RELIAS MEDIA

Critical Care [ALERT]

Vol. 27, Issue 5, August 2019
ReliasMedia.com

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

Heparin-Induced Thrombocytopenia: What's the Latest?

By Kathryn Radigan, MD, MSc

Attending Physician, Division of Pulmonary and Critical Care, Stroger Hospital of Cook County, Chicago

Dr. Radigan reports no financial relationships relevant to this field of study.

Heparin-induced thrombocytopenia (HIT) is a life-threatening, heparin-mediated, prothrombotic disorder caused by antibodies directed to complexes containing heparin and an endogenous platelet protein, platelet factor 4 (PF4).[1] Approximately 12 million patients are exposed to heparin each year in the United States.[2] Depending on the type of heparin, the duration of exposure, and the patient population, the incidence of HIT among those exposed ranges from < 0.1% to 7%.[3] Risk factors include surgical patients, exposure to unfractionated heparin (UFH) as opposed to low-molecular weight heparin (LMWH), use of therapeutic heparin as opposed to prophylactic heparin, and female sex.[4] Although patients with HIT are thrombocytopenic, bleeding is rare, with some studies showing a bleeding incidence of 6%.[5] Since the antibody that activates platelets can cause catastrophic arterial and venous thrombosis in one-third to one-half of cases, recognition, timely diagnosis, and treatment are crucial.[6,7]

PATHOPHYSIOLOGY

An autoantibody against PF4, after complex formation with heparin, induces platelet activation by cross-linking FcγIIA receptors.[6] Activated platelets increase both the release and surface expression of PF4, creating a positive feedback loop that stimulates further platelet activation. Thrombocytopenia occurs by way of removal of IgG-coated platelets by macrophages within the reticuloendothelial system and consumption of platelets caused by thrombosis. Platelet activation not only is accompanied by intense thrombin generation, but also occurs through intracellular signaling involving the spleen tyrosine kinase and the release of procoagulant microparticles,

Financial Disclosure: *Critical Care Alert*'s Physician Editor Betty Tran, MD, MSc, Nurse Planner Jane Guttendorf, DNP, RN, CRNP, ACNP-BC, CCRN, Peer Reviewer William Thompson, MD, Executive Editor Shelly Morrow Mark, Accreditations Manager Amy M. Johnson, MSN, RN, CPN, and Editorial Group Manager Leslie Coplin report no financial relationships relevant to this field of study.

placing the patient at increased risk of thrombosis.

TYPES OF HIT

Although there are two types of HIT, only HIT type II is of clinical significance with substantial clinical consequences.[6] Differentiation between HIT types I and II is based on clinical parameters. Type I typically is described as a transient drop in platelet count within the first two days of heparin exposure due to non-immune platelet aggregation, and the platelet count recovers without discontinuation of heparin. The platelet count nadir typically is around 100,000 platelets per microliter. HIT type II typically presents with a more dramatic, persistent drop in platelet count due to antibodies that form in response to PF4 complexed to heparin. The "HIT antibodies" may cause thrombosis in addition to thrombocytopenia or the syndrome of heparin-induced thrombocytopenia and thrombosis (HITT). Other HIT variants include delayed-onset HIT (HIT occurring more than five days after heparin withdrawal), refractory HIT (persistent thrombocytopenia or thrombosis that lasts for weeks after heparin has been removed), and spontaneous HIT (HIT in the absence of heparin exposure).[8] The exact cause of spontaneous HIT is unclear, but it may be related to exposure to a heparin-like proteoglycan, such as chondroitin sulfate, during surgery and/or it may be the result of proinflammatory events seen especially in postsurgical patients.[9]

PHASES OF HIT

HIT may be classified with respect to clinical presentation. Descriptors include suspected HIT, acute HIT, subacute HIT A and B, and remote HIT.[10] Suspected HIT is appropriate nomenclature when suspicion is high and thrombocytopenia is noted but heparin-PF4 assays are not yet available. Acute HIT is appropriate when thrombocytopenia is present and testing for heparin-PF4 antibodies (either the functional assay and/or immunoassay) is positive. Subacute HIT A may be used when thrombocytopenia has resolved, but HIT antibodies remain (functional and immunoassays are positive). Subacute HIT B is appropriate when thrombocytopenia has resolved with a negative functional assay, but immunoassays continue to be positive. The term remote HIT may be used with a prior history of HIT, but current assays are negative and no thrombocytopenia is noted.

