CASE REPORT

Sepsis-Induced Coagulopathy as a Risk for Postoperative Arterial Thrombosis: A Case Report

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ABSTRACT

Background: Venous thromboembolic disease and arterial thrombosis are recognized as common causes of hospital mortality, especially in postoperative patients, those who are immobilized, and individuals with sepsis. Coagulopathy is a significant factor due to the interaction between inflammation and coagulation, stemming from widespread endothelial damage.

Case: We report manifestations of sepsis-induced coagulopathy (SIC) in a 64-year-old woman who was treated at the intensive care unit (ICU) of RSUD Dr. Moewardi with peripheral arterial disease. The patient was treated for 20 days in the ICU with a multidisciplinary approach. The patient's clinical outcome was good and planned for follow-up during outpatient care.

Discussion: Thrombosis and inflammation are distinct yet closely interconnected physiological processes. In a normal physiological context, the activation of the coagulation system by inflammation is a component of the body's defense mechanism against pathogens, aiming to restrict their spread within the bloodstream. This protective response involves the interaction between innate immune cells and platelets.

Conclusion: By gaining a deeper insight into sepsis-associated coagulopathy (microthrombopathy), we can develop effective treatments that specifically target the microthrombotic pathway involved in endothelial damage.

Keywords: coagulopathy; intensivist; postoperative; sepsis; thrombosis

INTRODUCTION

Sepsis is a critical condition characterized by organ dysfunction resulting from an abnormal host response to infection. It is a syndrome with a prevalence of up to 2.5 per 1,000 individuals and has seen an annual increase of 8.7% over the past two decades. Sepsis affects approximately 19 million people each year, leading to nearly 5 million mortality cases, being the main cause of mortality worldwide.[1]

Notable clinical features of sepsis include thrombocytopenia, hemolytic anemia, vascular microthrombosis, multiorgan dysfunction syndrome (MODS), coagulopathy, and septic shock.[2]

Venous thromboembolism and arterial thrombosis are recognized as significant causes of in-hospital mortality, especially among patients following surgery, immobilization and sepsis.[3,4] Sepsis patients are at risk for thromboembolic events or thrombosis due to conventional risk factors including mechanical ventilation, endovascular catheters, inflammatory response, activation of hemostasis, and decreased fibrinolysis.[5] In addition, sepsis-related systemic hypotension, septic shock, tissue hypoxemia, and the requirement for vasopressor support can also induce venous thromboembolism and acute arterial thrombosis.[5]

Coagulopathy plays a crucial role through the interaction between inflammation and coagulation, causing systemic endothelial injury.[6] Disseminated intravascular coagulation (DIC) is marked by the abnormal systemic activation of the coagulation cascade, resulting in excessive thrombotic and hemorrhagic complications. This occurs due to fibrin formation, microangiopathic thrombosis, and the decrease of coagulation factors and platelets.[7]

This case report aims to report the manifestations of coagulopathy induced by sepsis in a 64-year-old female administered to the ICU of RSUD Dr. Moewardi with peripheral arterial disease.

CASE

We report a 64-year-old woman administered to the ICU of RSUD Dr. Moewardi with information about post-exploratory laparotomy for indications of generalized peritonitis et causa hollow viscous perforation (19 April 2023). The patient previously complained of pain throughout the abdominal area for 3 days before admitted to the hospital. Complaints of nausea, vomiting, fever, defecation, and urination were denied.

Physical examination on the 1st day of treatment (20 April 2023) in the ICU showed that the patient appeared to be moderately ill but alert and oriented, with vital signs within normal limits (blood pressure 105/90 mmHg, mean arterial pressure (MAP) ranging from 65 to 110 mmHg), respiratory frequency of more than 24 times per minute, pulse frequency 100 beats per minute), height 159 cm, weight 54kg with a body mass index (BMI): 21.42 kg/m2 (normoweight). On the local status examination, the stomach was not distended, bowel sounds were normal, and a nasogastric tube (NGT) was installed with a green product and a stoma. The patient's fluid balance is 250 ml/2 hours with a dwelling catheter (DC) and a deep yellow impression.

