Heparin-Induced Thrombocytopenia: Diagnostic and Therapeutic Considerations

Case Study and Commentary, William H. Matthai Jr, MD, and Jamie Ellen Siegel, MD

INTRODUCTION

Heparin use is ubiquitous in medicine today. It is used therapeutically in the management of arterial and venous thrombotic processes, such as acute myocardial infarction or deep venous thrombosis, and prophylactically to prevent thrombosis around the time of orthopedic procedures and to prevent prosthetic heart valve thrombosis or stroke in atrial fibrillation. Heparin is bonded to catheters such as pulmonary wedge catheters, and implanted catheters are sometimes flushed with a heparinized solution to prevent clotting. The chance of a significant exposure to heparin exceeds 50% when a patient is admitted to some medical services [1]. The widespread use of heparin exposes patients to the risk of heparin-induced thrombocytopenia (HIT), an antibody-mediated syndrome associated with significant morbidity and mortality. Serologically proven HIT occurs in 1.5% to 3% of patients with heparin exposure [2,3]. Paradoxically, the most feared consequence in these patients with a low platelet count is not bleeding but clotting. Arterial or venous thrombosis resulting in myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism, or limb ischemia and amputation complicate thrombocytopenia in at least 30% to 40% of cases [2,4,5], with a mortality estimated at approximately 30% [3,4,6] and a long length of hospital stay [3].

HIT is an important condition that is unrecognized by many clinicians. When thrombocytopenia is recognized, the diagnosis of HIT can be difficult to confirm, and until recently there was no therapeutic option other than discontinuation of heparin. Improved understanding of this syndrome increases the need for medical personnel to practice prevention, recognize the signs and symptoms of HIT, and know the treatment options available.

CASE STUDY

Initial Presentation and History

A 73-year-old woman presents to her local hospital with unstable angina. Treatment with aspirin, unfractionated heparin, and intravenous nitrates is initiated. Coronary angiography on the second hospital day demonstrates significant left main and 3-vessel coronary artery disease. The patient is transferred for emergent coronary artery bypass grafting. Surgery is performed on the second day of heparin therapy and is complicated by postoperative hypotension requiring administration of dopamine and dobutamine and placement of an intra-aortic balloon pump. The patient develops atrial fibrillation and oliguric renal failure. Peritoneal dialysis is begun. Intravenous heparin is restarted on her fifth hospital day due to persistent atrial fibrillation, and testing reveals a decreased platelet count. A hematology consultation is requested for diagnosis and management regarding the thrombocytopenia.

Physical Examination

The patient is intubated and sedated. Her blood pressure is 102/64 mm Hg, and her pulse is 64 bpm and irregularly irregular. She has a right internal jugular Swan-Ganz catheter in place, and a catheter is in place for peritoneal dialysis. There is an intra-aortic balloon pump in the right femoral artery. The patient’s right fourth and fifth toes are dusky purple. Her third left toe and her left thumb have a purple discoloration as well.

Serial platelet counts are as follows:

- Day 2 (preoperative) 255,000/mm$^3$
- Day 3 (postoperative) 94,000/mm$^3$
- Day 4 134,000/mm$^3$
- Day 5 (before heparin bolus) 59,000/mm$^3$
- Day 5 (after heparin bolus) 18,000/mm$^3$

William H. Matthai Jr, MD, Clinical Associate Professor of Medicine, Department of Medicine, University of Pennsylvania Medical School, Associate, Cardiac Catheterization Laboratory, Presbyterian Medical Center, Philadelphia, PA; and Jamie Ellen Siegel, MD, Associate Professor of Medicine, Department of Medicine, Division of Hematology, Robert Wood Johnson Medical School, New Brunswick, NJ.
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**Table 1. Differential Diagnosis of Acquired Thrombocytopenia in the Intensive Care Unit Setting**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Devices</th>
<th>Events</th>
</tr>
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<tbody>
<tr>
<td>Heparin</td>
<td>Membrane oxygenator</td>
<td>Hypotension and subsequent disseminated</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Intra-aortic balloon pump</td>
<td>intravascular coagulation</td>
</tr>
<tr>
<td>Diuretics (eg, furosemide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine, blockers (eg, cimetidine)</td>
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**Differential Diagnosis**