SCREENING OF ASYMPTOMATIC PATIENTS

The American Society of Hematology (ASH) guidelines have recommended regular screening of patients receiving heparin who are at intermediate (0.1-1.0%) or high (> 1.0%) risk of developing HIT.[3] Surgical and trauma patients receiving postoperative UFH are high-risk patients.[11] Medical and obstetrical patients receiving UFH and patients receiving LMWH after major surgery or trauma are intermediate-risk patients. Low-risk patients (those who do not need monitoring of platelets) include medical or obstetrical patients receiving LMWH, patients receiving LMWH after minor surgery or minor trauma, or those receiving fondaparinux. For patients with previous exposure to heparin within 30 days of reinitiating heparin, the ASH guidelines suggest screening for HIT on the day that heparin is initiated.[3] For those with no previous exposure, screening should occur from day 4 until day 14 after initial heparin exposure or until discontinuation of the heparin product. Every-other-day screening is recommended in high-risk patients, and screening every two to three days is recommended in intermediate-risk patients.

DIAGNOSIS

Typically, the platelet count falls more than half, with a nadir between 50 to 80 × 10^9/L and may occur with catastrophic arterial and venous thrombosis.[12] In one study that examined the timing in greater detail, 70% of HIT patients experienced a fall in platelets four or more days after the start of heparin therapy.[13] In these patients, a history of previous heparin exposure did not influence the timing of the thrombocytopenia. In 30% of patients, the onset of the thrombocytopenia was rapid, with a median time of onset approximately 10.5 hours after the start of heparin. All of these patients had been treated with heparin within the prior 100 days.

The probability of HIT in an ICU patient should be estimated using the 4Ts score (Thrombocytopenia, Timing, Thrombosis, and oThers).[14] Guidelines recommend

Critical Care [ALERT]
Authoritative, evidence-based summaries for the critical care clinician

Critical Care Alert (ISSN 1067-9502) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Critical Care Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Subscription Prices
United States
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Relias LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [2] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

against using a gestalt approach to the diagnosis.[3] A presumptive diagnosis of HIT is based solely on clinical findings and platelet counts until laboratory results are available. It is imperative to obtain accurate and complete information for the 4Ts score; incomplete information may lead to an inaccurate assessment of risk. If information is missing, it is recommended to err on the side of a higher 4Ts scores. In patients with suspected HIT and a low-probability 4Ts score, the ASH guidelines recommend against both further laboratory testing and empiric treatment.[3] In patients with intermediate- or high-risk 4Ts scores, discontinuation of heparin and treatment with non-heparin anticoagulants is important while a further workup proceeds.

Immunoassays, which detect PF4/heparin IgG antibodies, are quite sensitive (> 95%) and often are available within most institutions for a rapid turnaround time, but they have poor specificity.[15] The solid-phase ELISA is the most widely available test. If a patient has an intermediate or high probability 4Ts score, the ASH guidelines recommend an immunoassay with a follow-up functional assay if the immunoassay is positive and a functional assay is available.[3] Often the ELISA is reported as positive or negative, but it is important to know the optical density (OD) as well. A higher OD represents a higher titer of antibody in the patient's serum.

If an ELISA OD is less than 0.60, HIT typically is excluded.[16] In this setting, functional HIT antibody testing is not necessary unless the clinical picture changes or the clinical picture is discordant. This caveat may be especially important in patients with high-probability 4Ts score in the rare case of lab error or if the pathologic antigen involves a complex of heparin and a molecule other than PF4. Unless there is a special caveat, it is appropriate to discontinue non-heparin anticoagulation and resume heparin if clinically indicated. An ELISA OD > 2.00 or OD ≥ 1.5 and a high-probability 4Ts score confirms HIT. Although functional HIT antibody testing typically is not pursued in the setting of a high OD, some centers will send off the functional assay with the immunoassay to optimize efficiency and ensure quality. One of the most common functional assays, the serotonin release assay (SRA), has high specificity and positive predictive values. Another functional assay that is used commonly, especially in Europe, is the heparin-induced platelet activation (HIPA) assay.[17] An ELISA OD between 0.60 and 1.99 or OD between 0.60 and 1.49 with a high-probability 4Ts score is indeterminate. Assuming that heparin already has been discontinued, non-heparin anticoagulants are continued while functional assays are pending.[3] A positive functional assay in the appropriate clinical setting typically confirms a diagnosis of HIT, and a negative functional assay excludes it.

