients that derived the most benefit.

Unfractionated heparin (UFH) is a naturally occurring anticoagulant that is used in the treatment of thrombotic disorders. Its anticoagulant effects are achieved by binding antithrombin in the circulation(16). This interaction facilitates the ability of antithrombin to inactivate multiple coagulation factors (especially factors II and X) which effectively limits thrombin generation and prevents the formation of a fibrin clot. Because thrombin generation is inextricably linked to inflammation (thrombin promotes inflammation and inflammation causes thrombin generation), heparin is an anti-inflammatory drug(17;18). Heparin also possesses anti-inflammatory properties that are unrelated to its role as an anticoagulant(19-22).

Several live animal models of sepsis demonstrate a survival advantage due to heparin administration(23;24). A recent narrative review estimated that the overall odds ratio for death associated with heparin therapy to be 0.27 (95% confidence interval (CI) 0.16-0.46) when considering randomised animal studies(25). Post hoc subgroup analysis from 3 phase III trials demonstrate increased survival in patients receiving heparin, either alone or in combination with the intended study drug(26). A recently published propensity matched retrospective cohort study also demonstrated increased survival associated with heparin when administered to patients with septic shock(27). Though none of these published reports prove heparin is of certain benefit, they are hypothesis generating and suggest the need for future clinical trials of heparin and sepsis.

Given heparin's anticoagulant and inflammatory properties and the multiple lines of evidence highlighting therapeutic successes associated heparin in animals and humans, a sufficient evidenced-based framework to justify large clinical trials of heparin in patients with sepsis is warranted.

2.0 BACKGROUND

2.1 In vivo coagulation in humans

The maintenance of an intact vasculature is dependent upon a complex and interdependent system of cellular elements including platelets, red blood cells, and the endothelium, in addition to plasma components such as proteins, cytokines, glycosaminoglycans, and charged molecules. This system functions constitutively to ensure day-to-day vessel integrity, and is poised to immediately activate in the setting of vessel injury to initially control hemorrhage, but then to restore downstream blood flow when bleeding has ceased. The coagulation system responds to vascular damage by the sequential conversion of precursor zymogens to their active serine proteases. Serial activation of these zymogens occur on negatively charged phospholipid surface membranes of platelets and endothelial cells. These linked reactions constitute an amplification cascade that culminates in the conversion of fibrinogen to insoluble fibrin clot(28).

The major in vivo activator of the coagulation cascade is exposed tissue factor (TF) from damaged endothelial surfaces. Exposed TF binds to activated factor VII (VIIa). The TF-VIIa complex catalyzes the activation of factor X which then forms the prothrombinase complex along with factors Va, prothrombin (factor II), calcium, and a negatively charged phospholipid surface. The TF-VIIa complex can also activate factor IX, which then serves to also activate thrombin via the tenase complex. This serves as an essential amplification loop. Thrombin then serves to convert soluble fibrinogen to an insoluble fibrin clot. Essential to this haemostatic process are VonWillebrand factor and platelets. At the sites of vessel injury, VonWillebrand factor binds to exposed collagen

and undergoes a conformation change that exposes binding sites for platelets. Platelets are thus localised to the site of injury where they can become activated, associate with other platelets to form an initial platelet plug, and potentiate coagulation via the secretion of various haemostatic agents.

Prevention of unmitigated widespread thrombosis depends on the functioning of a series of circulating inhibitors and membrane-bound molecules. The three main inhibitors of coagulation include tissue factor pathway inhibitor (TFPI), antithrombin (AT), and the protein C anticoagulant pathway. TPFI binds to and inhibits the TF-VIIa complex and factor Xa. AT primarily targets thrombin (IIa) and factor Xa, but also inhibits factors IXa, XIa, XIIa, and VIIa. The rate of AT inhibition is accelerated over 1000 fold in the presence of heparin and endogenous heparan sulfate. The protein C anticoagulant pathway serves to inhibit thrombin formation via the interaction of multiple proteins on cell surfaces(29).

Fibrin clots provide the temporary scaffold on which wound healing takes place; however, these clots must eventually be dismantled and blood flow restored. This process is referred to as fibrinolysis and is mediated by a series of fibrinolytic enzymes. The major enzyme responsible for clot dissolution is plasmin, which is derived from the precursor molecule, plasminogen. Activators of plasminogen, include tissue-type plasminogen activator, and urokinase-type plasminogen activator. The major inhibitors of plasminogen, molecules that inhibit clot breakdown, include plasminogen activator inhibitor (PAI) 1 and 2(30).

2.2 The inflammatory response

In response to injury, infection, or a systemic insult, inflammation occurs. The cardinal signs of inflammation including redness (rubour), swelling (tumour), warmth (calour), and pain (dolour) have been recognised for thousands of years in clinical medicine. Acute inflammation occurs in response to a variety of stimuli, especially infection. This response is complex, and is thought to represent an adaptive and genetically evolved strategy to minimize infection, and maximize tissue repair.

Classically recognised mediators of inflammation include leukocytes (monocytes, neutrophils, basophils, eosinophils, and lymphocytes), cytokines, chemokines, complement proteins, adhesion protein molecules, reactive oxygen species, lysosomal granules, and vasoactive amines(31). In response to bacterial infection, endotoxin or lipoteichoic acid can activate neutrophils and monocytes. Chemokines secreted by activated neutrophils and monocytes (e.g. IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) serve to further activate, recruit, and to promote the adhesion of white blood cells to the site of infection or injury. Activated neutrophils and monocytes contribute further to the inflammatory response by releasing reactive oxygen species designed to eradicate offending pathogens. To increase blood flow, and thus increase numbers of white blood cells and immune mediators, vasoactive amines are released primarily from the activated endothelium and activated platelets(31).

In addition to these well recognised mediators of inflammation, the coagulation system contributes greatly to systemic inflammation. Factor Xa, thrombin, and fibrin can activate endothelial cells and elicit the synthesis of IL-6 and IL-8(32). Factor Xa, fibrin, and particularly thrombin are also potent activators of mononuclear cells. A consequence

of the feedback amplification of the coagulation cascade, the production of bradykinin results in increased vascular permeability. Platelet activation, due to thrombin, exposed collagen, and platelet activating factor, all promote inflammation (and coagulation) the by release of platelet alpha granules that contain several procoagulant and proinflammatory molecules.

Though evolutionarily adaptive, it must be recognised that any adaptive response may at times be excessive or insufficient, and thus maladaptive(33). Systematic inflammation, if sufficiently intense, can result in haemodynamic collapse, cellular destruction, and systemic thrombosis leading to widespread microvascular thrombosis and death.

2.3 Coagulation and inflammation in sepsis

Coagulation abnormalities are frequent in patients with sepsis, and range from subtle increases in laboratory markers of coagulation to disseminated intravascular coagulation (DIC), characterised by the simultaneous existence of systemic microvascular thrombosis and diffuse bleeding from multiple anatomic sites(32). In recent years, it has been increasingly recognised that inflammation and coagulation are inextricably linked and contribute to the pathobiology of the sepsis syndrome. Inflammation results in up-regulation of coagulation; coagulation promotes inflammation. If unabated, this cycle may culminate in multiorgan failure and death.

Evidence that activation of coagulation in concert with intense inflammation may lead to deleterious consequences has been demonstrated by several postmortem studies of patients with sepsis, coagulation abnormalities, and DIC. These studies show that,

despite diffuse bleeding at multiple anatomic sites, ischaemia and necrosis associated with thrombosis can be found in patients who have died from sepsis(34;35). The presence of these intravascular thrombi appears to be specifically related to the development of multiorgan dysfunction in these patients.

Inflammation up-regulates coagulation via several mechanisms. In severe sepsis, monocytes, stimulated by cell surface antigens and proinflammatory cytokines, express tissue factor, which leads to systemic activation of coagulation and increased thrombin generation(36). Thrombin facilitates the formation of fibrin, activates platelets, increases endothelial cell surface leukocyte adhesion molecules, and increases inhibitors of fibrinolysis. The end result is a relative upregulation of coagulation, and thus necessarily, amplification of systemic inflammation.

In addition to up-regulation of coagulation, systemic inflammation is associated with down-regulation of the major physiologic anticoagulant pathways (TFPI, AT, and the protein C anticoagulant pathway)(37). During severe inflammatory responses, AT levels are markedly reduced due to impaired synthesis, enhanced degradation by neutrophil elastase, and consumption related to thrombin generation(38). The degree of AT reduction has been associated with poor outcomes in several studies. The function of the protein C pathway is also impaired in severe sepsis. Plasma levels of the zymogen protein are low(39;40), reduced thrombomodulin levels occur(41), plasma levels of C4b increase(42), and the endothelial cell protein C receptor (EPCR) has been shown to be down-regulated(43). Together, these result in markedly reduced levels of activated protein C (APC), and propagation of coagulation and inflammation. Finally, severe inflammatory states are also associated with impaired fibrinolysis due to elevations in

PAI-1 and thrombin activatable fibrinolysis inhibitor, which further promote increased coagulation and thus inflammation(44).

2.4 Modulation of host inflammation in sepsis with anticoagulant therapies

Several studies have observed that reductions in natural anticoagulants, (e.g. AT, protein C, protein S, and TFPI) correlate with mortality in severe sepsis and septic shock(45). Given the bidirectional relationship of coagulation activation and inflammation, multiple programs of research have examined the efficacy of anticoagulant compound in patients with sepsis syndrome. Three such programs, studying AT, APC, and TFPI have progressed to phase III clinical trials.

Antithrombin (AT) has direct and indirect anti-inflammatory properties. Since it effectively inhibits thrombin generation, the activation of multiple inflammatory mediators are blunted as a consequence of AT supplementation. AT may also have inflammatory properties that are independent of coagulation(46;47). AT appeared effective in phase II studies(48), but a large phase III RCT of AT found no significant improvements in clinically relevant outcomes when this therapy was administered to patients with sepsis(8).

Likewise, tissue factor pathway inhibitor appeared promising in animal and pre-clinical human studies(49;50). However, when studied in large phase 3 RCTs, no effect on mortality was observed(51). Of these agents, only human recombinant activated protein C (APC), also known as drotrecogin alfa, has been shown to be efficacious in patients with sepsis.

Similar to AT and TFPI, levels of protein C and APC are low and associated with mortality in severe sepsis and septic shock(45). Pre-clinical research has shown that APC supplementation not only has the ability to down-regulate coagulation and increase fibrinolysis, but also decreases inflammation by independent mechanisms(52). In live animal models of septic shock, infusion of APC was shown to decrease mortality(53). In a phase II dose finding study, APC decreased inflammation and several markers of coagulation(54). In a phase III, multicentre RCT, APC was shown to decrease mortality and organ failure in patients with sepsis (PROWESS trial) (7). On the basis of this study, APC was licensed for use in patients with severe sepsis and septic shock. Regulatory approval of this agent was controversial(55-57), and the true effectiveness of this therapy is suspect. Longer term follow up data from this original study failed to confirm clinical benefit in the overall study population(58), and RCTs of APC in patients with decreased severity of illness and in paedriatic patients were stopped early for futility and for harm respectively(59). A follow up placebo controlled trial is underway to confirm the benefits of this agent in patients with septic shock. Uptake of this therapy into clinical practice has been less than expected, possibly due to uncertain benefits, industry involvement in the generation of the current evidence base and cost. A 4 day course of APC costs approximately CDN $10,000 per patient.

2.5 Use of heparin in sepsis and septic shock

Unfractionated heparin (UFH) is a naturally occurring anticoagulant that is produced in mast cells and basophils. Since the 1960's it has been used in the management of various thrombotic disorders. Heparin exerts its anticoagulant effect by primarily enhancing

antithrombin mediated inactivation of factors Xa and thrombin (IIa), but also factors IXa, XIa, and XIIa. By inactivating factors Xa and thrombin, heparin effectively limits thrombin generation. Because thrombin generation is intimately linked with inflammation, heparin thus acts as an inflammatory agent. Heparin also promotes fibrinolysis by enhancing the release of TFPI from the endothelium(60). The anticoagulant effects of heparin are mediated through a specific pentasaccharide sequence which binds with high affinity to antithrombin. Interestingly, this necessary pentasaccharide sequence is only present in approximately one third of the molecules in UFH mixtures(61). The majority of UFH, especially those glycosaminoglycan molecules that do not contain the key pentasaccharide that binds to antithrombin, binds non-specifically to endothelium and to many plasma constituents which contribute to the many anticoagulant-independent effects of heparin. Many of these non-specific, anticoagulant-independent interactions are partially responsible for the anti-inflammatory properties of heparin.

Anticoagulant-independent roles of heparin that serve to mitigate inflammation have been demonstrated in several experimental models(62). Heparin has been shown to neutralize endotoxin and increase serum TNF binding protein-I, limiting both activation of coagulation and inflammation(19;20;63). Heparin is also a known inhibitor of complement and of adhesion molecule expression in the microvasculature which may serve to limit haemolysis and decrease neutrophil adhesion in the setting of sepsis and endothelial injury(21;22;64). More recently, heparin has been shown to modulate HDL in the setting of infection and can reduce oxidant induced cellular damage(65;66).

As a consequence of heparin's potent anticoagulant effects and protean anticoagulant-independent effects, heparin appears well suited for rigorous scientific

study in the treatment of sepsis. Several animal models demonstrate that heparin administration reduces activation of coagulation and increases survival in endotoxin-equivalent models (including live organism infusion) of septic shock(23;62;67-69). A review and meta-analysis of animal RCTs found that heparin reduced the odds ratio for death (OR.27, 95%CI 0.16 to 0.46)(25). Prospectively collected, but non-randomised data from the placebo arms of three phase III trials in sepsis suggest a survival advantage associated with prophylactic dose heparin, independent of the study drug under investigation(26). In the first year of my Masters program at the University of Ottawa I completed and published a propensity matched retrospective cohort study of patients with septic shock. This study showed increased survival associated with heparin when given to patients within the first 48 hours of admission to an ICU(27).

The current literature supports a biologic rationale for the use of heparin in patients diagnosed with sepsis, but clinical trials are necessary to disprove the null-hypothesis that heparin has no such efficacy or the concern that heparin may be harmful. Thus, the objective of this thesis is to construct the evidence-based framework necessary to justify a multicentre prospective randomised trial of heparin in patients with severe sepsis and septic shock. This framework will be supported by two original studies; a systematic review and a cross-sectional survey.

3.0 SYSTEMATIC REVIEW

3.1 Objective

The objective of this study was to systematically investigate the clinical benefits and harms associated with the use of heparin in patients with sepsis, severe sepsis, septic shock, or disseminated intravascular coagulation (DIC) due to infection.

3.2 Methods

3.2.1 PICOS question

General Review Question

In patients diagnosed with sepsis, severe sepsis, septic shock, or disseminated intravascular coagulation due to infection, is the use of heparin associated with improvements in clinically important outcomes?

Population

Patients diagnosed with sepsis, severe sepsis, septic shock or with disseminated intravascular coagulation due to infection.

Intervention

Heparin administration; any dose, route of administration or timing of therapy. We included unfractionated heparin or low molecular weight heparins.

Comparator

Any comparator including no intervention or placebo.

