The Direct Medical Costs Associated with Suspected (Confirmed and Negative) Heparin-Induced Thrombocytopenia

by

Natasha Nanwa

A thesis submitted in conformity with requirements
for the degree of Master of Science

Graduate Department of
Pharmaceutical Sciences

UNIVERSITY OF TORONTO

Library and
Archives Canada

Published Heritage
Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et
Archives Canada

Direction du
Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence
ISBN: 978-0-494-45185-4
Our file Notre référence
ISBN: 978-0-494-45185-4

ABSTRACT

The Direct Medical Costs Associated with Suspected (Confirmed and Negative) Heparin-Induced Thrombocytopenia

Master of Science, 2008

Natasha Nanwa

Department of Pharmaceutical Sciences
UNIVERSITY OF TORONTO

Purpose: The objective of this study was to identify and quantify the direct medical costs associated with suspected (confirmed and negative) heparin-induced thrombocytopenia (HIT) from a Canadian hospital perspective.

Methods: A cost of illness analysis was conducted in patients with suspected HIT during 2005. Resource utilization variables included: (1) laboratory tests to investigate HIT, (2) HIT-safe anticoagulant use, (3) diagnostic imaging for HIT with thrombosis (HITT), and (4) additional hospital days attributed to HIT. The average cost per case of confirmed HIT, confirmed HITT, and negative HIT was calculated.

Results: Confirmed HITT cases incurred substantially greater average costs ($34,155, range $358-$202,069, n=12) than confirmed HIT cases without thrombosis ($4,575, range $39-$16,373, n=8). The average cost of a negative HIT case was $119 (range $39-$4,181, n=88).

Conclusions: This is the first study to quantify the costs associated with suspected HIT cases. These cases increase the costs of hospital care.

Acknowledgements

I would like to thank the following individuals. Without them, this project would have not been possible.

Dr. William Geerts, Dr. Nicole Mittmann, Sandra Knowles, Dr. Claudia Bucci, Scott Walker, Dr. Rita Selby and Dr. Neil Shear. You have all been wonderful mentors. I feel honored to have had this opportunity to work with you all. Thank you for your endless support, guidance, time, and patience.

Dr. Thomas Einarson and Dr. William Bartle. Thank you for being on my advisory committee. Your insights helped to shape this project.

Gail Elliot, Sunnybrook Health Sciences Centre Special Coagulation Laboratory, Sunnybrook Health Sciences Centre Pharmacy Department, John Iazzetta, Ted Winkle, Jeri Sever, and Natasha Speedie. Thank you all for your assistance. It was greatly appreciated.

My colleagues at the Health Outcomes PharmacoEconomics Research Centre: Soo Jin Seung, Peggy Kee, Marika Koo, Shazia Hassan, Pierre Isogai, Brian Chan, and Nancy Risebrough. Thank you for making the work environment an enjoyable one (and for putting up with my HIT puns).

The Glaxo Wellcome-Sunnybrook Drug Safety Clinic Graduate Student Fellowship. Thank you for supporting me financially.

Last but not least, my family: Dad, Mom, Amit, and Naveet. Thank you for all your encouragement and love.

Natasha

Table of Contents

Table of Tables

Table of Figures

List of Abbreviations

ADR	Adverse drug reaction
AP	Anterior-posterior
aPTT	Activated partial thromboplastin time
ASH	American Society of Hematology
CAN	Canadian
CBC	Complete blood count
CT	Computed tomography
CTPA	Computed tomography pulmonary angiogram
CVS	Cardiovascular surgery
DTI	Direct thrombin inhibitor
DVT	Deep vein thrombosis
ECG	Electrocardiography
ELISA	Enzyme-linked immunosorbent assay
EXP	Exploded
FXaI	Factor Xa Inhibitor
HIT	Heparin-induced thrombocytopenia
HITT	Heparin-induced thrombocytopenia with thrombosis
ICU	Intensive care unit
IgG	Immunoglobulin G
IV	Intravenous
IVC	Inferior vena cava
LAT	Lateral
LOS	Length of stay
LMWH	Low molecular weight heparin
MI	Myocardial infarction
MLT	Medical laboratory technologist
MRI	Magnetic resonance imaging
OCCI	Ontario Case Costing Initiative
OD	Optical density
OHIP	Ontario Health Insurance Plan
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
PF4	Platelet factor 4
PT	Prothrombin time
RA	Right atrial
SD	Standard deviation
SHSC	Sunnybrook Health Sciences Centre
SRA	Serotonin release assay
TE	Thromboembolism
TGA	Transient global amnesia
UFH	Unfractionated heparin
US	United States
VTE	Venous thromboembolism
V/Q	Ventilation/perfusion scan

1 INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a transient,[1] clinicopathological,[2-4] prothrombotic syndrome.[5] It occurs in up to 5% of patients exposed to unfractionated heparin (UFH).[6] It is a serious adverse drug reaction (ADR).[7] Of the patients who develop HIT, 30 to 60% of patients will develop a thrombotic complication,[8-10] resulting in rates of amputation as high as 20%,[10;11] and a mortality rate of up to 30%.[8;10;11] Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the most frequent thrombotic complication of HIT.[5;9;10] Other complications include acute limb ischemia,[10] stroke,[5;9;10] myocardial infarction (MI),[5;9;10] skin lesions,[12-15] and acute anaphylactoid reactions.[15] These HIT-related complications are referred to as HIT with thrombosis (HITT).

The detection and management of HIT consumes substantial hospital resources including diagnostic tests, use of HIT-safe anticoagulants, longer hospital stays, and potential lawsuits. Treatment with direct thrombin inhibitors (DTIs) is relatively expensive and requires frequent laboratory monitoring.[16] In 2004, treatment with one DTI cost Sunnybrook Health Sciences Centre (SHSC) $37,000 for one patient. In terms of expenditure, two DTIs (only used in the management of HIT) were among the top 50 drugs used at SHSC in 2004/2005 (argatroban and lepirudin were 41 and 49, respectively on this list). Previous studies have shown a more than doubling of hospital days and costs for medical and cardiovascular surgery (CVS) patients with HIT.[17;18] Hospitals have also faced lawsuits related to the adverse outcomes of HIT.[19]

1.1 Statement of Problem

Recent studies have shown that there is a substantial economic burden associated with HIT.[17;18;20] These studies provide information on resources utilized and the associated costs in the management of HIT. However, all of these studies were conducted in the United States (US) and each had a number of limitations, including lack of or poorly-defined HIT definitions, the cost of HIT and HITT were not separated, unclear perspectives (e.g., institutional, societal), incomplete cost lists, and lack of information on the burden of suspected HIT cases. As a result, these studies are not generalizable to Canada's healthcare system. A Canadian-specific burden of illness study on HIT has not previously been carried out.

1.2 Purpose of Study and Objective

The objective of this study was to identify and quantify the direct medical costs associated with suspected (confirmed and negative) cases of heparin-induced thrombocytopenia.

This study determined the costs and resource utilization related to suspected and proven cases of HIT, from the Canadian hospital perspective.

This study was also designed to:

(1) Estimate the costs of HIT management for use by Canadian hospital decision makers. For example, this study may assist with decisions that are made in relation to the hospital formulary and laboratory approaches to suspected HIT.

(2) Serve as a framework for other Canadian hospitals to determine the costs of HIT in their institutions.

(3) Serve as an input in a cost-effectiveness analysis comparing UFH to an alternative anticoagulant, considering differences in HIT rates.

(4) Serve as a model for future cost of illness studies focused on ADRs from the Canadian hospital perspective, since the last study appears to have been published in 1998 by Schlienger and colleagues.[21]

1.3 Review of Literature

1.3.1 Heparin-Induced Thrombocytopenia

Heparin is an anticoagulant that is commonly given to patients for the treatment or prevention of thrombosis.[22] It has been estimated that 30 to 40% of hospitalized patients are exposed to heparin.[23;24] Heparin is a glycosaminoglycan that is produced naturally in human mast cells or obtained from porcine intestinal mucosa or bovine lung tissue.[25] Heparin greatly increases the inhibition of the key coagulation factors, thrombin and factor Xa, thereby decreasing the rate of coagulation.[25] Unfractionated heparin and low molecular weight heparin (LMWH) are two general categories of heparin types used in clinical practice.[25]

An ADR is a complication caused by a patient's medication therapy rather than by their principal illness.[26-28] ADRs may lead to increases in hospital stay, disability, or death.[26-28] Despite the benefits of heparin, there are serious ADRs associated with it, including bleeding and HIT.[7]

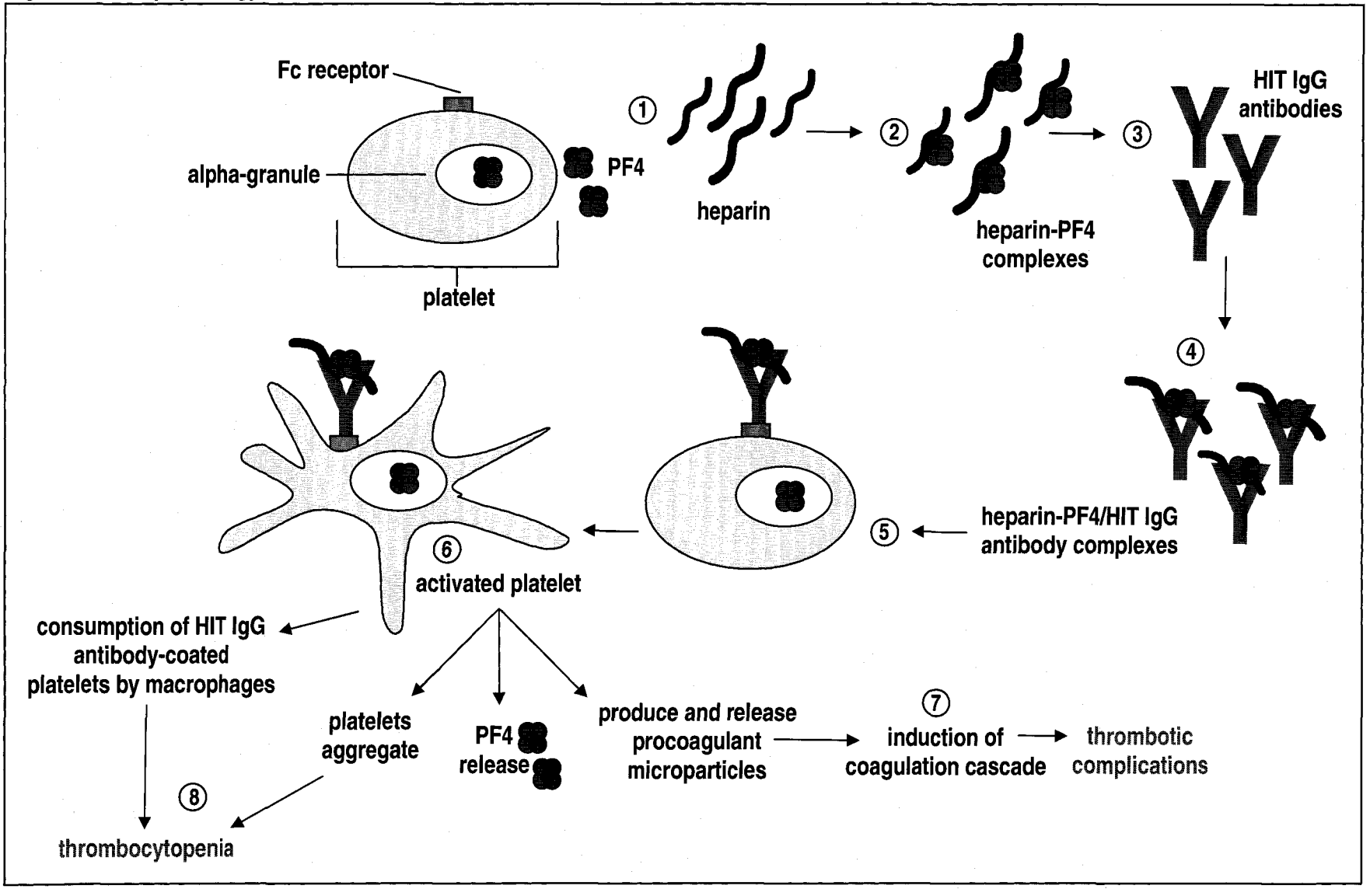
Heparin-induced thrombocytopenia occurs in up to 5% of patients exposed to UFH;[6] it has been estimated that 0.3% of all hospitalized patients develop HIT.[23] This transient,[1] prothrombotic syndrome[5] is a life-threatening ADR.[7] The paradox with HIT is that, although heparin is used to prevent and treat thrombosis, the development of HIT dramatically procedures a high thrombosis risk.[29]

1.3.1.1 Pathophysiology of HIT

Four components are essential to the pathophysiology of HIT: (1) heparin, (2) platelet factor 4 (PF4), (3) HIT immunoglobulin G (IgG) antibodies, and (4) Fc receptors on platelets. When a patient receives heparin for treatment of a thromboembolic disorder or DVT prophylaxis, the following processes may occur (Figure 1):

1) Heparin is introduced into the patient's circulation, where PF4 is present. PF4 is a protein released from the alpha-granules of platelets.[30]
2) Negative charges on heparin and positive charges on PF4 cause them to bind and form a complex.[31;32]
3) This interaction changes the shape of PF4[33] which results in the PF4 molecules becoming immunogenic. HIT IgG antibodies are developed to these altered PF4 molecules.[34]
4) The HIT IgG antibodies bind to the heparin-PF4 complexes.[34]
5) The heparin-PF4/HIT IgG antibody complexes then bind to the Fc receptors on the surface of platelets.[35]
6) This leads to a profound activation of the platelets causing them to release more PF4,[29] to produce and release into the circulation procoagulant microparticles[36] and to aggregate.[35]
7) The highly procoagulant microparticles induce the coagulation cascade leading to thrombotic complications.[36]
8) The platelet aggregation and the consumption of HIT IgG antibody-coated platelets by macrophages are the basis of the thrombocytopenia.[37]

Figure 1: Pathophysiology of HIT.



IgG - immunoglobulin G, PF4 - platelet factor 4

1.3.1.2 Factors Affecting the Frequency of HIT

The frequency of HIT depends on a number of factors:

(1) Type of heparin:
- A meta-analysis conducted by Martel et al[38] found the risk of HIT inpatients who were given for UFH was 2.6% and 0.2% for those who were given LWMH. This difference in risk may be due to molecule size.[38]

(2) Hospital patient population:
- Warkentin et al[39] found that surgical patients have a greater HIT risk than medical patients.