MANAGEMENT OF THE ACUTE PHASE

In patients with acute HIT without thrombosis (isolated HIT) or acute HIT complicated by thrombosis (HITT), ensure that all heparin has been stopped and that a non-heparin anticoagulant, such as argatroban, bivalirudin, danaparoid, fondaparinux, or a direct oral anticoagulant (DOAC) already has been started at a therapeutic dose.[3] Vitamin K antagonists should not be initiated. In critically ill patients, it is important to consider argatroban or bivalirudin in light of their short half-life, especially if there is a potential for invasive procedures and a risk of bleeding that may necessitate temporary discontinuation. Fondaparinux and DOACs may be an option in patients who are stable and not at increased risk of bleeding, but experience with DOACs in patients with HIT complicated by life- or limb-threatening thromboembolism is limited.

In cases of non-life-threatening or non-limb-threatening disease, rivaroxaban has been the DOAC with the most published literature.[3] Patients with acute HITT typically are started on rivaroxaban 15 mg twice daily for three weeks, followed by 20 mg daily. Patients with acute isolated HIT should be started at 15 mg twice daily until platelet recovery, followed by 20 mg daily if there is an indication for continued anticoagulation. In acute HITT or acute isolated HIT, the ASH guidelines recommend against an inferior vena cava (IVC) filter. Platelets should not be transfused in HIT unless the patient has active bleeding or a high risk of bleeding.

In patients with acute isolated HIT and no deep vein thrombosis (DVT) identified by compression ultrasound, the ASH guidelines suggest that anticoagulation be continued until proven platelet recovery. The guidelines suggest three months of therapy unless HIT persists without recovery of platelets. For 90% of patients, platelets will recover within seven days of the HIT diagnosis.[18] Among those with HITT, there are no specific recommendations regarding length of therapy. In patients with subacute HIT, treatment with DOACs, as opposed to vitamin K antagonists, is preferred. An emergency identifier with information including the allergy to heparin, the reaction of HIT, and the date of diagnosis is recommended for patients diagnosed with remote HIT.

DVT SCREENING AND PREVENTION

Thrombosis occurs in up to 50% of individuals with HIT who are not treated appropriately, and it is the presenting finding in 25% of patients.[19] The sequelae of thrombosis can be life-threatening and can include skin necrosis, limb gangrene, and organ infarction, including stroke, myocardial infarction, bowel infarction, and renal infarction. Per ASH guidelines, all patients with

acute HIT should receive a bilateral lower extremity compression ultrasound to screen for asymptomatic DVT.[3] All patients with upper extremity catheters should receive an upper extremity compression ultrasound. In patients with a history of HIT who require venous thromboembolism treatment or prophylaxis, administration of a non-heparin anticoagulant (e.g., apixaban, dabigatran, danaparoid, edoxaban, fondaparinux, rivaroxaban, or vitamin K antagonist), rather than UFH or LMWH, is recommended.[3]

SUMMARY

HIT is an iatrogenic, potentially life-threatening complication that occurs after exposure to heparin therapy in hospitalized patients. Even though the diagnosis ideally is established based on both clinical and laboratory findings, a presumptive clinical diagnosis using the 4Ts score often is necessary while awaiting laboratory confirmation. Early recognition and timely initiation of treatment are critical for improved prognosis. In addition to the typical non-heparin anticoagulant options, fondaparinux or DOACs may be options in patients who are stable without life-threatening or limb-threatening thromboembolism and not at increased risk of bleeding. Screening for asymptomatic DVT also is recommended for newly diagnosed HIT patients. ■