A complete blood test on 20 April 2023 can be seen in Table 1 which shows a decrease in hemoglobin values and an

increase in leukocytes. Preoperative and post-operative chest radiology examination showed differences (Figure 1), namely left unilateral pneumonia and inhomogeneous opacity with clear borders, partially irregular edges in the paravertebral projecting at the level of the corpus of thoracal vertebrae 1-4 on bilateral sides, suspecting a pathological process in the mediastinal organs.

Based on the history, physical, and supporting examination, the patient was assessed for sepsis and post-laparotomy exploration for indications of generalized peritonitis et causa hollow viscus perforation.

The patient was managed by an intensivist with triple antibiotics (ampicillin sulbactam IV 1.5 g per 8 hours, gentamicin IV 80 mg per 12 hours, and metronidazole IV 500 mg per 8 hours), fluid resuscitation (dextrose 5% 1/4 normal saline 60 cc/hour), antipyretic (paracetamol IV 1 gr per 8 hours), gastroprotective agent (omeprazole IV 40 mg per 12 hours) and vasopressor with norepinephrine 0.05 mcg/kg/hour at a rate of 1.5 cc/hour. Therapeutic targets for patients are airway safety, normoxia (SpO2 94-97%), normotension MAP 70-100 mmHg), normocardia (heart rate 70-90 bpm), and normocapnia (respiratory rate 14-16 brpm).

On the 2nd day of treatment in the ICU (21 April 2023), the patient showed a trend of worsening condition with a black NGT product and serial supporting examinations which showed anemia due to chronic disease, relative leukocytosis and hypoalbuminemia. The patient was planned for treatment in the high care unit (HCU). The patient was given additional treatment, namely tranexamic acid IV 1000 mg per 8 hours, albumin 25% 50 cc, and dose adjustment of the vasopressor norepinephrine 0.1 mcg/kg/minute. The patient was treated in the HCU unit until the 5th day of treatment (24 April 2023) and it was decided to transfer to the ICU unit based on consideration of the patient's condition.

On the 8th day of treatment in the ICU (26 April 2023), the patient complained of edema and redness in the upper extremities. The patient admitted that his left thumb had turned black 1 week after surgery. The patient has a history of hypertension but does not regularly take medication. The patient is suspected of a history of heart disease, diabetes mellitus, stroke, and smoking habits. A localized physical examination revealed bullae and necrosis on the left thumb. The patient was consulted by the Vascular Surgery and Cardiology Departments. The patient was assessed as suspected partial stenosis of the distal 1/3 of the radial and ulnar (S) Rutherford 5 Fontaine IV arteries. Therapies from Vascular Surgery are vascular repair and somatostatin every 24 hours, while the Cardiology prescribed ramipril 2.5 mg per 24 hours, carvedilol 3.25 mg per 12 hours, atorvastatin 40 mg per 24 hours, and clopidogrel 75 mg per 24 hours after vascular repair by the Thoracic and Cardiovascular Surgery Department. The patient was planned for further examination, namely computed tomography (CT) angiography and doppler ultrasound (DUS) of the superior extremities.

On the 9th day of treatment in the ICU (27 April 2023). Generalist status examination was within normal limits (normal vital signs, brown NGT product, yellowish stoma drain, and fluid balance >0.5 mg/kg/hour). Supporting examinations showed improvements in

hemoglobin, leukocyte, and albumin values but procalcitonin values were still elevated. Local status examination showed a bluish appearance from the thumb to the left wrist with tenderness and oxygen saturation in digit I was 0% (Figure 2). Patients with suspected peripheral arterial disease on the left upper extremity are planned for CT angiography and delayed heparinization.

CT angiography examination on May 2, 2023, showed partial stenosis in the distal 1/3 of left radial and ulnar vessels, decreased bone trabeculation in the left hand region accompanied by subcutaneous edema and soft tissue pneumatization in the distal the hand region to the left wrist joint leading to osteomyelitis, multiple lymphadenopathy in the left axillary region, and incidental finding, namely bilateral pneumonia.

Doppler ultrasound (DUS) examination of the left superior extremity (axillary artery, brachial artery, radial artery, and ulnar artery) showed partial stenosis in the distal 1/3 of the a. radial and ulnar.