Outcomes

Primary Outcome:

Mortality (ICU mortality, hospital mortality and 28 day mortality)

Secondary Outcomes:

Bleeding events

Red cell transfusion

Organ dysfunction

Duration of mechanical ventilation

Hospital and ICU length of stay

Studies

All controlled trials (ie., observational cohort or case-controlled studies [both prospective and retrospective] and randomised controlled trials).

3.2.2 Data Sources and search strategy

A systematic strategy to search OVID MEDLINE (1950–2008 May week 1) was developed with the assistance of an information specialist. This search strategy was adapted to search EMBASE (1980–2008 May week 1) and the Cochrane Central Register of Controlled Trials (to first quarter 2008). The search was updated on April 24, 2010.

The complete MEDLINE search strategy is presented in Appendix 1.The SCOPUS abstract and citation database was electronically searched to identify studies from relevant journals missed by the preceding search methods. To identify in-progress or planned studies, the search strategy included 3 trial registries: the UK National Research Register, the Australian New Zealand Clinical Trials Registry, and the ClinicalTrials.gov database. Attempts to find grey literature were made by searching the chemical abstracts database of the Scientific and Technical Information Network, and Google Scholar. The search strategy included abstracts and conference proceedings of the European Society of Intensive Care Medicine, the International Symposium on Intensive Care Medicine, the Society of Critical Care Medicine, the American College of Chest Physicians, the American Thoracic Society, the American Society of Hematology, and the International Society of Thrombosis and Haemostasis. Reference lists of all included studies and relevant reviews were searched for potentially suitable trials not identified by the electronic searches. No language restriction was applied, but for the purposes of this thesis, only English language studies were evaluated.

3.2.3 Study selection

3.2.3.1 Inclusion criteria

To meet our inclusion criteria, each study must have met each of the following 3 criteria:

1. Randomised controlled trial, Cohort-controlled or case-controlled study (full manuscript or abstracts were considered)

2. >80% of the study population consisted of patients diagnosed with sepsis, severe sepsis, septic shock or disseminated intravascular coagulation due to infection. No more than 20% of cases of DIC can be secondary to malignancy alone.
3. Heparin administration (unfractionated or low molecular weight).

3.2.3.2 Exclusion criteria

A study was excluded if it met any of the following criteria:

1. Studies involving non-humans.
2. Studies of disseminated intravascular coagulation that exclusively enroll patients with diagnoses other than sepsis (such as cancer, or amniotic fluid emboli).
3. Procedural heparin use (e.g. use of heparin for renal replacement therapy or plasma exchange).
4. Use of an alternate heparin as a control.
5. Studies exclusively enrolling patients < 1year of age.

3.2.4 Outcome measures

3.2.4.1 Primary outcome

Mortality (ICU mortality, hospital mortality and 28 day mortality)

3.2.4.2 Secondary outcomes

1. Bleeding events
2. Red cell transfusion
3. Organ dysfunction
4. Duration of invasive mechanical ventilation
5. ICU and hospital length of stay

3.2.5 Record review, data extraction and quality assessment

Title and abstracts of records that were found using the search strategy described above (section 3.2.2) were independently reviewed for relevancy by two individuals (Ryan Zarychanski and Danny Monsour)(Level 1 screen). Electronic records were reviewed using Reference Manager® version 11 (Thomson Reuters, Carlsbad, CA). Potentially eligible records were selected for full-text review. The full-text reports were evaluated by two reviewers (Ryan Zarychanski and Salman Kanji) for appropriateness of inclusion based on the pre-defined inclusion and exclusion criteria (Level 2 screen). Differences in decision making were resolved by further review and consensus. A third reviewer (Dean

Fergusson) could have been used if agreement after discussion was not attained; however, this was not required.

Two reviewers (Ryan Zarychanski & Salman Kanji) independently abstracted data from the English-language trials using a standardised data abstraction form, which had been piloted to ensure completeness and feasibility (Appendices 2 & 3). If essential data were ambiguous or missing, we contacted the first author or corresponding author by email. Discrepancies in extra data were reviewed and resolved by consensus. Methodologic quality of each randomised controlled trial using the Jadad scale(70), which generates a score based on the description of randomization (0 to 2 points), double-blinding (0 to 2 points) and participant withdrawals (1 point). Possible scores ranged from 0 to 5; a score of 3 or greater represented high methodologic quality (Appendix 2). Allocation concealment was assessed using the method developed by Schulz and colleagues and scored as "adequate," "unclear" or "inadequate(71)." The methodologic quality of observational studies was assessed using the Newcastle Ottawa Scale (NOS)(72). This scale adjudicates study characteristics using three domains: subject selection, comparability and outcome assessment. Points (or 'stars') are awarded based on defined study conditions (Appendix 3).

3.2.6 Data synthesis and analysis

Summary effect measures were calculated using Review Manager (version 5.0.23 for Windows, The Cochrane Collaboration, Oxford, England). Analyses were performed according to the intention-to-treat principle using eligible randomised patients. For all summary measures of effect, a random-effects model that weighted studies using the

inverse of its variance weights was employed and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). An OR of more than 1 suggests a higher odds of the outcome among patients receiving heparin compared to patients in the control group. A random effects model was used since the population parameters appeared to vary substantially and homogenous effect sizes were not expected and were not observed. Furthermore, studies were pooled to estimate the effect size in the entire population, not only the studies available.

We assessed statistical heterogeneity, that is, variability of the outcome estimates among included studies, using the I^2 statistic. This statistic is interpreted as the proportion of total variation across trials due to heterogeneity (minimum and maximum values 0% and 100%), and is both size invariant and scale invariant. I2 = 100% x [(Cochran *Q* – degrees of freedom) / Cochran *Q*]. An I^2 of 0%-40% does generally not induce caution when pooling; 30%-40% may represent moderate heterogeneity; 60%-90% may represent substantial heterogeneity; 75%-100% represents considerable heterogeneity(73). Perceived clinical heterogeneity (e.g. differences in the type of comparator studied, or in the methodologic quality of trials) was assessed with sensitivity analyses. Funnel plots were used to visually examine the potential for publication bias.

3.3 Results

3.3.1 Search Results

The systematic literature search identified 2103 records. Level 1 screening permitted the exclusion of 340 duplicate records, and 1667 additional records (Figure 1). Agreement between reviewers at this level of screening was substantial (kappa=0.77). Full text

manuscripts for 87 studies were retrieved and level 2 screening yielded 9 English language articles for inclusion. Non English articles are still to be analyzed. Agreement between reviewers at the second level of screening was almost perfect (kappa= 0.93), and the single discrepancy was resolved by discussion then consensus. Reasons for excluding studies at all levels of screening are listed in Figure 1. No records were identified through grey literature sources and no ongoing trials were identified. One previous systematic review of heparin in sepsis was identified that synthesized the results published animal studies(25).

3.3.2 Study Characteristics

A total 3892 patients were enrolled in 7 RCTs(74-80) and 2 retrospective cohort studies(27;81). One RCT was published in abstract form; the remaining RCTs and observational studies were published in peer reviewed journals. The total randomised population was 2478; the median RCT size was 48, and a single trial accounted for 78% of randomised patients(78). The 2 retrospective studies included 1390 and 24 patients respectively. All 9 studies enrolled patients with sepsis syndrome. Severity of illness scores were provided for 3 of 7 trials and 1 of 2 observational studies (Table 1). Given the Acute Physiology and Chronic Health Evaluation (APACHE II) scores reported and the baseline mortality rate among included patients, it appears that the majority of patients were critically ill with either severe sepsis or septic shock. Over 85% of patients were cared for in intensive care units (ICUs), and this figure is likely an underestimate due to incomplete reporting. The remaining patients were cared for in emergency departments or on hospital wards.

All RCTs and observational studies investigated unfractionated heparin (UFH) in the intervention arm. One RCT enrolled equal numbers of patients randomized either UFH or LMWH in a 3 arm trial(78). The control groups among the RCTs consisted of either placebo or no drug intervention in 4 RCTs, and was either antithrombin(75), recombinant thrombomodulin (ART-123)(79), or a synthetic protease inhibitor (Gabexate mesilate)(80) in the 3 remaining trials. Dosing of heparin varied and ranged from prophylactic dosing to full anticoagulation (activated partial thromboplastin time 2x normal). In all but 1 RCT(78), heparin was administered by continuous IV infusion. The duration of the study interventions ranged from approximately 2 days to 7 days.

In one large RCT (n=1935), all enrolled patients received drotrecogin alfa at 24 mcg/kg/min and patients were randomised to prophylactic heparin or placebo. In one observational study, 73% of patients in the control group received subcutaneous prophylactic dose UFH (i.e. 5000 units twice daily)(27), and in the second study, the control group received UFH at 'less than therapeutic' doses at the discretion of the medical team(81).

Figure 1: Study Flow Diagram

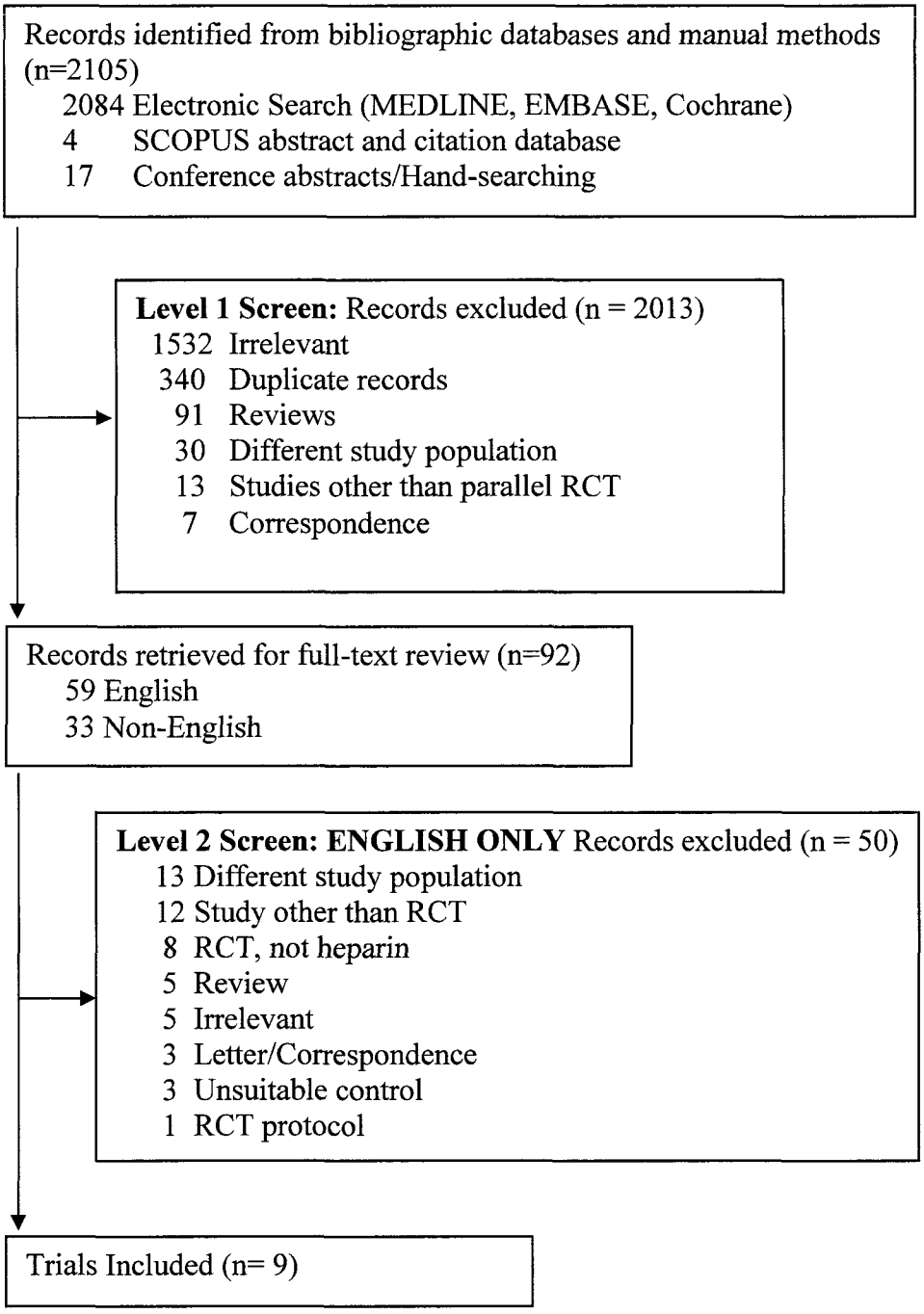


Table 1: Characteristics of the 9 studies included in the systematic review

Trial/Year	n Total Heparin/Control	Age in years Heparin/Control	Population	Severity of Illness Score Heparin/Control	Intervention Protocol	Control Protocol	Duration of Study Protocol
Randomised Controlled Trials							
Jaimes, 2009(77)	319 159 / 160	56 (IQR 40-71)	Suspected or confirmed infection presenting to an ER	APACHE II 9 (7-13) / 10 (6-14)	UFH: 500 units/hour by IV continuous infusion	Placebo: IV continuous infusion	7 days, or hospital discharge
Levi, 2007(78)	1935 976 / 959	Hep: 59.6 ±16.1 Cntrl: 58.4 ±16.0	Severe Sepsis	APACHE II 23.8 ±7.6 / 24 ±7.4	UFH: 5000 units S/Q BID OR LMWH: Enoxaparin 40mg S/Q OD (equal group sizes) **PLUS** drotrecogin alfa 24 mcg/kg/hr	Placebo (Saline) **PLUS** drotrecogin alfa 24 mcg/kg/hr	4 days
Saito, 2006(79)	99 51 / 48	<50: 8%/22% 50-69: 36%/39% ≥70: 56%/39%	DIC secondary to infection or malignancy[a]	NR	UFH: IV 8 Units/kg/hr	ART-123: IV 0.06 mg/kg over 30 min	6 days
Boldt, 1999(74)	28 14 / 14	Hep: 56.9 ±12.2 Cntrl: 58.2 ± 11.9	Sepsis or Trauma[b]	APACHE II 19.9 ±3.2 / 18.9 ±4.3	UHF: IV to keep aPTT 2x normal	No intervention	NR
Ghanem, 1997(75) (abstract)	48 24 / 24	NR	Sepsis and septic shock	NR	UFH: 150 units/kg/day by continuous IV infusion	Antithrombin concentrate: IV 1000 units every 12 hours	2 days (longer in the UFH group if thrombotic signs)
Haneberg, 1983(76)	26 11 / 15	<2: 36% / 27% 2-7: 45% / 47% 8-15: 18% / 27%	Meningococcal sepsis	NR	UFH: IV 100 unit/kg bolus, then 10,000 units/m^2 daily by infusion	No intervention	2 days
Taenaka, 1983(80)	23 8 / 15	Hep: 64.8 ±18.0 Cntrl: 60.6 ±15.7	Sepsis	83% required mechanical ventilation	UFH: IV 10 units/kg/hr targeting an activating clotting time of 150 sec.	Gabexate mesilate: IV 2 mg/kg/hr	7 days
Retrospective Cohort Studies							
Zarychanski, 2008(27)	1390 695 / 695	64.4 ±15.9 / 64.7 ±15.2	Septic Shock	APACHE II 24.1 ±7.6 / 24.2 ±7.9	UFH: IV by continuous infusion for aPTT 1.5-2.0x normal	No intervention	4.7 ±2.9 days
Kuppermann, 1994(81)	24 6 / 18	Hep: 1.9 Cntrl: 3.4	Meningococcal sepsis	NR	UFH: at least 50 units/kg by infusion within the first 72 hours of admission	No UFH or UFH at less than 50 units/kg by IV infusion	Range: 3-14 days