Evaluation of the causes of thrombocytopenia in a critically ill patient can be frustrating because a definitive answer often is not obtained. One must first differentiate between etiologic factors that may be life- or limb-threatening and interventions that must be maintained to permit continued critical care support. Heparin often fits both categories, and the decision to continue or interrupt heparin therapy may be difficult. The differential diagnosis of thrombocytopenia can be extensive. An outline of diagnoses to consider is provided in Table 1, with specific examples related to this case. Although there are multiple potential causes of thrombocytopenia in this patient and we cannot definitively say at this point that the patient has HIT, she is already showing signs of HIT and thrombosis. The changes in the patient’s right toes can be explained by the intra-aortic balloon pump in the right femoral artery, but the changes on her left side are less likely due to that device.

**Diagnosis**

The diagnosis of HIT can be a very difficult one to make. Five factors are considered when attempting to diagnose HIT: (1) the absence of another clear cause for thrombocytopenia, (2) the timing of thrombocytopenia, (3) the degree of thrombocytopenia, (4) concurrent clinical events, and (5) laboratory support of the diagnosis.

In patients exposed to heparin for the first time, thrombocytopenia typically develops 5 to 10 days after exposure [2,7]. If a patient has had 2 weeks of heparin therapy and then develops a low platelet count, a cause other than HIT is more likely. Patients with previous heparin exposure, especially within the previous few months, may develop thrombocytopenia much more rapidly, even within the first day of repeat exposure [7]. Even with a careful history, previous heparin exposure may have been hidden; thus, frequent platelet counts are recommended. Platelet counts should be obtained prior to heparin dosing, on the first day of treatment, and every 1 to 2 days for the first 2 weeks of heparin exposure. After discontinuation of heparin, thrombocytopenia should begin to resolve if the low platelet count was due to HIT. Platelet counts usually normalize within 7 to 10 days after heparin is discontinued [3], but recovery of the platelet count may be delayed, especially in severely ill patients.

The degree of thrombocytopenia is important in the diagnosis of HIT as well. The platelet count falls slightly in many patients shortly after exposure to heparin. This fall is a result of heparin-induced platelet aggregation and is known as type 1 HIT, or nonimmune heparin-associated thrombocytopenia. Type 1 HIT is a benign condition and rarely results in a platelet count below 100,000/mm³. Heparin may be continued as clinically indicated [8,9]. Type 2 HIT, immune-mediated HIT, is the diagnosis of concern, with the platelet count often falling to the 30,000–80,000/mm³ range; however, HIT with profound thrombocytopenia (platelet count < 20,000/mm³) or with a platelet count in the normal range can occur. Knowledge of the preheparin platelet count is important; a 50% decrease in the platelet count after initiation of heparin therapy should arouse suspicion of HIT.

Any thrombotic event in a patient with ongoing or recent heparin exposure should prompt consideration of HIT. Most thrombotic events are venous thromboses and include deep venous thrombosis, pulmonary embolism, venous limb gangrene, and bilateral adrenal vein thrombosis with acute adrenal insufficiency [2,5]. Arterial events occur most commonly after arterial manipulation, such as arteriography or coronary artery bypass surgery and may include limb ischemia, myocardial infarction, and stroke [10]. Other clinical events that should prompt consideration of HIT include heparin-induced skin necrosis at the site of heparin injections and acute systemic reactions following an intravenous bolus of heparin [11].

• What is the differential diagnosis of thrombocytopenia in this patient?

• How is the diagnosis of HIT made?
CASE-BASED REVIEW

Laboratory Testing

Numerous assays for the diagnosis of HIT are available, with varying reported sensitivities and specificities. High rates have been reported in individual studies, but the interpretation of each study is significantly affected by the study population [12,13].

