Surveillance of Scientific Literature (ARG LIT Service 2020-08)

- **Report Date:** 31.08.2020

New Literature on Argatroban and Related Topics

- **Source:** National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM).

- **Search:** "Argatroban"
  "Heparin-induced Thrombocytopenia"
  "Fondaparinux"

In the following the result of the routine literature search on Argatroban and related topics is given. After selection of action please return to sender.

Mainz, 31.08.2020

What's New for Argatroban and Related Topics in August 2020?

28 August 2020

Full text on file	**Argatroban**

Argatroban for therapeutic anticoagulation for heparin resistance associated with Covid-19 infection.

McGlynn F, McGrath J, Varghese C, Ryan B, McHugh J, Fahy A, Enright H.

J Thromb Thrombolysis. 2020 Aug 24:1–3. doi: 10.1007/s11239-020-02251-z. Epub ahead of print.

PMID: 32830309 Free full text

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28 August 2020

Full text on file	**Argatroban**

Fibrinolysis shut down in COVID-19 patients: Report on two severe cases with potential diagnostic and clinical relevance

Bakchoul T, Hammer S, Lang P, Rosenberger P

Thrombosis Update. 2020, August 26. doi: 10.1016/j.tru.2020.100008

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28 August 2020

Full text on file	**Argatroban**

Aortic Arch Thrombus and Pulmonary Embolism in a COVID-19 Patient

Gandotra P, Supariwala A, Selim S, Garra G, Gruberg L

The Journal of Emergency Medicine. 2020. doi: 10.1016/j.jemermed.2020.08.009

Abstract: Background: Coronavirus disease 2019 (COVID-19) is associated with endothelial inflammation and a hypercoagulable state resulting in both venous and arterial thromboembolic complications. We present a case of COVID-19 associated aortic thrombus in an otherwise healthy patient. Case Report: A 53-year-old woman with no past medical history presented with a 10-day history of dyspnea, fever and cough. Her pulse oximetry on room air was 84%. She tested positive for SARS-CoV-2 infection and chest radiography revealed moderate patchy bilateral airspace opacities. Serology markers for cytokine storm were significantly elevated with a serum D-dimer level of 8180 ng/mL (normal <230 ng/mL). Computer tomography (CT) of the chest with IV contrast was positive for bilateral ground glass opacities, scattered filling defects within the bilateral segmental and sub segmental pulmonary arteries, and a large thrombus was present at the aortic arch. The patient was admitted to the intensive care unit and successfully treated with unfractionated heparin, alteplase 50 mg, and argatroban 2 mcg/kg/min. Why should an emergency physician be aware of this? Mural aortic thrombus is a rare but serious cause of distal embolism and typically discovered during an evaluation of cryptogenic arterial embolization to the viscera or extremities. Patients with suspected hypercoagulable states such as that encountered with COVID-19, should be screened for thromboembolism, and when identified, aggressively anticoagulated.

Keywords: COVID-19; aortic thrombus; arterial thromboembolism; hypercoagulable state

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28 August 2020

Full text not on file	HIT II

Utility of the 4Ts score in excluding heparin-induced thrombocytopenia in lung transplant recipients.

Wu S, Converse MP, Alnuaimat HM, Veasey TM.

J Thromb Thrombolysis. 2020 Aug 20. doi: 10.1007/s11239-020-02249-7. Epub ahead of print.

Abstract: Heparin-induced thrombocytopenia (HIT) is a prothrombotic complication following heparin exposure. Data is limited on the incidence of HIT and validity of 4Ts score in the solid organ transplant population. This retrospective observational cohort included patients who underwent lung transplant between August 2015 and June 2018 and had a clinical suspicion of HIT with heparin-PF4 testing. The 4Ts score was correlated with the heparin-PF4 antibody and serotonin release assay (SRA) results, with positive SRA considered confirmed HIT. Of 146 patients evaluated, the overall incidence of HIT was low (2(1%)). Fifty-one patients had heparin-PF4 testing and were included in the cohort; 5 (10%) had positive heparin-PF4 and 1 (2%) had confirmed HIT. The median 4Ts score was 3 (3-4). Thirty (59%), 17 (33%), and 4 (8%) patients had low, intermediate, and high risk, respectively. The intermediate/high risk group compared to the low risk group had a higher use of alternative non-heparin anticoagulation [13 (62%) vs 7 (23%); p = 0.0086)] and a higher incidence of thrombosis [13 (62%) vs 1 (3%); p < 0.0001]. No patient with a low 4Ts score had confirmed HIT, supporting the utility of low 4Ts score to exclude HIT diagnosis in lung transplant recipients.

