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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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No 11 (344) 2023

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HEPARIN-INDUCED THROMBOCYTOPENIA (HIT) SYNDROME AMONG HEMODIALYSIS PATIENTS AND DISEASE MANAGEMENT STRATEGY

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Abstract.

The objective of this study is to investigate the impact of heparin-induced thrombocytopenia syndrome on individuals undergoing hemodialysis. Heparin-induced thrombocytopenia in hemodialysis patients (HD-HIT) is a condition believed to occur in hemodialysis patients who experience a sudden decrease in platelet count or unexplained blood clotting, particularly when there is evidence of thrombosis in the dialysis circuit despite adequate heparin dosage. HD-HIT is thought to be caused by a drug reaction and hyper immunoglobulin syndrome. It often occurs in the third to fifth session). Although the sensitivity ELISA test can yield a positive outcome for anti-PF4/heparin complex antibodies (HIT antibodies), the diagnosis is usually verified by a functional assay. Discontinue all sources of heparin, including those used for flushing or locking catheters, promptly upon the emergence of clinical suspicion of hemolysis. Alternative non-heparin anticoagulants should be resumed for dialysis, preferably a direct thrombin inhibitor. It is critical to start treatment as soon as possible because within 30 days of ceasing heparin, thrombus formation, including a clotting circuit, can become more complicated. This study used two cases from two patients who suffer from HD-HIT, and it concluded that it is necessary to diagnose heparin-induced thrombocytopenia syndrome as soon as possible, as it may lead to a high rate of infections and deaths if left untreated since dialysis patients are frequently exposed to heparin. Their condition may lead to moderate thrombocytopenia.

Key words. Colistin antibiotic, Hemocoagulation, Hemodialysis, Heparin-induced thrombocytopenia (HIT), Immunological test, Klebsiella pneumonia.

Introduction.

Heparin has traditionally been employed in hemodialysis facilities as an anticoagulant for securing long-term hemodialysis catheters and the extracorporeal circuit Furthermore, both low molecular weight heparin and unfractionated heparin have been employed. There has been a rise in the occurrence of type II heparin-induced thrombocytopenia (HIT) in recent years. The occurrence of this phenomenon is attributed to the creation of antibodies against the heparin-platelet factor complex, resulting in a decrease in platelet levels and an increased susceptibility to the development of blood clots in veins and arteries. A recent survey found that the prevalence of heparin-induced thrombocytopenia syndrome in hemodialysis patients was 0.26% (Dasgupta) in the United Kingdom. This is due to the widespread use of heparin in hemodialysis, whether to prevent blood clotting in the extracorporeal circuit or to lock catheters. It is, therefore, crucial to have a policy for specific and precise diagnosis and treatment of this syndrome in dialysis patients [1-7].

A significant and potentially deadly side effect of heparin use is heparin-induced thrombocytopenia, which can occur in a specific percentage of patients. Around 10% of patients diagnosed with HIT are categorized as Type 1 HIT or non-immune. This specific variety of HIT is distinguished by the aggregation or retention of platelets as a result of the direct interaction between heparin and platelets in the bloodstream. This interaction usually happens during the first three days after starting the medication and only causes mild thrombocytopenia (rarely less than 100,000/mm3), which generally goes back to normal after stopping the heparin. Autoantibodies related to the heparin-platelet factor 4 complex result in type 2 HIT, also called immune-mediated hemolysis. It typically appears 7–21 days after exposure, but it may appear suddenly in people who have taken heparin in the previous 90 days. The condition could deteriorate in these situations if an anaphylactoid reaction occurs within 30 minutes of delivery. In Japan, nafamostat mesylate, a versatile protease inhibitor with a wide range of activity, is occasionally employed as a substitute for heparin. There have been no clinical trials conducted to assess the effectiveness of HIT care, even though a small number of patients have demonstrated successful removal of blood clots and a gradual restoration of platelet count to its original level during a subsequent treatment session with nafamostat mesylate. Although (HD-HIT) can occur at the start of a heparin dialysis session, specific individuals with PF4/heparin complex antibodies are susceptible to developing late-onset thrombocytopenia syndrome [8-15].

Objective. The current study aims to determine the effect of heparin-induced thrombocytopenia syndrome on hemodialysis patients.

Methodology.

Case 1.

A 55-70-year-old female who suffers from chronic kidney disease stage 3 was admitted due to fever, edema, oliguria, and dyspnea, in addition to pallor and suprapubic tenderness. The results of the tests pointed to a urinary tract infection. She received HD treatment with unfractionated heparin (UFH) and intravenous (IV) antibiotics. On the 9th day of dialysis, platelets decreased, reaching a nadir of 59000/μL on day eleven. Her 4T score was 4. Moreover, her heparin-induced platelet aggregation test was positive, and it is one of the confirmatory functional assays for heparin-induced therapy (HIT) that examines how the patient's serum activates normal donor platelets in the presence of low-dose heparin [16-18], that shown in Tables 1 and 2.

Table 1. *Confirmatory functional tests for heparin-induced thrombocytopenia.*

4Ts	Defining Events	Score=2	Score=1	Score=0
Thrombocytopenia	Decrease from baseline to the lowest platelet count.	> -40-60% and ≥15,000-25,000/ µl without surgery within 3 days beforehand.	30-50% after 3 days of operation, platelet counts dropped by -17,000-20,000/ µL, or over 60% from baseline.	<30% Or <11,000/µL
Timing of platelet count drop	Onset of low platelet counts after starting heparin	5–10 days, Or less if heparin exposure began before 25-35 days.	Heparin exposure within 40-90 days is likely to occur within 5-10 days, after day 10, or within 2-5 days.	<7 days: no heparin exposure
Thrombosis (other clinical appearance)	---	Identify new cases of thrombosis associated with UFH, adrenal hemorrhage, or systemic response.	Therapeutic anticoagulation may result in venous thromboembolism, blood clots, or skin lesions at heparin injection sites.	N/A
Another source for thrombocytopenia	---	N/A	possible cause	possible cause

Table 2. *Compilation of different data of patient.*

Age	Comorbidities	Serum of procalcitonin (ng/mL)	culture of Blood	culture of Urine	Baseline creatinine (mg/dL)	CBC on presentation
60	HTN, 2 DM, CKD 3	5.6	-	*Klebsiella pneumoniae*	Approx 6.0	Hb-10 g/dL TLC-11750/µL Plt-170500/µL

Table 3. *Characteristics of Patients.*

Patient	History	Onset day/laboratory	Thrombotic events	Therapy	Follow-up
70-90 years female	December 9, 2015: G5D → G4 CKD Hypertension causes CKD. Sepsis and colistin nephrotoxicity cause AKI.	Hb D15: 10.4 g/dL Anti-PF4/ Hep+. Nadir Plt: 33 × 1094- T's Score: 5.	----	Heparin Citrate lock Warfarin	Plt 99 × 109 Hemodialysis

Table 4. *4T- Score of Patients.*

Classify	2 points	1 points	0 points
Thrombocytopenia	The platelet count drops by more than 60%, reaching a low of 150 × 10/l.	Platelet count decreases by 30-50% or minimum 10-19 × 109/l.	Platelet counts drop by <25-35% or nadir <10 × 109.
Time	Occurs within 7 days or 2 days if exposure occurs within 25-35 days.	Begin on 3 days ten or, if exposed within the preceding 25-35 to 90 days, occur in less than 2 days.	Early platelet decline without exposure to them.
other sequel of Thrombosis	Heparin bolus, skin necrosis, and new thrombosis.	Erythematosus skin lesions; potential thrombosis; repeated thrombosis	N/A
Another cause of thrombocytopenia	need a more precise reason.	There is an obvious possible reason.	A clear alternative reason is clear.