There are 3 types of laboratory assay for HIT. Evaluations of platelet function (platelet aggregometry and the serotonin release assay [SRA]) and measurements of the HIT antibody (enzyme-linked immunosorbent assay [ELISA]) are used most often clinically, and flow cytometry to measure markers of platelet activation is now being evaluated [14]. Platelet aggregometry has been reported to have a high specificity but low sensitivity, due in part to the many variables (ie, heparin concentration [15], platelet preparation procedure, platelet donor requirements [16], instrumentation, serum versus plasma) that can affect the assay’s outcome [17]. If any assay is to be considered the gold standard, it is the SRA. In this assay, radiolabeled serotonin is incorporated into donor platelets, and the rate of serotonin release is recorded after these platelets are mixed with a sample from the patient. The sensitivity of this assay approaches 90%, and false-positive results are relatively rare [18].

A patient with a positive SRA requires very careful evaluation.

The ELISA for the HIT antibody is technically easier to perform than the SRA, so it is the screening test for HIT in some institutions. In many populations, the sensitivity and specificity of the test is similar to that of the SRA [18]. Unfortunately, this test has a high false-positive rate in other populations. In particular, in patients who have had cardiopulmonary bypass, the proportion of patients who will have a positive ELISA exceeds 50%, while the proportion of these patients who will have a positive SRA or clinically diagnosed HIT is much lower [19]. In addition, there is poor concordance between the SRA and ELISA; if one of the assays is positive, it does not necessarily follow that the other will be positive as well [12,18]. When clinical suspicion is high, it is reasonable to do more than one type of assay for HIT. In the presence of multiple negative assays of different types, the diagnosis of HIT is highly unlikely [8]; however, this type of laboratory support is often not available. Ultimately, for many clinicians, the diagnosis must be made clinically.

Review of Data and Further Evaluation

Review of the clinical data reveals that thrombocytopenia developed on day 5 of heparin therapy. There was an initial drop in the platelet count and subsequent recovery resulting from cardiopulmonary bypass, followed by a second decline in the platelet count suggesting another insult. There is evidence of thrombosis. The laboratory reports a positive heparin antibody (ELISA) result. Because this assay is positive in approximately 50% of patients after cardiopulmonary bypass, the physician requests that the coagulation laboratory run an SRA; this assay is also positive. The physician now feels that a diagnosis of HIT is likely.

- What is the pathophysiology of HIT?

Pathophysiology

HIT was first noted in the surgical literature as “white clot syndrome”—arterial thrombi comprised mostly of platelets. Later, the association with heparin administration was made, and the syndrome became known as heparin-associated thrombocytopenia. Heparin was not thought to be causative because the combination of heparin, an anticoagulant, and thrombosis seemed to be inconsistent. For many years, investigators searched unsuccessfully for antibodies to heparin, but in the early 1990s an antibody against the heparin/platelet factor 4 (PF4) complex was identified [20,21]. PF4 is an endogenous glycoprotein that binds to and inactivates heparin; it is released from activated platelets. Antibodies to heparin/PF4 can bind to platelets, activating them and resulting not only in thrombocytopenia but also in the release of procoagulant microparticles that may lead to thrombosis [22]. PF4 also has a high affinity for endothelial glycosaminoglycans, and this complex is recognized by the HIT antibody as well [23]. The resulting antibody-mediated endothelial injury is another mechanism of HIT with thrombosis [24]. In general, HIT is a condition of abnormally increased thrombin generation, resulting in a generally procoagulant state [11]. Endothelial injury and thrombin generation may result in thrombosis in the absence of thrombocytopenia or after discontinuation of heparin (ie, HIT with delayed thrombosis).

- Is discontinuation of heparin adequate treatment for HIT?