APACHE, Acute Physiology and Chronic Health Evaluation; UFH, unfractionated heparin; LWMH, low molecular weight heparin; IQR, interquartile range; NR, not reported; IV, intravenous; S/Q; subcutaneous; ±, denotes standard deviation

[a] Patients with malignancy were excluded from all outcome analyses

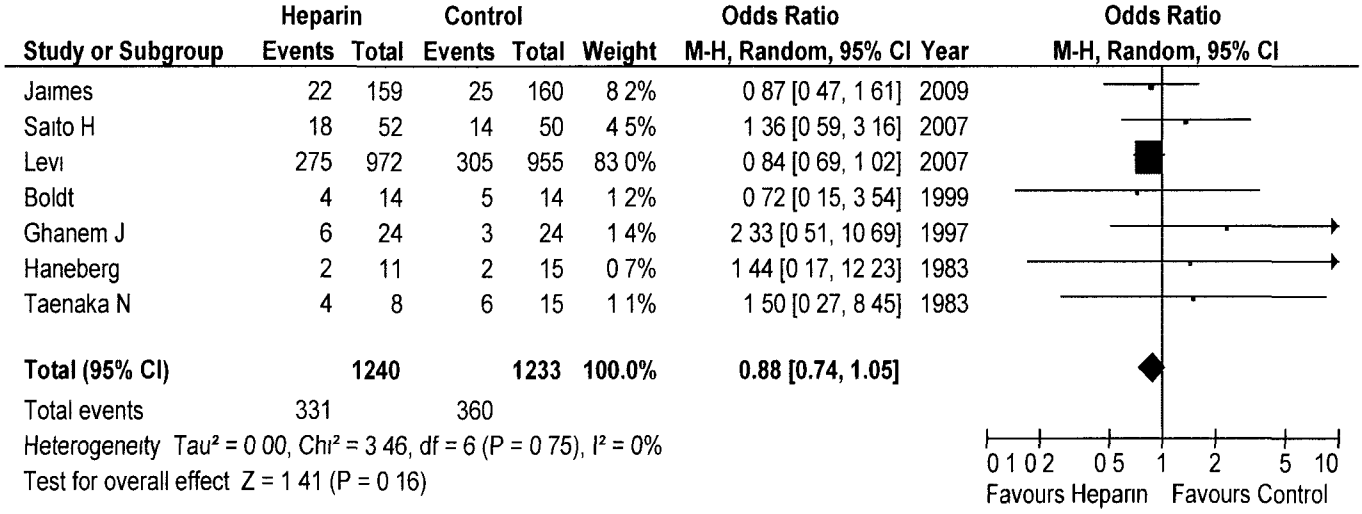
[b] Patients with trauma were excluded from all outcome analyses

3.3.3 Primary outcome – Mortality

Randomised Controlled Trials

Three RCTs reported 28 day mortality(77-79) and in the remaining 4 trials, the duration of follow up was not specified(74-76;80). The pooled OR for mortality in these 7 trials comparing heparin to any other intervention was 0.88 (95%CI 0.74 to 1.05, I^2 0%, n=2473) (Figure 2). In this analysis, 1 large high quality RCT accounted for 83% of the weighted estimate(78).

Figure 2: Pooled estimate of mortality in trials comparing heparin to other interventions



The pooled OR for mortality in 4 trials comparing heparin to either placebo or no intervention was 0.85 (95%CI 0.71 to 1.02, I^2 0%, n=2300) (Figure 3)(74;76-78). In 3 small trials comparing heparin to another anticoagulant agent, the pooled OR was (1.54 (95%CI 0.78 to 3.03, I^2 0%, n=51)(75;79;80) (Figure 4). In 3 trials of high methodologic quality (Jadad score of 5 with adequate allocation concealment), the pooled OR

associated with heparin administration was 0.86 (95%CI 0.72 to 1.03, I^2 0%, n=2348)(77-79). Among 3 trials with low methodological quality (Jadad score of 1 with unclear or inadequate allocation concealment), the OR associated with heparin administration was 1.10 (95%CI 0.39 to 3.06, I^2 0%, n=77)(74;76;80).

Figure 3: Pooled estimate of mortality in trials comparing heparin vs. placebo or no intervention

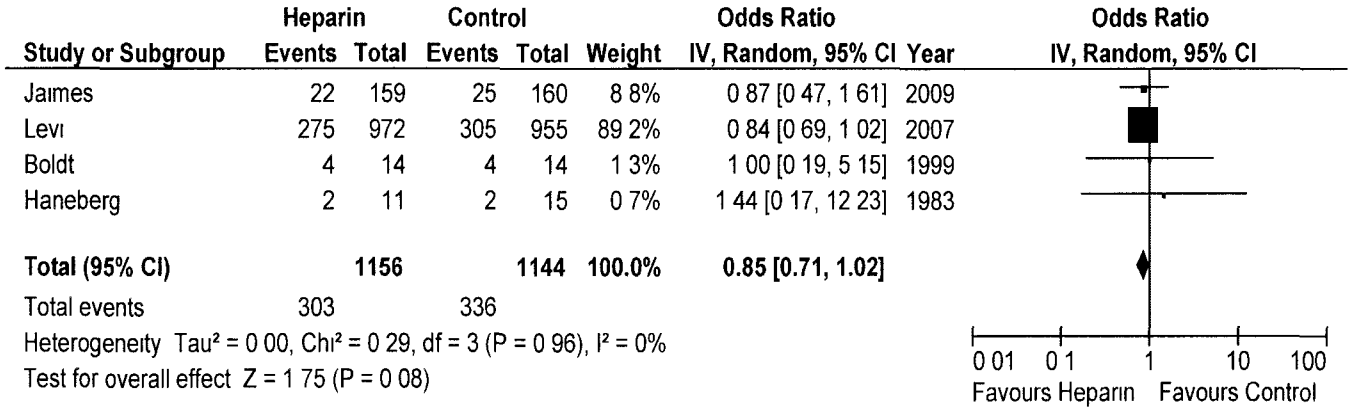
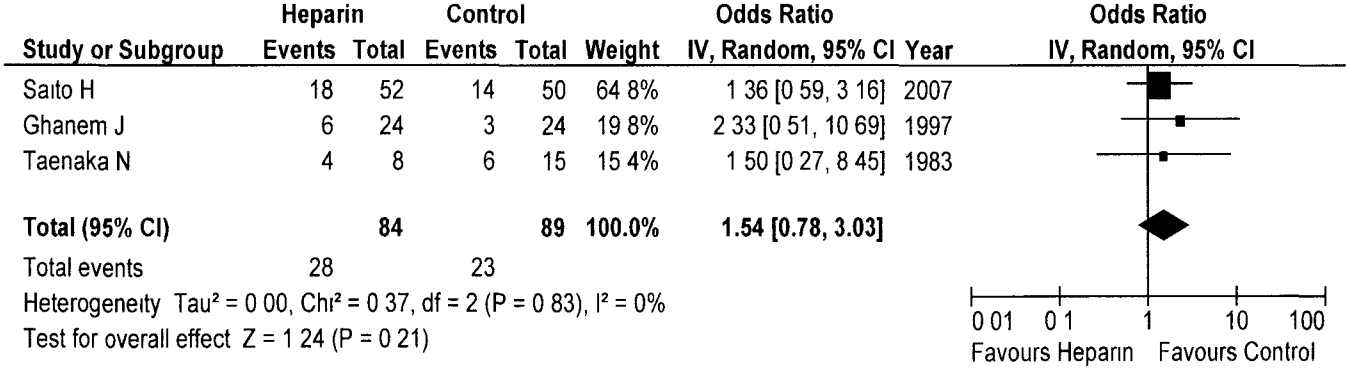


Figure 4: Pooled estimate of mortality in trials comparing heparin vs. other anticoagulants



Observational Studies

A single (n=1390) propensity matched cohort analysis of UFH in adult patients diagnosed with septic shock, a 4.1% reduction in death associated with heparin administration [279/695 (40.1%) vs. 307/695 (44.2%), Hazard Ratio (HR) 0.85, 95%CI 0.73 to 1.00)(27) was suggested. In this study, the reduction in mortality associated with heparin increased with increasing disease severity. Patients in the highest APACHE II quartile had a 13% absolute reduction in 28 day mortality associated with heparin administration (127/184 (69%) vs. 94/168 (56%), HR 0.70, 95%CI 0.54 to 0.92). The second observational study included young children with meningococcal sepsis(81). No difference in hospital mortality was observed between the UFH and no intervention groups [3/6 (50%) vs. 11/18 (61%), p=0.67], but this analysis was underpowered to detect a clinically significant mortality difference, and the authors of this second study did not adjust for important clinical confounders.

3.3.4 Secondary outcomes

Randomised Controlled Trials

Bleeding

Bleeding events were variably defined, inconsistently reported, and not amenable to pooled analyses. With UFH at 500 units/hr in patients with low severity of illness, Jaimes, et al, reported infrequent and equal (2/159 vs. 2/160) rates of minor bleeding consisting of nose, tracheal bleeding, and haematuria(77). Only 1 major bleeding event in a patient receiving heparin, a gastrointestinal hemorrhage requiring transfusion, was reported in this trial. Levi, et al, studied patients with severe sepsis, all of whom received

drotrecogin alfa, and randomised patients to either UFH, LMWH or placebo(78); data from either heparin group were pooled for the purpose of analysis. In this study, the rate of 'any bleeding' from study days 0-6 was marginally higher in the patients receiving heparin [105/976 (10.8%) vs. 78/959 (8.1%), p=0.05), but serious bleeding events were not different between groups [22/976 (2.3%) vs. 24/959 (2.5), p=0.72]. In the trial comparing UFH to a soluble thrombomodulin agent, at 7 days serious bleeding related adverse events were reported to be higher in the heparin group [65/115 (56.5%) vs. 50/116 (43.1%), p=0.05]; however, at 14 days no differences in serious bleeding events were found [75/115 (65.2%) vs. 64/116 (55.2%), p=0.14] (79). Units of red cells transfused during the study period was reported in 1 trial(74), and not statistically different between the heparin [8/14 (57%)] and non-intervention arms [6/14 (42%)], p=0.75.

Organ dysfunction/failure

One trial reported average daily change in the Multiple Organ Dysfunction score (MOD) which was not different between the heparin and placebo group at 28 days (-0.11 vs. -0.13, p=0.24)(77). The MOD score is a calculated value reflecting the severity of dysfunction of 6 organ systems (respiratory, hematologic, hepatic, cardiovascular, neurologic, and renal), and has been validated as a surrogate outcome for mortality in critically ill patients(82). No randomized trial reported the duration of mechanical invasive or non-invasive ventilation.

Hospital and ICU length of stay

Hospital length of stay was reported in 1 placebo controlled trial and was not different between the heparin and control group [12.0 days (IQR 8.0-19.5) vs. 12.5 days (IQR 8.0-20.0), p=0.98](77). In a single trial of heparin vs. a gabexate mesilate, a serine protease inhibitor, no statistical difference in ICU length of stay was identified [17.8 days (SD 6.6) vs. 22.8 days (SD 10.4), p=0.74](80).

Observational Studies

The study conducted by Zarychanski et. al was the only 1 of 2 observational studies to report relevant secondary outcomes(81).

Bleeding

The rates of gastrointestinal (5.2% vs. 3.7%, p=0.19) or central nervous system (1.0% vs. 1.0%, p=1.00), bleeding were similar in the heparin and control groups. Units of red cells transfused during the study period were no different [5.0 (SD 5.8) vs. 4.7 (SD 5.2), p=0.19].

Organ dysfunction/failure

Global measures of organ dysfunction were not reported. In the study conducted by Zarychanski et. al., the proportion of patients liberated from mechanical ventilation was higher (63% vs. 54%, p=0.003) in patients who received IV therapeutic dose UFH(27).

Hospital and ICU length of stay

Zarychanski et. al., reported that hospital length of stay was increased [19 days (IQR 8-36) vs. 14 days (IQR 5-31), $p<0.001$] among patients who received heparin. The authors postulated that this reflected decreased early deaths which may have been due to heparin.

3.3.5 Quality assessment

Randomised Controlled Trials

The methodological quality of the 3 most recent RCTs(77-79) were high (Jadad score 5 of 5 with adequate allocation concealment), while the 3 trials published before 2000(74;76;80) were of lowest methodologic quality (Jadad score 1 of 5 with unclear or inadequate allocation concealment) (Table 2). Three of 7 trials reported the source of sponsorship: 2 were industry funded(78;79), and 1 was funded by academic granting institutions(77). All trials were reported as RCTs, however, the method of allocation was not random but used alternating treatment allocation in 1 trial and thus quality points were deducted for an inappropriate randomization scheme(80). Blinding procedures, attrition information and adequate allocation concealment were reported in the three most recent randomized trials(77-79). Intention to treat analysis was used in 4 trials(76-79), and was either unclear(74;80) or non evaluable(75) in the remaining 3 trials. The methodological quality of the included abstract was not evaluable due to lack of detail(75).

Table 2: Methodological quality and risks of bias in the included randomized controlled trials

Study, Year	Study Type	Sponsor	Total	Randomization	Blinding	Withdrawals	Allocation Concealment	Intention-to-Treat Analysis
			Jadad Score*					
Jaimes, 2009(77)	Single centre	Academic grant funding	5	2	2	1	Adequate	Yes
Levi, 2007(78)	Multicentre	Eli Lilly (industry)	5	2	2	1	Adequate	Yes
Saito, 2006(79)	Multicentre	Asahi Kasei (industry)	5	2	2	1	Adequate	Yes
Boldt, 1999(74)	Single centre	NR	1	1	0	0	Unclear	Unclear
Ghanem, 1997(75) (abstract)	Multicentre	NE	NE	1	NE	NE	NE	NE
Haneberg, 1983(76)	Single centre	NR	1	1	0	0	Unclear	Yes
Taenaka, 1983(80)	Single centre	NR	1	0 (alternate patients)	0	0	Inadequate	Unclear

*The Jadad scale assigns methodological quality score based on the reported methods and description of randomization (0-2 points), blinding (0-2 points) and the reporting of participant withdrawals (0-1 point). Possible scores vary from 0 to 5, with a score of 5 indicating high methodological quality(70).
NR, not reported; NE, not evaluable.

Observational Studies

The methodological quality of the two retrospective cohort studies as assessed by the Newcastle-Ottawa Scale was high (Table 3). Criteria for items related to selection of patients, exposures, and outcomes were adequately met in both studies; however, only one study attempted to control for potential confounders between the exposed and non-exposed groups(27). In the study conducted by Zarychanski et. al., propensity matching on over 20 clinically relevant demographic, physiologic, and laboratory parameters was used to facilitate valid between group comparisons. Related statistical techniques to account for group differences were not used in the remaining observational study(81).

