Case Report

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Antithrombin-III for New Coronavirus Infection (COVID-19) Under Conditions of Extracorporeal Membrane Oxygenation (Clinical Observation)

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SUMMARY COVID-19 is a disease that, in addition to respiratory failure, leads to thrombosis and bleeding due to coagulation disorders. Extracorporeal membrane oxygenation (ECMO), required in cases of a deterioration of gas exchange function of the lungs, contributes to changes in blood coagulation indicators, which leads to an increased risk of hemorrhagic complications and thrombosis. In the article, a clinical case of a severe course of COVID-19 is reported, which required ECMO. During the treatment, antithrombin-III was used, which allowed avoiding life-threatening complications and successfully completing the procedure.

Keywords: COVID-19, SARS-COV-2, ECMO, thrombosis, bleeding, antithrombin, heparin, anticoagulant therapy

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ACT - activated clotting time
ALV - artificial lung ventilation
ARDS - acute respiratory distress syndrome
APTT - activated partial thromboplastin time
AT-III - antithrombin-III
CT - computed tomography
ECMO - extracorporeal membrane oxygenation
ELWI - extravascular lung water index
GEF - global exile faction
Ig - immunoglobulins
INR - international normalized ratio
RRT - renal replacement therapy
PT - prothrombin time
PCCI - continuous cardiac output index
PCR - polymerase chain reaction
PEEP - positive end-expiratory pressure
PICCO - cardiac output, determined by the shape of the pulse wave
SVRI - systemic vascular resistance index
SVV - stroke volume variability
VVECMO - veno-venous extracorporeal membrane oxygenation

The new coronavirus infection (*SARS-CoV*-2) has forced us to rethink the treatment of acute respiratory distress syndrome (ARDS) in many ways. One of the characteristic features of the course *of SARS-CoV*-2 is a high risk of thrombosis, which greatly complicates the use of extracorporeal support methods, in particular, extracorporeal membrane oxygenation (ECMO) [1], the technique that has no alternative in critical patients [2] . Unfortunately, when using ECMO in these patients, mortality exceeded 50% [3, 4], and thrombosis and bleeding were among the reasons contributing to an unfavorable outcome [5, 6]. Etiologically, thrombosis in these conditions may be closely associated with the development of multisystem inflammatory syndrome in patients with *COVID* -19 [7].

Patients in intensive care units with severe cases *of COVID*-19 often require extracorporeal therapies such as ECMO and renal replacement therapy (RRT) to compensate for partially or completely lost organ functions [8–10]. The use of ECMO and RRT, however, leads to excessive stimulation of the coagulation systems due to blood contact with various non-physiological surfaces and, as a result, thrombosis of the vascular bed or components of extracorporeal circuits [11], which can lead to the cessation of these auxiliary systems. In this regard, adequate anticoagulant therapy is required during such procedures, usually with unfractionated heparin [12, 13]. Moreover, the increased propensity for thrombosis, combined with an excessive systemic inflammatory response observed in patients with *COVID* -19, in view of the above, leads to the conclusion that more intensive anticoagulant therapy is needed [14, 15].

Monitoring the adequacy of heparinization is a key element in maintaining the delicate balance between bleeding and thrombosis. Activated partial thromboplastin time (APTT) reflects the state of the internal coagulation pathway and is taken into account most often [16, 17]. Parameters such as activated clotting time and activity of Antithrombin-III (AT-III) are also subject to measurement [17].

If it is necessary to use more than 35 000 IU of unfractionated heparin within 24 hours to achieve the target level of APTT, the development of heparin resistance due to AT-III deficiency can be assumed [18]. AT-III-independent forms of heparin resistance (the so-called "obvious" or "pseudo" forms) can also be caused by high concentrations of coagulation factor VIII, fibrinogen or platelets [19–21]

The control of AT-III activity during ongoing heparin infusion in ECMO is still a matter of debate. The optimal concentration of circulating AT-III remains unknown. Despite this, the use of recombinant antithrombin or antithrombin concentrate during ECMO is becoming increasingly common [22,23].

The aim of the clinical observation is to describe the experience of using AT-III during a long-term ECMO procedure in a patient with *SARS-CoV* -2-associated pneumonia and concomitant bacterial infection.