Discontinuation of Heparin

Although discontinuing heparin therapy will eventually result in resolution of thrombocytopenia, prevention of thrombosis is the goal of intervention. In one retrospective study, 52.8% of patients with HIT and isolated thrombocytopenia subsequently developed thrombosis [5]. In addition, up to 50% of patients with isolated thrombocytopenia and HIT may have an asymptomatic and clinically inapparent deep venous thrombosis at the time of the diagnosis of HIT that may be discovered only by systematic evaluation [25]. As discussed in the previous section, HIT is a condition of abnormally increased thrombin generation, resulting in a
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Generally procoagulant state [11]. Thrombotic events after the discontinuation of heparin have been well described [3]. Therefore, while discontinuation of heparin is a cornerstone of treatment of HIT, it is inadequate alone. Adequate treatment requires alternative methods of anticoagulation to reduce the possibility of thrombosis or to treat a thrombotic event. While patients with a thrombotic event will, on average, have a lower platelet count than those who do not, there is no way to predict which patient with HIT will suffer a thrombotic event and which will not [4].

All sources of heparin exposure must be eliminated if HIT is considered. In the case patient, there are multiple sources of heparin exposure in addition to the therapeutic infusion of heparin given after the development of atrial fibrillation. These sources include the heparin bonded to the Swan-Ganz catheter, the heparinized solutions used to flush the lumen of this catheter and the intra-aortic balloon catheter, the heparin in the peritoneal dialysate, and the heparin used to lock the dialysis catheter. These less obvious routes of heparin exposure will prolong HIT, thrombocytopenia, and the risk for thrombosis.

Anticoagulants

Although a number of treatment strategies for HIT have been employed, most provide inadequate anticoagulation. Use of low-molecular-weight heparin in a patient with active HIT is contraindicated. The antibodies that recognize the heparin/PF4 complex generally also recognize low-molecular-weight heparin when studied using in vitro platelet aggregation [26]. Low-molecular-weight heparins in a patient with HIT may maintain the condition, with continuing thrombocytopenia and a risk of thrombosis [27]. Additionally, agents such as the defibrinogenating agent anecrod, dextran, or platelet glycoprotein IIb/IIIa receptor inhibitors do not address the increased thrombin generation that occurs in HIT. However, a glycoprotein IIb/IIIa receptor inhibitor may have a beneficial role in conjunction with alternative anticoagulation [28]. The treatment options available in the United States that address the increased thrombin activity include danaparoid, which is a low-molecular-weight heparinoid, and lepirudin, a direct thrombin inhibitor (Table 2).

Lepirudin

Direct thrombin inhibitors are extremely powerful anticoagulants and have no cross-reactivity with the HIT antibody. Lepirudin is the only direct thrombin inhibitor approved for use and the only drug approved for treatment of HIT in the United States. The universally available activated partial thromboplastin time (aPTT) can be used to monitor the therapeutic effect of lepirudin, with treatment goals similar to those of heparin. Once therapeutic aPTT is achieved, there is much less intrapatient variability than with a heparin infusion and the aPTT needs to be checked only once a day. After several days, an antibody against lepirudin may develop in some patients, but there is no evidence the antibody is clinically significant [29]. The half-life of lepirudin is relatively short (1 to 2 hours), but the drug is excreted renally. Dose adjustment is possible and required for patients with renal insufficiency, as there is very limited experience with use of these drugs in patients requiring dialysis [30,31]. There is no antidote specific for lepirudin available. A prospective, historically controlled trial of lepirudin was published recently [4]. By 5 weeks after the laboratory diagnosis of HIT, the incidence of death, limb amputation, or new thromboembolic event was 52.1% in the historical controls and 30.9% in the lepirudin-treated group. The authors concluded that lepirudin reduced the incidence of these clinically important events with an acceptable safety profile. For these reasons, it has been our practice to use lepirudin as the anticoagulant of choice when intravenous anticoagulation is required, such as in patients with documented thrombosis. In addition, due to the high incidence of thrombosis in patients with active HIT, we have generally used lepirudin when the diagnosis of HIT has been confirmed or is strongly suggested. Other direct thrombin inhibitors, particularly argatroban, have been used in the management of HIT [32,33] and may become available for use in the United States. In countries where a direct thrombin inhibitor is unavailable, intravenous danaparoid may be used [6,34].