REFERENCES

1. Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. *Thromb Haemost* 1992;68:95-96.
2. Rice L. Heparin-induced thrombocytopenia: Myths and misconceptions (that will cause trouble for you and your patient). *Arch Intern Med* 2004;164:1961-1964.
3. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: Heparin-induced thrombocytopenia. *Blood Adv* 2018;2:3360-3392.
4. Salter BS, Weiner MM, Trinh MA, et al. Heparin-induced thrombocytopenia: A comprehensive clinical review. *J Am Coll Cardiol* 2016;67:2519-2532.
5. Goel R, Ness PM, Takemoto CM, et al. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. *Blood* 2015;125:1470-1476.
6. Arepally GM. Heparin-induced thrombocytopenia. *Blood* 2017;129:2864-2872.
7. Nand S, Wong W, Yuen B, et al. Heparin-induced thrombocytopenia with thrombosis: Incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution. *Am J Hematol* 1997;56:12-16.
8. Greinacher A, Selleng K, Warkentin TE. Autoimmune heparin-induced thrombocytopenia. *J Thromb Haemost* 2017;15:2099-2114.
9. Mallik A, Carlson KB, DeSancho MT. A patient with 'spontaneous' heparin-induced thrombocytopenia and thrombosis after undergoing knee replacement. *Blood Coagul Fibrinolysis* 2011;22:73-75.
10. Cuker A. Management of the multiple phases of heparin-induced thrombocytopenia. *Thromb Haemost* 2016;116:835-842.
11. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: A meta-analysis. *Blood* 2005;106:2710-2715.
12. Warkentin TE. Heparin-induced thrombocytopenia: A clinicopathologic syndrome. *Thromb Haemost* 1999;82:439-447.
13. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med* 2001;344:1286-1292.
14. 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;4:759-765.
15. Nagler M, Bachmann LM, ten Cate H, ten Cate-Hoek A. Diagnostic value of immunoassays for heparin-induced thrombocytopenia: A systematic review and meta-analysis. *Blood* 2016;127:546-57.
16. Raschke RA, Curry SC, Warkentin TE, Gerkin RD. Improving clinical interpretation of the anti-platelet factor 4/heparin enzyme-linked immunosorbent assay for the diagnosis of heparin-induced thrombocytopenia through the use of receiver operating characteristic analysis, stratum-specific likelihood ratios, and Bayes theorem. *Chest* 2013;144:1269-1275.
17. Leo A, Winteroll S. Laboratory diagnosis of heparin-induced thrombocytopenia and monitoring of alternative anticoagulants. *Clin Diagn Lab Immunol* 2003;10:731-740.
18. Pon TK, Mahajan A, Rosenberg A, et al. Platelet response to direct thrombin inhibitor or fondaparinux treatment in patients with suspected heparin-induced thrombocytopenia. *J Thromb Thrombolysis* 2018;45:536-542.
19. 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-e530S.

ABSTRACT & COMMENTARY

Impact of Early Low-Dose Norepinephrine in Adults Experiencing Sepsis With Hypotension

By Drayton Hammond, PharmD, MBA, BCPS, BCCCP

Clinical Pharmacy Specialist, Adult Critical Care, Rush University Medical Center, Chicago

Dr. Hammond reports no financial relationships relevant to this field of study.

SYNOPSIS: Adult patients experiencing sepsis with hypotension but who did not meet the definition of septic shock received a median of 800 mL of intravenous fluid prior to initiation of norepinephrine 0.05 mcg/kg/min as a non-titratable infusion. Patients in this early vasopressor group had much lower odds of failing to achieve their primary outcome of adequate mean arterial pressure and tissue perfusion when early norepinephrine was provided.

SOURCE: Permpikul C, Tongyoo S, Viarasilpa T, et al. Early use of norepinephrine in septic shock resuscitation (CENSER). A randomized trial. *Am J Respir Crit Care Med* 2019;199:1097-1105.

The initial management of sepsis includes recognizing and treating the causative infection with antimicrobial therapy and providing intravenous (IV) fluid resuscitation to support end-organ perfusion.[1] The current Surviving Sepsis Campaign guidelines provide a strong recommendation for administering at least 30 mL/kg of IV crystalloid fluid within the first three hours of resuscitation, but they are silent on the specific time to initiate vasopressor therapy.[1] Observational studies previously have suggested that earlier initiation of norepinephrine decreases the time to achieve target mean arterial pressure (MAP) and reduces in-hospital mortality.[2,3] This trial was performed to determine if administering low-dose norepinephrine soon after sepsis-induced hypotension is recognized accelerates shock control.[4]

Researchers conducted a randomized, double-blind trial in a large, tertiary referral center in Thailand.[4] Patients experiencing sepsis with hypotension (MAP < 65 mmHg) who had not been in shock for more than one hour were randomized to 24 hours of norepinephrine 0.05 mcg/kg/min as a non-titratable infusion or dextrose 5% in water at the same infusion rate. Patients were eligible to receive open-label norepinephrine at the discretion of the attending physician and received additional supportive care as guided by the 2012 Surviving Sepsis Campaign guidelines.[5] Patients who were hemodynamically stable without open-label norepinephrine, mechanical ventilation, or renal replacement therapy were transferred from the emergency department to the general medical ward, and all other patients received subsequent care in an intensive care unit. The primary outcome was shock control rate at six hours after sepsis diagnosis, defined as sustained MAP > 65 mmHg with evidence of adequate tissue perfusion (urine output > 0.5 mg/kg/hour for two consecutive hours or a decrease in serum lactate by > 10% from the initial level).