Table 3: Methodological quality and risks of bias in the included observational trials

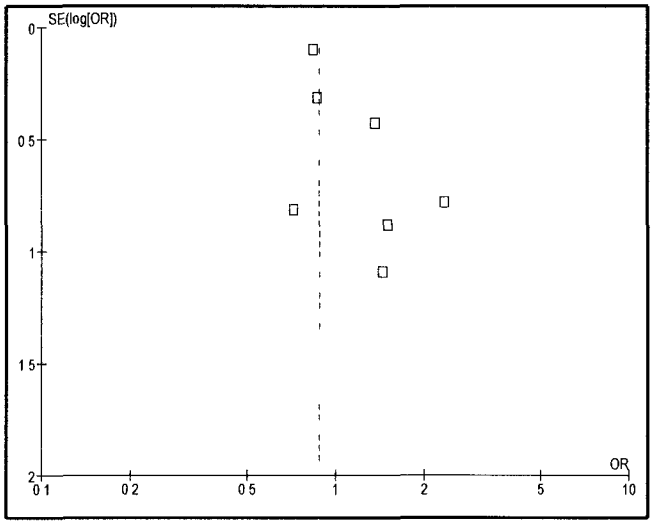
Zarychanski, 2008(27)	Multicentre, retrospective cohort	University of Manitoba	****	**	***	**9/9**
Kuppermann, 1994(81)	Multicentre, retrospective cohort	NR	****	-	***	**7/9**

NOS – Newcastle-Ottawa Scale: Comprised of 4 criteria for sample selection, 1 criteria to assess comparability of groups, and 3 criteria to examine the assessment of the study outcome(72).

3.3.6 Publication Bias

The potential for publication bias was minimized by conducting a thorough and systematic literature search that included grey literature searches and consultation with content experts. An inverse funnel plot for the mortality outcome, suggested an over-representation of studies demonstrating the superiority of novel agents compared to heparin; however, the inclusion of only 7 studies precludes reliable or valid inferences (Figure 5) (83). Variation observed in this plot could have been due to differences in methodological quality, target populations, or the treatment regimen.

Figure 5: Funnel plot assessing publication bias (Mortality Outcome)



3.4 Discussion

In this systematic review of patients with sepsis syndrome, we found no significant difference in mortality among the RCTs that compared heparin to any other intervention (OR 0.88, 95%CI 0.74 to 1.05). Pooled analysis suggest a trend towards decreased mortality in patients who received heparin compared to placebo or no intervention (OR 0.85, 95%CI 0.71 to1.02). This estimate was further supported by a large observational cohort-controlled study that similarly showed a reduction in death associated with heparin (HR 0.85, 95%CI 0.73 to 1.00). Changes in organ dysfunction, or length of stay due to heparin administration were not sufficiently described. Serious bleeding events or the need for transfusion were variably defined and inconsistently reported, but did not appear to be increased among in patients who received heparin.

Given the bidirectional relationship between coagulation and inflammation and the observation that natural coagulants are reduced in sepsis, several natural anticoagulants have been studied in phase III trials, including antithrombin, recombinant activated protein C (APC), and tissue factor pathway inhibitor. Only APC has been shown to reduce mortality in sepsis although a second large trial is underway to confirm or refute the original finding(84). Unfractionated heparin is also a natural anticoagulant with anti-inflammatory properties. The anticoagulant effects of heparin are mediated through a specific pentasaccharide sequence with high affinity to antithrombin; however, UFH binds non-specifically to endothelium and to many plasma constituents which contributes to the various anticoagulant-independent effects of heparin. These anticoagulant-independent effects of heparin are thought to mitigate inflammation in the setting of sepsis(19;21;22;64).

While phase III RCTs of unfractionated heparin in sepsis have not been performed, several lines of evidence support a potential role for heparin. For example, a recently published systematic review and meta-analysis of RCTs studying heparin in experimental animal models of sepsis demonstrated a reduction in death due to heparin administration (OR 0.27 (95%CI 0.16 to 0.46)(25). Prospectively collected, but non-randomised data from the placebo arms of phase III trials in sepsis also suggest a survival advantage associated with prophylactic dose heparin administration, independent of the study drug under investigation(26). Our results are consistent these previously published studies indicating a potential benefit of heparin and complement previously published observational work in this field(27). On the basis of these data, authors have openly called for prospective studies of heparin in patients with sepsis at high risk of death(27;85). In a recently presented national survey, 90% of critical care physicians practicing in Canada reported that future clinical trials of heparin are warranted(86).

3.4.1 Strengths and Limitations

One important strength of this systematic review includes the rigorous search methodology which was comprehensive, included non-English studies, and both randomized and observational studies. With these methods, it is unlikely that important scientific studies of heparin in sepsis were not omitted. Secondly, studies contributing the majority of data in the pooled analyses were of the highest methodological quality. Several limitations exist including the wide variability in heparin dosing, and duration of the study protocols. A single large RCT accounted for 83% of the summary effect measure for mortality; however, it is important to note that all patients in this trial

received APC(78). A trend towards reduced mortality with heparin was therefore observed in the context of concomitant activated protein C. Bleeding and other safety events were generally not reported, nor were other relevant outcomes such as organ dysfunction. Though important to consider, these limitations are a function of the included studies, and not a limitation of the review methods.

3.5 Conclusion

The results of this systematic review suggest that heparin may be beneficial when administered to patients with sepsis, especially in patients with severe sepsis or septic shock. Given the results of this study, and the results of previously published animal and other non-randomised observations, clinical trials of heparin in patients with severe sepsis or septic shock are justified.

4.0 Justification for a cross-sectional survey

The results of the systematic review indicate a potential role for heparin in severe sepsis and septic shock and highlight the need for further clinical trials. Further investigational work however is necessary inform the design and conduct of future trials. Heparin has been used in clinical practice since the 1970's, and was previous purveyed for use in disseminated intravascular coagulation (DIC) in the absence of clinical trials. Furthermore, activated protein C has been recently approved for use in severe sepsis, although cost, conflicting data, and controversy with the original trial appeared to limit uptake of this new therapy.

Using survey methodology, we intend to inform several aspects of future clinical trials including the willingness of the medical community to consider such investigations. If support exists for future trials, clinical equipoise would also need to exist, and therefore perceptions regarding heparin and alternate therapies will need to be explored. If another standard of care exists, future trials would need to include this standard. Given what appears to be slow uptake of activated protein C into clinical practice, information on potential barriers and facilitators regarding its use are important given that heparin is also an anticoagulant therapy. With this information, we could ideally design a program of research that could address potential barriers to the conduct of a trial and incorporate known facilitators of trial conduct.

5.0 NATIONAL SURVEY

5.1 Rationale

The pathobiology of severe sepsis and septic shock involves activation of coagulation, factor consumption and inhibition or reduction of circulating natural coagulants(37;87). To decrease coagulation and modulate host inflammation, several natural anticoagulants have been investigated(7;51;56). However, only human recombinant activated protein C (APC) has been shown to decrease mortality in a single multicentre randomised controlled trial (RCT)(7). Initial uptake of APC was slow due to cost (US 6,800 for a 4 day course), and safety concerns(88). Concerns pertaining to the conduct and reporting of the original trial and the subsequent publication of negative trials may also constitute barriers to its use(56;57).

Unfractionated heparin (UFH) is a naturally occurring anticoagulant that is used in the treatment of thrombotic disorders. Its anticoagulant effects are achieved by binding antithrombin in the circulation(16). Several live animal models of sepsis demonstrate a survival advantage secondary to heparin administration(23;24). A recent narrative review estimated the overall odds ratio for death associated with heparin therapy to be 0.27 (95% confidence interval (CI) 0.16 to 0.46) when considering all randomised animal studies(25). Post hoc subgroup analysis from phase III trials demonstrate increased survival in patients receiving heparin therapy, either alone or in combination with the intended study drug(26). A recently completed systematic review of all human randomised controlled trials of heparin demonstrated a trend towards reduced mortality with heparin (OR 85, 95%CI 0.71 to 1.02) (Zarychanski, unpublished

data) and a large observational study of patients with diagnosed with septic shock found a similar reduction in the hazard of death associated with unfractionated heparin (HR 0.85, 95%CI 0.73-1.00)(27). The cost of 4 a day IV infusion of unfractionated heparin at 1000 units/hr is approximately US $6.70.

In view of the available data suggesting a beneficial role for heparin in sepsis, in addition to the wide availability and low cost of this compound, calls for prospective trials have been made(27;85).

5.2 Objectives

With respect to patients diagnosed with severe sepsis or septic shock, the objectives of this survey were four fold:

a.) To evaluate the perceived utility and current use of anticoagulant therapies relative to other evidenced based therapies

b.) To enumerate potential barriers and facilitating factors to the use activated protein C

c.) To characterize the degree of certainty regarding the benefits and harms of unfractionated heparin

d.) To assess the willingness of critical care physicians to consider future clinical trials of heparin in this patient population

5.3 Methods

We conducted a cross-sectional, mixed-mode, self-administered survey of practicing critical care physicians in Canada. Research methods used in the construction, implementation, and reporting of this survey were based on published evidence,

including randomised controlled trials (RCTs), meta-analyses, and practice tools(89;90). Response rates were maximized by incorporating design and implementation elements that have been shown to have this favourable effect on response rates(91). Evidence based design elements included the use of short, user friendly, and relevant questions. Coloured ink was used, and endorsements from respected organizations (Canadian Critical Care Trials Group, Ottawa Hospital Research Institute, the University of Manitoba) were highlighted(91;92). Examples of evidenced-based implementation elements included the use of unconditional monetary incentives, delivery of a personalized cover letter in advance of the survey (for the web-based roll-out only), a stamped return envelope delivered with the questionnaire (paper-based roll-out only), and having at least 4 contacts with each potential respondent(91;92). The questionnaire, communication strategy and implementation procedure were structured to enhance clarity and readability based on principles of social exchange theory, principles designed to establish trust with potential respondents, and to increase rewards and decrease the perceived or real costs associated with participation(90). The survey was offered in French and English to respondents practicing in either Quebec or the rest of Canada. This study was approved by the Health Research Ethics Board at the University of Manitoba (Winnipeg, Manitoba).

5.3.1 Sample

The target population for this survey consisted of practicing critical care physicians working at Canadian academic centres, or centres affiliated with a Canadian university. For critical care physicians working in Quebec, names and contact information were

provided from a Provincial registry. For the rest of Canada, the physicians were identified by manually contacting the critical care departments of every University Hospital and centre affiliated with a Canadian university. Affiliated centres were defined as hospitals with formal agreements to teach residents and/or fellows.

5.3.2 Questionnaire Development

Item generation occurred via semi-structured interviews with 6 intensivists and 2 haemologists. Participants were presented with each survey objective and asked to list items necessary to fulfill that specific objective. Items were grouped into similar response categories, then reduced and revised using an iterative process based on expert opinion and interactive discussion. Items were also presented to members of the Centre for Transfusion (CTR) team at the University of Ottawa, and at two meetings of the Canadian Critical Care Trials Group (CCCTG) and further revised based member feedback. Response formats were either nominal, ordinal or interval and included indeterminate responses (e.g. I don't know, or I have no opinion) to reduce floor and ceiling effects and acknowledge uncertainty. The final questionnaire consisted of 19 questions, reflecting 3 major investigative domains reflecting the overall objectives of this survey (Appendix 4). The questionnaire and all correspondence were developed in English, translated into French by a professional translator, and then back-translated in to English to ensure appropriate connotation.

5.3.3 Questionnaire Pre-testing

To evaluate clinical sensibility, the questionnaire was assessed by 6 content experts using 5-point Likert scales (Appendix 5). After minor revision, the survey instrument was piloted on 12 Intensive Care fellows-in-training at 2 separate institutions. Time to completion, clarity of wording, and the usability of the instrument were assessed using 5-point Likert scales and post-survey interviews. Test-retest reliability of individual questions was examined by having the same fellows complete an identical questionnaire within 2 to 4 weeks.

5.3.4 Implementation Strategy

We used a mixed mode implementation strategy involving web-based and paper-based survey instruments, with up to 3 contacts per mode in the event of non-response. A pre-survey letter was first emailed to potential respondents with valid email addresses. Three days later, an email invitation containing an individualised web link to the web-based survey was sent to all potential respondents. Two email reminders were sent to non responders at 2 and 4 weeks following the initial invitation. Non-responders and individuals without valid email addresses were then mailed paper-based copies of the pre-survey letter and questionnaire followed by reminder cards at 2 and 4 weeks. All participants were mailed $5 Tim Horton gift cards regardless of participation. Individual survey responses were anonymous, but coded to allow efficient use of reminder cards.

5.3.5 Analyses

Descriptive statistics were presented as proportions with 95% confidence intervals. Test-retest reliability was analysed using chi square for nominal data; interval data was assessed by visually considering the proportion of respondents with exact matches or matches within 1 interval level on a 5 or 7 point Likert scale. A match within 1 interval level in greater than 80% of respondents was considered acceptable.

Factors associated with the use of activated protein C were assessed by multivariable logistic regression. Model parameters were estimated using the method of maximum likelihood and nested models were compared using the -2 log likelihood test. Variables included in the model were chosen based on clinical appropriateness. Confounding or effect modification were not explored. Results of regression analyses were expressed as odds ratios (OR) and 95% confidence intervals (CI). Odds ratios greater than 1 signify increased use of activated protein C compared to the referent group. 95% confidence intervals and p values reported reflect a two-tailed α level of 0.05.

5.4 Results

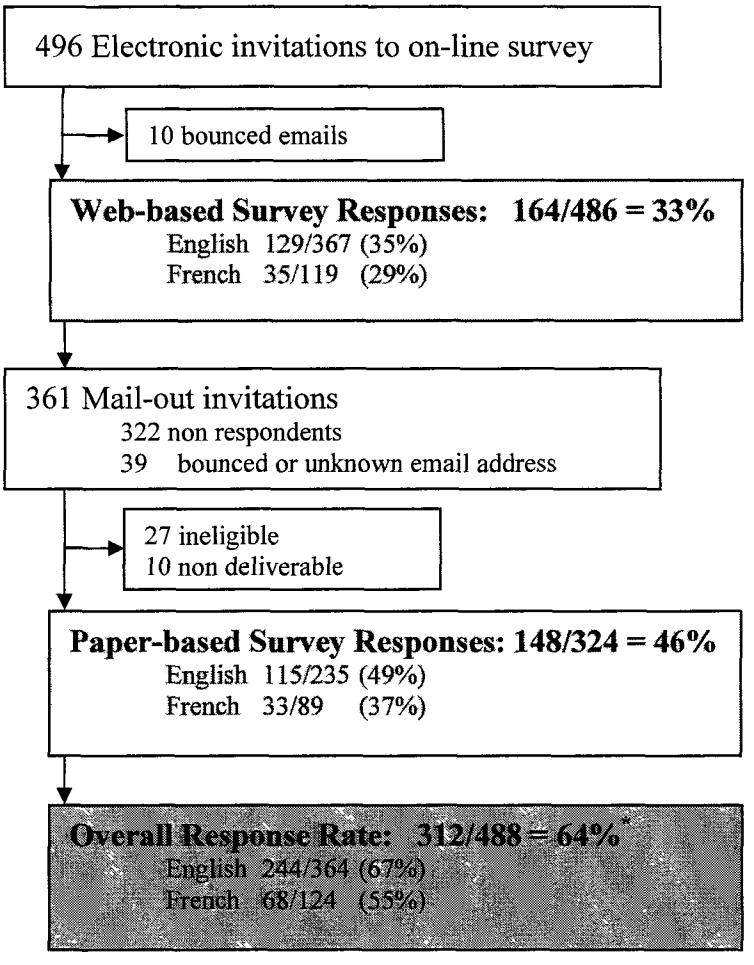
5.4.1 Pre Survey testing

All content experts stated that the survey questions were directed at important issues regarding the current and potential uses of anticoagulants in sepsis. Important or crucial omissions in the questionnaire were not identified. Reviewers stated that the response options were complete and easily understood to a moderate or large extent, and that the questionnaire was quite likely or very likely to inform the design of future clinical trials of heparin in sepsis. No significant differences in nominal or interval responses existed when evaluating test-retest reliability. The time to complete the web-based and paper-based questionnaires was 10.1 and 11.3 minutes respectively.