(3) Gender:
- Warkentin et al[39] also found that females have a greater risk of developing HIT. It has been suggested that this may be due to an up regulation of the immune system in females compared to males.[40]

(4) Heparin exposure:
- Lindhoff-Last et al[41] found that certain exposure periods to heparin resulted in increased HIT IgG antibody formation. These antibodies are detectable after day 5 of heparin exposure,[22] peak on days 9 to 11 after starting heparin and do not rise further after days 12 to 18.[41] The antibody levels become undetectable by day 100, making HIT a transient disease.[1]

1.3.1.3 Risks Associated with HIT

Of the 1 to 5% of patients exposed to heparin who develop HIT,[42] 30 to 60% of patients will develop a thrombotic complication,[8-10] resulting in rates of amputation as high as 20%,[10;11] and a mortality rate of up to 30%.[8;10;11] HIT is associated with a high thrombosis risk even when heparin is discontinued.[22] The first few days after discontinuation of heparin is still associated with a 5 to 10% thrombosis rate with an overall rate as high as 50% within 30 days.[5;22] Venous thromboembolism, which includes DVT and PE, is the most frequent thrombotic complication.[5;9;10] Other complications include acute limb ischemia,[10] stroke,[5;9;10] MI,[5;9;10] skin lesions,[12-15] and acute anaphylactoid reactions.[15]

1.3.1.4 HIT Investigations at SHSC

Sunnybrook Health Sciences Centre is a tertiary care, adult, university affiliated hospital located in Toronto, Ontario, Canada. At SHSC, all HIT cases are managed by a subspecialty Thromboembolism (TE) Service.

HIT is suspected when:

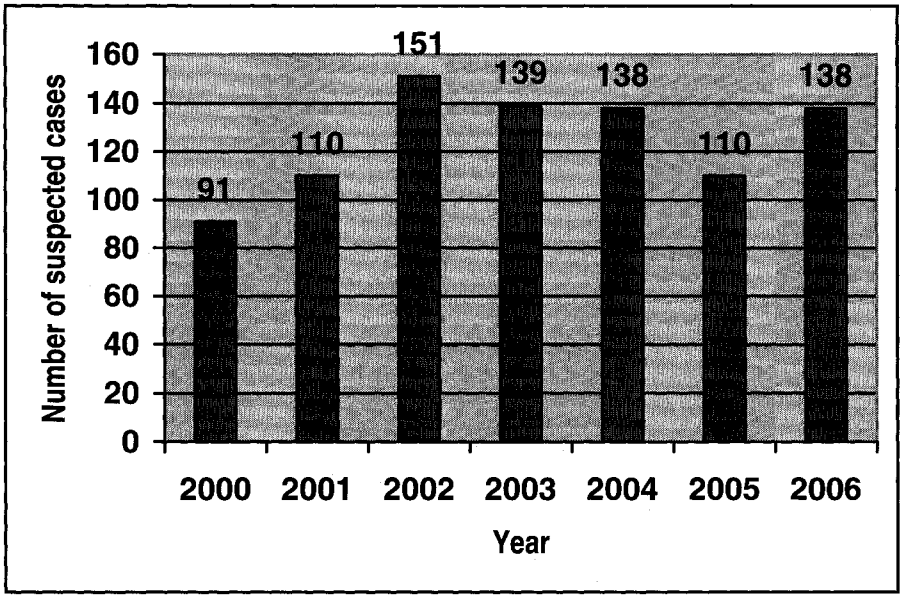
1) Platelet levels of a patient fall by at least 30% from baseline, 5 to 10 days after heparin exposure with no other likely cause,[43] and/or
2) A patient develops thrombosis while on or has recently been exposed to heparin,[43] and/or
3) A patient develops a systemic reaction after a heparin bolus or skin lesions at heparin injection sites.[22]

A high clinical probability for HIT is considered if a patient exhibits one or more of the above situations. This clinical impression is often supplemented by the use of the "Four T's" tool developed by Warkentin et al.[43]

It is standard procedure at SHSC for patients with suspected HIT to have heparin discontinued and a HIT enzyme-linked immunosorbent assay (ELISA) test ordered.

Heparin-induced thrombocytopenia ELISA testing was introduced at SHSC in 1998 as a diagnostic test for HIT. This test measures antibodies against the heparin-PF4 complex.[44] A positive result is classified as an optical density (OD) greater than 0.4.[44] In some suspected HIT cases, a serotonin release assay (SRA) may also be ordered to confirm HIT in patients with a positive ELISA. The SRA is a functional test, which measures the ability of HIT IgG antibodies to activate platelets.[2] When platelets are activated, serotonin is released.[45] If the serotonin in platelets has been pre-labeled with a radioactive tracer, the release of radioactive serotonin can be measured.[44;45] A positive result is classified as greater than 20% serotonin release.[44] The SRA may be ordered because it has a higher specificity than the HIT ELISA.[46] However, the SRA test is not done at SHSC and, therefore, blood samples are sent to the HIT reference laboratory at McMaster University. The SHSC Coagulation Laboratory maintains a complete database of all HIT ELISAs and SRA tests performed. From 2000 to 2006, an annual average of 125 patients have been suspected of HIT at SHSC as defined by a request for a HIT assay (Figure 2).

Figure 2: Suspected cases of HIT from 2000 to 2006.



1.3.1.5 Diagnosis of Confirmed Cases of HIT at SHSC

Heparin-induced thrombocytopenia is a clinicopathological syndrome.[2-4;47] Therefore, the diagnosis of HIT is based on: (1) the clinical picture such as thrombocytopenia with or without thrombosis, and (2) the pathological picture including the detection of HIT IgG antibodies.[2-4;47] Table 1 illustrates the criteria used to adjudicate HIT status among the suspected cases. Although HIT is usually diagnosed prospectively, the diagnostic criteria can also be used in a retrospective manner.

Table 1: Classifying the HIT status of a suspected case.

Status	Criteria
Confirmed HIT	Positive SRA or Positive HIT ELISA (OD: 0.4 - 1.0) + high clinical probability or Strongly positive HIT ELISA (OD > 1.0)
Negative HIT	Negative HIT ELISA or Negative SRA or Adjudicated negative by the TE Service
Indeterminate HIT	Positive HIT ELISA (OD: 0.4 - 1.0) + no SRA performed + adjudicated indeterminate by the TE Service

ELISA - enzyme-linked immunosorbent assay, OD - optical density, SRA - serotonin release assay, TE - thromboembolism

1.3.1.6 Management of HIT at SHSC

After the patient is suspected of HIT and a HIT ELISA is ordered, the following steps occur:

1) TE Service consultation (mandatory if the patient has a positive ELISA result).
2) Immediate withdrawal of all sources of heparin.[48]
3) Avoidance of LMWH.[49] Ranze et al[50] found that patients with HIT who were treated with LMWH developed new thrombosis at a significantly higher rate than with danaparoid.
4) Avoidance of platelet transfusions,[49] because this might increase the risk of a thrombotic event.[51]
5) Observation for symptoms or signs of thrombosis.[49]
6) Initiation of a HIT-safe anticoagulant.[49]
7) Avoidance of warfarin, if indicated, until the patient is on a HIT-safe anticoagulant and until recovery of thrombocytopenia,[49] due to the risk of developing warfarin-induced thrombosis such as skin necrosis and venous limb gangrene.[52]
8) Documentation of the HIT or HITT episode in the patient's chart. If the patient is considered to have HIT, a letter is sent to the patient and their relevant physician(s).

1.3.1.7 Prevention and Treatment of HITT at SHSC

Discontinuation of heparin eventually stops the body's immune response to the heparin-PF4 complexes and platelet activation, which is dependent on the presence of heparin.[48] However, the thrombosis risk persists for some time after heparin is discontinued.[48] Therefore, it is recommended that an alternative, HIT-safe anticoagulant be used to reduce the clinical impact of this extremely hypercoagulable state.[48;49]

The HIT-safe anticoagulants include: danaparoid, fondaparinux, argatroban, bivalirudin, and lepirudin. Danaparoid and fondaparinux are indirect factor Xa inhibitors (FXaIs).[48;53] Both drugs require limited laboratory monitoring and both are eliminated through the kidneys.[53;54] Argatroban, bivalirudin, and lepirudin are DTIs[48;55] and require laboratory monitoring using the activated partial thromboplastin time (aPTT).[48;55] Argatroban undergoes hepatic clearance,[56] bivalirudin is 80% cleared by proteolysis,[57] and 20% renally,[57-59] and lepirudin undergoes renal clearance.[60] Bleeding is the most common ADR associated with most of the HIT-safe anticoagulants.[53-55;60] Table 2 summarizes the characteristics of these HIT-safe anticoagulants.

Table 2: HIT-safe anticoagulants used at SHSC.

	Danaparoid	Fondaparinux	Argatroban	Bivalirudin	Lepirudin
Recommended uses at SHSC	Anticoagulation of patients with HIT or HITT[61]	Prevention and treatment of VTE in patients with HIT[61]	Anticoagulation of patients with HIT or HITT[61]	Patients with HIT requiring PCI[61]	Anticoagulation of patients with HIT or HITT[61]
Current formulary status	Removed from formulary in 2006	On formulary	On formulary	On formulary	On formulary
Mechanism	Indirect FXaI[48]	Indirect FXaI[53]	DTI[48]	DTI[55]	DTI[48]
Half-life	19 to 24 hours[62]	15 to 18 hours[63]	39 to 51 minutes[62]	10 to 24 minutes[62]	1.3 hours[62]
Clearance	Renal[48]	Renal[53]	Hepatic[56]	80% proteolysis[57-59] 20% renal[57;58]	Renal[60]

aPTT - activated partial thromboplastin time, DTI - direct thrombin inhibitor, FXaI - factor Xa inhibitor, PCI - percutaneous coronary intervention, VTE - venous thromboembolism

Although there are published recommendations on the management of HIT,[49] actual practice varies from hospital to hospital, depending on drug availability and the experience of the managing physicians. The current treatment guidelines at SHSC are summarized in Table 3. A suspected or confirmed case of HIT with no previous indication for an anticoagulant is given fondaparinux (or before 2006, danaparoid). A suspected or confirmed case of HIT with a previous indication for anticoagulation (e.g., mechanical heart valve) or with HITT is given one of the HIT-safe anticoagulants depending on their clinical situation (e.g., renal function).

Table 3: SHSC HIT treatment guidelines.

Type of case	Treatment
HIT + no indication for therapeutic anticoagulant	**fondaparinux** or **danaparoid***
HIT + indication for therapeutic anticoagulant	**argatroban** or **lepirudin** or **bivalirudin** or **fondaparinux** or **danaparoid*** followed by **warfarin** once thrombocytopenia has recovered
HITT	**argatroban** or **lepirudin** or **bivalirudin** or **fondaparinux** or **danaparoid*** followed by **warfarin** once thrombocytopenia has recovered

* in use until 2006

1.3.1.8 HIT Database at SHSC

In collaboration with the TE Service and SHSC Information Services, an electronic database of HIT cases was created. The HIT Database is password protected, maintained in Microsoft® ACCESS and resides on the secure SHSC intranet server.

The HIT Database was developed to systematically describe the epidemiology, clinical and temporal features of HIT, as well as its treatment and outcomes. A single reviewer (Natasha Nanwa) conducted a retrospective chart review to populate the database. All cases were assessed with a clinical expert. This database has not been validated and no previous studies have used data from this database.

The database contains detailed information on all suspected cases of HIT from January 1, 2005 to December 31, 2005: (1) demographic data and clinical history, (2) laboratory values, (3) inpatient medication data, and (4) clinical outcomes (Appendix A: HIT Database).

(1) Demographic Data and Clinical History

The demographic data in this database include: date of birth, gender, date of admission, date when HIT was suspected, and the discharge date. The HIT status was determined by the TE Service after all data was collected for each suspected case. Table 1 outlines how the HIT status was determined.

The patient's clinical history includes the clinical service the patient was on when they were suspected of HIT (e.g., cardiology, oncology, CVS). The number of TE Service visits are also available for each suspected case.

(2) Laboratory Values

The laboratory results included in the HIT Database are: all tests used to establish whether or not HIT was present, and tests used to monitor HIT-safe medications. For the HIT ELISA test, the OD is included.

(3) Inpatient Medication Data

The medication data section describes the doses and durations of the HIT treatments that are given to each of the cases of suspected HIT.

(4) Clinical Outcomes

This section relates to HIT-related complications. Diagnostic and surgical procedures associated with these complications are included. For example, if a HIT patient is suspected to have DVT, a Doppler ultrasound would be ordered. A HITT patient may undergo surgery such as an embolectomy or amputation. Bleeding episodes, possibly associated with HIT treatment, are also described in the database, along with interventions used to manage the bleed (e.g., blood transfusion).

1.3.2 Economic Burden of HIT

Recent studies reporting the economic burden associated with HIT,[17;18;20] provide information on the resources utilized and costs incurred in the management of HIT. These studies will be discussed in detail after a brief summary of economic evaluations in general.

1.3.2.1 Economic Evaluations

Full economic evaluations have two requirements: (1) they examine the costs and outcomes of alternatives (e.g., treatments, interventions, programs), and (2) they compare two (or more) alternatives.[64] An example of a full economic evaluation is a cost-effectiveness analysis, which involves the assessment of a common outcome (e.g., episode-free days, or years of life gained) and associated costs between two or more management alternatives.[64] ***Partial economic evaluations*** only meet one of the two characteristics of a full economic evaluation. For example, a ***cost of illness analysis*** describes the costs of a disease or intervention,[64] but is not considered a full economic evaluation as it does not include a comparison of two or more illnesses or interventions.[64;65]

Costs in economic evaluations are assigned to resource utilization variables, which include labor, supplies consumed and/or equipment used in the management of diseases.[66] There are three different types of costs: (1) direct medical costs, (2) direct non-medical costs, and (3) indirect costs. ***Direct medical costs*** are costs directly associated with the medical care of a patient (e.g., drugs, health professional fees).[67] ***Direct non-medical costs*** are not directly associated with the medical care of a patient, but are still attributable to the disease or intervention (e.g., parking, homecare).[68] ***Indirect costs*** are earnings lost by the patient as a result of the disease or intervention.[68]

An economic evaluation also requires that the perspective be specified; society, government, institution, or patient.[64] The perspective helps to identify which resource utilization variables and costs related to the alternatives are included.[69]

1.3.2.2 Economic Evaluations of HIT

To identify studies focused on the economics of HIT, a comprehensive search of the published literature was performed using HEALTHSTAR®, MEDLINE®, and EMBASE® on June 13, 2007. The search was subsequently repeated every two weeks in order to identify new studies. The subject headings "heparin," "costs and cost analysis," "economics," and "thrombocytopenia" were used in the HEALTHSTAR® and MEDLINE® searches. The searches yielded 28 studies as of January 1, 2008 (Table 4 and Table 5).