Case 2.

A 70–90-year-old Caucasian female patient with stage 4 chronic renal disease and hypertension had a multiresistant Klebsiella pneumoniae urinary tract infection that was treated with an intravenous Colistin antibiotic. She started getting hemodialysis via a central venous catheter as her kidney function declined. After fifteen days of initiating renal replacement medication, she developed thrombocytopenia. Her 4T score was 5, and the source of the disease was not evident. The use of anticoagulants during dialysis was stopped, and a serological examination was requested to detect antibodies associated with heparin-induced thrombocytopenia (HIT). Citrate was used as an anticoagulant for the central venous catheter. Antibodies against heparin-PF4 complex were identified. Following a two-week period, she was taken to a hemodialysis center and administered warfarin to halt the bleeding. [19-21], that shown in Tables 3 and 4.

Frequency of HIT in dialysis patients.

Studies suggest that between 1 to 5% of individuals who receive heparin may get heparin-induced thrombocytopenia (HIT). However, the incidence of HIT is considerably lower in patients treated with low-molecular-weight heparin. The variability in the specificity of the assays used to identify HIT antibodies may contribute to the differences in the occurrence rates of HIT. Furthermore, HIT antibody assays generally identify both pathogenic and non-pathogenic antibodies, irrespective of thrombocytopenia. A study is underway to assess the potential risk of thrombosis in individuals who do not have thrombocytopenia but exhibit a consistently high level of long-term HIT antibodies. However, the clinical implications of this finding is now uncertain. Although heparin is the most effective anticoagulant for dialysis, there is less data on the occurrence of heparin-induced thrombocytopenia (HIT) in dialysis patients.

It was anticipated that a survey aimed at all dialysis patients, encompassing both acute and chronic stages, would have a low frequency of HIT [22-26]. There is a notable disparity in the occurrence rate of HIT between two surveys that involve different groups of participants. A study found that among participants who had received dialysis therapy for less than three months, a relatively high frequency of 3.2% experienced the described condition. In contrast, among chronic dialysis patients who had received treatment for longer than three months, a low frequency of 0.6% experienced the condition. Consequently, there is a difference in the frequency of HIT in recently treated and chronically maintained dialysis groups within the dialysis population. The occurrence rate of HIT in the first group is comparable to that in the heparin-sensitive group. In the second type, HIT is infrequently recognized as a relapse of HIT when a patient undergoes alterations in immunological tolerance as a result of cardiovascular, orthopedic, and high-dose erythropoietin treatment, hence causing an unfavorable response that triggers platelet activity [27-30].

Diagnosing HD-HIT patients.

A step-by-step assessment is used to identify HD patients who are connected to HIT. First, the platelet count is evaluated using $<150\times10^9$/L and > 30% defined ranges. Examining the patient's thrombocytopenia during days 10–40 is the next step if there are no other explanations for the patient's circuit clotting. Due to heparin's limited usage in dialysis, which lasts about 5 hours daily, HD-HIT timing is often administered over a greater range than usual. A clotting circuit's existence, a positive ELISA added to characterize platelet decrease, and appropriate timing should all be regarded as indicators of HIT. A patient diagnosed with HD-HIT, who shows the predicted pattern of platelet decrease, clotting circuit, thrombocytopenia, and positive ELISA four-factor combinations, is likely to have a high likelihood of testing positive on the 14C serotonin release test. Patients who have thrombocytopenia and are undergoing hemodialysis, with positive ELISA results and no circuit clotting, exhibit a moderate occurrence of positive 14C serotonin release assays. There are four distinct diagnostic levels that can be identified: The phrase "HD-HIT most likely" suggests a high likelihood of HD-HIT, supported by a notable positive rate reported in 14C serotonin release tests. "HD-HIT likely" indicates a probable occurrence of HD-HIT, with a moderate rate observed in a functional assay. The term "unlikely" suggests that the timing is not within the expected range and there is a negative ELISA result despite the presence of a clotting circuit. The phrase "HIT less likely" suggests that the likelihood of clotting or thrombosis is low, notwithstanding a positive ELISA test [31,32].

When HD patients receive the recommended anticoagulation with heparin, unexpected platelet count declines occurring between 10 and 40 days, and the abrupt appearance of clots in the dialyzer and circuit are clear signs of HIT. Suppose thrombocytopenia, platelet fall timing, and an ELISA result are present in an HD patient with suspected HIT [33,34]. In such situations, these attributes might help validate the clinical significance of clotting in the circuit as a diagnosis of Heparin-Induced Thrombocytopenia (HIT), as specified in Table 5.

Pathophysiology.

Heparin-induced thrombocytopenia is defined as a decrease in the number of platelets that happens either during or shortly after being exposed to heparin. Despite heparin's discovery occurring about a century earlier, the specific attributes that identify heparin-induced thrombocytopenia (HIT) were initially recognized in the early 1970s. Subsequently, there was a rise in the number of reports regarding an illness that maybe has an immunological foundation. The user's text is empty. It is widely recognized that HIT occurs as a consequence of an immunological response in which antibodies (specifically IgG) are produced against heparin and platelet factor, leading to possible harm. The numeral 4. The IgG/PF4/heparin complexes engage with and stimulate platelets in the circulation via their Fc receptors, augmenting thrombin synthesis and promoting platelet aggregation [35-38].

Curiously, even while the number of platelets is decreasing, there is a clear clinical indication of an elevated likelihood of developing arterial or venous blood clots. Patients from medically vulnerable populations, such as those with renal failure or in need of renal replacement therapy, frequently develop the illness due to their pre-existing increased vulnerability to blood clot development. These individuals frequently experience thrombocytopenia due to concurrent factors unrelated to HIT [39-41].

Incidence.

Based on a thorough evaluation of immune-mediated heparin-induced thrombocytopenia (HIT), persons who are treated with heparin for more than four days may experience immune-mediated HIT at a rate ranging from 0.25% to 5.0%. A meta-analysis found that the overall incidence of immune-mediated HIT is 2.6%. The majority of patients have undergone challenging vaccination, typically with unfractionated or, less frequently, low-molecular-weight heparin (LMWH). It indicates that using LMWH instead of unfractionated heparin (UFH) can reduce the chance of getting HIT by up to 30 times, while it's still debatable if this risk reduction extends to long-term LMWH usage. Regarding pharmacokinetic features, LMWHs, with their shortened polysaccharide chains, are preferable to UFH in individuals with normal renal function [42-46]. However, it is debatable whether people suffering from renal failure may

Table 5. *Management strategy for (HIT) in hemodialysis patients.*

Step 1: The most crucial thing is to identify HIT.	**Step 2: Emergent procedure for a patient who may have HIT:**
1. Thrombus occlusion of the arteriovenous fistula/grafting and unexpected dialyzer/circuit clotting despite adequate heparin infusion. 2. Lack of clotting factors such raised hematocrit, increased ultrafiltration rate, intradialytic lipid transfusion, reduced blood flow, and elevated hematocrit. 3. Check main thrombocytopenia.	1. Immediately cease dialysis and install a complete extracorporeal circuit. 2. Return dialysis to argatroban (lepirudin); 3. Check for clots after switching heparin substitutes. 4. Avoid heparin flushing on non-session days.

benefit from these advantages. The primary constraint lies in the fact that LMWHs are primarily excreted through the kidneys, resulting in a significant prolongation of their biological half-life, and potentially leading to renal failure. Nonetheless, there is now a tendency in many dialysis centers in the UK to utilize LMWHs rather than UFH due to their effectiveness and simplicity (one-time bolus dosage) [47].