On the 20th day of treatment (08 May 2023) in the ICU the patient admitted that he had no complaints after necrotomy indicating partial stenosis of the distal 1/3 of the radial and ulnar arteries. The patient was transferred from inpatient care to the usual ward and can be decided to be outpatient on the 21st treatment day (09 May 2023) with discharge medication, namely N-acetylcysteine (NAC) 200 mg per 8 hours, folic acid per 24 hours, prorenal per 8 hours, ciprofloxacin per 12 hours and metronidazole every 8 hours. The patient was asked for follow-up control at the Vascular Surgery and Internal Medicine RSUD Dr. Moewardi.

Table 1. Laboratory examinations

Parameters	19/04/23	20/04/23	22/04/23	23/04/23	27/04/23	05/05/23
Hemoglobin	10.5*	10.5*	6.2*	5.6*	10.9*	10.0
Hematocryt	27	28*	17*	16*	33*	29
Leukocyte	11.5*	17.6*	16.9*	21.8*	14.6*	11.8
Thrombocyte	408.000	391.000	244.000	144.000*	180.000	325.00
Erythrocyte	3.52	3.54	2.10*	1.95*	3.73*	3.12
PT	15.0 s					
aPTT	32.5 s					
INR	1.150					
Random blood glucose	59 mg/dl					
Ureum	141					
Creatinine	1.7					
Albumin	3.4	2.7*	2.4*	2.1*	2.8*	
Natrium	139	139	149*		154*	150
Potassium	3.4	3.5	3.7		4.0	4.0
Calcium	1.27	1.11	1.19		114*	1.23
HbsAg	Nonreaktif					
Procalcitonin					1.76*	1.3