Patients in both groups received a median of 800 mL of crystalloid prior to study drug initiation and a median of approximately 30 mL/kg of crystalloid prior to open-label, titratable norepinephrine initiation (67.7% in the early norepinephrine group vs. 80% in the control group, $P = 0.01$). The early norepinephrine group had a median norepinephrine initiation time of 70 minutes (interquartile range 50-90 minutes). The total volume of IV fluid at all time points from hour 1 to day 3 was similar between groups; however, significantly more patients in the control group experienced cardiogenic pulmonary edema (14.4% vs. 27.7%, $P = 0.004$).

More patients in the early norepinephrine group achieved target MAP and tissue perfusion by hour 6 (76.1% vs. 48.4%, $P < 0.001$). More patients in the early norepinephrine group achieved all targets (i.e., MAP, urine output, and lactate clearance) by hour 6 (31% vs. 17.4%, $P = 0.005$) and target MAP and urine output by hour 6 (35.5% vs. 24.5%, $P = 0.04$). In contrast, achievement of target MAP and lactate clearance by 10% at hour 6 did not differ significantly between the groups (9.7% vs. 6.5%, $P = 0.30$). Mortality at 28 days was numerically lower in the early norepinephrine group (15.5% vs. 21.9%, $P = 0.15$), but it was not statistically significant. Intensive care unit and hospital lengths of stay as well as days alive and free from end-organ support to day 28 were similar between the groups.

■ COMMENTARY

Because vasodilation and capillary leakage are prominent features of sepsis with hypotension, restoring end-organ perfusion through an initial combination of IV fluid and vasopressor therapies theoretically may improve patient outcomes compared to IV fluid alone. Permpikul and colleagues found improved odds of achieving their primary outcome of adequate MAP and tissue perfusion when early norepinephrine was provided (odds ratio [OR], 3.4; 95% confidence interval, 2.09-5.53; $P < 0.001$). Although lactate clearance was similar between groups, this serves as an imperfect surrogate marker for disease status.[6] Additionally, although similar IV fluid amounts were provided between groups, patients who received early norepinephrine had lower odds of developing cardiogenic edema, suggesting that the vasoconstrictive and inotropic effects of this intervention were highly effective. They also had lower rates of new-onset arrhythmia development (11% vs. 20%, $P = 0.03$), which suggests improved management of sepsis and portends better outcomes.[7]

Although the 28-day mortality rates were similar between groups, the trial was inadequately powered to detect the observed 6.4% mortality difference because of the small sample size. Because the macrocirculation and microcirculation parameters favored the early norepinephrine group, a larger, multicenter trial evaluating mortality with the early initiation of

norepinephrine in adults experiencing sepsis and hypotension is warranted.

Clinicians looking to apply these findings to their practice should have at least a few considerations. Patients in this trial received a continuous, non-titratable norepinephrine infusion in the medical ward with 3:1 nurse staffing. If wards do not have that level of staff or prohibit continuous infusions from being administered, then care may need to be provided in an ICU or an intermediate care unit. Additionally, infusions were initiated through a peripheral line in most patients, which has been found to be safe for short periods of time with more proximal access sites, but may necessitate a change in practice and/or policy at some institutions.[8] Additionally, providers should not expect to provide a significantly smaller amount of IV resuscitative fluid, so the best practices of evaluating the patient's fluid status will remain essential. Similar rates of acute limb and/or intestinal ischemia occurred between the groups (3.2% vs. 1.9%, $P = 0.47$) when these other resuscitative measures were provided.