To prevent clotting in the extracorporeal circuit, unfractionated or LMWHs are currently employed in most renal units. Furthermore, heparin is utilized as a line-lock solution in certain patients with dialysis access by catheter alone. Therefore, heparin is administered three times a week for many patients receiving regular maintenance hemodialysis treatment, or it may be permanent for some of them. While the current study on the incidence rate for this particular demographic is limited, it has the potential to pose a serious issue for patients who require heparin for their routine hemodialysis treatment. The likelihood of experiencing HIT may be elevated in some patient populations, particularly in individuals who have undergone cardiac surgery and are of the feminine gender [48-50].

HIT was historically considered a neglected or undetected ailment, leading to a presumed low occurrence.

Scope.

This guide is intended for the use of nephrology medical staff and all registered and qualified nurses with experience in dialysis or who work under the direct supervision of specialized dialysis nurses.

Clinical guidelines are guidelines only, so interpretation and application of these guidelines remain the practitioner's responsibility. If you doubt anything, consult a specialist colleague or expert [51].

Anticoagulation for hemodialysis for patients diagnosed with HIT.

Heparin should not be used for anticoagulation when a patient has been diagnosed with heparin-induced thrombocytopenia or if it was highly suspected before testing (and further testing is needed). The recommended local policy is Fondoparinox, but it is important to note that although this drug is widely used, it is considered off-license use. Argatroban can also be used but is more complex and expensive [52].

Fondaparinux:

Fondaparinux is an artificial and specific activated Factor X (Xa) inhibitor. The specific inhibition of Factor Xa mediated by antithrombin (AT) is the cause of fondaparinux's antithrombotic action. Fondaparinux enhances the neutralization of Factor Xa by AT by roughly 300 times by its selective binding to AT. Fondaparinux, when taken at recommended doses, did not affect prothrombin time (PT)/International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), active clotting time (ACT), bleeding time, or fibrinolytic activity. Fondaparinux levels are used to monitor the possibility of fondaparinux's cumulative impact [53].

It is not recommended to utilize fondaparinux for anticoagulating the hemodialysis circuit.

The half-life of fondaparinux is prolonged up to 72 hours in individuals having a creatinine clearance of less than 30 mL/min. Fondaparinux is 64–77 percent eliminated in urine completely intact. Hemodialysis eliminates fondaparinux [54].

Dosing recommendations.

Initial dose:

- A starting dose of 0.05 mg/kg is advised, with a maximum dose of 3 mg.
- Using a 1 mL syringe, withdraw the recommended dosage and dilute it with 20 mL of 0.89% sodium chloride.
- At the beginning of dialysis, inject into the dialyzer's arterial side.

Dose adjustment:

- Consider raising the fondaparinux dose by 0.01 mg/kg during the subsequent dialysis session for individuals with three consecutive dialysis sessions when the circuit clots.
- A dosage decrease of 0.02 mg/kg should be considered for the next dialysis session if peak fondaparinux levels exceed 0.5 microgram/mL.
- Only peak levels should be used to guide dose adjustments.

Re-exposure to heparin.

The concept of heparin re-exposure relies on a distinct immunological reaction that entails the stimulation of B-cells independently of T-cell involvement. This reaction lacks memory, which may explain the temporary nature and absence of a recall response in the anti-PF4/heparin immune response. Patients with a history of heparin-induced thrombocytopenia (HIT) do not possess any immunological recollection of the PF4/heparin complex antigen. Therefore, it is safe to expose them to heparin again after their HIT antibodies have been eliminated from their bloodstream. However, there is limited consensus among medical professionals about the reintroduction of heparin for acute heparin-induced thrombocytopenia (HIT). Following the failure of ELISA to detect HIT antibodies, re-exposure is necessary for a minimum of 100 days. Upon discontinuation of heparin, there are significant variances in the reduction of optical density in ELISA. Even after several years, a short-duration type can still be detected, even if a positive ELISA test result remains. It is recommended that all patients undergo ELISA monitoring until the detection of HIT antibodies stops, as the different half-lives of these antibodies can reveal their unique characteristics. Re-exposure to heparin should be permitted under negative ELISA after implementing suitable emergency precautions, such as platelet counts. The majority of patients who are exposed to heparin again do not have a recurrence of heparin-induced thrombocytopenia (HIT), unless they undergo heart surgery or catheter intervention and, in exceptional circumstances, get platelet-stimulating medicines. Patients with HD who have a consistent titer with an optical density over 0.4 should avoid further exposure to heparin, as it would heighten the likelihood of HIT recurrence, which is linked to the reuse of heparin [55-60].

Bleeding complications with fondaparinux.

Fondaparinux does not have a particular antidote. In the event of significant bleeding issues, fondaparinux medication should be stopped immediately. Prompt investigation is also necessary to determine the underlying source of bleeding problems.

Consult a hematologist about the management of bleeding problems [61].

Argatroban:

Argatroban is a hepatic clearance agent with a short half-life (60 minutes) and thrombin inhibition. Because of this, it is the recommended medication for patients who have renal impairment or who have plans for invasive operations [62].

Argatroban dosing:

A bolus of 300 micrograms/kg of argatroban should be taken first, and then two micrograms/kg/min should be continuously infused. An hour before the hemodialysis treatment concludes, the maintenance infusion should be stopped [63].

If there is no visible thrombosis in the blood vessels or circuit of the patient, the dose can be lowered to 1 microgram/kg/min and titrated to a lower target APTT ratio of 2–3.5 (rather than the typical 2–3.5).

A 75-kilogram patient, for instance, would have 18.75 mg (18750 micrograms) ×80 = 19.50 micrograms; 18.75 milliliters of the 1 mg/ml infusion bag.

As instructed, please take the necessary amount from the infusion bag diluted earlier (1 mg/ml) and give it at least three minutes.

Monitoring of Argatroban treatment.

Achieve a systemic APTT ratio between 2 and 3.5. When using a direct argatroban test in the future, please refer to the recently updated UHL hematology guidelines (which are still in development) [64].

When initiating continuous therapy, measure the first APTT two hours after the commencement of the treatment at a rate of one or two micrograms/kg/min or four hours if the starting rate is 0.7 micrograms/kg/min.

To determine the maintenance dose of Argatroban, patients receiving chronic outpatient hemodialysis should have their APTT evaluated during their first three HD sessions. Subsequent observation should be predicated on clinical assessment, such as indications of hemorrhage or thrombosis, and any alteration in clinical state, such as acute sickness or liver function [65-67].

Locking of hemodialysis catheters in patients diagnosed with HIT.