Table 4: Ovid Healthstar® 1966 to December 2007.

#	Search History	Results
1	EXP Heparin/	18420
2	EXP "Costs and Cost Analysis"/	131888
3	EXP Economics/	375826
4	2 or 3	375826
5	1 and 4	445
6	limit 5 to (humans and English language)	413
7	thrombocytopenia.tw.	11674
8	6 and 7	28

EXP - exploded

Table 5: Ovid MEDLINE® 1950 to December 2007.

#	Search History	Results
1	EXP Heparin/	48110
2	EXP "Costs and Cost Analysis"/	133793
3	EXP Economics/	386514
4	2 or 3	386514
5	1 and 4	445
6	limit 5 to (humans and English language)	413
7	thrombocytopenia.tw.	24453
8	6 and 7	28

EXP - exploded

The subject headings "heparin-induced thrombocytopenia," "cost," and "economics" were used in the EMBASE® search, which yielded 55 studies as of January 1, 2008 (Table 6).

Table 6: EMBASE® 1980 to week 52 2007.

#	Search History	Results
1	EXP Heparin Induced Thrombocytopenia/	897
2	EXP "COST"/	115195
3	EXP ECONOMICS/	12898
4	2 or 3	126245
5	1 and 4	59
6	limit 5 to (human and English language)	55

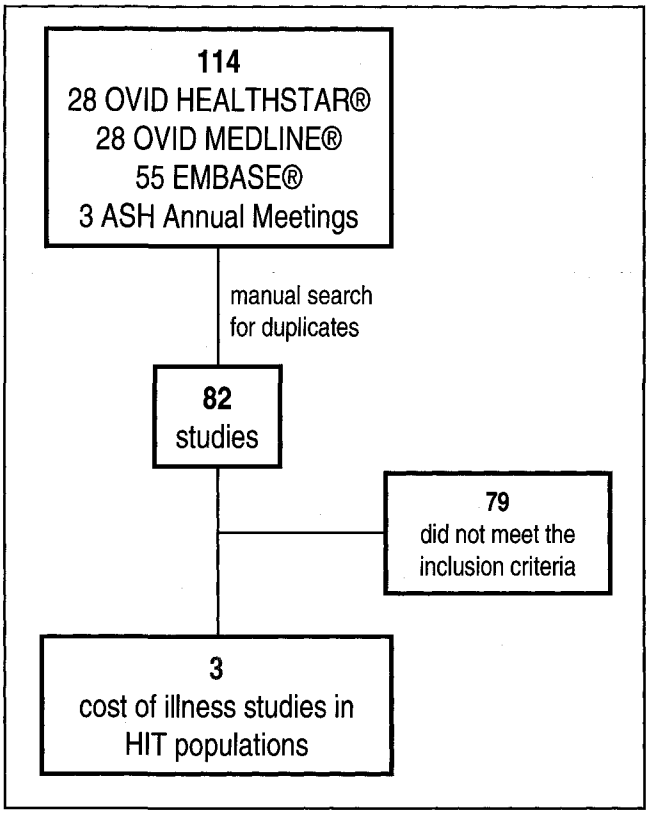
EXP - exploded

Abstracts that focused on the economics of HIT published in various conference proceedings were also reviewed. These included the International Society on Thrombosis and Haemostasis Congress (from 2001 to 2005), American Society of Hematology (ASH) Annual Meeting (from 2004 to 2007), and International Society for Pharmacoeconomics and Outcomes Research Annual Congress (from 2006 to 2007).

A broad search strategy was executed by "exploding" subject headings, which ensured that important articles were not missed. From the three databases and abstracts (n=114), a manual search for duplicates yielded 82 studies. Cost of illness studies that were conducted in HIT populations were of interest as this was the focus of the present study. Two published cost of illness studies[17;18] and one abstract[20] were found.

Seventy-nine studies did not meet the inclusion criteria of the literature review. The reasons for exclusion were: (1) other models of economic evaluations conducted in HIT populations, (2) studies that estimated HIT costs in their economic models, (3) review articles, (4) studies that only calculated the cost of HIT-safe anticoagulants, and (5) studies that mentioned "heparin-induced thrombocytopenia" and "cost" in their text, yet did not focus on the costs "associated" with HIT. Figure 3 summarizes the literature review search strategy and the results.

Figure 3: Literature review search strategy and results.



ASH - American Society of Hematology

1.3.2.2.1 Cost of Illness Studies Conducted in HIT Populations

Table 7 outlines the three cost of illness analyses that focused on HIT populations.[17;18;20]

Frame[18] presented the incremental cost associated with HIT by conducting a retrospective study in a population of valve surgery and cardiac bypass patients. Cases were identified from the hospital's HIT registry, while the non-HIT cases were identified using the diagnosis-related group code for open-heart surgery with UFH exposure. Frame found that hospital days and costs in the HIT group were double those determined for the non-HIT group. This study had a number of limitations. A definition for HIT was not provided, thus making it unclear if false positives were included in their cost analysis. The perspective used to carry out the study was unclear. It was assumed the study was from an institutional perspective. There was no mention of a discounting rate, and a sensitivity analysis was not performed. Statistics were not

presented to show significant differences between the two groups. Finally, the average cost for HIT alone and HITT were not presented separately.

Creekmore et al[17] performed a similar study but focused on medical inpatients. Patients were considered to have HIT if the following criteria were met: (1) platelet count fell at least 50% below baseline, and (2) they had a positive HIT ELISA, or (3) they were treated with lepirudin or argatroban. The controls were matched by hospital service, birth date, and international classification of diseases classes (ninth revision). Hospital days and costs were three times greater in the HIT group compared to the controls. This study had a number of limitations. The definition of HIT indicated that false positives were very likely included in their cost analysis. The type of economic analysis and perspective used to carry out the study were unclear. It was assumed the study was a cost of illness analysis with an institutional perspective. A sensitivity analysis was not performed. Moreover, the average cost for HIT alone and HITT were not presented separately. Finally, the case sample consisted of medical patients who had HIT while on prophylactic doses of heparin and is, therefore, not representative of HIT burden.

The final cost of illness study was an abstract by Smythe et al[20] who conducted a cost of illness analysis to assess the impact of HIT at their institution. There were significant differences in hospital days and costs, with both variables twice as high in the HIT group compared to the control group. As with the other two studies, the perspective and HIT definition were uncertain. Also, the average cost for HIT alone and HITT were not presented separately. Finally, the type of HIT patient population was not reported.

In summary, these three American studies concluded that there is an increase in hospital days and costs with HIT, when compared to controls. However, these studies have a number of major limitations. This is why it is of interest to identify and quantify the direct medical costs associated with suspected (confirmed and negative) HIT cases from a Canadian hospital perspective.

Table 7: Cost of illness studies conducted in HIT populations.

	Frame[18]	Creekmore et al[17]	Smythe et al[20]
Publication year	2005	2006	2005
Country	United States	United States	United States
Year and currency	2002 US dollars	2004 US dollars	2005 US dollars
Time horizon	4 1/2 years	4 1/3 years	1 year
Perspective	Undefined	Undefined	Undefined
Patient population	Heart valve surgery and cardiac bypass patients receiving UFH: 129 HIT vs. 10,648 Non-HIT	Adult medical patients receiving thromboprophylaxis: 44 HIT vs. 212 controls	72 HIT patients with matched controls for 31 of them
Methods	Retrospective analysis	Retrospective analysis with nested case-control	Retrospective analysis with case-control
Source of data and cost values	Institutional sources, Healthcare Cost and Utilization Project Nationwide Inpatient Database	Institutional sources	Institutional sources, Medicare
Outcome measures related to HIT	Average direct medical cost per patient (pharmacy, lab, supplies, room rates, operating room, utilities, infrastructure, maintenance)	Average direct medical cost per patient (physician, laboratory, pharmacy, dialysis, supplies, procedures, radiology, blood bank, nutrition, operating room)	Average hospital costs
Summary of results (mean cost per patient)	HIT $54,818 (average LOS = 21.6 days) Non-HIT $21,590 (average LOS = 9.7 days)	HIT $56,364 (average LOS = 18.8 days) Control $15,231 (average LOS = 6.3 days)	HIT $55,440 (average LOS = 22.8 days) Control $26,505 (average LOS = 11.6 days)
Limitations	1) Perspective used was unclear 2) Definition of HIT not provided 3) Cost of HIT alone and HITT not presented separately 4) Only CVS patients were studied	1) Type of economic analysis unclear 2) Perspective used was unclear 3) False positives included in the cost analysis 4) Cost of HIT alone and HITT not presented separately 5) Only medical patients were studied	1) Perspective used was unclear 2) Definition of HIT not provided 3) Cost of HIT alone and HITT not presented separately 4) Type of HIT patient population not reported
Pharmaceutical industry involved in funding	No	No	No

CVS - cardiovascular surgery, LOS - length of stay, UFH - unfractionated heparin, US - United States

2 METHODS

A retrospective cost of illness analysis was conducted to examine the direct medical costs associated with suspected cases of HIT from January 1 to December 31, 2005.

2.1 Study Site

The study was carried out at Sunnybrook Health Sciences Centre, a tertiary care, adult, university-affiliated hospital located in Toronto, Ontario, Canada. Sunnybrook Health Sciences Centre has a large Cardiac Surgery Program and a comprehensive TE Service that manages all cases of HIT.

2.2 Patient Sample

The patient sample included all suspected (confirmed and negative) HIT cases from the HIT Database. Patients in whom a diagnosis of HIT could not be confirmed or ruled out were excluded from the study.

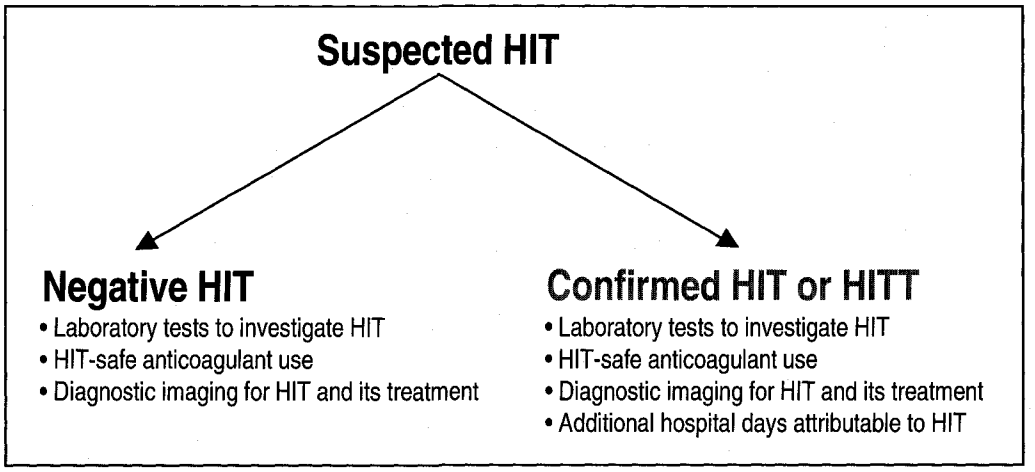
2.3 Perspective

This study was conducted from the hospital perspective because HIT is almost exclusively an hospital-acquired and hospital managed disorder, and is relatively common with approximately 0.3% of all hospitalized patients developing this ADR.[23] In addition, the SHSC HIT Database is a hospital-based database in which resource utilization variables related to the overall healthcare and societal perspectives were not included.

2.4 Resource Utilization Variables

The HIT Database was used to identify the resource utilization variables associated with direct medical costs in the management of HIT. These included: (1) laboratory tests to investigate suspected HIT, (2) HIT-safe anticoagulant use, (3) diagnostic imaging related to HIT or its treatment, and (4) additional hospital days attributable to HIT. Information not available in the HIT Database was gathered through a detailed patient chart review. Figure 4 outlines the resource utilization variables associated with each HIT status.

Figure 4: The resource utilization variables associated with each HIT status.



2.4.1 Laboratory Tests to Investigate Suspected HIT

The HIT Database provided the number of HIT ELISA, and SRA tests performed for each suspected HIT case. The HIT ELISA was carried out on-site at SHSC and a micro-cost analysis was done to determine the overall cost of HIT ELISA testing (Appendix B: Cost Components Associated with Laboratory Tests). Included in this cost was the Medical Laboratory Technologist's (MLT) time to conduct the test, as determined by a time-and-motion study that was carried out by the SHSC Department of Clinical Pathology. The costs of HIT ELISA kits and reagents were included. The cost of the Personal Lab (the machine used to process the test) was excluded in the cost analysis, because this machine has been at the hospital for the past eight years and was also used for other tests (Cathy Sparling, Chief Medical Laboratory Technologist, SHSC Department of Clinical Pathology, personal communication, February 3, 2006). Serotonin release assays were performed at the McMaster University HIT Reference Laboratory, and SHSC was charged a fee for this test. The hospital global budget covers the costs for these two tests (Jacqueline King, Hematology Supervisor, SHSC Department of Clinical Pathology, personal communication, May 24, 2007).

Table 8 summarizes the laboratory tests in terms of data source, cost source, and cost assumptions.

Table 8: Laboratory testing: sources and assumptions.

Description	Data source	Cost source	Cost analysis rules and assumptions
HIT ELISA	HIT Database		The Personal Lab cost was not included in the test cost because the machine has been at SHSC for the last eight years and is used for other tests
▪ MLT time (time to conduct tests)	Time-and-motion study	SHSC Human Resources	
▪ Supplies to carry out tests (e.g., test kits, regents)	SHSC Coagulation Laboratory	SHSC Coagulation Laboratory	
SRA	HIT Database	SHSC Coagulation Laboratory	This test is performed off-site; therefore, the cost to SHSC was the test charge plus shipping cost

ELISA - enzyme linked immunosorbent assay, MLT - medical laboratory technologist, SHSC - Sunnybrook Health Sciences Centre, SRA - serotonin release assay

2.4.2 HIT-Safe Anticoagulant Use

The SHSC Department of Pharmacy database (WORx©) provided a list of medications that each suspected case received during his/her admission at SHSC, along with the dose, duration, and cost. All of the HIT-safe drugs that are ordered at SHSC are included in this database, with the exception of bivalirudin which is only used in the catheterization lab for percutaneous coronary interventions (PCIs),[61] and is not captured in the WORx® database. For each drug, the dose recorded in the HIT Database was multiplied by the cost from the SHSC formulary to calculate the drug acquisition cost.