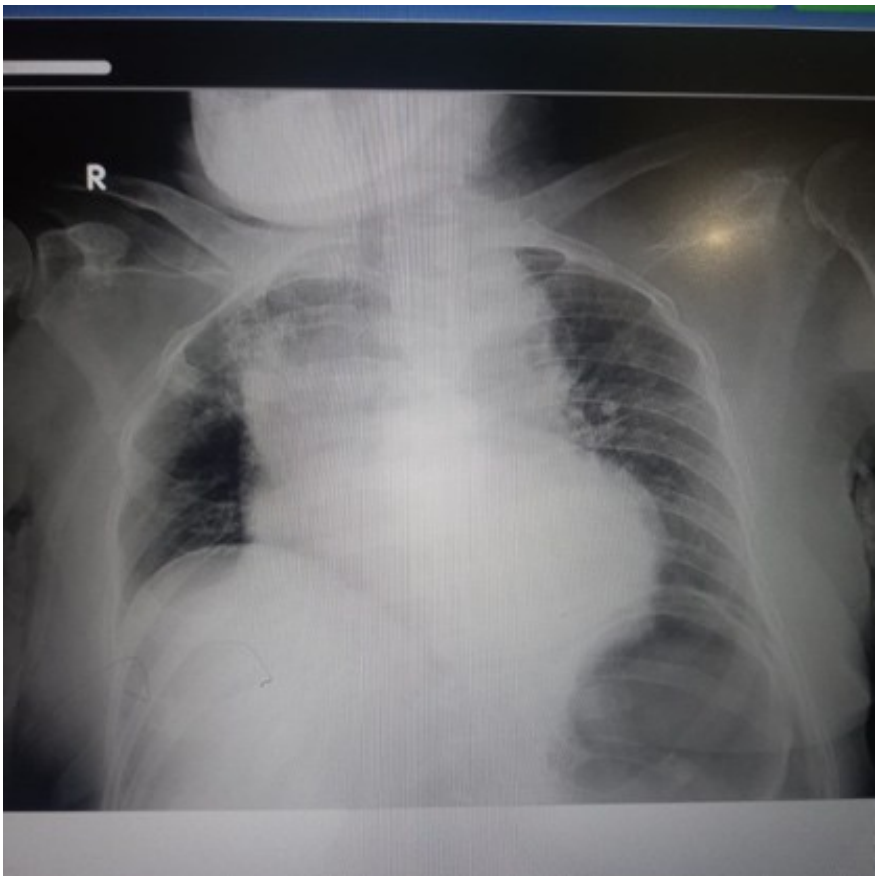

Figure 1. Chest x-ray of the patient

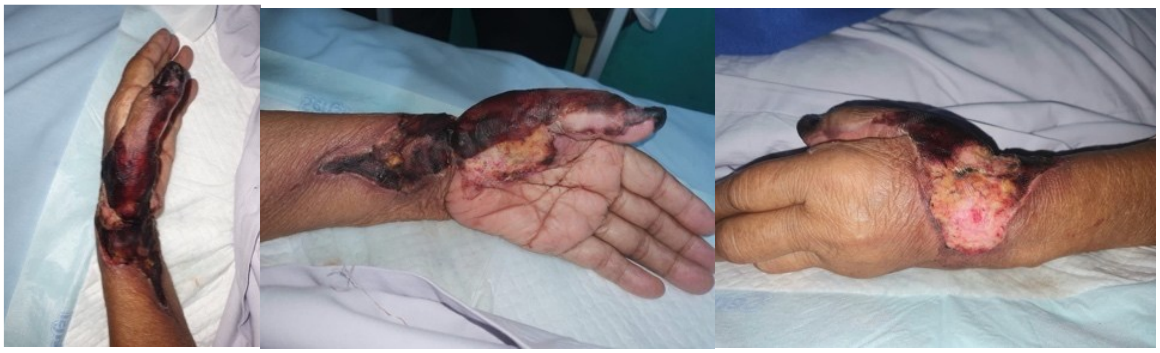

Figure 2. Local status of the left upper extremity

DISCUSSION

Thrombosis and inflammation are distinct yet intimately linked physiological processes. Inflammation-driven activation of the coagulation system is a component of the body's defense mechanism against pathogens, designed to restrict their systemic distribution in the bloodstream. This process, known as immunothrombosis, is facilitated through interactions between innate immune cells and platelets, leading to the activation of the coagulation system. Through this study, we reported a case of thrombosis due to sepsis in patients requiring intensive care support.

The occurrence of thrombotic events in ICU patients remains unclear. Research by Bleck et al., reported the occurrence of thrombosis in the form of stroke reaching 2.7% among 1,758 critically ill patients. The study by Wijdicks et al reported 0.7% of hemorrhagic stroke patients among 2,555 ICU patients.[8] Ischemic stroke, acute coronary syndrome, and venous thromboembolism are the most frequently observed events whereas peripheral arterial occlusion and arterial thromboembolism are much less common.

Individuals with thrombosis were typically older, had a history of hypertension, and presented with higher baseline APACHE II scores.[9,10] In this case, we report a 60-year-old female with a history of hypertension who was treated in the ICU for indications of postoperative sepsis who showed thrombosis 7 days after hospitalization.

Endotheliopathy-associated microthrombosis is central to the clinical phenotype of advanced sepsis. A key feature of severe sepsis is microvascular dysfunction caused by widespread microthrombi, which are primarily composed of platelets. Ultralarge multimers of von willebrand factor (ULVWF) complexes are present in multiple organs and are enhanced by microthrombogenesis. This pathophysiological mechanism, known as vascular microthrombosis (VMTD), induces circulatory dysfunction that leads to organ ischemia.[11]

In sepsis, unexplained thrombocytopenia is a crucial early indicator of endotheliopathy, with on going microthrombogenesis leading to consumptive thrombocytopenia. Often, thrombocytopenia in critically ill patients is mistakenly attributed to heparin, but the term “thrombocytopenia in critically ill patients” (TCIP) is used for cases where known causes have been excluded (heparin-induced, drug-related, transfusion-related, DIC, bone marrow suppression, hypersplenism, autoimmune, and others). The significance of mild to moderate TCIP in the early stages of sepsis is frequently overlooked due to the lack of clear understanding and the rarity of hemorrhagic syndrome. However, TCIP has been identified as a common and predictable hematologic feature in sepsis-associated coagulopathy, resulting from consumptive thrombocytopenia through an activated ULVWF pathway. In critical care, there is a notable correlation between the onset, duration, and severity of thrombocytopenia and the overall severity and outcome of critical illness. These findings highlight that TCIP is an important hematological phenotype and plays a significant role in the endothelial pathogenesis of sepsis.[13]

According to the International Society on Thrombosis and Haemostasis (ISTH) DIC subcommittee on disseminated intravascular coagulation (SSC) criteria, the presence of increased fibrin degradation products (FDP) or D-dimer levels, decreased platelet count, prolonged prothrombin time (PT), and reduced fibrinogen levels are indicative of DIC. Additionally, other scoring systems for DIC include the Japanese Association of Acute Medicine (JAAM) DIC diagnostic criteria, which also assess platelet count, FDP concentration, PT, and systemic inflammation.[14] There are several other examinations of markers of systemic inflammatory response.