Eliminate all heparin sources in patients with a diagnosis of HIT or with a high or moderate pretest likelihood (waiting for findings of further investigations) to avoid significant thrombotic consequences. HD catheters (both tunneled and non-tunneled catheters) should not be locked with heparin or in conjunction with TauroLock (see the protocol). Taurolock alone should be used to lock catheters. In cases where this is inappropriate or does not keep the catheter in place, urokinase 13000 units or a solution containing citrate should be used [68,69], that shown in Table 6.

Management of HD-HIT patients.

Medical professionals can quickly identify visible clotting in the circuit, such as in blood chambers, tubes, and dialyzers, during the session. Consequently, care of HIT may commence promptly upon suspicion that clotting is caused by HD-HIT. When a diagnosis of HIT is confirmed based on a strong clinical suspicion, it is crucial to immediately stop the use of all types of heparin, including low-molecular-weight heparin, heparin flushing, and heparin-coated catheters or devices. Timely identification of HIT in the extracorporeal circuit is essential for the dissolution of blood clots, and if clot formation is suspected to be due to a shortage of heparin, additional heparin infusion should be abstained from. To proceed with the dialytic operation, it is necessary to install a new dialyzer and extracorporeal circuit devices. If the circuit clotting prevents the completion of the operation, it is imperative to initiate the session promptly using an alternative anticoagulant. The assessment presented in Table 7 can be utilized to validate the diagnosis of HIT [70-73].

Argatroban, lepirudin, and danaparoid are the preferred alternative anticoagulants for hemodialysis patients with heparin-induced thrombocytopenia (HIT). Danaparoid is a low molecular weight molecule that resembles heparin. Despite repeated administration of danaparoid to HD-HIT patients, it does not adequately prevent bleeding in these individuals due to its significant cross-reactivity in clinical settings. Lepirudin is a recombinant thrombin inhibitor derived from hirudin. It is

Table 6. *Monitoring and Audit Criteria.*

Key achievement indicator	Evaluation method	Repetition	Lead
HIT is not seen in kidney disease patients.	Total positive HIT assays.	frequent	N/A
every year			-
use make use of Argatroban	-	frequent	-

Table 7. *Evaluate patients with three clinical factors and ELISA.*

Regular	Identification of HIT	Platelet fall ($\leq 150\times10^9$/L)	Limits of coagulation	Timing of reduced (15-35 days)	ELISA (IgG, IgA, IgM)	Estimates of positive SRA
ONE	most probable	+	+	+	Pos.	high (~80-100%)
TWO	probable	+	−	+	Pos.	moderate (~85%)
THREE	less probable	+	−	+	Pos.	Less moderate (~80%)
FOUR	unprobable	+	+	+	Neg.	- (0%)

+, clinical factor present, −, not present, SRA, 14C serotonin release assay.

Table 8. *Estimating the pretest probability of HIT; the 4Ts score.*

4Ts	Two degree	One degree	Zero degree
Thrombocytopenia.	>60% platelet count falls to nadir ≥20.	30–50% platelet count fall or nadir 10–19.	Low platelet count <25-35% or rare <14
Timing of low platelet counts or other HIT effects.	Days 7–14 or before Day 2 with 40-day heparin exposure.	Day 10-14 with unclear timing or Day 2 with recent heparin exposure 25-90 days ago.	<Day 4 (Heparin unexposure).
Thrombosis or other consequences.	Skin necrosis, acute systemic response to an unfractionated heparin bolus, or new blood clot.	Unconfirmed thrombosis, erythematous skin lesions, and progressive thrombosis.	N/A
Another response to thrombocytopenia.	N/A		specified
			possibility

The maximum possible score is 8, and the pretest probability score of 6–8 indicates high, 4–5 intermediate, and 0–3 low. Adapted from Warkentin TE, HIT Diagnosis and Management, Circulation, 2004, A first day of immunizing heparin exposure is considered Day 0.

tough to regulate the dose appropriately for HD-HIT patients since the kidneys primarily remove the medication and have a noticeably longer half-life in uremic patients. Argatroban, a synthetic direct thrombin inhibitor formerly known as MD805, is non-immunogenic and does not bind to HIT antibodies. Unlike lepirudin, Argatroban is predominantly metabolized by the liver and its elimination time is slightly extended in those undergoing hemodialysis. As an alternate anticoagulant, argatroban is primarily used to avoid extracorporeal circuit clotting in patients with HD-HIT. The medication is administered continuously at a rate of 2 micrograms per kilogram per minute, as long as the patient's liver function is normal. The treatment begins with an initial dose of 250 micrograms per kilogram at the commencement of dialysis. The empirical goal of dose adjustment is to achieve a 2–3.5-fold increase in the activated partial thromboplastin time (APTT), which is equivalent to prolonging the duration of heparin administration. After the acute phase of HIT is over, the dosage can be reduced to less than 2μg/kg/min, resulting in a 2–3.5 times longer APTT. In order to avoid unforeseen hemorrhagic complications, it is necessary to reduce the dosage to a level below 2μg/kg/min, taking into account the extent of liver failure. The resolution of HIT symptoms can only be achieved by substituting heparin with argatroban during dialysis. While there is a lack of data supporting the use of systemic argatroban medicine on non-session days, it is possible that argatroban anticoagulation could decrease the occurrence of new and worsening thrombotic events [74-79].

Diagnosis.

Since HIT is a clinical–pathological disease, a doctor should consider the possibility of making a clinical diagnosis of the syndrome before making an initial assessment in response to a noted decrease in platelet count.

The most used scoring method, the 4T scoring system, evaluates the level to which the clinical picture supports a HIT diagnosis that shown in Table 8). Scoring systems can be used to identify patients who have an equal chance of having both heparin-induced thrombocytopenia (HIT) and other conditions that cause low platelet count, such as kidney difficulties. These scoring methods assess the probability of HIT before doing clinical tests [80,81].

Physicians mostly rely on laboratory testing since clinical diagnosis might be difficult. However, it's crucial to understand that HIT antibody production can happen without thrombocytopenia or the whole clinical presentation of HIT.

The two main categories of laboratory tests used to identify antibody development in HIT are immunological assays directed towards PF4 or heparin and platelet activation assays. Greater specificity can be obtained using functional tests, such as the serotonin release assay and heparin-induced platelet aggregation. Nevertheless, these techniques are complex and require advanced technical skills to assess platelet activity while considering the patient's serum and heparin. Consequently, the majority of centers commonly employ the ELISA technique, which is subject to the constraint that antibodies with low titer do not have an impact on the clinical outcome. Consequently, the majority of centers frequently employ the ELISA technique, which has the drawback of potentially detecting tiny levels of antibodies that have little impact on the clinical outcome. Commercially available immunological diagnostics that specifically target IgG antibodies have been accessible due to the fact that platelets can solely be triggered by IgG antibodies. The absolute optical density (OD) assessments, which quantify antibody levels and indicate a greater risk of HIT with higher levels, should be taken into account when interpreting the test results. The 2012 BCSH Guidelines propose the utilization of a threshold value for determining a positive outcome when employing an immunological ELISA to identify HIT antibodies, as opposed to merely indicating a positive or negative result. An examination of successive quantitative outcomes acquired by an ELISA immunoassay revealed that initial elevated negative OD values (0.6–1.1) had a significant likelihood of transitioning into positive values (>1.0) upon retesting. In such cases, it is recommended to conduct consecutive tests to confirm the trend [82-89].