Danaparoid

There is little experience with subcutaneous administration of lepirudin, so use of this drug as a prophylactic agent is difficult. For instance, in a patient at bedrest who needs prophylaxis against deep venous thrombosis but has a known history of HIT, subcutaneous heparin (either standard unfractionated or low-molecular-weight) would not be appropriate; however, a subcutaneously administered agent would be most convenient in this setting. There is good experience with subcutaneous administration of the heparinoid danaparoid in HIT [6]. This mixture of low-molecular-weight glycosaminoglycans acts as an anticoagulant via its action on antithrombin. Its activity can be assessed only by measuring anti-factor Xa activity, an assay that is generally not readily available. Danaparoid has a long half-life (25 hours) and is also renally excreted. Therefore, laboratory availability of the anti-factor Xa assay is necessary in patients with abnormal renal function. Also, danaparoid cross-reacts somewhat with the HIT antibody in 10% to 40% of patients, but the clinical significance of cross-reactivity is not clear. No antidote specific for danaparoid is available. Although there is experience with intravenous danaparoid as treatment for HIT, we have generally used lepirudin in this setting due to greater experience with lepirudin in the United States, its shorter half-life, easy monitoring capability with the aPTT, and lack of cross-reactivity with the HIT antibody.
Should platelets be transfused in patients with HIT?

Patients with HIT generally do not bleed and therefore do not benefit from platelet transfusion. In fact, episodes of thrombosis have occurred after transfusion of platelets in patients with HIT, presumably from activation of the transfused platelets by the antibody-heparin complex [30].

Initial Treatment and Follow-up

The physician discontinues heparin therapy. In the setting of atrial fibrillation and with evidence of thrombosis, the physician starts intravenous lepirudin after the dose is adjusted for the patient’s renal insufficiency. An aPTT checked 4 hours after lepirudin is started is 65 seconds (2 x control). The lepirudin provides anticoagulation to reduce the risk of new thromboembolic events related to HIT as well as the anticoagulation required for the atrial fibrillation and indwelling intra-aortic balloon pump. Lepirudin is continued, and on day 10 the platelet count is 105,000/mm³. The patient’s hemodynamics improve, and the intra-aortic balloon pump is removed. The Swan-Ganz catheter is replaced with one that is not heparin bonded, and it is flushed with unheparinized saline. Over 24 hours, urine output improves and peritoneal dialysis is discontinued. The dialysis catheter is flushed with unheparinized saline.

What is the role of warfarin in treating patients with HIT?

What can be done to prevent HIT in the first place?

Warfarin Therapy

Warfarin should not be used alone as initial therapy for HIT, but several months of continued anticoagulation with warfarin may be appropriate in patients with HIT-associated thrombosis. However, warfarin-induced limb gangrene has been reported in HIT patients given warfarin without other anticoagulation [35]. HIT is a procoagulant state that may result in increased consumption of protein C, a natural anticoagulant. A low level of protein C within a few days of initiation of warfarin therapy in conjunction with increased thrombin generation that occurs in HIT is the pathophysiologic set up for warfarin-induced thrombosis. Therefore, it is necessary to start alternative anticoagulation with an agent such as lepirudin or danaparoid along with warfarin in patients with HIT. Initiation of warfarin therapy when the platelet count rises above 100,000/mm³ is a reasonable guideline. Longer-term anticoagulation with warfarin also may be appropriate in patients with HIT but with no thrombosis after initiation of an alternative anticoagulant. As mentioned earlier, the risk of thrombosis does not end when heparin is discontinued. In a patient with a firm diagnosis of HIT, especially in association with a condition that predisposes to thrombosis such as congestive heart failure or immobility, several months of anticoagulation with warfarin may be reasonable to reduce the risk of delayed thrombosis and to allow the level of the HIT antibody to fall. As with acute HIT, we are unable to select those patients at the greatest risk of delayed thrombosis due to HIT, and there are no data regarding the true utility of long-term anticoagulation in this condition.