5.4.2 Respondents

The overall survey response rate was 64% (312/488) (Figure 6). The response rates for the web-based and paper-based survey were 33% and 46% respectively. The response rate for individuals receiving English questionnaires was 67% while the response rate for those sent French questionnaires was 55%. Demographic details of the respondents are summarised in table 4. Respondents most commonly identified Internal Medicine as their primary specialty (55%), followed by Anaesthesiology (29%). The majority of respondents were either between the ages of 36-45 (48%) or 46-55 (31%). Physicians from Ontario comprised 34% of the study population, followed by Quebec (17%) and Alberta (13%). Respondents reported practicing mostly in mixed medical/surgical ICUs in 83% of the time and the majority worked 11-15 (43%) or 16-20 (25%) clinical weeks per year in an intensive care unit (ICU).

Figure 6: Mixed-mode survey response



*Denominator for overall response (n=488) equals the total number of web-based responses (n=164) plus the number of paper-based invitations delivered to eligible recipients (n=324)

Table 4: Survey respondents (n=312)

Specialty	
Internal Medicine	173 (55%)
Anaesthesiology	91 (29%)
General Surgery	31 (10%)
Emergency Medicine	11 (4%)
Other	6 (2%)
Age	
25 - 35	28 (9%)
36-45	151 (48%)
46-55	98 (31%)
>55	35 (11%)
Clinical weeks per year in ICU	
<5	2 (0.6%)
5-10	63 (20%)
11-15	132 (42%)
16-20	78 (25%)
20-30	34 (11%)
>30	3 (1%)
Province	
BC	25 (8%)
Alberta	41 (13%)
Saskatchewan	13 (4%)
Manitoba	27 (9%)
Ontario	107 (34%)
Quebec	52 (17%)
NB	15 (5%)
NS	27 (9%)
PEI	-
NFLD	5 (2%)

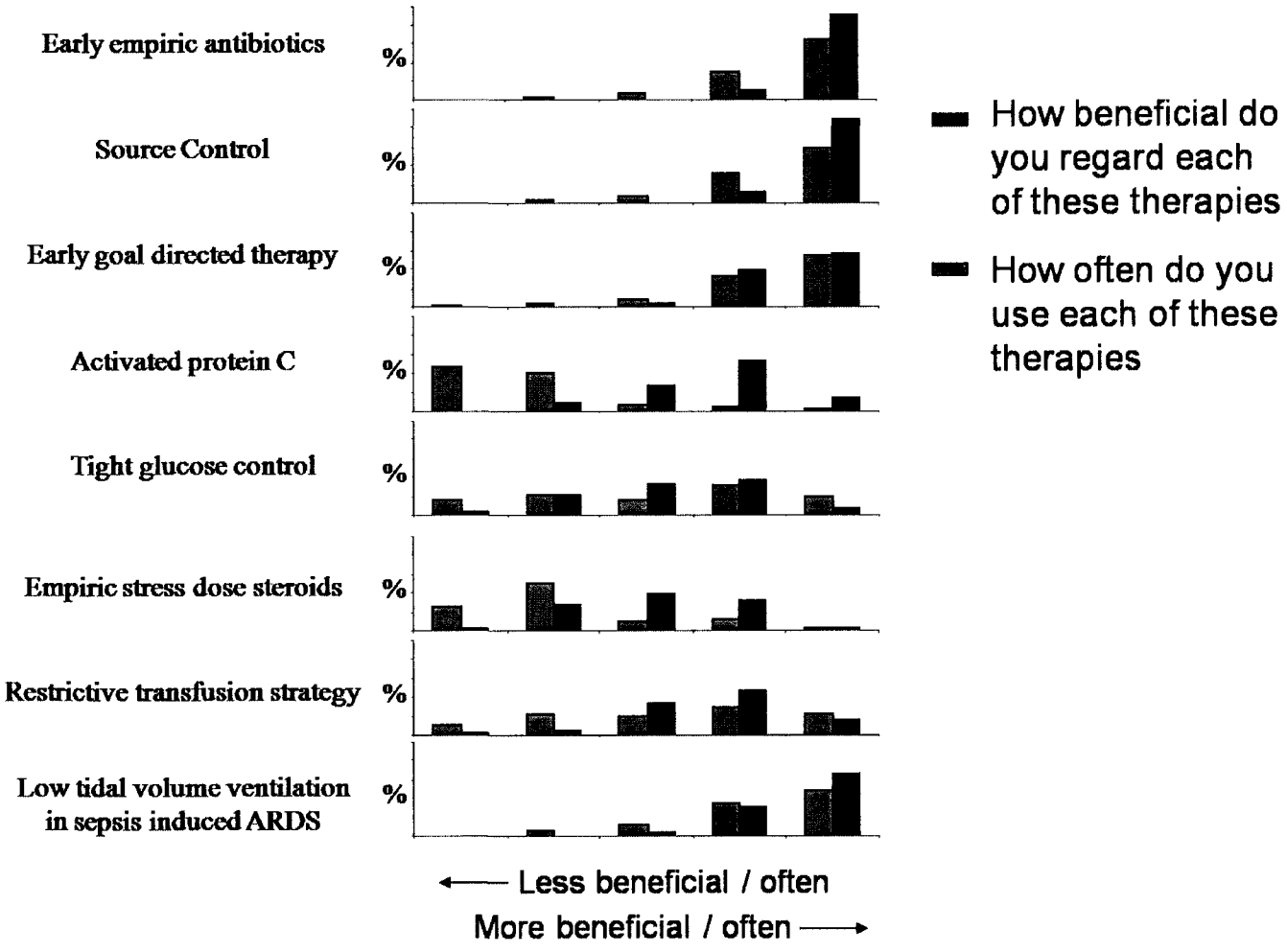
5.4.3 Objective 1: Benefit and use of evidenced based therapies in sepsis and septic shock

In the early management of severe sepsis or septic shock, 89% (n=278) of respondents indicated that anticoagulant therapies were either important (26%) or potentially important (63%) when given to modulate the host inflammatory response or activation of coagulation. From a list of 9 anticoagulants, the top 3 agents considered clinically beneficial or potentially beneficial in the early management of severe sepsis or septic shock were activated protein C (97%), unfractionated heparin (71%), and low molecular weight heparin (LMWH) (63%). Of respondents (n=34) who believed that anticoagulant therapies were not important, inadequate quality of evidence (52%), inconsistent evidence (39%) or an inadequate quantity of evidence (39%) were the 3 most frequently selected reasons.

When asked to rank the perceived benefits and current use of 8 different therapies in severe sepsis or septic shock on a Likert scale, early empiric antibiotics, source control, early goal directed therapy (EGDT) and low tidal volume ventilation for ARDS were perceived to be 'definitely beneficial' in 89%, 85%, 56%, and 63% of patients and reportedly used 'almost always/always' (meaning 75-100% of patients) in 93%, 88%, 86%, and 81% of respondents (Figure 7). Conversely, 'definite benefit' and use 'almost always/always' were substantially lower for restrictive transfusion strategies (16% and 49%), activated protein C (14% and 6%), tight glucose control (6% and 46%), or empiric stress dose steroids (1.4% and 14%). Activated protein C was the therapy most

commonly never or rarely used (meaning 0-10% of patients), as reported by 47% of respondents (Figure 7).

Figure 7: Perceived benefits and stated use of therapies in severe sepsis and septic shock



Benefits were rated on a Likert scale as definitely not beneficial, probably not beneficial, neutral, probably beneficial, or definitely beneficial. Degree of usage reflected the following categories: never/rarely (0-10% of patients), sometimes (11-25%), often (26-50%), usually (51-75%), almost always/always (76-100%).

5.4.4 Objective 2: Barriers and facilitators to the use of APC

In a case based scenario designed to assess the reported use of activated protein in patients with sepsis with no signs of bleeding or contraindications to APC, 98% (n=306) of critical care physicians indicated they would never or rarely (meaning 0-10% patients) prescribe APC to a septic patient diagnosed with pneumonia without refractory hypotension or signs of organ failure. Conversely, when presented the same patient, but with persistent hypotension requiring vasopressors despite fluid resuscitation, acute renal failure, and an APACHE II score of 28, who had no contraindications to APC and in whom APC is a Surviving Sepsis Campaign Grade B recommendation(93), 26% (n=81) of physicians indicated they would use APC almost always or always (meaning 75-100% of patients).

A multivariable logistic model was constructed to explore factors associated with the use of APC in a patient meeting all clinical criteria for APC use according to the Surviving Sepsis Campaign guidelines(93). These guidelines synthesize current evidence and expert opinion pertaining to the management of patients with sepsis. Factors included in the model were age, primary specialty, years of fellowship training in Critical Care Medicine, province of practice, and the number of patients per week admitted with severe sepsis or septic shock. Only years of fellowship training and the province where the respondent practiced critical care were associated with APC use (Table 5). The odds ratio associated with almost always/always use of APC in physicians with 1 year of fellowship training compared with no fellowship training was 3.32 (95%CI 1.31 to 8.40). The odds ratio associated with 2 or more years of fellowship training (compared to no fellowship training) was not significantly increased (OR 1.71, 95%CI 0.71 to 4.38).

Compared with APC use in the Province of Ontario, the odds of almost always/always using APC in a patient defined according to the Surviving Sepsis Campaign guidelines was 2.76 greater in Alberta (95%CI 1.11 to 6.90).

Table 5: Factors associated with almost always/always use of activated protein C (n=308)

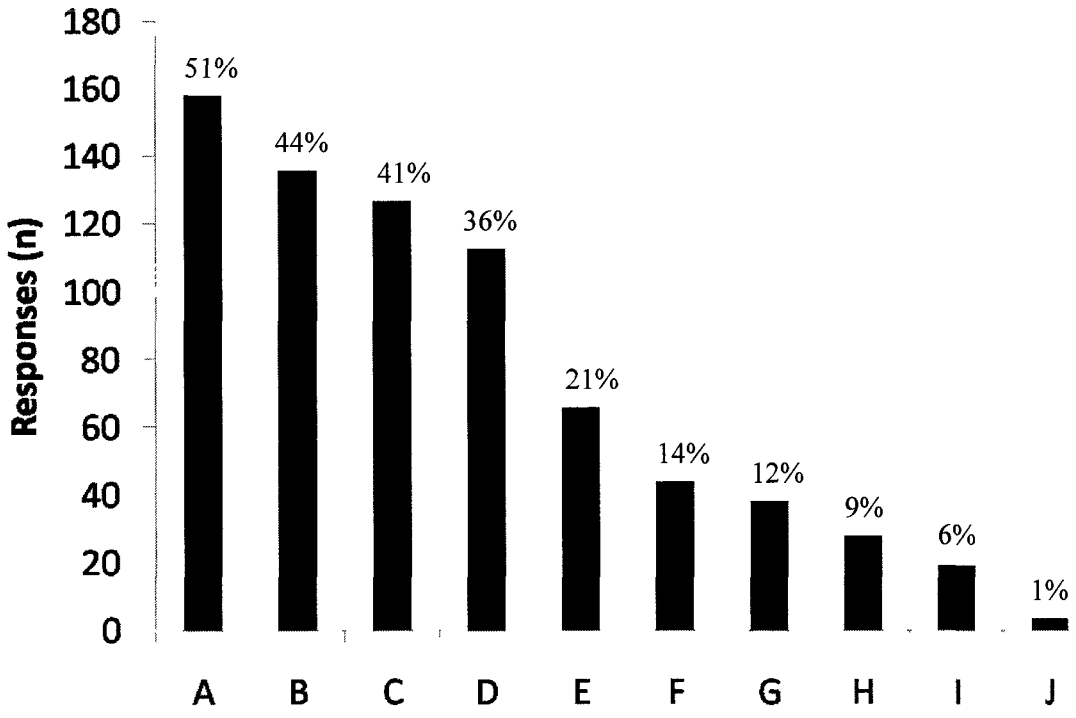
	[illegible]	[illegible]
Age		
>55	2 (0.5, 7.94)	0.33
46-55	1.15 (0.36, 3.69)	0.82
36-45	1.14 (0.37, 3.49)	0.82
25-35	-	-
Base specialty		
Other	2.29 (0.29, 17.76)	0.43
Anesthesiology	1.59 (0.53, 4.71)	0.41
Internal medicine	1.43 (0.5, 4.03)	0.50
Emergency Medicine	0.48 (0.05, 5.1)	0.54
General surgery	-	-
Years of critical care fellowship training		
1 year	3.32 (1.31, 8.4)	0.01
2 or more	1.76 (0.71, 4.38)	0.22
None	-	-
Province of practice		
Atlantic	2.76 (1.11, 6.9)	0.03
British Columbia	2.4 (0.83, 6.87)	0.10
Alberta	1.2 (0.48, 2.99)	0.70
Manitoba/Saskatchewan	0.96 (0.37, 2.5)	0.94
Quebec	0.65 (0.25, 1.65)	0.36
Ontario	-	-
Patients with severe sepsis or septic shock admitted per week		
>10	0.32 (0.03, 3.69)	0.36
7-10	0.89 (0.21, 3.8)	0.87
4-6	0.97 (0.34, 2.81)	0.96
1-3	0.98 (0.39, 2.49)	0.97
<1	-	-

*Adjusted for age, base specialty, years of critical care training, province of practice, and patient with severe sepsis or septic shock admitted per week.

Industry involvement in the generation of the current evidence base was the most frequently cited barrier to the use of APC, selected in 51% (n=158) of potential respondents (Figure 8). A belief that the harms associated with APC may outweigh the potential benefits was selected by 44% (n=136) of respondents. Industry involvement in the generation of practice guidelines was selected 40% (n=127) of the time. In respondents who thought use of APC was not supported by the current evidence base (n=38), an insufficient number of completed RCTs (66%), inconsistent results of individual studies (60%), and high risk of bias due to industry sponsorship or involvement (45%) were the 3 most frequent issues identified by respondents.