In conclusion, a diagnosis of HIT should only be considered in cases when the clinical picture is consistent. To determine the post-test probability, one must take into account the assay type, the quantitative result, and a pretest probability of at least 5 as determined by the 4T Scoring System. It is advisable to seek guidance from the hematology team and laboratory when managing suspected cases and investigations in routine clinical practice, as many practitioners lack direct access to comprehensive laboratory testing [90-92].

Treatment.

When there is a clinical suspicion, the therapeutic guidelines require stopping all heparin formulations and starting a suitable alternative anticoagulant. Stopping the trigger on its own is insufficient; patients also require specific treatment to prevent the thrombin storm and following thrombotic events, which affect up to 40–50% of them over the next several days or weeks. To avoid aggravating the risk of thrombosis, reflex platelet transfusion intended for thrombocytopenia or mild bleeding is likewise inappropriate and is to be saved for catastrophic bleeding [93,94].

Dialysis should be administered without the use of heparin if a patient is suspected of having HIT. Multiple methods are at one's disposal, including as short-term, daily dialysis, as well as dialysis with continuous pre-dilution using saline or frequent bolus injection of saltwater. Regular dialysis may not always be possible, and the utilization of saline infusions appears to have a substantial probability of therapy ineffectiveness and necessitates considerable exertion. Opting for an alternative anticoagulant may prove to be a more effective and sustainable approach in the long run. There are three non-heparin anticoagulants that can be used for anticoagulation in HIT: Argatroban, lepirudin, and danaparoid are anticoagulant medications. These anticoagulants do not cross-react with HIT antibodies. Because LMWH can have up to 50% cross-reactivity with unfractionated heparin, it should not be administered as a substitute when HIT occurs. When considering alternate anticoagulant therapies, it is important to be cautious due to the potential danger of bleeding, despite the fact that bleeding is not commonly related with HIT syndrome [95,96].

Argatroban, a synthetic thrombin inhibitor, is an ideal option for individuals undergoing hemodialysis as it is not eliminated by the kidneys and does not require a dosage modification. It is advisable to employ the activated partial thromboplastin time (APTT) for the purpose of monitoring, with the goal of achieving a target range of 1.5–3.0. With the exception of critical care patients, who are advised to receive a dosage of 0.5 ug/kg/min according to the SmPC, the typical initial dose for others is two ug/kg/min administered as a continuous infusion. It is important to take into account the increase in prothrombin time caused by argatroban before initiating warfarin therapy for oral anticoagulation in patients. Prior to quitting argatroban, it is necessary to overlap the two drugs for a minimum of five days, and achieve a parallel INR of 6 for two days. The dialyzability of argatroban remains uncertain. While one study found that the amount of argatroban removed by dialysis was insignificant compared to natural elimination, the product label states that approximately 20-30% of the medicine can be eliminated with hemodialysis [97,98].

Although individuals with severe kidney disease should undergo lower dose regimens, dalapidogan can also be utilized. Danaparoid is a compound composed of heparin sulfate, dermatan sulfate, and chondroitin sulfate. It has been approved by the FDA for the prevention of venous thromboembolism (VTE) in surgical patients after surgery. Danaparoid exhibits a higher ratio of anti-factor Xa to anti-factor IIa activity compared to heparin, with a ratio of around 28:1 versus 1:1. Monitoring is typically required only for specific patient groups, specifically those with severe kidney disease and body weights of either 60 or 100 kg, due to the medication's constant dosage response. There are dosage regimens for prevention and treatment; however, research indicates that low-dose regimens could be related to an increased incidence of new thrombotic events. Using danaparoid sodium as the reference, the anti-Xa test is used for monitoring. A study has been carried out on the application of Danaparoid in critically ill patients and persons undergoing hemofiltration or dialysis. Haemofiltration procedures include administering 40 U/kg intravenously for hemodialysis and 100-400 U/h intravenously to achieve anti-Xa levels of 0.5-1 U/m. Examples of hemofiltration and hemodialysis regimens have been published. The dialysability of danaparoid is unknown. Recombinant hirudin, or lepirudin, is a natural thrombin inhibitor that has been demonstrated to lower treatment-related mortality risks, new thromboembolic events, and limb amputation. The typical regimen for administration comprises a bolus of 0.4 mg/kg followed by 0.15 mg/kg/hr.

Additionally, the APTT is used for monitoring, with a target range of 1.5–2.5. If the APTT is more than 2.5 times normal, lepirudin should not be administered. When creatinine levels are 1.5–2.0 mg/dL, a 50% lower dose for bolus and infusion is recommended; extra caution is advised when renal impairment is severe. This is because lepirudin's half-life is greatly extended when renal function is compromised. To effectively maintain anticoagulation during dialysis, individuals with a t1/2 of about 50 hours have been advised to take different dosages before treatment. When employed with high flux polysulfone dialyzers, lepirudin can be dialyzed [99,100].

Fondaparinux, a man-made complex carbohydrate, has demonstrated efficacy in treating individuals with heparin-induced thrombocytopenia (HIT), while lacking official approval for this indication. It is doubtful to induce HIT because it lacks the sugar domain required for complexing with PF4. Numerous studies have documented its beneficial application in HIT, in individuals suffering from renal failure, and in patients receiving hemodialysis. Anti-Xa levels are employed to ascertain the appropriate dosages, while the initial daily dose remains unchanged (7.5 mg/d for a patient weighing between 50 and 100 kg). Maintenance dosages may require only 2.5 or 5 mg each day [101-103].

The same practices do not always determine treatment length for individuals with HIT. A minimum of two months has been recommended due to the possibility of thrombosis lasting up to six weeks, as suggested by prospective studies. Warfarin can be started if the patient's platelet count has returned to its original level, after following a treatment plan that corresponds to the specific alternative anticoagulant they have been given. Discontinuing heparin and switching to warfarin alone is not recommended due to the danger of venous limb gangrene induced by the depletion of protein C resulting from warfarin use, along with the continuous blood clotting process.

Ultimately, it is essential to instruct persons who are impacted by the sickness and offer them guidance concerning the potential danger of thrombosis in the acute setting. It is also important to emphasize that antibody testing and alternative anticoagulation

may be necessary if they need heparin within the next 150 days. It is important for doctors to carefully examine the patient's case notes, just like they would for any drug-induced adverse events, in order to identify any potential hazards [104].

It is still challenging to accurately diagnose, assess, and treat HIT in renal patients, and there currently needs to be more clinical data to support the best course of treatment. Significantly, there has been a recent increase in the over diagnosis of HIT due to the restricted capability of the commonly used PF4-dependent immunoassays to precisely detect HIT antibodies. This should be improved by limiting testing to IgG class antibodies when more precise functional tests are unavailable. It would appear reasonable to explore managing crossspeciality in specific dose regimens for medications not commonly utilized outside of the HIT arena, given the diversity of patients and diagnoses. It is unclear if the present trend of increased LMWH usage for dialysis would eventually result in a lower incidence of HIT in patients receiving chronic hemodialysis. The therapeutic function of the new oral anticoagulants in this specialized field is still unknown [105-107].

Discussion.