Keywords: 4Ts score; HIT; Heparin-induced thrombocytopenia; Lung transplant.

PMID: 32816196

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28 August 2020

Full text on file	**HIT**

The challenges of diagnosing heparin-induced thrombocytopenia in patients with COVID-19.

May JE, Siniard RC, Marques M.

Res Pract Thromb Haemost. 2020 Aug 2:10.1002/rth2.12416. doi: 10.1002/rth2.12416. Epub ahead of print.

PMID: 32838112 Free full text

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28 August 2020

Full text on file	**HIT**

Response to: The challenges of diagnosing heparin-induced thrombocytopenia in patients with COVID-19.

Riker RR, May TL, Fraser GL, Gagnon DJ, Bandara M, Zemrak W, Seder DB.

Res Pract Thromb Haemost. 2020 Jul 9:10.1002/rth2.12417. doi: 10.1002/rth2.12417. Epub ahead of print.

Abstract: We thank May et al for their comments, expanding the number of reported cases of suspected and confirmed heparin-induced thrombocytopenia (HIT) associated with COVID-19, and reemphasizing the complexity of the prothrombotic state observed (1). We agree that false-positive enzyme immunoassay (EIA) detection of anti-platelet factor 4 (PF4)/heparin antibodies could explain the results we observed in patients #2 and #3 (2), and this has been the conventional interpretation when functional testing (such as the serotonin-release assay [SRA]) returns negative. We suggested that a false negative SRA result could have explained our findings, as opposed to the contention by May et al that we concluded they were falsely positive, to broaden our discussion about SRA-negative HIT, a relatively new and evolving clinical condition (3-6).

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28 August 2020

Full text on file	**HIT**

COVID-19 versus HIT hypercoagulability.

Warkentin TE, Kaatz S.

Thromb Res. 2020 Aug 10; 196:38-51. doi: 10.1016/j.thromres.2020.08.017. Epub ahead of print

Abstract: A striking feature of COVID-19 is the high frequency of thrombosis, particularly in patients who require admission to intensive care unit because of respiratory complications (pneumonia/adult respiratory distress syndrome). The spectrum of thrombotic events is wide, including in situ pulmonary thrombosis, deep-vein thrombosis and associated pulmonary embolism, as well as arterial thrombotic events (stroke, myocardial infarction, limb artery thrombosis). Unusual thrombotic events have also been reported, e.g., cerebral venous sinus thrombosis, mesenteric artery and vein thrombosis. Several hematology abnormalities have been observed in COVID-19 patients, including lymphopenia, neutrophilia, thrombocytopenia (usually mild), thrombocytosis, elevated prothrombin time and partial thromboplastin times (the latter abnormality often indicating lupus anticoagulant phenomenon), hyperfibrinogenemia, elevated von Willebrand factor levels, and elevated fibrin d-dimer. Many of these abnormal hematologic parameters-even as early as the time of initial hospital admission-indicate adverse prognosis, including greater frequency of progression to severe respiratory illness and death. Progression to overt disseminated intravascular coagulation in fatal COVID-19 has been reported in some studies, but not observed in others. We compare and contrast COVID-19 hypercoagulability, and associated increased risk of venous and arterial thrombosis, from the perspective of heparin-induced thrombocytopenia (HIT), including the dilemma of providing thromboprophylaxis and treatment recommendations when available data are limited to observational studies. The frequent use of heparin-both low-molecular-weight and unfractionated-in preventing and treating COVID-19 thrombosis, means that vigilance for HIT occurrence is required in this patient population.

Keywords: COVID-19; Disseminated intravascular coagulation; Heparin; Thrombocytopenia; Thrombosis..

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21 August 2020

Full text on file	**Argatroban**

Heparin-induced thrombocytopenia in COVID-19 patients with severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation: two case reports.

Bidar F, Hékimian G, Martin-Toutain I, Lebreton G, Combes A, Frère C.

J Artif Organs. 2020 Aug 12. doi: 10.1007/s10047-020-01203-x. Epub ahead of print.