The HIT Database was not able to provide information on non-HIT-safe anticoagulant drugs used in the treatment of HIT (e.g., tissue plasminogen activator, warfarin). It was assumed that HIT-safe anticoagulants would contribute the most to inpatient medication costs (for example, $410 per 250 mL vial of bivalirudin)[61] compared to drugs like warfarin that range from $0.10 to $0.57 per tablet.[61]

HIT-safe anticoagulant use requires pharmacy preparation time and supplies for administration. These were considered in the overall treatment cost. To estimate the cost of pharmacy time, a time-and-motion study was conducted with the SHSC Department of Pharmacy (Appendix C: Cost Components Associated with HIT-Safe Anticoagulant Use). The time it took to prepare an order for lepirudin was studied and these results were applied to the other DTIs. Lepirudin was chosen since it was the most common DTI used among the study cohort. Because the FXaIs do not require any preparation, pharmacy time was not included in their costs.

Supplies used to administer the drugs such as syringes, needles, and intravenous (IV) bags, were not included. These costs are minimal (e.g., bulk order of 1000 hypodermic needles can range from $0.08 to $0.46 per needle US $[70]).

Only DTIs require laboratory monitoring. Thus, all of the aPTT and prothrombin time (PT) tests performed during the DTI treatment were included. The hospital global budget covers the costs for these two tests for inpatients (Jacqueline King, Hematology Supervisor, SHSC Department of Clinical Pathology, personal communication, May 24th 2007).

Bleeding is a relatively common ADR associated with most of the HIT-safe anticoagulants;[53-55;60] therefore, the cost of blood transfusions were included (Appendix C: Cost Components Associated with HIT-Safe Anticoagulant Use).

Table 9 summarizes HIT-safe anticoagulant use in terms of data source, cost source, and assumptions. Table 10 outlines the drug cost components included in the overall costs associated with HIT-safe anticoagulant use.

Table 9: HIT-safe anticoagulant use: sources and assumptions.

Description	Data source	Cost source	Cost analysis rules and assumptions
Drug costs for: ▪ HIT ▪ HITT ▪ ADRs related to the HIT-safe drugs (e.g., bleeding)	HIT Database	SHSC Pharmacy Database (WORx©), SHSC Formulary, Ontario Regional Blood Coordinating Network	All costs of HIT-safe anticoagulants were included in the analysis because they are only indicated for the treatment or prevention of HITT
Pharmacy (time to prepare drugs): ▪ Pharmacist ▪ Pharmacy technician	Time-and-motion study	SHSC Human Resources, SHSC Department of Pharmacy	Only applied to DTIs; FXaIs do not require preparation
Supplies to administer drugs (e.g., syringe, needle, IV bag, alcohol swab)	SHSC Pharmacy	SHSC Supplies	Not included because minimal cost compared to the overall cost of the HIT-safe anticoagulants
Inpatient medication monitoring tests (e.g., aPTT, PT)	HIT Database	SHSC Coagulation Laboratory	The number of tests performed during the HIT-safe treatment

ADR - adverse drug reaction, aPTT - activated partial thromboplastin time, DTI - direct thrombin inhibitor, FXaI - factor Xa inhibitor, IV - intravenous, PT - prothrombin time, SHSC - Sunnybrook Health Sciences Centre

Table 10: Components included in the overall costs associated with HIT-safe anticoagulant use

Drug	Included in overall inpatient medication cost	Pharmacy time	Supplies	Monitoring	ADR
DTIs	Yes	Yes	No	Yes	Yes
FXaIs	Yes	No	No	No	Yes

DTI - direct thrombin inhibitor, FXaI - factor Xa inhibitor

2.4.3 Diagnostic Imaging for HIT or Its Treatment

The HIT Database provided information on the diagnostic imaging that patients underwent when HITT was suspected or when patients suffered an ADR due to HIT treatment. To determine the cost of diagnostic imaging, the technical portion listed in the Ontario Health Insurance Plan (OHIP) Schedule of Benefits was used as a proxy for the cost, as specific hospital costs were not available (Appendix D: Cost Components). Table 11 summarizes the procedures in terms of data source, cost source, and assumptions.

Table 11: Diagnostic imaging: sources and assumptions.

Description	Data source	Cost source	Cost analysis rules and assumptions
Diagnostic imaging (e.g., CT, MRI, ultrasound)	HIT Database	OHIP Schedule of Benefits (technical portion)	NA

CT - computed tomography, MRI - magnetic resonance imaging, NA - not applicable, OHIP - Ontario Health Insurance Plan

2.4.4 Additional Hospital Days Attributed to HIT

The HIT Database and the hospital chart review were used to estimate the number of additional hospital days, if any, for each confirmed case. Sunnybrook Health Sciences Centre Decision Support supplied the hospitalization costing data based on budget estimates of the average cost per day for a medical, surgical, intensive care unit (ICU) level 2, or ICU level 3 bed. The bed costs include: (1) administration, (2) nursing, (3) pharmacy (Pharmacist + Pharmacy Technician + non HIT-safe drugs), (4) Allied Health Professionals (Physiotherapist, Social Worker, Speech Therapist, Occupational Therapist), (5) laboratory, (6) diagnostics, and (7) other (e.g., supplies). Refer to Appendix E: Cost Components Associated with Hospitalization.

Sunnybrook Health Sciences Centre Decision Support could not provide the overhead costs. Overhead costs relate to the running of the institution, such as lighting, heating, porters, transportation, cleaning and medical supports.[71] The source for overhead costs was the Ontario Case Costing Initiative (OCCI). The Ontario Ministry of Health and Long-Term Care uses the costing information obtained by OCCI to assess hospital funding.[72] The 2005/2006 OCCI database collected case costing data from 12 hospitals in Ontario.[73] Although SHSC was not part of this database, there four other major teaching hospitals that contributed to the OCCI database: Mount Sinai, St. Michael's, University Health Network, and Ottawa General hospitals. The average overhead reported for the top 50 most responsible diagnoses in 2005/2006 was approximately 40% of the total hospitalization costs for these four teaching hospitals. This value was applied to hospitalization costs in this study.

Some HIT cases were readmitted to hospital because of a HIT-related complication. The entire length of stay (LOS) for these readmission was counted in the analysis. For the other cases, five different clinical scenarios were established in order to identify and quantify additional hospital days attributable to HIT. Hospital days could be prolonged as a result of: (1) diagnosing HIT (e.g., waiting for lab or imaging results), (2) HIT-related surgery, (3) waiting for platelets to recover or PT to normalize while the patient was on a HIT-safe anticoagulant, (4) the need for anticoagulation for another condition (e.g., atrial fibrillation), requiring the use of a HIT-safe anticoagulant in hospital, or (5) a HIT-safe anticoagulant ADR such as bleeding.

Additional hospital days were not considered for negative HIT cases. Table 12 summarizes the additional hospital days in terms of data source, cost source, and assumptions.

Table 12: Additional hospital days: sources and assumptions.

Description	Data source	Cost source	Cost analysis rules and assumptions
Additional days in hospital	HIT Database, Patient chart review	SHSC Decision Support, OCCI	Additional hospital days attributed to confirmed cases when: 1) Patient re-admitted because of a HIT complication 2) Diagnosing HIT (e.g., waiting for lab or imaging results) 3) HIT-related surgery 4) Patient given a HIT-safe anticoagulant: a) Waiting for platelet counts to recover ($\geq 150 \times 10^9$) or PT to normalize b) There is an indication for anticoagulation, where HIT-safe anticoagulants are the only alternatives available and are administered in hospital c) ADR caused by the HIT-safe anticoagulants, such as bleeding

ADR - adverse drug reaction, OCCI - Ontario Case Costing Initiative, PT - prothrombin time, SHSC - Sunnybrook Health Sciences Centre

3 ANALYSIS

3.1 Quantification of Cost Variables

Descriptive statistics (mean, standard deviation, median, and range) were used to characterize each resource utilization variable cost.

The resource utilization cost for each patient equaled the unit cost multiplied by the number of units. These costs were averaged across all patents to arrive at a mean cost per patient.

Costs incurred by the suspected cases of HIT at SHSC from 2005 were evaluated in 2007 Canadian (CAN) dollars. When 2007 dollars were not available the costs were adjusted by the Canadian inflation rate by using the Consumer Price Index.[74] When multiple costs were available for a resource variable, the lowest cost estimate was used.

3.2 Cost Outcomes

The following cost outcomes were calculated for each resource utilization variable and overall total average cost:

- Average cost per negative HIT case
- Average cost per confirmed case
  - Average cost per confirmed HIT case
  - Average cost per confirmed HITT case

There was a secondary analysis that was carried out for these cost outcomes, which was adopted from a study by Mittmann et al,[75] called the actually managed analysis. This analysis presents the average consumed resource cost. For example, among the 88 HIT negative cases, 12 received some specific treatment for HIT. In the primary analysis, the denominator for the average HIT-safe anticoagulant cost would be based on the 88 cases, while, in the actually managed analysis, the denominator for the average

HIT-safe anticoagulant cost would be based on the 12 treated cases. The results of this analysis are presented in Appendix F: The Actually Managed Results.

3.3 Sensitivity Analysis

A sensitivity analysis was not conducted, as plausible ranges for costs from published literature were not available. It was considered to use ±25% as utilized in various costing studies;[76-78] however, the largest cost driver for the entire analysis was additional hospital days attributable to HIT. Therefore, varying the other costing components would contribute very little to the overall average total cost attributable to HIT.

3.4 Discounting

Discounting was not applied due to the short time horizon of this study.

3.5 Ethics

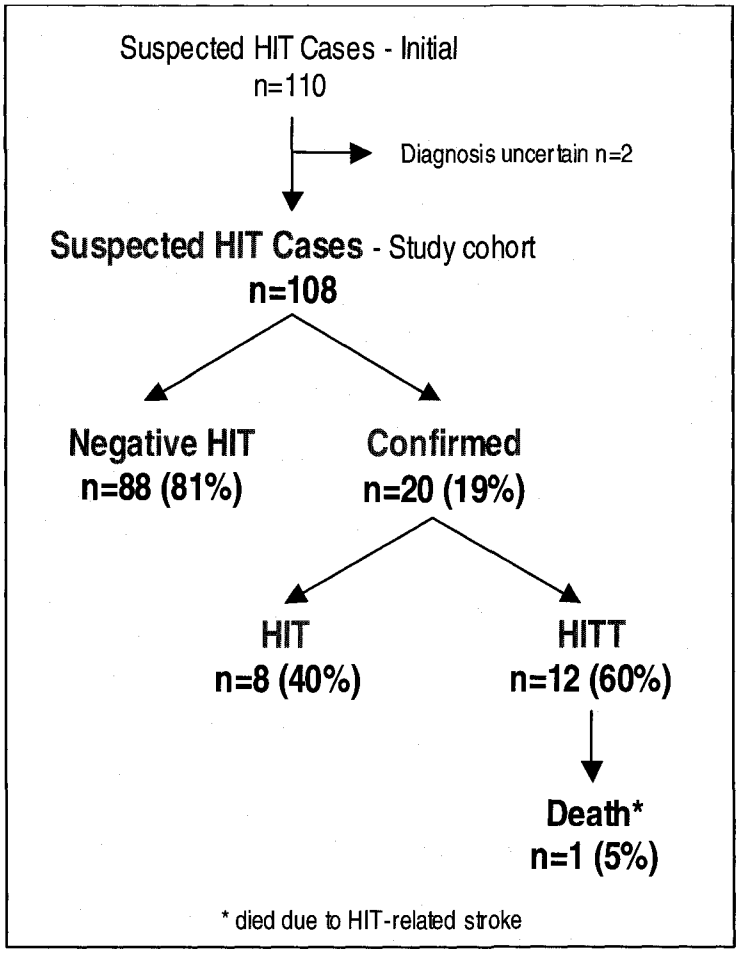
The SHSC Research Ethics Board approved this study in December 2006 (refer to Appendix G: Research Ethics Board Approval Letter). Consent from the patients included in this study was not required because there was no patient interaction and the study was based on a retrospective chart review.

4 RESULTS

4.1 Demographics

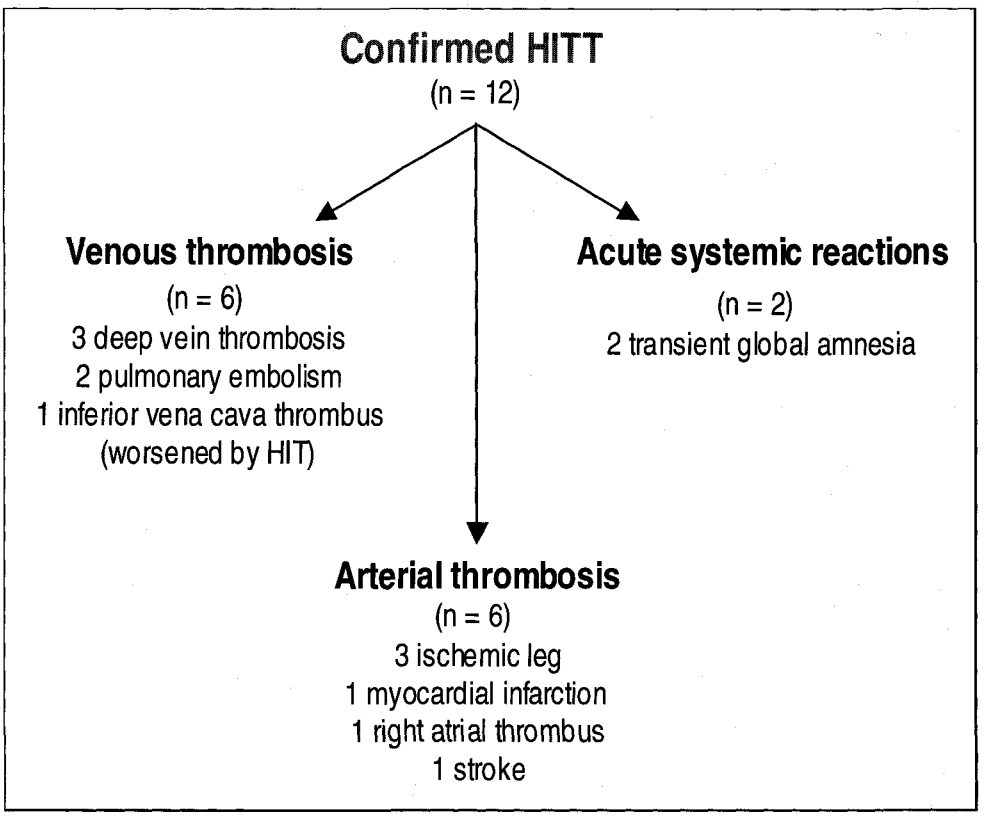
In 2005, there were 110 suspected HIT cases based on a request for a HIT ELISA test (Figure 5). However, two patients with suspected HIT were excluded because their HIT status could not be confirmed. Therefore, the study cohort consisted of 108 cases: 88 negative for HIT and 20 confirmed (8 HIT and 12 HITT). One confirmed HITT case died due to a HIT-related stroke.