Antibodies developed against the HPF4 complex induce the prothrombotic disease known as HIT. Numerous variables influence the frequency of HIT, including the kind of heparin administered (LMWH causes 10-fold less HIT than UFH, and even less with fondaparinux), the treatment environment (surgical patients experience higher rates of HIT than medical patients, likely because of the large volumes of PF4 released during operations), and the diagnostic tests conducted. According to estimates, the incidence of dialysis patients is 4% for those starting treatment and 0.6% for those receiving treatment on a chronic basis; however, there are no statistics from India at this time. In our environment, we had a 0.63% incidence with five incidents out of 9579 HD sessions in 600 patients. On the other hand, as with IV catheter flushes, HIT antibody formation may be initiated with very little heparin exposure. Positively charged platelet factor-4 produced from activated platelet granules binds negatively charged proteins and anions like heparin on the endothelium when it comes into contact with the platelet surface. IgG antibodies bind to neoepitopes on HPF4 complexes, which cross-link FC-receptors on platelets and monocytes, activating them and causing the production of thrombin.

Several scoring systems have been proposed to predict HIT; only the 4T score has proven accurate. HIT can be ruled out with a low 4T score because of its strong 100% NPV. However, because of their poor positive predictive value (PPV), intermediate (6) and high (7) ratings are not diagnostic. Both functional assays and immunoassays are used in laboratory testing for HIT.

70–100% of patients have thrombocytopenia, the most common symptom brought on by the consumption of active platelets within thrombi and the evacuation of platelets coated with IgG. In 25% of cases, the presentation type is thrombosis. Arterial thrombosis is less prevalent compared to venous thrombosis. Pulmonary embolism is the most prevalent occurrence that has the potential to be lethal. The thromboembolic repercussions arise from heightened thrombin production by active platelets and monocytes, as well as from the injury and activation of vascular cells. Circuit coagulation and vascular access thrombosis are frequent manifestations of HIT in dialysis patients; nonetheless, it is essential to investigate other potential causes of access thrombosis.

HIT can occur with any dosage, at any time, or with any administration method. Heparin-platelet-4 complex formation is minimal when fondaparinux is employed, less effective when heparin has a low molecular weight, and most effective when heparin is not fractioned. It is more common in females, older people, and surgical patients.

Because they are exposed to heparin regularly, dialysis patients are at risk of acquiring HIT. Up to 12% of them do. Once heparin is introduced, HIT usually occurs early in the dialysis session, while delayed-onset HIT is uncommon in individuals with the PF4/heparin complex antibodies. HD-HIT is characterized by specific clinical manifestations such as sudden decrease in platelet count, formation of blood clots in the external circulation after administering heparin, successful removal of clots when using a different anticoagulant, and occasionally, blockage of blood vessels due to blood clots in the vascular access.

Conclusion.

Untreated HIT can lead to high rates of morbidity and death. It is critical to detect and treat HIT as soon as possible because hemodialysis patients regularly come into contact with heparin and because their disease may cause significant thrombocytopenia.

Thrombocytopenia occurring within the initial five to fourteen days following heparin administration in dialysis patients who are receiving heparin should elevate the likelihood of HD-HIT. Although heparin and heparin-containing medications must be stopped immediately to rule out an HD-HIT diagnosis, each patient needs a customized approach. A tailored strategy for anticoagulant medication and renal replacement treatment is required, considering the thrombotic risk that is specific to this case.

Authors' contributions:

Qutaiba Qasim defined the methodology, validated, analyzed and verified the data, and organized it, thus finalizing the manuscript in the final version.

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Data Availability Statement: Upon reasonable request, the corresponding author will provide all the data that support this study's conclusions. Please contact Dr. Qutaiba Kasim with requests for access to this data (e-mail: qutaiba.qasim@alayen.edu.iq).

Conflict of interest.

There are no conflicts of interest on the part of the authors with any scientific or medical entity.

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REFERENCES

1. Benjamin S. Salter, Menachem M. Weiner, Muoi A. Trinh, et al. Heparin-Induced Thrombocytopenia, Journal of the American College of Cardiology. 2016;67.
2. Dasararaju R, Singh N, Mehta A. Heparin induced thrombocytopenia: review. Expert Rev Hematol. 2013;6:419-28.
3. Battistelli S, Genovese A, Gori T. Heparin induced thrombocytopenia in surgical patients. Am J Surg. 2010;199:43-51.
4. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141:e495S-530S.
5. Lovecchio F. Heparin-induced thrombocytopenia. Clin Toxicol (Phila). 2014;52:579-83.
6. Lanzarotti S, Weigelt JA. Heparin-induced thrombocytopenia. Surg Clin North Am. 2012;92:1559-72.
7. Anand SX, Viles-Gonzalez JF, Mahboobi SK, et al. Bivalirudin utilization in cardiac surgery: shifting anticoagulation from indirect to direct thrombin inhibition. Can J Anesth. 2010;58:296-311.
8. Glenn M. LaMuraglia, Rabih Houbballah, Michael Laposata. The identification and management of heparininduced thrombocytopenia in the vascular patient. Journal of Vascular Surgery. 2012;55:562-570.
9. Matsuo T, Matsuo M, Sugimoto T, et al. Anti-heparin/PF4 complexes by ELISA in patients with disseminated intravascular coagulation. Pathophysiol Haemost Thromb. 2007;36:305-10.
10. Warkentin TE, Roberts RS, Hirsh J, et al. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. Chest. 2005;127:1857-61.
11. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med. 2001;344:1286-92.
12. Rice L, Attisha WK, Drexler A, et al. Delayed onset heparininduced thrombocytopenia. Ann Intern Med. 2002;136:210-5.
13. Lubenow N, Kempf R, Eichner A, et al. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. Chest. 2002;122:37-42.
14. Warkentin TE, Cook RJ, Marder VJ, et al. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. Blood. 2005;106:3791-6.
15. Lubenow N, Hinz P, Thomaschewski S, et al. The severity of trauma determines the immune response to PF4/heparin and the frequency of heparin-induced thrombocytopenia. Blood. 2010;115:1797-803.
16. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005;106:2710-5.
17. Battistelli S, Genovese A, Gori T. Heparin-induced thrombocytopenia in surgical patients. Am J Surg. 2010;199:43-51.
18. Mattioli AV, Bonetti L, Carletti U, et al. Thrombotic events in patients with antiplatelet factor 4/heparin antibodies. Heart. 2009;95:1350-4.
19. Menajovsky LB. Heparin-induced thrombocytopenia: clinical manifestations and management strategies. Am J Med. 2005;118:21S-30S.
20. Schindewolf M, Schwaner S, Wolter M, et al. Incidence and causes of heparin-induced skin lesions. CMAJ. 2009;181:477-81.
21. Selleng K, Schütt A, Selleng S, et al. Studies of the anti-platelet factor 4/heparin immune response: adapting the enzyme-linked immunosorbent spot assay for detection of memory B cells against complex antigens. Transfusion. 2010;50:32-9.
22. Hassell K. The management of patients with heparin-induced thrombocytopenia who require anticoagulant therapy. Chest. 2005;127:1S-8S.
23. Baron SJ, Yeh RW, Cruz-Gonzalez I, et al. Efficacy and safety of argatroban in patients with heparin induced thrombocytopenia undergoing endovascular intervention for peripheral arterial disease. Catheter Cardiovasc Interv. 2008;72:116-20.
24. Ignacio Cruz-González, María Sánchez-Ledesma, Pedro L. Sánchez, et al. Heparin-Induced Thrombocytopenia. Rev Esp Cardiol. 2007;60:1071-82.
25. Warkentin TE, Roberts RS, Hirsh J, et al. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. Arch Intern Med. 2003;163:2518-24.
26. Hong AP, Cook DJ, Sigouin CS, et al. Central venous catheters and upper-extremity deep-vein thrombosis complicating immune heparin-induced thrombocytopenia. Blood. 2003;101:3049-51.
27. Girolami B, Prandoni P, Stefani PM, et al. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with subcutaneous unfractionated heparin: a prospective cohort study. Blood. 2003;101:2955-9.
28. Napolitano LM, Warkentin TE, Almahameed A, et al. Heparin-induced thrombocytopenia in the critical care setting: diagnosis and management. Crit Care Med. 2006;34:2898-911.
29. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:S311-37.
30. Everett BM, Yeh R, Foo SY, et al. Prevalence of heparin/platelet factor 4 antibodies before and after cardiac surgery. Ann Thorac Surg. 2007;83:592-7.