Steps to Prevent HIT

Although anticoagulation with heparin cannot and should not be avoided in many patients, there are several steps that

Table 2. Treatment Options for Heparin-Induced Thrombocytopenia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Lepirudin</td>
<td>0.4 mg/ kg load, then 0.15 mg/ kg/hr</td>
<td>Preferred therapy, if available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjust dose for renal insufficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Check aPTT 4 hours after any dose adjustment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Goal aPTT is 1.5 to 3 x control</td>
</tr>
<tr>
<td>IV Danaparoid</td>
<td>400 U/hr x 4 hr, then 300 U/hr x 4 hr, then 100 to 370 U/hr</td>
<td>Use if direct thrombin inhibitor cannot be used</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor anti-factor Xa levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adjust dose for renal insufficiency</td>
</tr>
<tr>
<td>SC Danaparoid</td>
<td>750 U every 12 hr</td>
<td>May be used for low-risk cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Must have ability to monitor anti-factor Xa levels if renal insufficiency is present</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>Consider for long-term anticoagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not start warfarin without concurrent alternative anticoagulation</td>
</tr>
</tbody>
</table>

aPTT = activated partial thromboplastin time; IV = intravenous; SC = subcutaneous.
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can reduce the likelihood of HIT. It is now thought that bovine heparin may be more likely to produce HIT than porcine heparin [7]. For this reason, porcine heparin is used almost universally. Heparin exposure should be reduced if possible. Oral anticoagulation should be started as early as possible if indicated to reduce the duration of heparin exposure. Intravenous prim adaptors should not be flushed with heparin. Although low-molecular-weight heparin is contraindicated in patients who have already developed HIT, it is less likely to produce HIT than is standard unfractionated heparin [2]. Substitution of one of the low-molecular-weight heparins for clinically appropriate prophylactic or therapeutic indications is expected to significantly reduce the risk for HIT. Nonetheless, monitoring platelet counts for developing thrombocytopenia has been recommended whether standard or low-molecular-weight heparin is used.

Continuation of Therapy and Patient Discharge

With initiation of alternative anticoagulation with lepirudin, adequate circulation to all digits is maintained and evidence of digital ischemia gradually resolves, with minimal necrosis of the skin of the toes. Atrial fibrillation is converted to sinus rhythm. The central lines and dialysis catheters are removed on hospital day 11. Due to the diagnosis of HIT with evidence of thrombosis, the physician starts the patient on warfarin; lepirudin is discontinued when the prothrombin time/INR is therapeutic. The patient is discharged on hospital day 21. She is advised to wear a medical alert bracelet [36].

• What issues regarding HIT need further study?

Easily available methods of establishing a firm diagnosis of HIT and identifying patients at increased risk of thrombosis who require therapy more aggressive than discontinuation of heparin must be developed. Identification of those at risk for HIT with delayed thrombosis and the role, if any, for prolonged anticoagulation with warfarin must be defined. The ideal duration of treatment with warfarin is not known. Lepirudin or danaparoid provide adequate anticoagulation for HIT patients who require intravenous or subcutaneous prophylactic anticoagulation; however, there is no well-established method of providing alternative anticoagulation during cardiopulmonary bypass [37,38]. At the present time, if surgery can be performed electively, it may be best to postpone surgery for several months to allow antibody levels to fall. If repeat testing for HIT is negative, it may be possible to perform surgery with a single bolus of unfractionated heparin, with consideration of alternative anticoagulation in the postoperative period [39].

Summary

HIT is now recognized as an important immune-mediated complication of the use of any form of heparin by any route. Paradoxically, the adverse effect is thrombosis, both venous and arterial. This side effect of heparin must be recognized early to prevent limb-threatening morbidity and mortality. Serial platelet counts are the cornerstone of diagnosis. Laboratory diagnosis is difficult because testing is not 100% predictive, is highly specialized, and is not available at all centers. A diagnosis of HIT carries with it significant limitation in future treatment that requires heparin. Once a diagnosis of HIT is seriously entertained, heparin must be discontinued. Alternative anticoagulation can be instituted until the etiology of thrombocytopenia is better understood and a decision regarding avoidance of heparin or prolonged anticoagulation can be made. Alternative anticoagulation is now available that can reduce the morbidity and mortality associated with HIT.

References