Figure 5: Suspected HIT cases in 2005.



The complications experienced by the confirmed HITT cases are outlined in Figure 6. There were six episodes of venous thrombosis, six episodes of arterial thrombosis and two patients with acute systemic reactions. Two patients had greater than one HIT complication.

Figure 6: Complications experienced by confirmed HITT cases (n=12).



Of the 88 negative HIT cases, 42% were female with an average age of 69 (standard deviation = ±13) years and an average LOS of 36.5 (standard deviation = ±43.6) days. Among the 8 confirmed cases, 75% were female with an average age of 64 (standard deviation = ±12) years and an average LOS of 28.5 (standard deviation = ±21.4) days. Finally, among the 12 confirmed HITT cases, 58% were female with an average age of 73 (standard deviation = ±7) years and an average LOS of 36.5 (standard deviation = ±35.2) days (Table 13).

Table 13: Demographics for suspected HIT cases (n=108).

	Negative HIT	Confirmed HIT + HITT	Confirmed HIT	Confirmed HITT
Number of patients	88	20	8	12
Average age ± SD (range)	69 ± 13 (19 - 94)	69 ± 9 (47 - 83)	64 ± 12 (47 - 83)	73 ± 7 (59 - 83)
Average number of hospital days ± SD (range)	36.5 ± 43.6 (3 - 244)	33.3 ± 30.0 (5 - 128)	28.5 ± 21.4 (5 - 62)	36.5 ± 35.2 (12 - 128)
Median number of hospital days (range)	23.0 (3 - 244)	22.5 (5 - 128)	20.5 (5 - 62)	26.5 (12 - 128)
Female	42%	65%	75%	58%

SD - standard deviation

It was found that 68 (63%) of the suspected cases were surgical patients (Table 14). Seventy-five percent of these suspected HIT cases had cardiac surgery.

Table 14: Suspected HIT in the surgical group (n=68).

Patient group	Negative HIT	Confirmed HIT + HITT	Confirmed HIT	Confirmed HITT
Oncology	0	2	1	1
Urology	1	0	0	0
Vascular	1	0	0	0
Orthopedic	1	0	0	0
Plastic	2	0	0	0
Trauma	2	0	0	0
General	3	0	0	0
Burn	5	0	0	0
Cardiac	38	13	6	7
Total	53	15	7	8

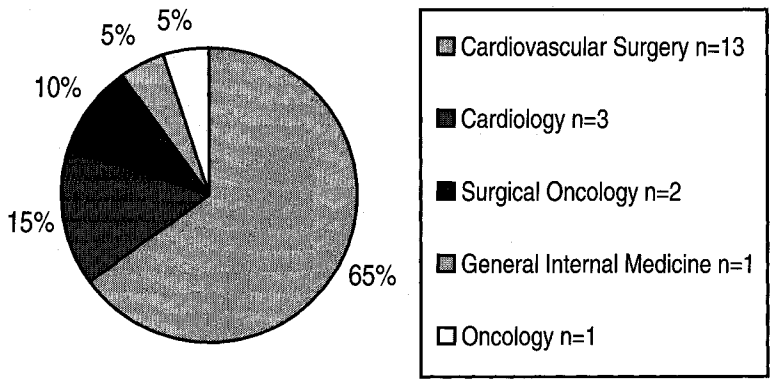
It was found that 40 (37%) of the suspected cases were medical patients (Table 15). Most of these were general medicine patients, although cardiology patients experienced the greatest number (n=3) of confirmed cases.

Table 15: Suspected HIT in the medical group (n=40).

Patient group	Negative HIT	Confirmed HIT + HITT	Confirmed HIT	Confirmed HITT
Neurology	1	0	0	0
Nephrology	5	0	0	0
Oncology	6	1	0	1
Cardiology	7	3	1	2
General Medicine	16	1	0	1
Total	35	5	1	4

Figure 7 presents the confirmed cases (n=20) by patient group (both medical and surgical). Overall, cardiovascular surgery made up 46% of the suspected HIT cases and 65% of the confirmed HIT cases. Together, cardiovascular surgery and cardiology accounted for 80% of all the confirmed cases.

Figure 7: Confirmed HIT cases by patient group (n=20).



4.2 Laboratory Tests to Investigate HIT

All 108 suspected HIT cases had an HIT ELISA ordered. When the HIT ELISA result was indeterminate, an SRA was ordered (eight were ordered in 2005). The average and median laboratory costs per negative HIT case were $54 and $39, respectively (Table 16). The average and median laboratory costs for a confirmed case were $68 and $39, respectively.

Table 16: Cost of laboratory tests to investigate HIT.

	Negative HIT (n = 88)	Confirmed HIT + HITT (n = 20)	Confirmed HIT (n = 8)	Confirmed HITT (n = 12)
Average laboratory cost ± SD (range)	$54 ± $41 ($39 - $272)	$68 ± $62 ($39 - $233)	$39 ± $0 ($39 - $39)	$88 ± $74 ($39 - $233)
Median laboratory cost (range)	$39 ($39 - $272)	$39 ($39 - $233)	$39 ($39 - $39)	$39 ($39 - $233)

SD - standard deviation

4.3 HIT-Safe Anticoagulant Use

Thirty-one (29%) of the suspected HIT cases were treated with a HIT-safe anticoagulant (Table 17). One confirmed case did not receive treatment because he died the same day he was suspected of HIT. Six cases were treated with more than one HIT-safe anticoagulant (one negative HIT case and five confirmed HITT cases).

Lepirudin accounted for 64% of the total HIT-safe medication costs in 2005. Four patients each were given argatroban and danaparoid although the total costs were very different. Bivalirudin was administered to only one confirmed HIT case, with a cost of $9,302. Seventeen patients were treated with fondaparinux, eight of whom were negative HIT cases.

Table 17: Average cost of HIT-safe anticoagulants by HIT status and drug.

Drug	Negative HIT	Confirmed HIT	Confirmed HITT	Total cost
Lepirudin	$221 n = 1	$3,562 ± $23 ($3,545 - $3,578) n = 2	$4,793 ± $4,842 ($1,099 - $16,744) n = 9	$50,481
Argatroban	$3,987 n = 1	$0	$4,023 ± $4,211 ($693 - $8,757) n = 3	$16,058
Bivalirudin	$0	$9,302 n = 1	$0	$9,302
Fondaparinux	$91 ± $58 ($28 - $196) n = 8	$81 ± $67 ($42 - $182) n = 4	$263 ± $100 ($140 - $365) n = 5	$2,367
Danaparoid	$228 ± $135 ($90 - $359) n = 3	$0	$54 n = 1	$737
Total number treated	12[1]	7[2]	18[3]	

SD - standard deviation, [1] One patient received both lepirudin and fondaparinux, [2] One patient died before receiving any treatment, [3] Five patients received more than one HIT-safe anticoagulant

Table 18 shows the average and median HIT-safe anticoagulant costs for all suspected HIT cases. The average HIT-safe anticoagulant cost per negative HIT case was $64. The average HIT-safe anticoagulant cost per confirmed HIT case was $2,094. The average HIT-safe anticoagulant cost per confirmed HITT case was $4,725.

Table 18: Cost of HIT-safe anticoagulant use.

	Negative HIT (n = 88)	Confirmed HIT + HITT (n = 20)	Confirmed HIT (n = 8)	Confirmed HITT (n = 12)
Average HIT-safe anticoagulant cost ± SD (range)	$64 ± $428 ($0 - $3,987)	$3,667 ± $4,356 ($0 - $16,744)	$2,094 ± $3,314 ($0 - $9,302)	$4,725 ± $4,776 ($252 - $16,744)
Median HIT-safe anticoagulant cost (range)	$0 ($0 - $3,987)	$2,579 ($0 - $16,744)	$119 ($0 - $9,302)	$3,156 ($252 - $16,744)

SD - standard deviation

4.4 Diagnostic Imaging Associated with HIT

Table 19 summarizes the average and median diagnostic imaging costs for all suspected HIT cases. Overall, the costs of diagnostic imaging for patients with suspected HIT were very low. As expected, the imaging costs were greatest with patients with HITT.

Table 19: Cost of diagnostic imaging associated with HIT.

	Negative HIT (n = 88)	Confirmed HIT + HITT (n = 20)	Confirmed HIT (n = 8)	Confirmed HITT (n = 12)
Average diagnostic imaging costs ± SD (range)	$1 ± $7 ($0 - $67)	$44 ± $65 ($0 - $212)	$8 ± $24 ($0 - $67)	$68 ± $73 ($0 - $212)
Median diagnostic imaging costs (range)	$0 ($0 - $67)	$0 ($0 - $212)	$0 ($0 - $67)	$56 ($0 - $212)

SD - standard deviation

4.5 Additional Hospital Days Attributable to HIT

Table 20 provides the average and median additional hospital days and costs for the 8 confirmed HIT and 12 confirmed HITT cases. The average additional hospital days were 2.5 (standard deviation = ±2.7) days for the confirmed HIT cases, with an average cost associated with these hospital days of $2,424. For the confirmed HITT group, the average additional hospital days were 14.6 (standard deviation = ±21.8) days with an average cost associated with the hospital days of $29,274.

Table 20: Number and cost of additional hospital days attributable to HIT.

	Confirmed HIT + HITT (n = 20)	Confirmed HIT (n = 8)	Confirmed HITT (n = 12)
Average additional hospital days ± SD (range)	9.8 ± 17.7 (0 - 60)	2.5 ± 2.7 (0 - 6)	14.6 ± 21.8 (0 - 60)
Median additional hospital days (range)	4.5 (0 - 60)	2.0 (0 - 6)	5.0 (0 - 60)
Average cost associated with additional hospital days ± SD (range)	$18,538 ± $48,100 ($0 - $198,238)	$2,434 ± $2,779 ($0 - $7,032)	$29,274 ± $60,637 ($0 - $198,238)
Median cost associated with additional hospital days (range)	$3,888 ($0 - $198,238)	$1,944 ($0 - $7,032)	$3,888 ($0 - $198,238)

SD - standard deviation

4.6 Summary of Results

Table 21 presents the overall average costs attributable to HIT. The average total attributable cost for a negative HIT case was $119, and for a confirmed case was $22,317. The average total attributable cost for a case of HIT was $4,575 and for a case of HITT was $34,155.

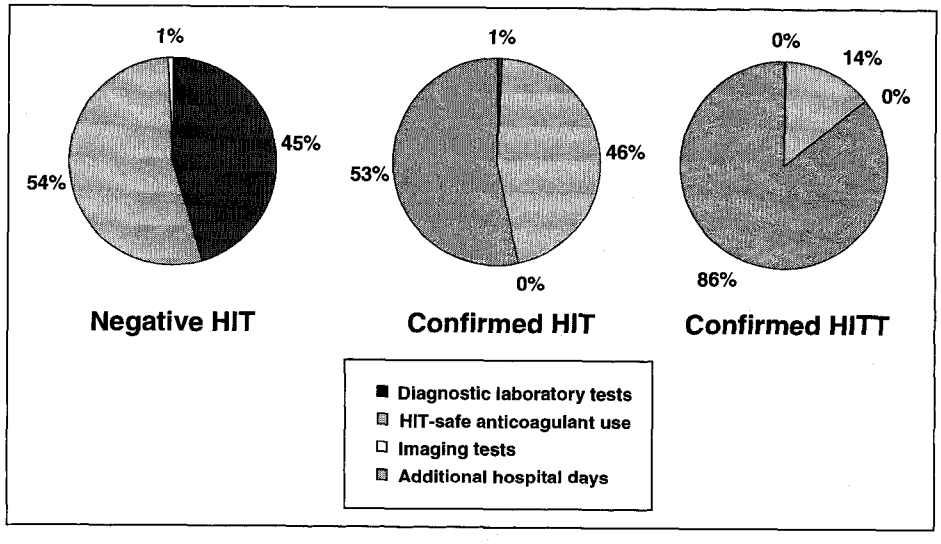
Table 21: The total attributable costs of HIT.

	Attributable cost (mean ± SD)
Negative HIT (n = 88)	
Laboratory testing	$54 ± $41 median: $39, range: $39 - $272
HIT-safe anticoagulant use	$64 ± $428 median: $0, range: $0 - $3,987
Diagnostic imaging	$1 ± $7 median: $0, range: $0 - $67
Total	**$119** ± $448 range: $39 - $4,181
Confirmed HIT + HITT (n = 20)	
Laboratory testing	$68 ± $62 median: $39, range: $39 - $233
HIT-safe anticoagulant use	$3,667 ± $4,356 median: $2,579, range: $0 - $16,744
Diagnostic imaging	$44 ± $65 median: $0, range: $0 - $213
Additional hospital days	$18,538 ± $48,100 median: $3,888, range: $0 - $198,238
Total	**$22,317** ± $48,860 range: $39 - $202,069
Confirmed HIT (n = 8)	
Laboratory testing	$39 ± $0 median: $39, range: $39 - $39
HIT-safe anticoagulant use	$2,094 ± $3,314 median: $119, range: $0 - $9,302
Diagnostic imaging	$8 ± $24 median: $0, range: $0 - $67
Additional hospital days	$2,434 ± $2,779 median: $1,944, range: $0 - $7,032
Total	**$4,575** ± $5,873 range: $39 - $16,373
Confirmed HITT (n = 12)	
Laboratory testing	$88 ± $74 median: $39, range: $39 - $233
HIT-safe anticoagulant use	$4,725 ± $4,776 median: $3,156, range: $252 - $16,744
Diagnostic imaging	$68 ± $73 median: $56, range: $0 - $213
Additional hospital days	$29,274 ± $60,637 median: $3,888, range: $0 - $198,238
Total	**$34,155** ± $60,992 range: $358 - $202,069

SD - standard deviation

Figure 8 outlines the distributions of costs by HIT status. The largest cost driver for the negative HIT cases was HIT anticoagulant use, accounting for 54% of the total average cost. The largest cost driver for the confirmed cases was additional hospital days.

Figure 8: Distribution of costs by HIT status.



The total costs for HIT in 2005 are presented in Table 22.

Table 22: Total HIT costs.

	Negative HIT	Confirmed HIT	Confirmed HITT	Total
Total hospital costs	$10,448	$36,604	$409,735	$456,787

5 GENERAL DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 General Discussion

Overall, in 2005, the management of suspected (confirmed and negative) cases of HIT cost SHSC $456,787.