31. Foo SY, Everett BM, Yeh RW, et al. Prevalence of heparin-induced thrombocytopenia in patients undergoing cardiac catheterization. Am Heart J. 2006;152:290 e291-7.
32. Yeh RW, Everett BM, Foo SY, et al. Predictors for the development of elevated antiheparin/ platelet factor 4 antibody titers in patients undergoing cardiac catheterization. Am J Cardiol. 2006;98:419-21.
33. Warkentin TE, Sheppard JA, Moore JC, et al. Laboratory testing for the antibodies that cause heparininduced thrombocytopenia: how much class do we need? J Lab Clin Med. 2005;146:341-6.
34. Prandoni P, Siragusa S, Girolami B, et al. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. Blood. 2005;106:3049-54.
35. Warkentin TE, Aird WC, Rand JH. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. Hematology Am Soc Hematol Educ Program. 2003:497-519.
36. Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost. 2006;4:759-65.
37. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood. 2005;106:2710-5.
38. Hourigan LA, Walters DL, Keck SA, et al. Heparin-induced thrombocytopenia: a common complication in cardiac transplant recipients. J Heart Lung Transplant. 2002;21:1283-9.
39. Klenner AF, Lubenow N, Raschke R, et al. Heparin-induced thrombocytopenia in children: 12 new cases and review of the literature. Thromb Haemost. 2004;91:719-24.
40. I Ahmed, A Majeed, R Powell. Heparin induced thrombocytopenia: diagnosis and management update, Postgrad Med J. 2007;83:575-582.
41. Franchini M. Heparin induced thrombocytopenia: an update. Thrombosis Journal. 2005;3:14-20.
42. Rice L. Heparin-induced thrombocytopenia: myths and misconceptions. Arch Intern Med. 2004;164:1961-4.
43. Katzung BG. Basic and clinical pharmacology, 9th ed. McGraw Hill. 2004:545-9.
44. Reilly RF. The pathophysiology of immune-mediated heparin-induced thrombocytopenia. Semin Dial. 2003;16:54-60.
45. Jang IK, Hursting MJ. When heparins promote thrombosis: review of heparininduced thrombocytopenia. Circulation. 2005;111:2671-83.
46. Elizabeth J. Benge1, Yi McWhorter, Triple threat: bilateral renal artery thrombosis and heparin induced thrombocytopenia in a patient with COVID-19, a case report. J Emerg Crit Care Med. 2022;6:3.
47. Miesbach W, Makris M. COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149.
48. Bidar F, Hékimian G, Martin-Toutain I, et al. Heparin-induced thrombocytopenia in COVID-19 patients with severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation: two case reports. J Artif Organs. 2021;24:277-81.
49. Acharya S, Anwar S, Siddiqui FS, et al. Renal artery thrombosis in COVID-19. IDCases. 2020;22:e00968.
50. Iba T, Levy JH, Connors JM, et al. The unique characteristics of COVID-19 coagulopathy. Crit Care. 2020;24:360.
51. Sauerberg N, Khan YS. Renal Artery Thrombosis. Treasure Island (FL): StatPearls Publishing; 2021.
52. Takefumi Matsuo, Keiko Wanaka. Heparin-Induced Thrombocytopenia and Hemodialysis, Matsuo. J Blood Disord Transfus. 2011:S2.
53. Sonawane S, Kasbekar N, Berns JS. The safety of heparins in end-stage renal disease. Semin Dial. 2006;19:305-310.
54. Chang JJ, Parikh CR. When heparin causes thrombosis: significance, recognition, and management of heparin-induced thrombocytopenia in dialysis patients. Semin Dial. 2006;19:297-304.
55. Nakamoto H, Shimada Y, Kanno T, et al. Role of platelet factor 4-heparin complex antibody (HIT antibody) in the pathogenesis of thrombotic episodes in patients on hemodialysis. Hemodial Int. 2005;9:S2-S7.
56. Hursting M, Murray P. Argatroban anticoagulation in renal dysfunction: a literature analysis. Nephron Clin Pract. 2008;109:c80-c94.
57. Lena M. Napolitano, Theodore E. Warkentin, Amjad AlMahameed, et al. Heparin-induced thrombocytopenia in the critical care setting: Diagnosis and management. Crit Care Med. 2006;34:2898-2911.
58. Warkentin TE. Clinical picture of heparininduced thrombocytopenia. In: Heparin- Induced Thrombocytopenia. 3rd ed. Warkentin TE, Greinacher A (Eds). New York, Marcel Dekker. 2004:53-106.
59. Zwicker JI, Uhl L, Huang WY, et al. Thrombosis and ELISA optical density values in hospitalized patients with heparin-induced thrombocytopenia. J Thromb Haemost. 2004;2:2133-2137.
60. Bartholomew JR. Transition to oral anticoagulant in patients with heparin-induced thrombocytopenia. Chest. 2005;127:27S-34S.
61. Levy JH, Winkler AM. Heparin-induced thrombocytopenia, and cardiac surgery. Curr Opin Anaesthesiol. 2010;23:74-9.
62. Bakchoul T, Giptner A, Najaoui A, et al. Prospective evaluation of PF4/heparin immunoassays for the diagnosis of heparin-induced thrombocytopenia. J Thromb Haemost. 2009;7:1260-5.
63. Warkentin TE, Sheppard JI, Moore JC, et al. Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. J Thromb Haemost. 2008;6:1304-12.
64. Greinacher A, Ittermann T, Bagemühl J, et al. Heparin-induced thrombocytopenia: towards standardization of platelet factor 4/heparin antigen tests. J Thromb Haemost. 2010;8:2025-31.
65. Zwicker JI, Uhl L, Huang WY, et al. Thrombosis and ELISA optical density values in hospitalized patients with heparin-induced thrombocytopenia. J Thromb Haemost. 2004;2:2133-7.
66. Altuntas F, Matevosyan K, Burner J, et al. Higher optical density of an antigen assay predicts thrombosis in patients with heparin-induced thrombocytopenia. Eur J Haematol. 2008;80:429-35.