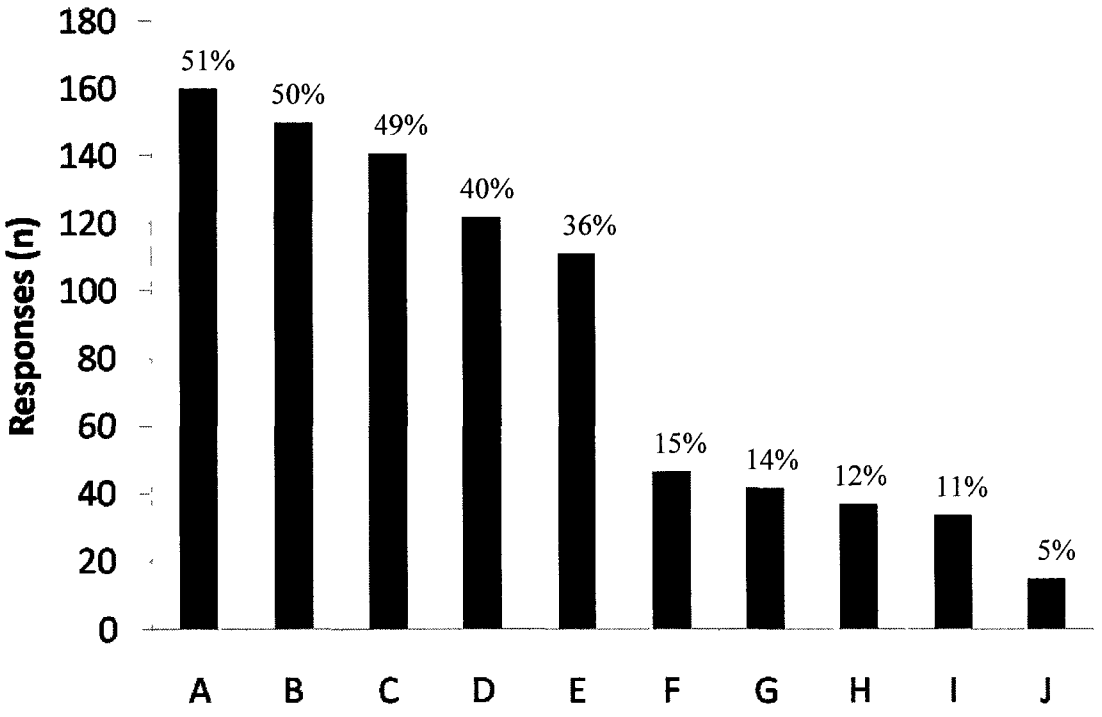
The most common factor believed to facilitate the use of APC as recommended by the Surviving Sepsis Campaign guidelines is agreement with the guideline itself, identified by 51% (n=160) of respondents (Figure 9). A belief that the benefits of APC outweigh the possible harms (50%, n=157), and an easy and efficient ICU approval process (49%, n=152) were the next most commonly selected factors reported to facilitate the use of APC. In respondents who thought the use of APC was facilitated by a strong evidence base (n=48), the substantial magnitude of the effect size (60%), low risk of bias due to high study quality (58%), and precise estimates of potential benefit (47%) were the 3 most frequent aspects identified.

Figure 8: Perceived barriers to the use of activated protein C as recommended by the Surviving Sepsis Campaign guidelines



A – Industry involvement in the generation of the current evidence
B – Harms may out-weigh the potential benefits
C – Industry involvement in the generation of the current practice guidelines
D – APC is not cost effective
E – Use not supported by the current evidence base
F – Disagree with the Surviving Sepsis Campaign recommendation
G – Other
H – Local experts do not support the use of APC in the above patient population
I – Difficult or inefficient ICU approval processes decrease appropriate use of APC
J – APC is associated with increased physician/nurse work load demands

Figure 9: Factors facilitating the use of activated protein C as recommended by the Surviving Sepsis Campaign guidelines

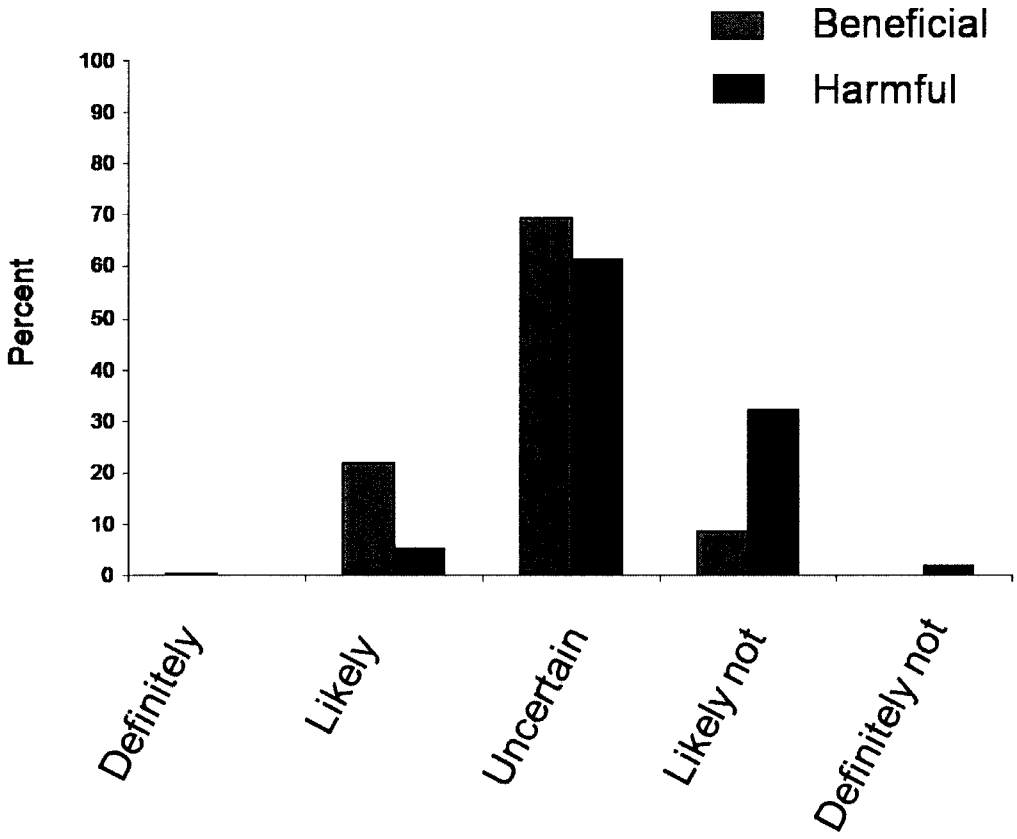


A – Agree with the Surviving Sepsis Campaign recommendation
B – Benefits of therapy outweigh the possible harms
C – Easy and efficient ICU approval processes are in place to facilitate use of APC
D – Local experts support the use of APC in the above patient population
E – APC is not associated with increased physician/nurse work load demands
F – Its use is supported by a strong evidence base
G – APC is cost effective
H – No concerns relating to industry involvement in the generation of the current evidence
I – No concerns relating to industry involvement in the generation of the current practice guidelines
J – Other

5.4.5 Objective 3: Degree of uncertainty regarding the benefits and harms of unfractionated heparin

When respondents were asked to report how certain they were that either UFH or LMWH are beneficial or harmful when used in the early treatment of severe sepsis or septic shock, 67% (n=211) indicated they were uncertain that UFH or LWMH were beneficial, and 61% (n=189) indicated they were uncertain that either UFH or LMWH were harmful in this context (Figure 10).

Figure 10: Degree of certainty that unfractionated heparin or low molecular weight heparin are beneficial or harmful when used in the early treatment of severe sepsis or septic shock (n=312)



5.4.6 Objective 4: Assessing the willingness of physicians to consider future clinical trials of heparin

In our sample population, 90% (n=281) of critical care physicians believed that future clinical trials of either UFH or LMWH are warranted in patients diagnosed with severe sepsis or septic shock. The most common reasons in support of future trials reflected the ready availability (79%), ease of administration (78%), and low cost of heparin. In the 31 respondents who believed that future trials of heparin were not warranted, the most frequently cited reasons were uncertainty whether sufficient biologic rationale exists to support clinical trials (52%), and uncertainty (48%) whether a beneficial role of heparin is suggested by the current evidence base.

5.5 Discussion

In this cross-sectional survey of Canadian critical care physicians, we found the majority (89%, n=278) believed anticoagulant therapies are important when used to modulate host inflammation and activation of coagulation in patients with severe sepsis or septic shock. Early empiric antibiotics, source control, EGDT, and low tidal volume ventilation in ARDS were highly valued, and reported to be used in most patients. Perceived benefits and reported use of activated protein C and empiric stress dose steroids were comparatively low. The majority of practicing critical care physicians are uncertain about the benefits and harms associated with UFH or LMWH in the early treatment of severe sepsis and septic shock, and that 90% believe future clinical trials are warranted.

Individual decisions around planned behavior and practice patterns are complex and include factors such as attitudes, subjective norms, and perceptions concerning an individual's sense of control(94). In our survey, when presented with a case description of a patient with septic shock for whom APC is recommended according to published guidelines(93), only 26% of critical care physicians indicated they used this therapy almost always or always in the advocated patient population. Concerns regarding industry involvement in the generation of the current evidence base and practice guidelines, and an unfavorable cost-benefit ratio were believed to be barriers to its use. Though our survey was not designed to characterize the entire range of factors affecting individual decisions, these data will need to be considered when planning research programs and clinical trials of anticoagulants or other therapies in patients with severe sepsis or septic shock.

Many factors influence the feasibility and design of a given clinical trial; clinical equipoise and a willingness to participate are essential. Clinical equipoise is said to exist when there is genuine uncertainty within the medical community regarding the comparative therapeutic merit of each arm in a trial(95). In this regard, our survey indicated that two-thirds of physicians (67%) are uncertain if UFH or LMWH are beneficial or harmful (61%) when used in the early treatment of severe sepsis or septic shock, leading one to reason that a state of clinical equipoise exists for this therapy. With respect to comparative therapeutic merit, a clear standard of care does not appear to exist given that 14% of respondents believed that APC was definitely beneficial, and that 1.4% reportedly used the agent almost always or always in severe sepsis and septic shock. Even when presented with the ideal patient for whom this drug is indicated as per the

Surviving Sepsis Campaign guidelines, 26% said they would consider using this agent in almost all patients. Support for future clinical trials of heparin in sepsis appears to exist with 90% of Canadian academic critical care physicians specifying that, in their opinion, future clinical trials of heparin are warranted.

5.5.1 Strengths and Limitations

As with any study, limitations exist that merit discussion. With the intention of identifying centres that might prospectively enroll patients in future clinical trials, the target population for this survey were critical care physicians working in academic centres or centres affiliated with an academic institution. Physician attitudes and responses may therefore not be generalizable to community hospitals. To ensure feasibility and maximize the overall response rate, questions were concise, and closed-ended. This format permitted enumeration of physician attitudes and opinions, but our survey instrument was not able to formally examine all relevant factors influencing practice such as individual prior beliefs and heuristics, or past, present and future personal physician incentives. Given the anticipated sample size, survey pre-testing, including the assessment of clinical sensibility and test-retest reliability, was conducted on ICU fellows in training. It is therefore possible that their perceptions of the survey, performance on repeat testing, may not have represented the results obtained if pre-survey testing had been conducted on fully qualified critical care physicians.

Strengths of our survey include the use of rigorous scientific methodology including a systematic approach to questionnaire development and pre-survey testing to optimize internal validity(89). External validity, or generalizability, was maximized by

achieving a robust response rate of 64%. Multiple evidence based strategies were employed to maximize the survey response rate including the formulation of short questions, using a pre-survey letter, multiple reminder letters, and including a non-monetary incentive(91;92). Additional survey elements incorporated and supported by clinical research included the use of personalised correspondence, demonstrating evidence of University/academic endorsement, and including pre-stamped return envelopes (paper-based survey) with the survey questionnaire(90;91).

5.6 Conclusions

Anticoagulant therapies used to modulate host inflammation in patients with severe sepsis or septic shock are reported to be clinically important to practicing critical care physicians, but not routinely used. The majority of critical care physicians believe that unfractionated heparin or low molecular weight heparin may be potentially beneficial in severe sepsis or septic shock, and agree that further clinical trials are warranted. Uncertainty exists regarding the potential clinical benefits or harms of unfractionated heparin or LWMH in patients diagnosed with sepsis or septic shock.

6.0 SUMMARY AND FUTURE DIRECTIONS

The overall objective of this thesis was to construct the evidence based-framework necessary to justify prospective clinical trials of unfractionated heparin in patients with severe sepsis and septic shock. This objective was carried out by planning and conducting 2 original research studies: a systematic review of the clinical literature, and a national cross-sectional self-administered survey.

The goal of the systematic review was to investigate the clinical benefits and harms associated with the use of heparin in patients with sepsis, severe sepsis, septic shock, or disseminated intravascular coagulation (DIC) due to infection. Nine studies met our inclusion criteria, 7 randomised controlled trials and 2 retrospective cohort studies. Pooled analysis from randomised controlled trials suggested a trend towards decreased mortality in patients who received heparin compared with placebo or no intervention (OR 0.85, 95%CI 0.70 to 1.02), and this estimate was further supported by my own observational cohort-controlled study that similarly showed a reduction in death associated with heparin (HR 0.85, 95%CI 0.73 to 1.00). Changes in organ dysfunction, or length of stay due to heparin administration were not sufficiently described among the included RCTs. Likewise, serious bleeding events or the need for transfusion were variably defined and inconsistently reported, but did not appear to be increased among patients who received heparin. The conclusion from this systematic review was that heparin may be beneficial when administered to patients with sepsis, particularly patients with severe sepsis or septic shock. Further trials are necessary to definitively establish the efficacy and safety of this intervention.

Prior to the design and potential conduct of future clinical trials, a survey was undertaken. With regard to patients diagnosed with severe sepsis or septic shock, the objectives of the survey were to evaluate the perceived utility and current use of anticoagulant therapies in relation to other evidenced based therapies, to enumerate potential barriers and facilitating factors to the use of activated protein C, to characterize the degree of certainty regarding the benefits and harms of unfractionated heparin, and to assess willingness of critical care physicians to consider future clinical trials of heparin.

In our cross-sectional survey of Canadian critical care physicians, we found that a majority (89%) of respondents believed anticoagulant therapies are important when used to modulate host inflammation and activation of coagulation in patients with severe sepsis or septic shock. Early empiric antibiotics, source control, EGDT, and low tidal volume ventilation in ARDS were highly valued, and reported to be used in most patients. Perceived benefits and use of activated protein C, or empiric stress dose steroids were comparatively low. We found that the majority of practicing critical care physicians are uncertain about the benefits and harms associated with UFH or LMWH in the early treatment of severe sepsis and septic shock, and that 90% believe future clinical trials are warranted. We therefore concluded that anticoagulant therapies used to modulate host inflammation in patients diagnosed with severe sepsis or septic shock are reported to be clinically important, but not routinely used. The majority of critical care physicians believed that unfractionated heparin or low molecular weight heparin may be potentially beneficial in severe sepsis or septic, and believed that further clinical trials are warranted.

Based on the results of the systematic review and survey, future clinical trials of unfractionated heparin or low molecular weight heparin, are justified and would be

supported by critical care physicians practicing in Canada. Clinical equipoise regarding the benefits and harms of UFH or LWMH appears to exist, and an alternative standard of care is not readily apparent. The direct implication is that either placebo controlled trials, or trials of heparin vs. 'standard therapy' are ethically justifiable given current practice patterns in Canada. After much discussion with my mentors and with members from the Canadian Critical Care Trials Group, the next step in this research program is to conduct a multicentre dose-finding study of unfractionated heparin in patients with septic shock.