The average costs incurred by confirmed HITT cases were substantially greater than the average costs incurred by confirmed HIT cases. This is due to the costs associated with additional hospital days associated with the complications and their management. Confirmed HITT cases stayed in hospital for a longer duration and spent more days in the ICU. Three of these cases had additional hospital days ranging from 21 to 60 days. One patient suffered a HIT-related stroke and had an additional LOS of 60 days. Two patients underwent HIT-related surgeries. One patient underwent an embolectomy of a leg thrombus and an amputation (LOS = 59 days) and the other patient underwent an embolectomy of a leg (LOS = 21days).

In the confirmed HIT group, the additional hospital stay averaged 2.5 days. The LOS was prolonged in this group primarily because these patients were on a HIT-safe anticoagulant and their platelet count levels had to normalize before they were discharged from hospital. Figure 8 demonstrates that the additional hospital days contributed to greater proportion of the overall costs in the confirmed HITT group (86%) than in the confirmed HIT group (53%).

The largest cost driver for the negative HIT cases was HIT-safe anticoagulant use. The majority of the negative HIT cases received FXaIs, but one of the patients received argatroban, which is much more expensive than FXaIs (Table 17).

This is the first study to determine the costs associated with suspected HIT cases. Smythe et al[24] appears to be the only other study to report data on suspected cases. However, their definition of suspected HIT differs from the definition used in this study. Smythe et al[24] defined suspected HIT as one or more of the following: (1) cases that are managed like newly diagnosed HIT cases, (2) cases that have a negative or inconclusive HIT ELISA result, or (3) cases that have the suspicion of HIT written in their hospital charts. They did not include cases that had negative SRA results.[24] The HIT Database was the source of the

patient population for this study. The SHSC HIT Database defined suspected HIT as cases that had a HIT ELISA test ordered, regardless of the HIT ELISA or SRA result. Thus, the patient sample presented in the Smythe et al[24] study cannot be compared to those in this study.

One limitation of this study was the underestimation of costs attributed to HIT. A conservative view was taken to cost allocation for the following: (1) laboratory tests to investigate HIT, (2) HIT-safe anticoagulant use, (3) diagnostic imaging for HIT, (4) additional hospital days, (5) additional nursing time due to HIT, (6) surgical procedures due to HITT, (7) additional inpatient rehabilitation due to HIT, and (8) physician visits.

(1) Laboratory Tests to Investigate HIT

On average, a HIT ELISA cost $39. This cost was derived by adding all the costs associated with HIT ELISA kits, reagents, and MLT time for the year 2005 and then dividing this cost by the number of tests carried out in that year. Sunnybrook Health Sciences Centre also conducts HIT ELISA testing for 10 other hospitals in the greater Toronto area. In 2005, 22% (133/618) of the HIT ELISA tests were for SHSC. Since the costs presented were from batched samples, these may be lower than in other institutions that perform fewer tests.

Complete blood counts (CBCs) are frequently ordered in patients with suspected HIT. However, since CBCs are also ordered for other reasons, it is difficult to separate which tests were ordered for HIT. As a result, they were not included in this analysis.

(2) HIT-Safe Anticoagulant Use

Pharmacy preparation time was included in the HIT-safe anticoagulant costs. These costs could be underestimated for the following reasons: (1) the time-and-motion study was uninterrupted rather than representing the true pharmacy setting (e.g., varying drug orders and number of working staff), and (2) the time spent clarifying the order with the physician, or a nurse inquiring about how to prepare or administer the drug can prolong the preparation process.

(3) Diagnostic Imaging for HIT

This resource variable was also underestimated in this study. The technical component from the OHIP Schedule of Benefits was used as a proxy for the actual diagnostic imaging costs. Costs from OCCI were considered but were not used because of the broad ranges associated with these costs. For example, the total average cost of a leg Doppler ultrasound was reported to be $242 (standard deviation= ±$131) with a range of $77 to $685 in 2005/2006.[79] The range indicates that imaging costs are not consistent from hospital to hospital.

The OHIP Schedule of Benefits did not provide technical costs related to computed tomography (CT) and magnetic resonance imaging (MRI). Consequently, five CTs and one MRI were not included in this analysis.

Diagnostic imaging for negative HIT cases were also underestimated. Some imaging tests may have been related to HIT but, unless it was certain that the tests were done because of HIT, they were not included.

(4) Additional Hospital Days Attributable to HIT

It is uncertain if the costs per hospital day used in this study reflect the real life costs at SHSC, as the overhead cost was not included in the estimates given by the SHSC Decision Support Department. Therefore, hospitalization costs were increased by 40% to account for the overhead. There was the option to use hospitalization costs (that included overhead) published in burden of illness studies carried out in Ontario teaching hospitals. For example, Heemstra et al[80] reported the hospitalization cost to be $880 per day in 2002 ($987 2007 CAN) at the Hospital for Sick Children, and Dranitsaris et al[81] reported the average hospitalization cost to be $550 per day in 1993 ($708 2007 CAN) at an Ontario teaching hospital. These costs were not used because, they are unlikely to be accurate and, at SHSC, there are four levels of hospitalization with the daily costs ranging from $699 to $3,304 (Appendix E: Cost Components Associated with Hospitalization). The cohort for this study consisted of various patient types, so their level of hospitalization varied as well.

Additional hospital days were ascribed by chart review by a single reviewer in conjunction with a clinical expert, following the criteria outlined in Table 12. A comparative approach with matched pairs was not possible due to the various patient groups that made up the study cohort. The single reviewer and clinical expert were biased to be conservative in allocating hospital days to HIT (i.e., if there was uncertainty about whether hospital stay could be attributable to HIT, it was not counted).

Negative HIT cases did not have costs associated with additional hospital days included in their total average attributable HIT costs. However, their hospital days could be increased by HIT for the following reasons: (1) diagnosing HIT (e.g., waiting for lab results or imaging results), (2) treating HIT, with a HIT-safe anticoagulant until HIT is ruled out, or (3) the patient may suffer from an ADR when exposed to a HIT-safe anticoagulant. This study involved a retrospective chart review; therefore, separating which days were attributable to HIT from days attributable to their concomitant illnesses was not always possible and a conservative view of hospital days was taken.

(5) Additional Nursing Time due to HIT

At SHSC there is a nursing workload measurement database called GRASP©, which is used by the Ministry of Health to assist in funding hospital nursing care.[82] In this study, we wanted to assess if HIT increased nursing time, but the GRASP© database was not up to date with 2005 data. It was also difficult to attribute nursing time to HIT without a comparator group. Therefore, it was not counted in the cost analysis as a separate variable, although it was not completely lost as the hospitalization costs accounts for nursing time. Depending on the level of hospitalization, the nursing ratio differs. For example, in some of the ICUs at SHSC there is a one-to-one nurse-to-patient ratio compared with a ratio of one-to-four to one-to-seven on other nursing units.

(6) Surgical Procedures due to HITT

The costs of surgical procedures were not counted in this study. We were unable to directly determine the hospital costs related to two embolectomies and one above knee amputation that were experienced by two confirmed HITT cases. Therefore, the costs of similar procedures were considered, such as lower limb amputation in the diabetic population as reported by O'Brien et al.[83] However, they obtained this cost from OCCI, which includes all hospitalization costs. To avoid double counting in this analysis, the cost of these surgical procedures were not included.

(7) Additional Inpatient Rehabilitation due to HIT

Patients who suffer HITT may require inpatient rehabilitation services. For example, a patient who suffers a HIT-related stroke may require physiotherapy and/or speech therapy. However, it was difficult to determine rehabilitation costs retrospectively. Therefore, it was not counted in the cost analysis as a separate variable, but additional rehabilitation costs were not completely lost as the hospitalization costs already account for allied health professionals.

(8) Physician Visits

The HIT Database provided the number of consults and visits from the TE Service. Physician costs were not included in the final analysis as this study was from the hospital perspective.

A sensitivity analysis could address the underestimation of the costs of HIT, although this was not conducted because plausible ranges were not available. Although a conservative view was taken with cost allocation in this study, it is felt that the important costs were captured from the hospital perspective.

The other limitation to this study was generalizability. This study was conducted at SHSC, which is a large teaching hospital. For example, drugs available at this institution may not be available at community hospitals. It also has a Cardiac Surgery Program, which produced the majority of the confirmed cases of HIT. Finally, SHSC has a HIT management team (e.g., the TE Service) that attempts to optimize the

efficiency of patient care. Other institutions may have higher costs because they do not have such a service.

5.2 Conclusions

Suspected (confirmed and negative) cases of HIT increase the costs of hospital care. The conservative institutional costs for HIT at SHSC were $456,787 in 2005. Confirmed HITT cases made up almost 90% of the total HIT costs.

This is the first study to identify and quantify the direct medical costs associated with all aspects of HIT, including negative HIT, confirmed HIT, and confirmed HITT. Previous burden of illness studies in HIT were conducted in the US and each had a number of limitations, including lack of or poorly-defined HIT, unclear perspectives (e.g., institutional, societal), incomplete cost lists, the cost of HIT and HITT were not separated out, and lack of information on the burden of suspected HIT cases. Thus, the results presented in these earlier studies could not be compared to the results of this study.

This is also the first comprehensive study on the direct medical costs associated with HIT from a Canadian hospital perspective. Canadian hospital decision makers can use this study to estimate the costs of HIT management. For example, this study may assist with decisions that are made in relation to the hospital formulary and laboratory approaches to suspected HIT. It can also serve as a framework for other Canadian hospitals to determine the costs of HIT in their institution. Moreover, it can serve as an input in a cost-effectiveness analysis comparing UFH to an alternative anticoagulant. Some cost-effectiveness studies comparing UFH to an alternative anticoagulant[84-87] used elements a HIT cost in their economic models. However, these surrogate costs for HIT do not reflect the true cost of HIT and the results of this study would be a more accurate estimate to use. Finally, this study can serve as a model for future cost of illness studies focused on ADRs from the Canadian hospital perspective, since the last study appears to have been done in 1998.

5.3 Recommendations

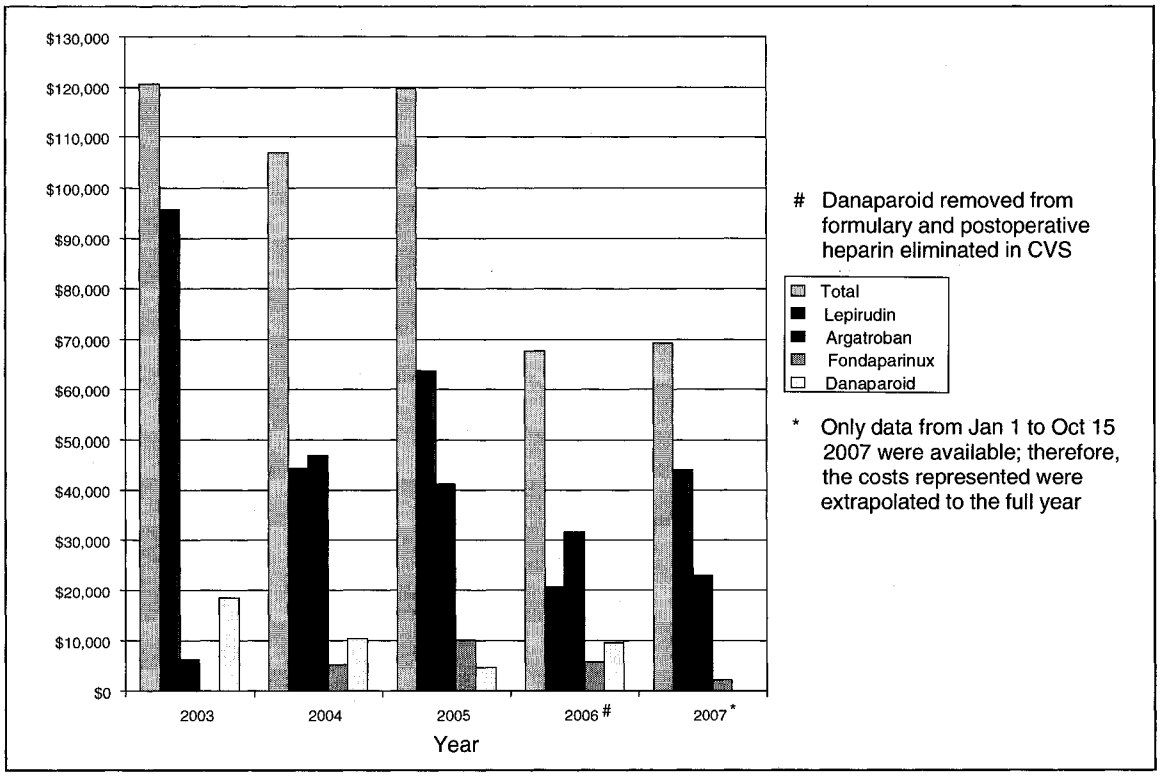
This study could be expanded to examine the following: (1) other perspectives, (2) a prospective analysis, (3) comparator groups, and (4) other institutions.

(1) Other Perspectives

This study focused on hospital related costs such as hospital days, inpatient medication, laboratory tests, and imaging. If the study were from the healthcare perspective, then physician fees, outpatient visits, and outpatient medication use would also be included.

A longitudinal perspective can also be investigated, such as the changes in the disease over time, changes in diagnostic criteria, and changes inpatient management. The introduction of new HIT-specific interventions can be studied. For example, the following have occurred at SHSC in the past few years that may impact on HIT: (1) the introduction of fondaparinux as HIT treatment in 2004, (2) the removal of danaparoid from the formulary in 2006, and (3) the elimination of postoperative heparin in CVS patients in 2006. Figure 9 displays the HIT-safe anticoagulant expenditures at SHSC from 2003 to 2007. These drugs are not used for any non-HIT indication. The overall expenditures for HIT-safe drugs per year may be decreasing, possibly as a result of one or more of the changes above.

Figure 9: HIT-safe anticoagulant expenditures at SHSC from 2003 to 2007.



(2) A Prospective Analysis

A prospective study could be conducted. The TE Service could populate the HIT Database prospectively, making it easier to sort out which components of patient care are attributable to HIT. Patients with confirmed HITT could be followed after discharge to study loss in productivity, outpatient visits, and outpatient medication use.