67. Baroletti S, Hurwitz S, Conti NAS, et al. Thrombosis in suspected heparin-induced thrombocytopenia occurs more often with high antibody levels. Am J Med. 2012;125:44-9.
68. Chan CM, Woods CJ, Warkentin TE, et al. The role for optical density in heparin-induced thrombocytopenia: a cohort study. Chest. 2015;148:55-61.
69. Whitlatch NL, Kong DF, Metjian AD, et al. Validation of the high-dose heparin confirmatory step for the diagnosis of heparin-induced thrombocytopenia. Blood. 2010;116:1761-6.
70. McFarland J, Lochowicz A, Aster R, et al. Improving the specificity of the PF4 ELISA in diagnosing heparin-induced thrombocytopenia. Am J Hematol. 2012;87:776-81.
71. Bakchoul T, Giptner A, Bein G, et al. Performance characteristics of two commercially available IgG-specific immunoassays in the assessment of heparin-induced thrombocytopenia (HIT). Thromb Res. 2011;127:345-8.
72. Warkentin TE. Platelet microparticle generation assay for detection of HIT antibodies: advance, retreat, or too soon to tell? Thromb Res. 2014;133:957-8.
73. Warkentin TE, Arnold DM, Nazi I, et al. The platelet serotonin-release assay. Am J Hematol. 2015;90:564-72.
74. Bakchoul T, Zöllner H, Greinacher A. Current insights into the laboratory diagnosis of HIT. Int J Lab Hematol. 2014;36:296-305.
75. Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. Blood. 1986;67:27-30.
76. Mullier F, Minet V, Bailly N, et al. Platelet microparticle generation assay: a valuable test for immune heparin-induced thrombocytopenia diagnosis. Thromb Res. 2014;133:1068-73.
77. Cosmi B. Current management of heparininduced thrombocytopenia. Expert Rev Hematol. 2015;8:837-49.
78. Warkentin TE. Heparin-induced thrombocytopenia. Hematol Oncol Clin North Am. 2007;21:589-607.
79. Warkentin TE, Maurer BT, Aster RH. Heparininduced thrombocytopenia associated with fondaparinux. N Engl J Med. 2007;356:2653-5.
80. Rota E, Bazzan M, Fantino G. Fondaparinuxrelated thrombocytopenia in a previous lowmolecular-weight heparin (LMWH)-induced heparin-induced thrombocytopenia (HIT). Thromb Haemost. 2008;99:779-81.
81. Salem M, Elrefai S, Shrit MA, et al. Fondaparinux thromboprophylaxis-associated heparininduced thrombocytopenia syndrome complicated by arterial thrombotic stroke. Thromb Haemost. 2010;104:1071-2.
82. Greinacher A, Völpel H, Janssens U, et al. Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparininduced thrombocytopenia: a prospective study. Circulation. 1999;99:73-80.
83. Skrupky LP, Smith JR, Deal EN, et al. Comparison of bivalirudin and argatroban for the management of heparin-induced thrombocytopenia. Pharmacotherapy. 2010;30:1229-38.
84. Kiser TH, Burch JC, Klem PM, et al. Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. Pharmacotherapy. 2008;28:1115-24.
85. Dang CH, Durkalski VL, Nappi JM. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. Pharmacotherapy. 2006;26:461-8.
86. Vun CM, Evans S, Chong BH. Cross-reactivity study of low molecular weight heparins and heparinoid in heparin-induced thrombocytopenia. Thromb Res. 1996;81:525-32.
87. Stratmann G, deSilva AM, Tseng EE, et al. Reversal of direct thrombin inhibition after cardiopulmonary bypass in a patient with heparin-induced thrombocytopenia. Anesth Analg. 2004;98:1635-9.
88. Bijsterveld NR, Moons AH, Boekholdt SM, et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. Circulation. 2002;106:2550-4.
89. Yee AJ, Kuter DJ. Successful recovery after an overdose of argatroban. Ann Pharmacother. 2006;40:336-9.
90. Sheth SB, DiCicco RA, Hursting MJ, et al. Interpreting the international normalized ratio (INR) in individuals receiving argatroban and warfarin. Thromb Haemost. 2001;85:435-40.
91. Warkentin TE, Greinacher A, Craven S, et al. Differences in the clinically effective molar concentrations of four direct thrombin inhibitors explain their variable prothrombin time prolongation. Thromb Haemost. 2005;94:958-64.
92. Arpino PA, Demirjian Z, Van Cott EM. Use of the chromogenic factor X assay to predict the international normalized ratio in patients transitioning from argatroban to warfarin. Pharmacotherapy. 2005;25:157-64.
93. Hirsh J, Heddle N, Kelton JG. Treatment of heparin-induced thrombocytopenia: a critical review. Arch Intern Med. 2004;164:361-9.
94. Fulco PP. Treatment dosage recommendation for fondaparinux in a patient with heparin induced thrombocytopenia. J Thromb Thrombolysis. 2006;22:69.
95. Warkentin TE, Cook RJ, Marder VJ, et al. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. Blood. 2005;106:3791-6.
96. Jang IK, Lewis BE, Matthai WH Jr, et al. Argatroban anticoagulation in conjunction with glycoprotein IIb/IIIa inhibition in patients undergoing percutaneous coronary intervention: an open-label, nonrandomized pilot study. J Thromb Thrombolysis. 2004;18:31-7.
97. Pinto DS, Sperling RT, Tu TM, et al. Combination platelet glycoprotein IIb/IIIa receptor and lepirudin administration during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia. Catheter Cardiovasc Interv. 2003;58:65-8.
98. Gosselin RC, Dager WE, King JH, et al. Effect of direct thrombin inhibitors, bivalirudin, lepirudin, and argatroban, on prothrombin time and INR values. Am J Clin Pathol. 2004;121:593-9.
99. Maloney JP. Lessening the punch of heparin-induced thrombocytopenia. Chest. 2002;122:5-6.
100. Harenberg J, Jorg I, Fenyvesi T. Treatment of heparin-induced thrombocytopenia with fondaparinux. Haematologica. 2004;89:1017-8.
101. Fischer KG. Hirudin in renal insufficiency. Semin Thromb Hemost 2002;28:467-82.
102. Murray PM, Reddy BV, Grossman EJ, et al. A prospective comparison of three argatroban treatment regimens during in end-stage renal disease. Kidney Int. 2004;66:2446-53.

103. Bradner J, Hallisey RK, Kuter DJ. Fondaparinux in the treatment of heparininduced thrombocytopenia. Blood. 2004;104:492a.
104. Pinto DS, Sperling RT, Tu RM, et al. Combination platelet glycoprotein IIb/IIIa receptor and lepirudin administration during percutaneous coronary intervention in patients with heparin-induced thrombocytopenia. Cath Cardiovasc Interv. 2003;58:65-8.
105. Gosselin RC, Dager WE, King JH, et al. Effect of direct thrombin inhibitors, bivalirudin, lepirudin, and argatroban, on prothrombin time and INR values. Am J Clin Pathol. 2004;121:593-99.
106. Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the Bivalirudin Angioplasty Study. Am Heart J. 2001;142:952-9.
107. Alsoufi B, Boshkov LK, Kirby A, et al. Heparin-induced thrombocytopenia (HIT) in pediatric cardiac surgery: an emerging cause of morbidity and mortality. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual. 2004;7:155-71.