The thrombin-antithrombin complex (TAT) serves as a marker of thrombin generation and is beneficial to identify patients with DIC, as excessive thrombin generation is a hallmark of this process. Elevated TAT levels have been observed in patients with DIC at admission or in those who subsequently develop DIC, compared to patients without DIC. Increased TAT levels are also associated with higher mortality in sepsis patients. Combining TAT with other biomarkers has been shown to offer greater prognostic value than using TAT alone.[1]

Although fibrinolysis is often impaired in sepsis-induced DIC, this dysfunction is not readily detectable using standard coagulation parameters. The antifibrinolytic protein PAI-1 has been extensively investigated as a potential marker for hypofibrinolysis in septic patients with DIC. Elevated PAI-1 levels can help distungish patients with DIC and predict its development. Like TAT, combining PAI-1 with other biomarkers enhances its prognostic accuracy. High levels of PAI-1 are correlated to a higher risk of of death.[1]

Endogenous thrombin potential—a test that indicates thrombin formation—is evaluated in sepsis. The results regarding biomarkers in sepsis are still conflicting, and further research is required. However, recent evidence indicates a relationship between the increased severity of infection and a decreased ability to generate thrombin. These biomarkers could be valuable in predicting the development of multiorgan dysfunction and poor outcomes in sepsis patients.[1]

Prothrombin fragment 1.2 (F1.2) is an activating peptide generated during the conversion of prothrombin to thrombin. It is used as a marker of thrombin generation and is included in the DIC criteria of the Japanese Society on Thrombosis and Hemostasis (JSTH).[1]

ADAMTS-13 is a protease that regulates the size of von Willebrand factor multimers. By cleaving these multimers, ADAMTS-13 reduces their prothrombotic properties, as larger von Willebrand factor molecules enhance hemostatic competence. A deficiency in ADAMTS-13 leads to the accumulation of ultra-large von Willebrand factor multimers, contributing to thrombotic microangiopathy in sepsis. This deficiency is associated with increased severity of sepsis and poor prognosis.[1,13]

In this case, the patient was diagnosed with sepsis based on clinical and supporting examinations (increased leukocytes, decreased platelets, and findings of bilateral pneumonia). Meanwhile, thrombosis has manifestations in the form of peripheral arterial disease which is confirmed through CT angiography and DUS examination of the extremities.

Currently, no specific therapy is established for sepsis-induced coagulopathy (SIC). The International Surviving Sepsis Campaign guidelines for managing sepsis and septic shock strongly recommend pharmacological thromboprophylaxis with low molecular weight heparin for patients with sepsis or septic shock. The most updated Surviving Sepsis Japan Campaign guidelines from 2020 advise early diagnosis of DIC and strongly discourage the use of anticoagulants for sepsis-associated DIC. Various treatment strategies for SIC have been evaluated, primarily focusing on suppressing prothrombotic effects. These strategies include the administration of heparin/heparinoids or anticoagulant proteins.[2,4] In this case, the patient was given antithrombosis, clopidogrel 75 mg per 24 hours, resuscitation therapy, triple antibiotics, and vasopressors.

Monitoring coagulation biomarkers, such as D-dimer and other indicators, and tracking the progression from SIC to overt DIC, should significantly influence the management of sepsis. SIC is evaluated using routine, cost-effective laboratory tests, which are crucial for assessing disease progression. Studies have shown that detecting and monitoring coagulation abnormalities can help predict adverse outcomes in sepsis. Patients with severe sepsis and DIC have a 20% lower survival rate compared to those without DIC, with SIC-associated mortality around 30% and overt DIC mortality nearing 40%. Using the SIC scoring system for DIC screening is an effective method to ensure that DIC is not missed. Additionally, SIC screening can help identify patients with sepsis who may benefit from targeted therapies.[14,15] In our case we reported a patient with good clinical outcomes after 20 days of treatment in the ICU and was planned for outpatient follow-up.