(3) Comparator Groups

Three studies have examined HIT-related costs with comparator groups; Creekmore et al[17] presented costs for medical patients, Frame[18] presented costs for CVS patients, and Smythe et al[20] presented costs for a undefined patient population. Each of these studies concluded that there was an increase in hospital days and costs associated with HIT. In this study, the majority of the cases were CVS patients, which accounted for 46% of the suspected HIT cases and 65% of the confirmed HIT cases. A sub-analysis of the CVS patients showed that patients with suspected HIT had significantly longer postoperative hospital stays then CVS patients without HIT. However, given the problem with diagnostic uncertainty, differences in patient management and variability in costing assumptions, it is not appropriate to compare HIT costs between studies. Table 23 presents the comparison of postoperative LOS in CVS patients.

Table 23: Comparison of postoperative LOS in CVS patients.

Patient group	Mean postoperative LOS ± SD (range)	p-value for postoperative LOS
CVS (HIT not suspected) n = 808	10.7 ± 8.7 (0.0 - 132.0)	-
CVS suspected HIT n = 51	27.5 ± 28.8 (3.0 - 129.0)	0.0001*
CVS Negative HIT n = 38	*26.8 ± 31.4 (3.0 - 129.0)*	*<0.001#*
CVS HIT n = 6	*21.0 ± 15.9 (15.0 - 21.0)*	*>0.05#*
CVS HITT n = 7	*34.0 ± 23.6 (14.0 -71.0)*	*<0.001#*

CVS - cardiovascular surgery, LOS - length of stay, SD - standard deviation * unpaired t-test, # one-way analysis of variance with Tukey-Kramer multiple comparison test to determine the probability of observed difference from the patient group CVS (HIT not suspected)

(4) Other Institutions

Data from other institutions would be important in order to generalize to all hospitals in Ontario or elsewhere in Canada.

REFERENCES

(1) Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. New England Journal of Medicine 2001; 344(17):1286-1292.

(2) Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards consensus. Thrombosis & Haemostasis 1998; 79(1):1-7.

(3) Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. British Journal of Haematology 2003; 121(4):535-555.

(4) Warkentin TE. Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. Archives of Pathology & Laboratory Medicine 2002; 126(11):1415-1423.

(5) Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. American Journal of Medicine 1996; 101(5):502-507.

(6) Greinacher A, Warkentin TE. Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. Thrombosis Research 2006; 118(2):165-176.

(7) Jappe U. Allergy to heparins and anticoagulants with a similar pharmacological profile: an update. Blood Coagulation & Fibrinolysis 2006; 17(8):605-613.

(8) Wallis DE, Workman DL, Lewis BE, Steen L, Pifarre R, Moran JF. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. American Journal of Medicine 1999; 106(6):629-635.

(9) Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thrombosis & Haemostasis 2005; 94(1):132-135.

(10) Nand S, Wong W, Yuen B, Yetter A, Schmulbach E, Gross FS. Heparin-induced thrombocytopenia with thrombosis: incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution. American Journal of Hematology 1997; 56(1):12-16.

(11) King DJ, Kelton JG. Heparin-associated thrombocytopenia. Annals of Internal Medicine 1984; 100(4):535-540.

(12) White PW, Sadd JR, Nensel RE. Thrombotic complications of heparin therapy: including six cases of heparin-induced skin necrosis. Annals of Surgery 1979; 190(5):595-608.

(13) Warkentin TE. Heparin-induced skin lesions. British Journal of Haematology 1996; 92(2):494-497.

(14) Platell CF, Tan EG. Hypersensitivity reactions to heparin: delayed onset thrombocytopenia and necrotizing skin lesions. Australian & New Zealand Journal of Surgery 1986; 56(8):621-623.

(15) Warkentin TE, Roberts RS, Hirsh J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. Chest 2005; 127(5):1857-1861.

(16) Rosove M.H. New Insights on Heparin-induced Thrombocytopenia. Blood 2005; 105(1):4-5.

(17) Creekmore FM, Oderda GM, Pendleton RC, Brixner DI. Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. Pharmacotherapy 2006; 26(10):1438-1445.

(18) Frame JN. The heparin-induced thrombocytopenia Task Force model: Implementing quality improvement and economic outcome initiatives. Seminars in Hematology 2005; 42(Suppl. 3):S28-S35.

(19) Samama M, Valdes JC, Natali J. Medico-legal implications of anticoagulant treatments. Journal des Maladies Vasculaires 1996; 21(4):250-255.

(20) Smythe MA, Koerber JM, Mattson JC. Capturing the Financial Impact of Heparin-Induced Thrombocytopenia. Blood (ASH Annual Meeting Abstracts) 106, 3127. 11-16-2005.

(21) Schlienger RG, Oh PI, Knowles SR, Shear NH. Quantifying the costs of serious adverse drug reactions to antiepileptic drugs. Epilepsia 1998; 39(Suppl. 7):S27-S32.

(22) Warkentin TE. Clinical Picture of Heparin-induced Thrombocytopenia. In: Warkentin TE, Greinacher A, editors. Heparin-Induced Thrombocytopenia. 4 ed. New York: Informa Healthcare; 2007. 21-66.

(23) Shuster TA, Silliman WR, Coats RD, Mureebe L, Silver D. Heparin-induced thrombocytopenia: twenty-nine years later. Journal of Vascular Surgery 2003; 38(6):1316-1322.

(24) Smythe MA, Koerber JM, Mattson JC. The incidence of recognized heparin-induced thrombocytopenia in a large, tertiary care teaching hospital. Chest 2007; 131(6):1644-1649.

(25) Baglin T, Barrowcliffe TW, Cohen A, Greaves M, British Committee for Standards in Haematology. Guidelines on the use and monitoring of heparin. British Journal of Haematology 2006; 133(1):19-34.

(26) Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. New England Journal of Medicine 1991; 324(6):370-376.

(27) Baker GR, Norton PG, Flintoft V, Blais R, Brown A, Cox J et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. Canadian Medical Association Journal 2004; 170(11):1678-1686.

(28) Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The Quality in Australian Health Care Study. Medical Journal of Australia 1995; 163(9):458-471.

(29) Warkentin TE. Heparin-induced thrombocytopenia, Part 1: The diagnostic clues. Journal of Critical Illness 2005; 20(1):6-13.

(30) Kaplan KL, Broekman MJ, Chernoff A, Lesznik GR, Drillings M. Platelet alpha-granule proteins: studies on release and subcellular localization. Blood 1979; 53(4):604-618.

(31) Stuckey JA, St CR, Edwards BF. A model of the platelet factor 4 complex with heparin. Proteins 1992; 14(2):277-287.

(32) Mayo KH, Ilyina E, Roongta V, Dundas M, Joseph J, Lai CK et al. Heparin binding to platelet factor-4. An NMR and site-directed mutagenesis study: arginine residues are crucial for binding. Biochemical Journal 1995; 312(Pt 2):357-365.

(33) Li ZQ, Liu W, Park KS, Sachais BS, Arepally GM, Cines DB et al. Defining a second epitope for heparin-induced thrombocytopenia/thrombosis antibodies using KKO, a murine HIT-like monoclonal antibody. Blood 2002; 99(4):1230-1236.

(34) Visentin GP, Ford SE, Scott JP, Aster RH. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. Journal of Clinical Investigation 1994; 93(1):81-88.

(35) Kelton JG, Sheridan D, Santos A, Smith J, Steeves K, Smith C et al. Heparin-induced thrombocytopenia: laboratory studies. Blood 1988; 72(3):925-930.

(36) Warkentin TE, Hayward CP, Boshkov LK, Santos AV, Sheppard JA, Bode AP et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. Blood 1994; 84(11):3691-3699.

(37) Chong BH. Heparin-induced thrombocytopenia. British Journal of Haematology 1995; 89(3):431-439.

(38) Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005; 106(8):2710-2715.

(39) Warkentin TE, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. Blood 2006; 108(9):2937-2941.

(40) Alving BM. Heparin-induced thrombocytopenia: the female factor. Blood 2006; 108(9):2884.

(41) Lindhoff-Last E, Eichler P, Stein M, Plagemann J, Gerdsen F, Wagner R et al. A prospective study on the incidence and clinical relevance of heparin-induced antibodies in patients after vascular surgery. Thrombosis Research 2000; 97(6):387-393.

(42) Arepally GM, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. New England Journal of Medicine 2006; 355(8):809-817.

(43) Warkentin TE, Heddle NM. Laboratory diagnosis of immune heparin-induced thrombocytopenia. Current Hematology Reports 2003; 2(2):148-157.

(44) Warkentin TE. Laboratory testing for heparin-induced thrombocytopenia. Journal of Thrombosis & Thrombolysis 2000; 10(Suppl. 1):35-45.

(45) Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. Blood 1986; 67(1):27-30.

(46) Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. Blood 2000; 96(5):1703-1708.

(47) Warkentin TE. Heparin-induced thrombocytopenia: a clinicopathologic syndrome. Thrombosis & Haemostasis 1999; 82(2):439-447.

(48) Greinacher A, Warkentin TE. Treatment of Heparin-Induced Thrombocytopenia: An Overview. In: Warkentin TE, Greinacher A, editors. Heparin-Induced Thrombocytopenia. 4 ed. New York: Informa Healthcare; 2007. 283-317.

(49) Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: Recognition, treatment, and prevention - The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(Suppl. 3):311S-337S.

(50) Ranze O, Eichner A, Lubenow N. The use of low-molecular-weight heparins in heparin-induced thrombocytopenia (HIT): a cohort study. Annals of Hematology 2000; 79(Suppl. 1):198.

(51) Warkentin TE. Current agents for the treatment of patients with heparin-induced thrombocytopenia. Current Opinion in Pulmonary Medicine 2002; 8(5):405-412.

(52) Warkentin TE. Coumarin-induced skin necrosis and venous limb gangrene. In: Colman RW, Marder VJ, Clowes AW, George JN, Goldhaber S.Z., editors. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. 1663-1671.

(53) Bradner JE, Eikelboom JW. Emerging Anticoagulants and Heparin-Induced Thrombocytopenia: Indirect and Direct Factor Xa Inhibitors and Oral Thrombin Inhibitors. In: Warkentin TE, Greinacher A, editors. Heparin-Induced Thrombocytopenia. 4 ed. New York: Informa Healthcare; 2007. 441-461.

(54) Chong BH, Magnani HN. Danaparoid for the Treatment of Heparin-Induced Thrombocytopenia. In: Warkentin TE, Greinacher A, editors. Heparin-Induced Thrombocytopenia. 4 ed. New York: Informa Healthcare; 2007. 319-343.

(55) Bartholomew JR. Bivalirudin for the Treatment of Heparin-Induced Thrombocytopenia. In: Warkentin TE, Greinacher A, editors. Heparin-Induced Thrombocytopenia. 4 ed. New York: Informa Healthcare; 2007. 409-439.

(56) Lewis BE, Hursting MJ. Argatroban Therapy in Heparin-Induced Thrombocytopenia. In: Warkentin TE, Greinacher A, editors. Heparin-Induced Thrombocytopenia. 4 ed. New York: Informa Healthcare; 2007. 379-408.

(57) Robson R, White H, Aylward P, Frampton C. Bivalirudin pharmacokinetics and pharmacodynamics: effect of renal function, dose, and gender. Clinical Pharmacology & Therapeutics 2002; 71(6):433-439.

(58) Fox I, Dawson A, Loynds P, Eisner J, Findlen K, Levin E et al. Anticoagulant activity of Hirulog, a direct thrombin inhibitor, in humans. Thrombosis & Haemostasis 1993; 69(2):157-163.

(59) Scatena R. Bivalirudin: a new generation antithrombotic drug. Expert Opinion on Investigational Drugs 2000; 9(5):1119-1127.

(60) Greinacher A. Lepirudin for the Treatment of Heparin-Induced Thrombocytopenia. In: Warkentin TE, Greinacher A, editors. Heparin-Induced Thrombocytopenia. 4 ed. New York: Informa Healthcare; 2007. 345-378.

(61) Drug Formulary: http://alecto/departments/pharmacy/drugsearch.cfm. Sunnybrook Health Sciences Centre 2007.

(62) Dager WE, White RH. Treatment of heparin-induced thrombocytopenia. Annals of Pharmacotherapy 2002; 36(3):489-503.

(63) Hirsh J. New anticoagulants. American Heart Journal 2001; 142(Suppl. 2):S3-S8.

(64) Basic Types of Economic Evaluations. In: Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL, editors. Methods for the Economic Evaluation of Health Care Programmes. 3 ed. New York: Oxford; 2005. 7-26.

(65) Drummond M. Cost-of-illness studies: a major headache? Pharmacoeconomics 1992; 2(1):1-4.

(66) Larson LN. Cost Determination and Analysis. In: Bootman JL, Townsend RJ, McGhan WF, editors. Principle of Pharmacoeconomics. 3 ed. Cincinnati: Harvey Whitney Books Company; 2005. 47-63.

(67) Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. Milbank Memorial Fund Quarterly - Health & Society 1982; 60(3):429-462.

(68) Bonk RJ. Categorization of Pharmacoeconomic Costs. Pharmacoeconomics in Perspective: A Primer on Research, Techniques, and Information. New York: Pharmaceutical Products Press; 1999. 71-76.

(69) Rychlik R. Basics and Methods. Strategies in Pharmacoeconomics an Outcomes Research. New York: The Haworth Press, Inc.; 2002. 13-67.

(70) Needles Only: http://www.researchsupply.net/needles.html. Research Supply 2008.

(71) Ontario Guide to Case Costing: http://www.occp.com/. Ontario Case Costing Initiative 2007.

(72) About the OCCI: http://www.occp.com/. Ontario Case Costing Initiative 2007.

(73) Ontario Case Costing Facilities: http://www.occp.com/. Ontario Case Costing Initiative 2007.

(74) Inflation Calculator: http://www.bankofcanada.ca/en/rates/inflation_calc.html. Bank of Canada 2008.

(75) Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, FitzGerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respiratory Medicine 2008; 102(3):413-421.

(76) Reynolds MR, Essebag V, Zimetbaum P, Cohen DJ. Healthcare resource utilization and costs associated with recurrent episodes of atrial fibrillation: the FRACTAL registry. Journal of Cardiovascular Electrophysiology 2007; 18(6):628-633.

(77) Thomas KC, Nosyk B, Fisher CG, Dvorak M, Patchell RA, Regine WF et al. Cost-effectiveness of surgery plus radiotherapy versus radiotherapy alone for metastatic epidural spinal cord compression. International Journal of Radiation Oncology, Biology, Physics 2006; 66(4):1212-1218.

(78) Angus DC, Linde-Zwirble WT, Clermont G, Ball DE, Basson BR, Ely EW et al. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. Critical Care Medicine 2003; 31(1):1-11.

(79) Costing Analysis Tool: http://www.occp.com/. Ontario Case Costing Initiative 2007.