A 46-year-old patient was transferred to N.V. Sklifosovsky Institute from another hospital on Jan 16, 2021 on the 25th day from the onset of the disease with a diagnosis of: "Coronavirus infection caused by the *COVID-19 virus*, community-acquired polysegmental pneumonia, acute respiratory failure of the hypoxic type." Resection of the upper lobe of the left lung in history.

Upon admission to the hospital, the patient's condition was regarded as extremely serious, due to severe respiratory failure against the background of progressive pneumonia, which could not be compensated by artificial lung ventilation (ALV) in the *A/C mode (IPPV)* with a controlled volume, oxygen fraction in the inhaled

gas mixture (FiO_2), equal to 100%, positive end-expiratory pressure (PEEP) 10 cm of water column, low blood oxygen saturation - SpO_2 was 88%, intoxication and developing multiple organ failure.

On the day of admission, computed tomography (CT) was performed, which revealed CT signs of severe infiltrative-inflammatory changes in both lungs (CT-3, right lung — 50–75%, left lung — 25–50%), bilateral hydrothorax and unexpressed intrathoracic lymphadenopathy.

Tracheobronchoscopy revealed erosive mucopurulent tracheobronchitis with hemorrhagic component.

At the same time, a study was performed for antibodies to *SARS-CoV*-2: the content of *IgM* was 01.78, and *IgG* - 387.91, and a polymerase chain reaction (PCR) study was performed: ribonucleic acid (RNA) *SARS-CoV*- 2 was detected.

According to the results of ultrasound examination: echocardiographic (EchoCG) signs of thrombosis in the visualized veins of the lower extremities were not detected, echo signs of occlusive thrombosis of the saphenous veins of both upper extremities were found.

In the period from Jan 17, 2021 to Jan 23, 2021, the patient's condition was characterized as extremely severe, without significant dynamics. In accordance with the results of laboratory tests, antibiotic therapy was adjusted. Medical sedation was discontinued, the patient was clearly conscious.

On Jan 24, 2021, a negative trend was noted — an increase in respiratory acidosis and a significant decrease in SpO_2. The level of consciousness was a superficial stunning. Decompensation of respiratory failure was an indication for veno-venous (VV) peripheral ECMO (in accordance with the interim guidelines of the Ministry of Health of the Russian Federation "Prevention, diagnosis and treatment of a new coronavirus infection (*COVID* - 19)" dated 10/26/2020: decrease in the PaO index$_2$/FiO_2 below 80 mm Hg and (or) hypercapnia with pH less than 7.2, despite protective ventilation in the prone position for 10-12 hours, with PaO_2 45 mm Hg, $PaCO_2$ 115 mm Hg, FiO_2 100%, pH 7.15 PEEP 10 mm Hg, tidal volume (TV) 300 ml and SpO_2 75%).

Cannulation was performed through the femoral vein on the right and the jugular vein on the right with cannulas 24 *Fr* and 18 *Fr*, respectively. At the beginning of the ECMO procedure, the following support parameters were set: 4 l/min of the volumetric blood flow rate and 7 l/min of the flow of 100% oxygen to the oxygenator. Laboratory indicators of the gas composition of arterial blood were determined at the level: pO_2 64 mm Hg, $paCO_2$ 37 mm Hg, SpO_2 - 95% with an ECMO recirculation fraction of less than 15%.

PICCO monitoring was initiated: PCCI 4.5, SVV 8%, ELWI 14, SVRI 1500, GEF 28%. Hemodynamics was stable, without vasotropic support. Consciousness was clear. RRT, respiratory support, VV ECMO, dynamic monitoring with symptomatic therapy, procedures for the prevention of thromboembolic and infectious complications, as well as antibiotic therapy were carried out.

In the period from Jan 26, 2021 to Jan 30, 2021, the patient's condition remained stable.

On Jan 31, 2021, there was a need for a progressive increase in FiO_2 on a ventilator, while during a routine preventive examination of the ECMO circuit, a dysfunction of the oxygenator membrane was observed due to its thrombosis, after which the set was replaced.

From Feb 1, 2021, the patient's condition was assessed as extremely serious and stable. The degree of respiratory support progressively decreased in accordance with the patient's capabilities, anticoagulant therapy with sodium heparin, antibacterial and symptomatic therapy, and gradual activation of the patient were performed.