Implementation of this type of practice should be coordinated with emergency medicine physicians and intensivists as well as nurses in emergency departments and ICUs to streamline the process and reduce the risk of complications. Finally, the results of a multicenter trial comparing early vasopressor initiation to liberal IV crystalloid therapy will provide more insight into the benefits and harms of both practices.[9] ■

REFERENCES

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017;45:486-552.
2. Morimatsu H, Singh K, Uchino S, et al. Early and exclusive use of norepinephrine in septic shock. Resuscitation 2004;62:249-254.
3. Bai X, Yu W, Ji W, et al. Early versus delayed administration of norepinephrine in patients with septic shock. *Crit Care* 2014;18:532.
4. Permpikul C, Tongyoo S, Viarasilpa T, et al. Early use of norepinephrine in septic shock resuscitation (CENSER). A randomized trial. *Am J Respir Crit Care Med* 2019;199:1097-1105.
5. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including The Pediatric Subgroup. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* 2013;39:165-228.
6. Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. *JAMA* 2019;321:654-664.
7. Bosch NA, Cohen DM, Walkey AJ. Risk factors for new-onset atrial fibrillation in patients with sepsis: A systematic review and meta-analysis. *Crit Care Med* 2019;47:280-287.
8. Cardenas-Garcia J, Schaub KF, Belchikov YG, et al. Safety of peripheral intravenous administration of vasoactive medication. *J Hosp Med* 2015;10:581-585.
9. Schoenfeld DA. Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS). Available at: https://clinicaltrials.gov/ct2/show/NCT03434028. Accessed June 2, 2019.

ABSTRACT & COMMENTARY

Trajectory of Physical Function Recovery May Help Inform Prognosis for Survivors of Acute Respiratory Failure

By Elaine Chen, MD

Assistant Professor, Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Section of Palliative Medicine, Rush University Medical Center, Chicago

Dr. Chen reports no financial relationships relevant to this field of study.

SYNOPSIS: There are several distinct trajectories of recovery after acute respiratory failure. The group with the highest physical function consisted primarily of younger women who experienced less continuous sedation time and shorter ICU length of stay.

SOURCE: Gandotra S, Lovato J, Case D, et al. Physical function trajectories in survivors of acute respiratory failure. *Ann Am Thorac Soc* 2019;16:471-477.

Persistent physical function impairment for months to years is common after mechanical ventilation for acute respiratory failure.[1] Patients have identified physical strength, fatigue, and decreased walking distance as important outcomes after critical illness. Prior studies have revealed that factors such as hospital length of stay, sex, ethnicity, and prior smoking status may influence physical function recovery after a critical illness. The authors of this study sought to determine whether common patterns

of physical function recovery occur over a six-month period after a critical illness and to assess the characteristics of such trajectory groups.

Researchers performed a secondary analysis of a previously designed randomized clinical trial that evaluated standardized rehabilitation therapy among patients with acute respiratory failure.[2] In this was single-center trial, investigators recruited 300 mechanically ventilated patients, 18 years of age or older, over a five-year period. The duration of mechanical ventilation was limited to 80 hours or less, and the duration of hospitalization was limited to seven days or less. Patients were previously independently ambulatory, but the use of a cane or walker was allowed. In-person physical function testing was evaluated at hospital discharge and again at two, four, and six months after enrollment. The Short Physical Performance Battery (SPPB), which assesses gait speed, balance, and lower extremity strength with a score from 0 to 12, was chosen as the objective physical function variable. Statistical analysis included group-based trajectory modeling.

Of the 300 patients randomized, 260 were discharged alive and had at least one SPPB data point available for analysis. The mean SPPB score for all patients at the time of discharge was in the "low function" category and increased to a plateau in the "intermediate function" category by month 2. Patients were grouped into four different trajectories based on physical function recovery. Characteristics of the groups were evaluated using chi-square tests, one-way analysis of variance, and multinomial logistic regression. Group 1 included patients discharged with physical function disability that did not improve by six months. Patients in group 2 were discharged with physical function disability with some improvement, but they remained functionally disabled by six months. Group 3 patients exhibited low physical function at discharge and improved to intermediate physical function. Patients in group 4 had intermediate physical function at discharge and improved to high physical function at two months; this level was sustained at six months. The greatest change in physical function appeared to occur within the first two months after discharge. In the final regression model, age, sex, ICU length of stay (LOS), and continuous intravenous (IV) sedation days were found to influence trajectory group membership.

Group 4, the group with highest physical function, was comprised of mostly younger females with shorter ICU LOS and duration of sedation. Group 1, the group with the most persistent physical disability, consisted primarily of older patients who had longer sedation time and longer ICU LOS. Ventilator days and hospital LOS were excluded in this study because of their close correlation with ICU LOS. The median age in group 4 was 45 years, and the youngest patient in group 1 was 40 years old.