(80) Heemstra HE, Zwaan T, Hemels M, Feldman BM, Blanchette V, Kern M et al. Cost of severe haemophilia in Toronto. Haemophilia 2005; 11(3):254-260.

(81) Dranitsaris G, Tran TM, McGeer A, Narine L. Pharmacoeconomic analysis of empirical therapy with ceftazidime alone or combination antibiotics for febrile neutropenia in cancer patients. Pharmacoeconomics 1995; 7(1):49-62.

(82) GRASP Self Learning Guide for Nurses: http://mysb.ca/data/1/rec_docs/1210_intranetgrasp.pdf. Sunnybrook Health Sciences Centre 1999.

(83) O'Brien JA, Patrick AR, Caro JJ. Cost of managing complications resulting from type 2 diabetes mellitus in Canada. BMC Health Services Research 2003; 3(1):7.

(84) Shorr AF, Jackson WL, Moores LK, Warkentin TE. Minimizing costs for treating deep vein thrombosis: The role for fondaparinux. Journal of Thrombosis & Thrombolysis 2007; 23(3):229-236.

(85) Shorr AF, Jackson WL, Weiss BM, Moores LK. Low-molecular weight heparin for deep vein thrombosis prophylaxis in hospitalized medical patients: Results from a cost-effectiveness analysis. Blood Coagulation & Fibrinolysis 2007; 18(4):309-316.

(86) McGarry LJ, Thompson D, Weinstein MC, Goldhaber SZ. Cost effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients. American Journal of Managed Care 2004; 10(9):632-642.

(87) Aujesky D, Smith KJ, Cornuz J, Roberts MS. Cost-effectiveness of low-molecular-weight heparin for treatment of pulmonary embolism. Chest 2005; 128(3):1601-1610.

(88) Barty R, Thompson T, Cameron T. Developing a Cost Model for Transfusion of Blood Components in Ontario. Canadian Society of Transfusion Medicine (conference) 2007.

(89) Rock G, Akerblom O, Berseus O, Herve P, Jacobs P, Kelly T et al. The supply of blood products in 10 different systems or countries. Transfusion Science 2000; 22(3):171-182.

(90) Schedule of Benefits- Physician Services Under the Health Insurance Act (October 1, 2007): http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html. Ministry of Health and Long Term Care 2007.

Appendix A: HIT Database

Demographic data
Date of birth
Gender
Year HIT suspected
Important dates:
Date of admission
Date HIT suspected
Date of discharge/death
HIT status:
HIT
HITT
Negative
Indeterminate
Clinical history
Primary clinical service at the time of heparin exposure:
Surgery:
Cardiac surgery
General surgery
Orthopedic surgery
Trauma
Vascular surgery
Other surgery
Medicine:
Cardiology
General internal medicine
Nephrology
Neurology
Other internal medicine
Visits from the TE Service
Date of consultation + dates and number of follow-up visits
Laboratory values
HIT testing:
HIT ELISA:
Date requested
Date reported
Optical density value
Result
SRA:
Date requested
Date reported
Result
Number of medication monitoring tests (related to use of HIT-safe anticoagulant):
aPTT

PT
Medication data
Treatment for HIT (dose and duration):
HIT-safe anticoagulants:
Argatroban
Bivalirudin
Danaparoid
Fondaparinux
Lepirudin
Clinical outcome data
HIT-related complications and diagnostic imaging:
Venous:
DVT:
Doppler ultrasound
Venogram
Other
PE:
CTPA
V/Q scan
Pulmonary angiogram
Other
Adrenal infarction:
CT
US
MRI
Other
Other
Arterial:
MI:
Cardiac enzymes
ECG
Coronary angiogram
Other
Peripheral arterial occlusion:
Arterial Doppler
Arteriogram
CT angiogram
MR angiogram
Other
Stroke:
CT
MRI
Angiogram
Other
Bypass graft occlusion:
Angiogram

Other
Other
Other:
Transient global amnesia:
CT
MRI
Other
Clotting of dialysis circuit
HIT-related surgery:
Amputation
Other
Bleeding episode:
Overt bleeding location
Bleeding outcome
Death during hospital stay (specify reason)
Other

aPTT - activated partial thromboplastin time, CT - computed tomography, CTPA - computed tomography pulmonary angiogram, DVT - deep vein thrombosis, ECG - electrocardiography, MRI - magnetic resonance imaging , PE - pulmonary embolism, PT - prothrombin time, V/Q - ventilation/perfusion scan

Appendix B: Cost Components Associated with Laboratory Tests

Cost components related to the HIT ELISA.

Components	Cost (2007 CAN $)
Supplies to carry out test	
GTI PF4 Enhanced® kit (number used in the year multiplied by the unit cost)	30 x $641 = $19,230
Conjugate (number used in the year multiplied by the unit cost)	20 x $13 = $ 260
Wash buffer (number used in the year multiplied by the unit cost)	30 x $13 = $390
Sample diluents (number used in the year multiplied by the unit cost)	10 x $13 = $130
Substrate (number used in the year multiplied by unit cost)	5 x $13 = $65
Yearly total	$20,075
MLT time	
Hourly rate + 30% benefits	$38
Hands on MLT time for ELISA (hours per year)	110
Yearly total	$4,180
Number of HIT ELISA performed in 2005 for all hospitals	618
Total average cost for HIT ELISA [($20,075 + $4,180)/618]	$39 per test

ELISA - enzyme linked immunosorbent assay, MLT - medical lab technologist, PF4 - platelet factor 4

SRA charges to SHSC.

Test type	Charge (2007 CAN $)
SRA	$150 + $5 shipping and handling fee to deliver to McMaster University $155 per test

SRA - serotonin release assay

Appendix C: Cost Components Associated with HIT-Safe Anticoagulant Use

(1) Pharmacy Preparation Time

A prospective time-and-motion study was carried out at SHSC on January 31, 2007 to determine the labor costs required to prepare the DTIs: lepirudin, argatroban and bivalirudin. For lepirudin, an average infusion rate of approximately 21 mL/hr was found among the cohort of patients who received this drug as treatment in 2005. The preparation time for this dose was studied (Table 24).

A Pharmacist receives an order for lepirudin, which is then entered into the SHSC Pharmacy Database, WORx©. Labels are printed and given to the Pharmacy Technician, along with an instruction sheet. The Pharmacy Technician then prepares a bolus dose that requires one IV bag and a vial of the drug. Other items needed for a continuous drug infusion (three vials of the drug, three IV bags, and three vials of sterile water) are collected. The Pharmacist then reviews the items being sent to the hospital nursing unit and signs off on the order.

Table 24: Time and cost of preparing lepirudin.

Task	Time	Cost (salary x time)
- Drug order received by Pharmacist - Entered into Pharmacy Database WORx© - Labels printed and given to Pharmacy Technician, along with instruction sheet	2 minutes and 49 seconds (~ 3 minutes)	$44.31/60 (Pharmacist pay/ 60 minutes) x 3 minutes = $2.22
- Prepare bolus dose - Prepare IV bags and vials - Labels bags	15 minutes and 31 seconds (~ 16 minutes)	$26.62/60 (Pharmacy Technician pay/ 60 minutes) x 16 minutes = $7.10
Pharmacist reviews and signs off	52 seconds (~ 1 minute)	$44.31/60 (Pharmacist pay/ 60 minutes) x 1 minute = $0.74
Total	~ 20 minutes	$10.06 (~ $10)

IV - intravenous

For argatroban, an average infusion rate of approximately 9 mL/hr was found among the study cohort who received this drug. Argatroban does not require a bolus. The continuous infusion is prepared by the Pharmacy staff, and nurses reconstitute the drug just before administration to avoid wastage of drug. The

continuous infusion requires an IV bag, vial of drug, and vial of sterile water. The time-and-motion study on the preparation of lepirudin indicated that approximately 16 minutes is needed to prepare a dose, which requires four vials of drug. It was decided to divide this time by four to calculate the time it takes to prepare a dose using one vial of drug. The Pharmacist time would be the same as the time recorded in the lepirudin study. Therefore, it was assumed that it takes roughly four minutes to prepare argatroban (Table 25).

Only one patient received bivalirudin as treatment (7.5 mg/hr). The supplies were one vial of drug, one IV bag and one vial of sterile water. The same time-and-motion assumption made for argatroban was also made for bivalirudin (Table 25).

Table 25: Time and cost of preparing argatroban and bivalirudin.

Task	Time	Cost (salary x time)
- Drug order received by Pharmacist - Entered into Pharmacy Database WORx© - Labels printed and given to Pharmacy Technician, along with instruction sheet	2 minutes and 49 seconds (~ 3 minutes)	$44.31/60 (Pharmacist pay/ 60 minutes) x 3 minutes = $2.22
- Prepare IV bag and vial - Labels bags	~ 4 minutes (preparation of 1 vial)	$26.62/60 (Pharmacy Technician pay/ 60 minutes) x 4 minutes = $1.77
Pharmacist reviews and signs off	52 seconds (~ 1 minute)	$44.31/60 (Pharmacist pay/ 60 minutes) x 1 minute = $0.74
Total	~ 8 minutes	$4.73 (~ $5)

IV - intravenous

The drug infusion rates are variable because they depend on the weight of the patient, and the patient's renal or hepatic function. The drug expiry date for the DTIs, once prepared, is 24 hours. Thus, the assumption was made that these preparation costs would be applied to each day of DTI treatment. Table 26 provides a summary of these costs.

Table 26: Summary of drug preparation costs per day.

Drug	Drug preparation cost per day
Lepirudin	$10
Argatroban or bivalirudin	$5

No preparation time was counted for fondaparinux, as it is given subcutaneously using pre-loaded syringes. No preparation time was also counted for danaparoid, because the patients in this study cohort had received the drug subcutaneously rather than by infusion.

2) Monitoring Tests and Treatment of ADRs

Table 27: Costs related to monitoring and treatment of ADRs.

Variable	Cost (2007 CAN $)	Reference
Monitoring tests for DTIs: aPTT cost PT cost	 $4 $3	Jacqueline King, Hematology Manager, SHSC Department of Clinical Pathology, personal communication, May 24th 2007
Treatment of ADRs (bleeds): Transfusion cost (phlebotomy + transfusion service + nursing)	$63*	Barty R et al 2007[88]

aPTT - activated partial thromboplastin time, CAN - Canadian, ADR - adverse drug reaction, DTI - direct thrombin inhibitor, PT - prothrombin time, SHSC - Sunnybrook Health Sciences Centre, * blood product costs not included because hospitals receive blood free of charge[89]

Appendix D: Cost Components Associated with Diagnostic Imaging

Complication	Procedure	Codes[90]	Technical fees (2007 CAN $)[90]
DVT	Leg Doppler ultrasound	J202 J163	$34 $33
DVT	Leg bilateral Doppler ultrasound	J202 J163	$34x2=$68 $33
IVC thrombus	Abdominal Doppler ultrasound	J135 J206	$50 $23
MI, PE	Chest AP	X090	$15
MI, PE	Chest AP + LAT routine	X091	$23
PE	Chest CT	X125	no technical fee
Peripheral arterial occlusion	Femoral angiogram	X174	$31
RA thrombus, MI	Echocardiography	G560	$35
Stroke	Brain without contrast MRI	X421 X425 X499	no technical fee
Stroke, TGA	Head without contrast CT	X400	no technical fee

AP - anterior posterior, CAN - Canadian, CT - computed tomography, DVT - deep vein thrombosis, IVC - inferior vena cava, LAT - lateral, MI - myocardial infarction, MRI - magnetic resonance imaging, PE - pulmonary embolism, RA - right atrial, TGA - transient global amnesia

Appendix E: Cost Components Associated with Hospitalization

Average cost per day by bed type.

Type of bed	Cost per day (2007 CAN $)
Medical	$699
Surgical	$778
ICU level 2	$1,758
ICU level 3	$3,304

ICU - intensive care unit, cost includes: administration + nursing + pharmacy + allied health + laboratory + diagnostics + other (e.g., supplies) + overhead (40% of total hospitalization cost)

Appendix F: The Actually Managed Results

	Average cost (mean ± SD)
Negative HIT	
Laboratory testing	$54 ± $41(n=88) median: $39, range: $39-$272
HIT-safe anticoagulant use	$468 ± $1,115 (n=12) median: $98, range: $28-$3,987
Diagnostic imaging	$67 (n=1) median: NA, range: NA
Total	**$589**
Confirmed HIT + HITT	
Laboratory testing	$68 ± $62 (n=20) median: $39, range: $39-$233
HIT-safe anticoagulant use	$3,859 ± $4,386 (n=19) median: $2,674, range: $42-$16,744
Diagnostic imaging	$98 ± $64 (n=9) median: $67, range: $35-$213
Additional hospital days	$28,520 ± $57,920 (n=13) median: $4,195, range: $2,797-$198,238
Total	**$32,545**
Confirmed HIT	
Laboratory testing	$39 ± $0 (n=8) median: $39, range: $39-$39
HIT-safe anticoagulant use	$2,393 ± $3,460 $ (n=7) median: $182, range: $42-$9,302
Diagnostic imaging	$67 (n=1) median: NA, range: NA
Additional hospital days	$4,868 ± $1,488 (n=4) median: $4,277, range: $3,888-$7,032
Total	**$7,367**
Confirmed HITT	
Laboratory testing	$88 ±$74 (n=12) median: $39, range: $39-$233
HIT-safe anticoagulant use	$4,725 ± $4,776 (n=12) median: $3,156, range: $252-$16,744
Diagnostic imaging	$102 ± $67 (n=8) median: $67, range: $35-$213
Additional hospital days	$39,032 ± $68,024(n=9) median: $4,195, range: $2,797-198,238
Total	**$43,947**

SD - standard deviation

Appendix G: Research Ethics Board Approval Letter

MEMO R A N D U M

To: Scott Walker
Pharmacy
Room KB333

From: Philip Hébert MD

Date: December 8, 2006

Subject: **The Direct Medical Costs Associated with Suspected and Confirmed Cases of Heparin-Induced Thromboytopenia**

Project Identification Number: 451-2006
Approval Date: December 8, 2006

The Research Ethics Board of Sunnybrook Health Sciences Centre has conducted an expedited review of the research protocol referenced above on the above captioned date and approved the involvement of human subjects as specified in the protocol Version 1 dated October 31, 2006.

The quorum for approval did not involve any member associated with this project.

Should your study continue for more than one year you must request a renewal on or before one year from the approval date. Please advise the Board of the progress of your research annually and/or any adverse reactions or deviations which may occur in the future.

The above Project Identification Number has been assigned to your project Please use this number on all future correspondence.

Philip C. Hébert, MD PhD FCFPC
Chair, Research Ethics Board
/cap