On Feb 8, 2021, there was a need to increase heparinization, accompanied by an increase in the volume of the hemorrhagic component in the discharge from the respiratory tract during sanitation. According to the results of laboratory data, the level of activity of AT-III was 67%. When calculating according to the formula: Required dose (ME) of AT-III = body weight (kg) × (target level - initial level of activity [%]) × 0.5. AT-III was prescribed in the amount of 1 000 IU.

In the period from Feb 9, 2021. As of Feb 13, 2021, the trend towards an increase in the volume of spontaneous breathing continued with a decrease in the parameters of respiratory support both on mechanical ventilation and on ECMO. On Feb 14, 2021, training was started with a short-term shutdown of the gas supply to the oxygenator, which the patient tolerated mainly without clinically significant changes, until Feb 22, 2021, an increase in $PaCO_2$ was observed up to 85 mm Hg, which did not affect the clinical picture. The activation on the bed was initiated, sessions of physiotherapy exercises were performed.

On Feb 22, 2021, after a successful preliminary shutdown of the gas supply to the oxygenator for more than 24 hours, a decision was made to terminate ECMO (table).

Table

Dynamics of coagulation indices and dosages of sodium heparin

Indicator	Reference - values	Date/day of ECMO														
		24.01/1	25.01/2	26.01/3	27.01/4	28.01/5	01/29/6	30.01/7	31.01/8	01.02/9	02.02/10	03.02/11	04.02/12	05.02/13	06.02/14	07.02/15
		Day of disease														
		32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
APTT, sec	25.4–38.4	60.6	159.9	53.4	38	29.6	44.6	29.3	44	50	37.1	42.6	33.3	39.9	34.9	35.0
Prothrombin, %	70–130	62.5	53	77	87	57.6	100	97	68.7	100	83	73	61		91	
INR	0.80–1.20	1.32	1.62	1.20	1.11	1.60	1.00	1.02	1.23	1.00	1.14	1.25	1.44		1.07	
PT, sec	9–13		19	14	13		12	12		12	13	15	17		13	
Fibrinogen, g/l	2.0–3.93	2.75	2.83	3.10	2.67	2.15	3.01	2.52	1.82	3.68	4.42	3.77	4.36		4.08	
AT-III,%	75–125															
Heparin, IU/hour		1200	1100	600	750	1000	2500	700	800	800	1000	1500	1500	1000	750	750

Indicator	Reference - values	Date/day of ECMO														
		08.02/16	09.02/17	10.02/18	11.02/19	12.02/20	02/13/21	14.02/22	02/15/23	16.02/24	02/17/25	18.02/26	02/19/27	02/20/28	02/21/29	02/22/30
		Day of disease														
		47	48	49	50	51	52	53	54	55	56	57	58	59	60	61
APTT, sec	25.4–38.4	41.6	29.9	30.3	30.0	40.0	47.7	39.9	35.3	36.6	31.0	113	33.3	34.4	44.5	56.5
Prothrombin, %	70–130	101	72.9	88	95	93	79	68.1	89	72.3	66.4	44	65.0	77	70.4	44
INR	0.80–1.20	0.99	1.31	1.10	1.04	1.05	1.19	1.38	1.09	1.32	1.42	1.55	1.23	1.13	1.34	1.55
PT, sec	9–13	12		13	12	12	14		13			18	14	13		18
Fibrinogen, g/l	2.0–3.93	3.21	1.98	1.88	2.44	2.16	2.65	1.23	1.45	1.89	1.50	1.45	1.49	1.42	1.99	1.55
AT-III,%	75–125	67		74					68			65				82
Heparin, IU/hour	-	1600	900	1500	1500	1500	1050	900	1400	1750	1000	1500	900	1000	900	900

Notes: APTT — activated partial thromboplastin time; INR - international normalized ratio; PT, prothrombin time; AT-III - antithrombin-III

The patient was successfully weaned off ECMO on the 30th day of the procedure. During the observation period, a relation was noted between episodes of coagulation disorders and a decrease in the level of AT-III in the blood, which complications were avoided by timely replenishment of its deficiency (figure).