In other ICU survivorship studies, pre-existing comorbidities were associated with some factors in recovery. In this study, prehospital oxygen use, dialysis, or Acute Physiology and Chronic Health Evaluation (APACHE) III scores were not associated with recovery trajectory. In this study, female sex showed an advantage for long-term physical function recovery. In other studies, female sex was shown to be associated with higher mortality and increased ICU-acquired weakness. The authors agreed that sex-related differences in ICU outcomes are complex and need further elucidation. The time receiving continuous IV sedation was the only modifiable factor that was shown to influence the recovery trajectory. This finding supports other studies that encourage minimizing the duration of continuous sedation in critically ill patients.

Limitations to this study included missing data due to death or loss to follow-up. Prehospitalization functional status was not well defined, but the patients in this study were younger and less ill at baseline compared to subjects in other studies. Follow-up time of six months, with only a small number of measurements at each follow-up, limits the complexity of the regression models. Additionally, hospitalization time was limited to seven days or less, but the authors of other studies have looked at longer durations of mechanical ventilation or hospitalization.

In summary, this study defined four distinct trajectories of recovery after mechanical ventilation for acute respiratory failure, limited to adult ambulatory patients with a maximum of seven days of hospitalization. Trajectory membership was associated with age, sex, ICU LOS, and continuous IV sedation days. The researchers found that the group with the highest physical function was primarily younger women with a shorter LOS and fewer IV sedation days.

■ COMMENTARY

This study adds to the extensive literature on outcomes after critical illness. The authors described four distinct trajectories of recovery over the first six months after hospital discharge. As with many studies of recovery after critical illness, the study is limited by subject selection and loss to follow-up. The inclusion criteria for this study were predetermined to be relatively higher functioning, since the parent study was designed to evaluate standardized rehabilitation therapy. All patients were ambulating independently prior to critical illness, while many critically ill patients have lower levels of premorbid function. APACHE III score at enrollment was used as a surrogate for prehospitalization illness. Although it appeared significant in univariate analysis,

the multivariate *P* value was not significant. Perhaps with a larger cohort, this could become a significant factor in the recovery trajectory. In addition to the limitations described earlier, the number of ICU organ failures was not assessed in this study, and the severity of illness during hospitalization was not evaluated as a factor in recovery. Because these patients were followed for only six months, it would be interesting to see the trajectories of recovery at one and five years after discharge.

This study shows that there are distinct trajectories of physical function recovery after critical illness. Although the information found in this study does not provide targeted interventions to improve function and recovery, it may help identify patients at greater risk of physical function disability after critical illness. It helps inform prognosis in those who are expected to recover and provides a basis for designs of further clinical trials to tailor interventions to specific subgroups. ■

REFERENCES

1. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364:1293-1304.
2. Morris PE, Berry MJ, Files DC, et al. Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: A randomized clinical trial. *JAMA* 2016;315:2694-2702.

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.

2. Log on to **ReliasMedia.com** and click on My Account. First-time users must register on the site. Tests are taken after each issue.

3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the completed evaluation is received, a credit letter will be emailed to you.

CME/CE QUESTIONS

1. Which test should be done to screen for clinically silent deep vein thrombosis (DVT) in individuals with heparin-induced thrombocytopenia but without DVT symptoms?
a. Bilateral leg ultrasound
b. D-dimer
c. Bilateral computed tomography angiogram
d. Wells' criteria

2. Which medication may be considered as an additional option for non-heparin anticoagulants in the setting of heparin-induced thrombocytopenia?
a. Warfarin
b. A direct oral anticoagulant
c. Enoxaparin
d. Aspirin

3. In the trial by Permpikul et al, what norepinephrine dosage was provided as a non-titratable continuous infusion to patients in the early vasopressor group?
a. 0.02 mcg/kg/min
b. 0.05 mcg/kg/min
c. 0.1 mcg/kg/min
d. 0.15 mcg/kg/min

4. In the trial by Permpikul et al, what volume of intravenous fluid was provided for resuscitation prior to norepinephrine initiation in the early vasopressor group?
a. 0 mL
b. 500 mL
c. 800 mL
d. 1.2 L

5. In the study by Gandotra et al, which of the following factors was associated with rapid improvement in physical function after acute respiratory failure?
a. Appropriate use of low tidal volume ventilation
b. Lower maximum positive end-expiratory pressure received
c. Fewer days of mechanical ventilation
d. Fewer days of continuous intravenous sedation

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.