Though heparin has been used in clinical practice for decades, the mechanism of action of this agent in sepsis is unclear, and the dose necessary to achieve clinical benefit in the absence of adverse outcomes is speculative. A dose finding trial will be useful to assess the underlying mechanisms of action (anticoagulant or anti-inflammatory), and the feasibility of a randomised controlled trial (consent, enrolment, protocol adherence, etc). Though not finalized, this trial is currently designed as a 3-arm study investigating two different IV doses of unfractionated heparin compared with a control group receiving subcutaneous heparin (5000 units twice daily) for the prevention of deep vein thrombosis. It is our expectation that this dose finding study will inform the design of a future multicentre randomised controlled trial designed to assess the efficacy and safety of unfractionated heparin in patients with severe sepsis or septic shock.

7.0 MUSINGS AND RUMINATIONS

The background to this work originated in 2005, when as a clinical fellow, I wondered if unfractionated heparin would be as clinically efficacious as a new, very expensive drug that had been recently introduced into clinical practice. A colleague of mine, Anand Kumar, invited me to undertake an analysis of heparin in his own database of patients with septic shock. Together, we found what appeared to be clinical benefit associated with heparin, but our manuscript was critiqued by reviewers who did not believe the results could be valid. Based on reviewer comments, and with the help of Steve Doucette and Dean Fergusson, we repeated the analysis using increasingly sophisticated methods to control for systematic bias; our conclusions however remained unchanged.

The widespread availability and low cost of heparin, combined with the lethality of septic shock motivated me to pursue the notion that heparin may actually be effective in patients with septic shock. If correct, the implications for clinical practice would be enormous. The agent is so inexpensive that virtually any country - resource rich, or resource limited - could afford it. However, because the drug is generic and inexpensive, corporate and academic motivation to study it was relatively low, and thus I knew considerable background work would be necessary before this agent was ready to be investigated in randomised trials.

"If a man is to shed the light of the sun upon other men, he must first of all have it within himself" (Romain Rolland)

Although the ideas for this thesis were my own, they were cultivated and made operational with expert help from my mentors, Dean Fergusson and Paul Hébert, thesis committee members (Drs. Alan Tinmouth, Deborah Cook, Anand Kumar, and Donald Houston), and members of the Canadian Critical Care Trial Group (CCCTG). Design elements and operational details of the systematic review and the survey were presented at several CCCTG meetings where I received invaluable advice and collective mentorship. With continued input and direction from CCCTG members, the pilot dose finding trial will be designed and conducted. If I have learned one thing from 18 years of post-secondary education, it is the importance of mentorship. None of this work would have advanced to this level without the input of the aforementioned individuals and the collective membership of the CCCTG.

"There is an easy solution to every problem – neat, plausible, and wrong" (H.L. Mencken).

Of course no one expected any of this process to be easy. Thankfully it is by confronting challenge that we learn the most. This thesis, and my experience in the epidemiology programme in Ottawa has definitely instilled the value of planning and attention to detail in clinical research. Keeping track of 2105 citations from over 10 sources is inherently problematic and a recipe for frustration. I am grateful that David Moher and Margaret Sampson encouraged me to become a Reference Manager power-user. Finding Chinese medical literature is a nightmare - translating these and other

foreign language citations only increases the level of difficulty. Though I think the routine inclusion of Asian language literature in systematic reviews would be valuable, practical mechanisms to locate, translate, and adjudicate these studies do not currently exist.

Given that this was my first experience designing and conducting a scientifically valid survey, the learning curve was admittedly steep. Who knew survey methodology could be so involved? Thankfully, I had experts on my team to show me the ropes and I am particularly grateful that Karen Burns had recently published a comprehensive and practical guide on this topic and that my close colleague and friend Alexis Turgeon had completed a survey in a similar target population. Mixed mode surveys are complicated, and I would think twice about walking this road again. Both web-based and paper-based surveys have unique challenges and mixed-mode surveys necessarily mandate that all of these encumbrances be addressed.

The day I 'went live' with the web-based survey, sent to almost 500 colleagues around the country, I was immediately deluged with emails from respondents who said the web-based tool did not work! To my disappointment, I realised I made a last minute programming error in the internal response logic and was forced to re-tool, and re-invite everyone to participate. Though some had managed to complete the survey, all previous responses had to be deleted, and thus I had to ask all potential respondents to complete the survey a second time…how embarrassing. As if that was not awkward enough, when people received their unconditional token of appreciation, a $5 Tim Hortons gift card, another round of emails arrived saying they did not work! It turns out that the cards were not activated by the company before they were sent to me. The cards were able to

be activated centrally, but this seemingly unavoidable disaster necessitated a second explanatory 'humble-pie' email from yours truly.

"Every end is a new beginning" (a recent fortune cookie)

Though this is the end of this my thesis, it is just the beginning for clinical trials of heparin in sepsis. It is equally only the beginning of what I hope will be a long and productive career of scientific discovery that will better the lives of those most in need.

8.0 CONCLUSION

Based on the work conducted and data presented, it is my thesis that unfractionated heparin may be beneficial when administered to patients with severe sepsis or septic shock. Future clinical trials are warranted and supported by a medical community who believe that this avenue of research is clinically important and who are genuinely uncertain regarding the potential therapeutic benefits or harms of heparin used in this patient population.

Appendix 1: Medline search for systematic review

```
1     exp Sepsis/ (69087)
2     (sepsis or septic$).tw. (77452)
3     Disseminated Intravascular Coagulation/ (9297)
4     or/1-3 (125638)
5     exp Heparin/ (49075)
6     Heparin, Low-Molecular Weight/ or Heparinoids/ or Enoxaparin/ or Dalteparin/
or Nadroparin/ (7670)
7     (heparin or unfractionated heparin or low molecular weight heparin or
fondaparinux or idraparinux or enoxaparin or dalteparin or tinzaparin or reviparin
or nadroparin or parnaparin or certoparin or ardeparin or LMWH).tw. (54847)
8     or/5-7 (71532)
9     animals/ not humans/ (3233627)
10     (4 and 8) not 9 (2258)
11     comparative study/ or follow-up studies/ or prospective studies/ or risk
factors/ or cohort.mp. or compared.mp. or groups.mp. or multivariate.mp. (3808301)
12     Epidemiologic studies/ (4170)
13     exp case control studies/ (399889)
14     exp cohort studies/ (686468)
15     (cohort adj (study or studies)).tw. (40109)
16     Cohort analy$.tw. (1973)
17     (Follow up adj (study or studies)).tw. (29291)
18     (observational adj (study or studies)).tw. (19257)
19     Longitudinal.tw. (87504)
20     Retrospective.tw. (161397)
21     Cross sectional.tw. (87337)
22     Cross-sectional studies/ (91087)
23     or/11-22 (4096747)
24     randomized controlled trial.pt. (261792)
25     controlled clinical trial.pt. (79616)
26     Randomized Controlled Trials as Topic/ (55793)
27     random allocation.sh. (62095)
28     double blind method.sh. (99250)
29     single-blind method.sh. (12315)
30     clinical trial.pt. (456604)
31     exp Clinical Trials as Topic/ (208828)
32     (clin$ adj25 trial$).ti,ab. (159956)
33     ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw. (102819)
34     placebo$.sh. (29407)
35     placebo$.ti,ab. (117339)
36     random$.ti,ab. (452900)
37     research design.sh. (53575)
38     comparative study.pt. (1419883)
39     exp evaluation studies/ (107570)
40     follow up studies.sh. (374722)
41     prospective studies.sh. (249296)
42     (control$ or prospectiv$ or volunteer$).ti,ab. (2087534)
43     or/24-42 (4047689)
44     animals/ not humans/ (3233627)
45     43 not 44 (3191985)
46     10 and 23 (479)
47     10 and 45 (554)
48     10 and (23 or 45) (686)
```

Appendix 2: RCT data extraction form for eligible studies

Reviewer's Initials: _____ Date of data extraction:_____
(dd/mm/yyyy)

Article Identification

Ref ID number: _____

Title: _____

_____

_____

First Author: _____

Journal name/
Reference Source _____

☐Journal article ☐Published Abstract ☐Conference Proceeding ☐Other_____

Year:_____ Volume:_____ Starting Page:_____

Language of Publication: _____

Source of sponsorship (Study) _____

Study - country of origin _____

Comments: _____

_____

Verification of Eligibility

Inclusion Criteria	Verify by a "tick" mark
1. Randomised Clinical Trial	
2. >80% of the study population consisted of patients diagnosed with sepsis, severe sepsis, septic shock or disseminated intravascular coagulation due to infection. No more than 20% of cases of DIC can be secondary to malignancy alone	
3. Heparin administration (unfractionated or low molecular weight)	

Study Design

☐Single Centre ☐Multicentre

Type of ICU/centre (eg. medical, surgical, mixed med/surg, burn, trauma)

_____

_____

Comments/Clarification:_____

_____

_____

Inclusion Criteria:

1. _____

2. _____

3. _____

4. _____

Exclusion Criteria:

1. _____

2. _____

3. _____

4. _____

5. _____

6. _____

If admitted with DIC, what were the criteria for DIC: _____

_____

_____

If admitted with sepsis, what were the criteria for sepsis:_____

_____

_____

Screening and Enrollment

Total patients randomized _____

Total patients with sepsis _____

	Heparin	**Control**
No. of patients assigned to group	_____	_____
No. of patients who completed the study	_____	_____
No. of patients included in analysis	_____	_____
Description of losses to Follow up: **n (%)**	_____	_____

Were details and reasons given to explain the losses to follow up?: ☐Yes ☐No

Was the analysis intention to treat? ☐Yes ☐No ☐Not reported

Stated outcome Measures

Stated Primary outcomes:
1. _____
2. _____
3. _____
4 _____

Secondary outcomes:
1. _____
2. _____
3. _____
4 _____

Intervention Details:

HEPARIN

Type of Heparin administered: ☐Unfractionated
☐Low Molecular Weight Heparin (Type: _____)

Duration of intervention period: (hours, days) _____

Dosing regimen: _____

_____

Co-interventions during trial:
Use of concomitant anticoagulant therapies:_____

_____

Other Cointerventions:_____

CONTROL GROUP

Type of control: _____

Duration of intervention period: (hours, days) _____

Dosing regimen: _____

_____

Co-interventions during trial:
Use of concomitant anticoagulant therapies:_____

_____

Other Cointerventions:_____

Baseline Characteristics

	Heparin N = _____	CONTROL N = _____
Age (mean/SD or median/IQR)		
APACHE 2 or 3 (mean/SD or median/IQR) **Injury Severity Score (ISS)** (mean/SD or median/IQR)		
DIC Score:		
SOFA (mean/SD or median/IQR)		
LODS/MODS (mean/SD or median/IQR)		
SAPS (mean/SD or median/IQR)		
Specific admission Diagnosis (n)		
Sepsis		
Malignancy		
Other: _____		
Source of sepsis:		
Respiratory		
Abdominal/GU		
Other		
INR (mean/SD or median/IQR)		
aPTT (mean/SD or median/IQR)		
Platelets (mean/SD or median/IQR)		
Number of patients requiring mechanical ventilation		

Outcome measures and Results (1)

Length of follow up:

	Heparin	CONTROL
DICHOTOMOUS OUTCOMES		
EFFICACY		
Mortality **Length of follow up?: _____**		
Need for renal replacement therapy		
Measure of organ dysfunction (SOFA or MODS score, or some description)		
Resolution of DIC **Length of follow up?: _____**		
SAFETY		
Bleeding events? (whatever is reported and specify definitions of bleeding)		
Need for red cell transfusion		
CONTINUOUS OUTCOMES		
ICU Length of stay (mean/SD or median/IQR)		
Duration of mechanical ventilation Units: _____ (usually days) (mean/SD or median/IQR)		
Red cell units transfused		

Assessment of Methodological Quality

Randomization	**0** **Not randomized**	**1** **randomized**	**2** **method to generate the randomization sequence was described and appropriate**
Double blinding	**0** **Not double blinded**	**1** **Double blind**	**2** **of blinding was described and appropriate**
Withdrawals and drop outs	0 no description of participants who were included in the study but did not complete the observation period	1 explicit description of participants who were included in the study but did not complete the observation period or were not included in the analysis The number and reasons for withdrawal in each group must be stated	
Allocation Concealment	Inadequate	Unclear	Adequate

Method of randomization: _____ ☐Not Stated

Method of blinding: _____ ☐Not Stated

Method of allocation concealment: _____ ☐Not Stated

Appendix 3: Observational data extraction form

Reviewer's Initials: _____ Date of data extraction:_____
(dd/mm/yyyy)

Article Identification

Ref ID number: _____

Title: _____

_____

_____

First Author: _____

Journal name/
Reference Source _____

☐Journal article ☐Published Abstract ☐Conference Proceeding ☐Other_____

Year:_____ Volume:_____ Starting Page:_____

Language of Publication: _____

Source of sponsorship (Study) _____

Study - country of origin _____

Comments: _____

_____

Verification of Eligibility

Inclusion Criteria	Verify by a "tick" mark
4. Cohort-controlled or case-controlled study	
5. >80% of the study population consisted of patients diagnosed with sepsis, severe sepsis, septic shock or disseminated intravascular coagulation due to infection. No more than 20% of cases of DIC can be secondary to malignancy alone	
6. Heparin administration (unfractionated or low molecular weight)	

Study Design

☐Cohort ☐Case-controlled

☐Retrospective ☐Prospective

☐Single Centre ☐Multicentre

Type of ICU/centre (eg. medical, surgical, mixed med/surg, burn, trauma)

_____

_____

Comments/Clarification:_____

_____

_____

Inclusion Criteria:

1. _____

2. _____

3. _____

4. _____

Exclusion Criteria:

1. _____

2. _____

3. _____

4. _____

5. _____

6. _____

If admitted with DIC, what were the criteria for DIC: _____

_____

_____

If admitted with sepsis, what were the criteria for sepsis:_____

_____

_____

Screening and Enrollment

Total patients _____

Total patients with sepsis _____

Other patients (specify type and %) _____

	Heparin	**Control**
No. of patients assigned to group	_____	_____
No. of patients included in analysis	_____	_____
Description of losses to Follow up: **n (%)** (if prospective study)	_____	_____

Were details and reasons given to explain the losses to follow up?: ☐Yes ☐No ☐N/A

Was the analysis intention to treat? ☐Yes ☐No ☐Not reported ☐N/A

Stated outcome Measures

Stated Primary outcomes: 1. _____

2. _____

3. _____

4 _____

Secondary outcomes: 1. _____

2. _____

3. _____

4 _____

Intervention Details:

HEPARIN

Type of Heparin administered: ☐Unfractionated
☐Low Molecular Weight Heparin (type: _____)

Duration of intervention period: (hours, days) _____

Dosing regimen: _____

_____

Co-interventions during trial:
Use of concomitant anticoagulant therapies:_____

_____

Other Cointerventions:_____

CONTROL GROUP

Type of control: _____

Duration of intervention period: (hours, days) _____

Dosing regimen: _____

_____

Co-interventions during trial:
Use of concomitant anticoagulant therapies:_____

_____

Other Cointerventions:_____

Controlling for confounders:

Describe the method used to control for confounders:

Which confounders were controlled for:

Baseline Characteristics

	Heparin N = _____	**CONTROL** N = _____
Age (mean/SD or median/IQR)		
APACHE 2 or 3 (mean/SD or median/IQR) **Injury Severity Score (ISS)** (mean/SD or median/IQR)		
DIC Score:		
SOFA (mean/SD or median/IQR)		
LODS/MODS (mean/SD or median/IQR)		
SAPS (mean/SD or median/IQR)		
Specific admission Diagnosis (n)		
Sepsis		
Malignancy		
Other: _____		
Source of sepsis:		
Respiratory		
Abdominal/GU		
Other		
INR (mean/SD or median/IQR)		
aPTT (mean/SD or median/IQR)		
Platelets (mean/SD or median/IQR)		
Number of patients requiring mechanical ventilation		

Outcome measures and Results (1)

Length of follow up:

	Heparin	CONTROL
DICHOTOMOUS OUTCOMES		
EFFICACY		
Mortality **Length of follow up?: _____**		
Need for renal replacement therapy		
Measure of organ dysfunction (SOFA or MODS score, or some description)		
Resolution of DIC **Length of follow up?: _____**		
SAFETY		
Bleeding events? (whatever is reported and describe the definitions)		
Need for red cell transfusion		
CONTINUOUS OUTCOMES		
ICU Length of stay (mean/SD or median/IQR)		
Duration of mechanical ventilation Units: _____ (usually days) (mean/SD or median/IQR)		
Number of RBC units transfused		

NEWCASTLE OTTAWA SCALE - COHORT STUDIES

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✱
   b) somewhat representative of the average _____ in the community ✱
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✱
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

Selection score: ___ / 4

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✱
   b) structured interview ✱
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✱
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✱
   b) study controls for any additional factor ✱ (This criteria could be modified to indicate specific control for a second important factor.)