Abstract: Veno-venous (VV) extracorporeal membrane oxygenation (ECMO) is increasingly used in Coronavirus disease-19 (COVID-19) patients with the most severe forms of acute respiratory distress syndrome (ARDS). Its use is associated with a significant hemostatic challenge, especially in COVID- 19 patients who have been demonstrated to otherwise present a COVID-19-associated coagulopathy. The systematic use of unfractionated heparin therapy to prevent circuit thrombosis is warranted during ECMO support. The clinical presentation and management of heparin-induced thrombocytopenia, which is a rare but life-threatening complication of heparin therapy, has not been described in those patients yet. We report herein two cases of laboratory-confirmed HIT in COVID-19 patients with severe ARDS admitted to our intensive care unit for VV-ECMO support and the successful use of argatroban as an alternative therapy. We also provide a brief literature review of best evidence for managing such patients. The diagnosis and management of HIT is particularly challenging in COVID-19 patients receiving ECMO support. An increased awareness is warranted in those patients who already present a procoagulant state leading to higher rates of thrombotic events which can confuse the issues. Argatroban seems to be an appropriate and safe therapeutic option in COVID-19 patients with HIT while on VV-ECMO.

Keywords: Argatroban; COVID-19; Extracorporeal membrane oxygenation; Heparin-induced thrombocytopenia.

PMID: 32789604 Free full text

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21 August 2020

Full text on file	**HIT**

Heparin-induced thrombocytopenia among incident hemodialysis patients anticoagulated with low molecular weight heparin: A single-center retrospective study.

Doi Y, Koga K, Sugioka S, Inoue Y, Arisato T, Nishioka K, Ishihara T, Sugawara A.

Nefrologia. 2020 Aug 14:S0211-6995(20)30093-X. English, Spanish. doi: 10.1016/j.nefro.2020.05.012. Epub ahead of print.

PMID: 32807578 Free full text

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21 August 2020

Full text on file	**HIT**

Heparin-induced thrombocytopenia and thrombosis in a patient with Covid-19.

Huang CT, Hsu SY, Chang KW, Huang CG, Yang CT, Cheng MH.

Thromb Res. 2020 Aug 3; 196:11-14. doi: 10.1016/j.thromres.2020.07.056. Epub ahead of print.
PMID: 32810772 Free full text

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21 August 2020

Full text not on file	HIT II

Adverse outcomes associated with managing suspected heparin induced thrombocytopenia in the critically ill.

Patterson S, Al Nabhani I, Linkins LA.

Thromb Res. 2020 Aug 6;193:218-220. doi: 10.1016/j.thromres.2020.08.011. Epub ahead of print.

PMID: 32798962

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21 August 2020

Full text not on file	HIT II

The role of fluid-phase immune complexes in the pathogenesis of heparin-induced thrombocytopenia.

Huynh A, Arnold DM, Smith JW, Elliott TD, Ivetic N, Kelton JG, Nazy I.

Thromb Res. 2020 Jun 6;194:135-141. doi: 10.1016/j.thromres.2020.06.012. Epub ahead of print.

Abstract: Immune complexes assemble on the platelet surface and cause Fc-mediated platelet activation in heparin-induced thrombocytopenia (HIT); however, it is not known if fluid-phase immune complexes contribute to HIT. The objective of this study was to understand the role of fluid-phase immune complexes in platelet activation and HIT. Binding of wild-type and 15 platelet factor 4 (PF4) mutants to platelets was measured using flow cytometry. Platelet activation was measured using the PF4-dependent 14C-serotonin release assay (PF4-SRA) with KKO and a HIT-patient plasma in the presence of wild-type or PF4 mutants. To activate platelets, we found that a minimal level of wild-type PF4 is required to bind the platelet surface in the presence of KKO (2.67 relative MFI) or HIT-patient plasma (1.71 relative MFI). Only a subset of PF4 mutants was able to support platelet activation, despite having lower surface binding than the minimum binding required of wild-type PF4 (9 mutants with KKO and 2 mutants with HIT-patient plasma). Using individual PF4 mutants, we identified that HIT immune complexes can be formed in fluid-phase and induce platelet activation. Further studies are required to investigate the role of fluid-phase HIT immune complexes in the development of thrombocytopenia and thrombosis associated with clinical HIT.

PMID: 32788105

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14 August 2020

Full text on file	Argatroban

Thrombolysis and use of argatroban for the treatment of massive pulmonary embolism following anticoagulation failure in a patient with COVID-19.

Sagardia LM, Daniels LM.

Am J Health Syst Pharm. 2020 Aug 11:zxaa287. doi: 10.1093/ajhp/zxaa287. Epub ahead of print.