CONCLUSION

The endothelial pathogenesis of sepsis and septic shock is driven by the activated ultralarge von Willebrand factor (ULVWF) pathway. In sepsis, complement activation induces an endotheliopathy that initiates two separate molecular events: the activation of the inflammatory pathway and the microthrombotic pathway. This leads to inflammation-associated endotheliopathy and Endotheliopathy-Associated Vascular Microthrombotic Disease (EA-VMTD). In the big picture, the physiological protective immune system defends the host and removes invading pathogens. However, when this protective system is compromised and antibiotics are not fully effective, the pathological destructive endothelial system can cause harm to the host. A deeper understanding of sepsis-associated coagulopathy (microthrombopathy) could lead to the development of effective treatments targeting the microthrombotic pathway of endothelial pathogenesis.

REFERENCES

1. Tsantes AG, Parastatidou S, Tsantes EA, Bonova E, Tsante KA, Mantzios PG, et al. Sepsis-Induced Coagulopathy: An Update on Pathophysiology, Biomarkers, and Current Guidelines. Vol. 13, Life. MDPI; 2023.
2. Matevosyan K, Sarode R. Thrombosis, Microangiopathies, and Inflammation. Semin Thromb Hemost. 2015 Aug 15;41(6):556–62.

3. Nowroozpoor A, Bank MA, Jafari D. Limb Ischemia due to Extensive Arterial Thrombosis in the Absence of Venous Occlusion as an Unusual Complication of Critical Illness from COVID-19. Case Reports in Acute Medicine. 2021 Mar 19;4(1):23–31.
4. Olinic DM, Stanek A, T A Taru DA, Homorodean C, Olinic M. Acute limb ischemia: An update on diagnosis and management. Vol. 8, Journal of Clinical Medicine. MDPI; 2019.
5. Iba T, Arakawa M, Di Nisio M, Gando S, Anan H, Sato K, et al. Newly Proposed Sepsis-Induced Coagulopathy Precedes International Society on Thrombosis and Haemostasis Overt-Disseminated Intravascular Coagulation and Predicts High Mortality. J Intensive Care Med. 2020 Jul 1;35(7):643–9.
6. Iba T, Levi M, Thachil J, Helms J, Scarlatescu E, Levy JH. Communication from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis on sepsis-induced coagulopathy in the management of sepsis. Journal of Thrombosis and Haemostasis. 2023 Jan 1;21(1):145–53.
7. Simmons J, Pittet JF. The coagulopathy of acute sepsis. Vol. 28, Current Opinion in Anaesthesiology. Lippincott Williams and Wilkins; 2015. p. 227–36.
8. Tsantes AG, Parastatidou S, Tsantes EA, Bonova E, Tsante KA, Mantzios PG, et al. Sepsis-Induced Coagulopathy: An Update on Pathophysiology, Biomarkers, and Current Guidelines. Vol. 13, Life. MDPI; 2023.
9. Donzé JD, Ridker PM, Finlayson SRG, Bates DW. Impact of sepsis on risk of postoperative arterial and venous thromboses: Large Prospective cohort study. BMJ (Online). 2014;349.
10. Levine RL, LeClerc JR, Bailey JE, Monberg MJ, Sarwat S. Venous and arterial thromboembolism in severe sepsis. Thromb Haemost. 2008 May;99(5):892–8.
11. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. Vol. 18, Nature Reviews Cardiology. Nature Research; 2021. p. 666–82.
12. Chang JC. Sepsis and septic shock: Endothelial molecular pathogenesis associated with vascular microthrombotic disease. Vol. 17, Thrombosis Journal. BioMed Central Ltd.; 2019.
13. Levi M, Scully M, Singer M. The role of ADAMTS-13 in the coagulopathy of sepsis. Vol. 16, Journal of Thrombosis and Haemostasis. Blackwell Publishing Ltd; 2018. p. 646–51.
14. Iba T, Levy JH, Raj A, Warkentin TE. Advance in the management of sepsis-induced coagulopathy and disseminated intravascular coagulation. Vol. 8, Journal of Clinical Medicine. MDPI; 2019.
15. Takeshita K, Izumisato T, Takane T, Nishihara K. A case of disseminated intravascular coagulation of sepsis that caused extreme-thrombocytopenia treated at a remote-island-hospital. J Gen Fam Med. 2023 Jan 1;24(1):50–3.