Comparability score: ___ / 2

Outcome

1) Assessment of outcome
   a) independent blind assessment ✱
   b) record linkage ✱
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✱
   b) no

Outcome score: ___ / 3

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✱
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✱
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

TOTAL score: ___ / 9

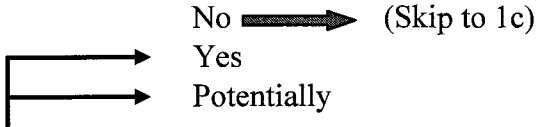
Appendix 4: Survey Questionnaire

Part 1:

The aims of these first two questions are to evaluate the perceived utility and current use of anticoagulant therapies in sepsis in relation to other evidenced based therapies.

1. **Consider a clinical environment with no institutional barriers and where cost is NOT a factor:**

   Is the concept of administering anticoagulant therapies clinically important in the early management of severe sepsis or septic shock when given to modulate the host inflammatory response or the activation of coagulation? *(i.e., NOT for the prevention or treatment of venous thrombosis)*



1b. (If Yes OR Potentially), Which anticoagulants would you consider clinically beneficial (e.g., improved survival, or decreased morbidity) in the early management (e.g., first 48 hours) **of severe sepsis or septic shock?** *(Select ONE response for EACH of the following therapies)*

Unfractionated heparin	Yes	No	Potentially
Low molecular weight heparins	Yes	No	Potentially
Protein C concentrate	Yes	No	Potentially
Activated Protein C	Yes	No	Potentially
Antithrombin	Yes	No	Potentially
Tissue factor pathway inhibitor	Yes	No	Potentially
Aspirin	Yes	No	Potentially
Clopidogrel	Yes	No	Potentially
Glycoprotein IIb/IIIa inhibitors	Yes	No	Potentially

1c. (If no, why not *(check all that apply)*

Risks generally outweigh potential benefits
Inadequate quality of evidence to support the use of any such agent
Inadequate quantity of evidence to support the use of any such agent
At present, there is inconsistent evidence to support the use of any such agent
I am unfamiliar with the current evidence in this field
Other(s) (please specify) _____

2. **How often do YOU use the following therapies for patients diagnosed with severe sepsis or septic shock?** *(Please consider the previous 1 year of your clinical practice)*

	Never (0% of patients)	**Rarely** (1-10% of patients)	**Sometimes** (11-25% of patients)	**Often** (26-50% of patients)	**Usually** (51-75% of patients)	**Almost always** (76-100% of patients)	**Always** (100% of patients)
Early empiric antibiotics (within the first hour of diagnosis)							
Source Control							
Early goal directed fluid resuscitation (within the first 6 hours of shock onset)							
Activated Protein C							
Tight glucose control							
Empiric stress dose steroids							
Restrictive transfusion strategy							
Low tidal volume ventilation in sepsis induced ARDS							

3. **How BENEFICIAL would you consider each of the following therapies for patients with severe sepsis or septic shock with regard to improving clinical outcomes? (e.g., improved survival, or decreased morbidity)**
(Again, please consider only the evidence base to date and a practice environment with no institutional barriers or cost constraints)

	Definitely NOT beneficial	**Probably NOT beneficial**	**Neutral**	**Probably beneficial**	**Definitely beneficial**	**Uncertain of the evidence-base**
Early empiric antibiotics (within the first hour of diagnosis)						
Source Control						
Early goal directed fluid resuscitation (within the first 6 hours of shock onset)						
Activated Protein C						
Tight glucose control						
Empiric stress dose steroids						
Restrictive transfusion strategy						
Low tidal volume ventilation in sepsis induced ARDS						

Part 2:

The following questions are designed to evaluate current practice regarding the use of activated protein C in sepsis and to outline potential barriers and facilitating factors that impact its use.

4. To approximately what percentage of septic patients with the following characteristics would YOU typically prescribe APC?

	Never (0% of patients)	**Rarely** (1-10% of patients)	**Sometimes** (11-25% of patients)	**Often** (26-50% of patients)	**Usually** (51-75% of patients)	**Almost always** (76-100% of patients)	**Always** (100% of patients)
4a. A 46 year old patient with newly diagnosed sepsis due to pneumonia. Initial hypotension corrected with only IV fluids. No signs of organ failure or ARDS, and no bleeding or contraindications to APC							
4b. A 46 year old patient with newly diagnosed sepsis due to pneumonia. Persistent hypotension after initial fluid resuscitation necessitating the use of norepinephrine. No other signs of organ failure or ARDS, and no bleeding or contraindications to APC							

(Question 4 – continued)

4. To approximately what percentage of septic patients with the following characteristics would YOU typically prescribe APC?

	Never (0% of patients)	**Rarely** (1-10% of patients)	**Sometimes** (11-25% of patients)	**Often** (26-50% of patients)	**Usually** (51-75% of patients)	**Almost always** (76-100% of patients)	**Always** (100% of patients)
4c. A 46 year old patient with newly diagnosed sepsis due to pneumonia. Persistent hypotension after initial fluid resuscitation necessitating the use of norepinephrine. New onset acute renal failure. No other signs of organ failure or ARDS, and no bleeding or contraindications to APC. CALCULATED APACHE SCORE IS 21							
4d. A 46 year old patient with newly diagnosed sepsis due to pneumonia. Persistent hypotension after initial fluid resuscitation necessitating the use of norepinephrine. New onset acute renal failure. No other signs of organ failure or ARDS, and no bleeding or contraindications to APC. CALCULATED APACHE SCORE IS 28							

5. **Please select the factor(s) that you believe constitute a <u>BARRIER</u> to the use of APC as recommended in the Surviving Sepsis Campaign guidelines.** *(Check all that apply)*

Grade B recommendation:

Adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥25 or multiple organ failure) if there are no contraindications

You disagree with the Surviving Sepsis Campaign recommendation
You are concerned that harms may outweigh the potential benefits of therapy
Your local experts do not support the use of APC in the above patient population
You have concerns relating to industry involvement and the generation of the **current evidence base**
You have concerns relating to industry involvement and the generation of the **current practice guidelines**
You are concerned that APC is not cost effective
Administration of APC is associated with increased physician/nurse work load demands
Difficult or inefficient ICU approval processes decrease appropriate use of APC
→ Its use is not supported by the current evidence base
Other (please specify) _____

If you chose: "Its use is not supported by the current evidence base" - Which aspects of the current evidence are important <u>BARRIERS</u> to the use of APC? *(Check all that apply)*

Insufficient number of completed randomized controlled trials
High risk of bias due to poor study quality
High risk of bias due to industry sponsorship or involvement
Inconsistent results among individual studies
Small magnitude of effect size (e.g., statistically significant, but not clinically important)
Imprecise estimates of potential benefit
Imprecise estimates of potential harm
Other (please specify) _____

6. **Please select the factor(s) that you believe <u>FACILITATE</u> the use of APC as recommended in the Surviving Sepsis Campaign guidelines.** *(Check all that apply)*

Grade B recommendation:

Adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥25 or multiple organ failure) if there are no contraindications

- You agree with the Surviving Sepsis Campaign recommendation
- You believe that the potential benefits of therapy outweigh the possible harms
- Your local experts support the use of APC in the above patient population
- You have no concerns relating to industry involvement and the generation of the **current evidence base**
- You have no concerns relating to industry involvement and the generation of the **current practice guidelines**
- APC is cost effective
- Administration of APC is not significantly associated with increased physician/nurse work load demands
- Easy and efficient ICU approval processes are in place to facilitate appropriate use of APC
- → Its use is supported by a strong evidence base
- Other (please specify) _____

If you chose: "Its use is supported by a strong evidence base" - Which aspects of the current evidence are important <u>FACILITATORS</u> to the use of APC? *(Check all that apply)*

- Adequate number of completed randomized controlled trials
- Low risk of bias due to high study quality
- Low risk of bias due to minimal industry sponsorship or involvement
- Consistent results among individual studies
- Substantial magnitude of effect size (e.g., both statistically significant and clinically important)
- Precise estimates of potential benefit
- Precise estimates of potential harms
- Other (please specify) _____

Part 3:

The third section explores heparin as a potential therapy in sepsis and will ask you to consider future clinical trials of heparin in patients with severe sepsis and septic shock.

7. Post hoc analyses of 3 randomized trials of anticoagulant therapies in sepsis (n=5758) have shown that concomitant heparin appears to mitigate or abolish the clinical effects of newer anticoagulants and suggests that heparin alone may be clinically beneficial:

   How certain are you that either unfractionated heparin or low molecular weight heparin is beneficial when used in the early treatment of severe sepsis or septic shock?

   Definitely beneficial
   Likely beneficial
   Uncertain
   Likely not beneficial
   Definitely not beneficial

8. **How certain are you that either unfractionated heparin or low molecular weight heparin is harmful when used in the early treatment of severe sepsis or septic shock?**

   Definitely harmful
   Likely harmful
   Uncertain
   Likely not harmful
   Definitely not beneficial

9. **Do you believe that future clinical trials of either unfractionated heparin or low molecular weight heparin are warranted to assess its potential benefit in patients diagnosed with severe sepsis/septic shock?**

No ⟶ (Skip to 9c)
Yes

9b. (If Yes), Why? *(Check all that apply)*

Biologic rationale exists to support clinical trials of heparin in this field
A beneficial role of heparin is currently suggested in the current evidence base
Heparin is inexpensive
Heparin is relatively easy to administer
Heparin is readily available
Other(s) (please specify) _____

9c. (If No), Why not? *(Check all that apply)*

I am unsure if sufficient biologic rationale exists to support clinical trials of heparin in this field
No biologic rationale exists to support clinical trials of heparin in this field
I am unsure if a beneficial role of heparin is suggested by the current evidence base
No beneficial role of heparin is suggested by the current evidence base
Proven therapies currently exist; further research is not justified
Other(s) (please specify) _____

Part 4:

This last section surveys important demographic characteristics of respondents. Once again, all responses are completely anonymous.

10. What is your age? *(in years)*

25 - 35
36 - 45
46 - 55
> 55

11. What is your primary specialty?

Internal medicine or a subspecialty thereof
General Surgery, or a subspecialty thereof
Anesthesiology
Emergency medicine
Other (please specify) _____

12. How many years have you been in independent practice?

< 1 year
1 - 5 years
6 - 10 years
11 - 20 years
> 20 years

13. How many years of formal fellowship training in critical care medicine did you complete?

I have not completed fellowship training in critical care
1 year
2 or more years

14. In which province do you practice intensive care medicine?
(main province if more than one)

British Columbia	Quebec
Alberta	New Brunswick
Saskatchewan	Nova Scotia
Manitoba	Prince Edward Island
Ontario	Newfoundland/Labrador

15. In what type of hospital do you <u>mostly</u> practice?

Teaching (a center affiliated with a university)
Community (no university affiliation)
Other (please specify) _____

16. In what type of ICU do you <u>mostly</u> practice?

Medical
Surgical or Trauma
Mixed medical/surgical
Cardiac surgery
Neuro
Other (please specify) _____

17. On average how many clinical weeks per year do you work in an ICU?

<5 weeks
5 - 10 weeks
11 - 15 weeks
16 - 20 weeks
20 - 30 weeks
>30 weeks

18. How many active beds are there in the ICU where you <u>mostly</u> practice?

<10
10 - 15
16 - 20
21 - 25
26 - 30
>30

19. On average, how many patients per week are diagnosed with severe sepsis or septic shock in the ICU where you <u>mostly</u> practice?

<1
1 - 3
4 - 6
7 - 10
>10

Appendix 5: Clinical sensibility

Thank you in advance for taking the time to provide feedback to the survey. This form is designed to convey information related to issues of clinical sensibility and content validity.

Please Highlight your response, save the document, and then email the completed form back to me.

1. To what extent are the questions directed at important issues regarding the current and potential uses of anticoagulants in sepsis?

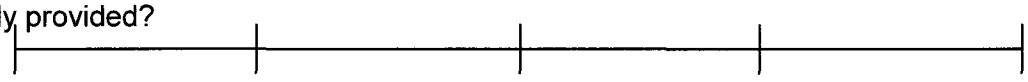
Small Extent	Limited Extent	Fair Extent	Moderate Extent	Large Extent

2. Are there important omitted issues regarding the current and potential uses of anticoagulants in sepsis that should be included in the questionnaire?

Crucial Gaps	Important Gaps	Minor Gaps	Minimal Gaps	Insignificant Gaps

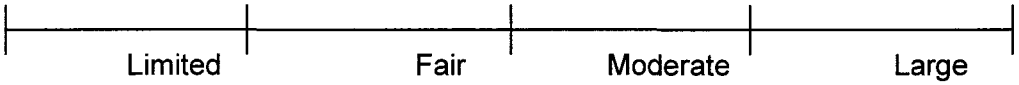
Please identify any omissions:_____

3. To what extent are the response options complete (ie. important response options are appropriately provided?



Small Extent	Limited Extent	Fair Extent	Moderate Extent	Large Extent

4. To what extent are the response options provided simple and easily understood?



Small Extent	Limited Extent	Fair Extent	Moderate Extent	Large Extent

5. How likely is the questionnaire to elicit practice variability regarding the use of anticoagulants?

Very unlikely Unlikely Likely Quite Likely Very Likely

6. How many items are inappropriate or redundant?

Very many Many Some A few Hardly any

Please identify redundant or inappropriate items:_____

7. How likely will this questionnaire be able to sufficiently inform the design of a future clinical trial of heparin in severe sepsis/septic shock?

Very unlikely Unlikely Likely Quite Likely Very Likely

Thank you again for this important feedback. Please feel free to email me with any other feedback that you would like to pass along.

Ryan Zarychanski

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