Abstract: Disclaimer: In an effort to expedite the publication of articles related to the COVID-19 pandemic, AJHP is posting these manuscripts online as soon as possible after acceptance. Accepted manuscripts have been peer-reviewed and copyedited, but are posted online before technical formatting and author proofing. These manuscripts are not the final version of record and will be replaced with the final article (formatted per AJHP style and proofed by the authors) at a later time. Purpose: Successful use of alteplase and argatroban to treat a patient with coronavirus disease 2019 (COVID-19)-associated massive pulmonary embolism with cardiac arrest is reported. Summary: This case report describes a 42-year-old male with COVID-19 who developed a massive pulmonary embolism resulting in cardiac arrest after suspected failure of low-molecular-weight heparin therapy for a deep venous thrombosis. Administration of two 50-mg doses of intravenous alteplase resulted in return of spontaneous circulation, and low-dose argatroban was used as follow-up anticoagulation therapy without complications. This is the first case report of use of argatroban in a patient with COVID-19 with cardiac arrest-associated massive pulmonary embolism after failure of previous anticoagulation efforts. Conclusion: Argatroban may be used as an alternate anticoagulation strategy in COVID-19 patients who fail low-molecular weight therapy. A risk versus benefit discussion should be had regarding appropriateness of therapy as well as dosing. More data is needed to understand the unique hypercoagulable condition in COVID-19 patients as well as research that further highlights the role of argatroban and bivalirudin therapy in this patient population.

Keywords: COVID-19; anticoagulants; argatroban; heart arrest; pulmonary embolism; tissue-plasminogen activator.

PMID: 32780853 Free full text

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14 August 2020

Full text on file	**Argatroban**

Argatroban therapy for heparin-induced thrombocytopenia in a patient with coronavirus disease 2019.

Ogawa Y, Nagata T, Akiyama T, Nishida K, Kumasawa J, Kohno M, Kohata H, Gohma I.

J Thromb Thrombolysis. 2020 Aug 11:1–3. doi: 10.1007/s11239-020-02248-8. Epub ahead of print.

PMID: 32780355 Free full text

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07 August 2020

Full text not on file	**Argatroban**

Utilization and Outcomes of Children Treated with Direct Thrombin Inhibitors on Paracorporeal Ventricular Assist Device Support.

VanderPluym CJ, Cantor RS, Machado D, Boyle G, May L, Griffiths E, Niebler RA, Lorts A, Rossano J, Sutcliffe DL, Lytrivi ID, Buchholz H, Fynn-Thompson F, Hawkins B, Conway J.

ASAIO J. 2020 Aug;66(8):939-945. doi: 10.1097/MAT.0000000000001093.

Abstract: Thrombotic and bleeding complications have historically been major causes of morbidity and mortality in pediatric ventricular assist device (VAD) support. Standard anticoagulation with unfractionated heparin is fraught with problems related to its heterogeneous biochemical composition and unpredictable pharmacokinetics. We sought to describe the utilization and outcomes in children with paracorporeal VAD support who are treated with direct thrombin inhibitors (DTIs) antithrombosis therapy. Retrospective multicenter review of all pediatric patients (aged <19 years) treated with a DTI (bivalirudin or argatroban) on paracorporeal VAD support, examining bleeding and thrombotic adverse events. From May 2012 to 2018, 43 children (21 females) at 10 centers in North America, median age 9.5 months (0.1-215 months) weighing 8.6 kg (2.8-150 kg), were implanted with paracorporeal VADs and treated with a DTI. Diagnoses included cardiomyopathy 40% (n = 17), congenital heart disease 37% (n = 16; single ventricle n = 5), graft vasculopathy 9% (n = 4), and other 14% (n = 6). First device implanted included Berlin Heart EXCOR 49% (n = 21), paracorporeal continuous flow device 44% (n = 19), and combination of devices in 7% (n = 3). Adverse events on DTI therapy included; major bleeding in 16% (n = 7) (2.6 events per 1,000 patient days of support on DTI), and stroke 12% (n = 5) (1.7 events per 1,000 patient days of support on DTI). Overall survival to transplantation (n = 30) or explantation (n = 8) was 88%. This is the largest multicenter experience of DTI use for anticoagulation therapy in pediatric VAD support. Outcomes are encouraging with lower major bleeding and stroke event rate than that reported in literature using other anticoagulation agents in pediatric VAD support.

PMID: 32740356

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07 August 2020

Full text on file	**HIT**

Detection of anti-heparin-PF4 complex antibodies in COVID-19 patients on heparin therapy.

Dragonetti D, Guarini G, Pizzuti M.

Blood Transfus. 2020 Jul;18(4):328. doi: 10.2450/2020.0164-20.

PMID: 32697931 Free full text

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