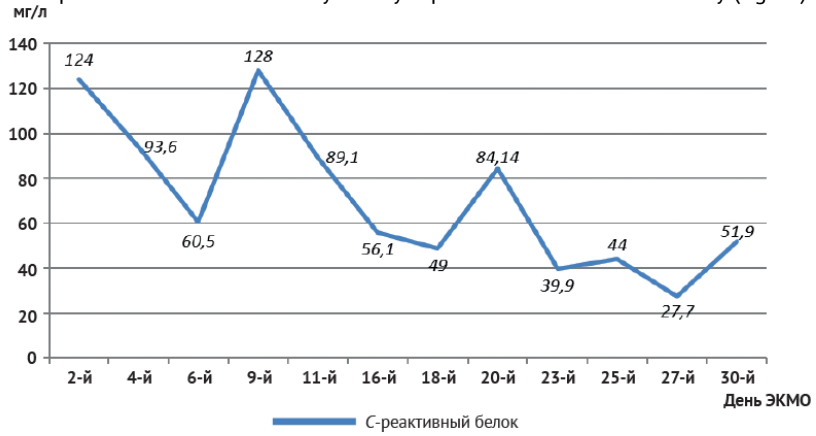

Figure. Dynamics of an inflammatory response marker during extracorporeal membrane oxygenation (ECMO)

DISCUSSION

In this case, it should be noted that the severity of clinical manifestations of coagulopathic disorders remained clear throughout the entire period of ECMO use, in particular, episodes of bleeding from the respiratory tract that were well visualized at the patient's bedside in case of erosive purulent-hemorrhagic tracheobronchitis, as well as well-traced dynamics of extracorporeal thrombosis contour, expressed in a decrease in the function of the oxygenator. Prior to the use of AT-III, thrombosis of the extracorporeal circuit in the absence of clear predictors, maintaining a sufficiently high volumetric blood flow velocity along the circuit, existing heparin coverage in a relatively recent ECMO setting, and difficulty in finding a balanced dosage of sodium heparin due to active coagulation disorders associated with severe systemic inflammatory response in *SARS-COV*-2, prompted the search for an additional method of monitoring the blood coagulation system in order to prevent critical disorders. Attention is drawn to the fact that already on the 8th day thrombosis of the circuit occurred, suggesting its immediate replacement, while the previous routine practice of using IV-V ECMO allowed the use of an oxygenator for a much longer period [24]. Setting high values of assisted perfusion parameters at the start of ECMO was due to the need to correct clinically significant respiratory acidosis [25], since the use of extracorporeal circulation circuits, as a rule, leads to a decrease in the level of blood plasma proteins responsible for coagulation, such as AT-III, fibrinogen and von Willebrand factor [26]. Considering that the new coronavirus disease is associated with an increased risk of thrombosis [27] and requires anticoagulant therapy even without the use of the aforementioned circuits, the issue of maintaining coagulation balance is particularly acute. The effectiveness of sodium heparin directly depends on the level of antithrombin, and a hyperinflammatory systemic response leads to its decrease, due to which anticoagulant therapy may lose its properties in the development of heparin resistance [28]. According to the mechanism of action of AT-III, its use leads to a decrease in the need for excessive heparinization, which in our case corresponded to the expected effect and made it possible to avoid significant hemorrhagic complications with a safe amount of anticoagulant therapy in terms of the risk of thrombosis.

CONCLUSIONS

1. Successful weaning of a patient with a critical course of COVID-19 from extracorporeal membrane oxygenation is an extremely difficult task and requires the use of all modern technologies of modern resuscitation.

2. Control and correction of the state of hemostasis is one of the important tasks in long-term extracorporeal membrane oxygenation.

3. The use of Antithrombin-III (as a result of a decrease in its level in the blood) makes it possible to provide optimal conditions for the long-term operation of the extracorporeal membrane oxygenation system.

REFERENCES

1. Zhuravel SV, Evseev AK, Kolokoltsev AD, Kuznetsova NK, Utkina II, Petrikov SS. Historical Development and Prospects of Extracorporeal Membrane Oxygenation in Clinical Practice. *Vysokotekhnologichnaya meditsina* . 2020;7(1):51–58. (in Russian)
2. Brygin PA, Zhuravel SV, Troitskiy DA, Utkina II. Predictors of extracorporeal membrane oxygenation efficacy in patients with acute respiratory failure. *Transplantology. The Russian Journal of Transplantation* . 2020;12(3):220–230. (in Russ.). https://doi.org/10.23873/2074-0506-2020-12-3-220-230
3. Bartlett RH, Ogino MT, Brodie D, McMullan DM, Lorusso R, MacLaren G, et al. Initial ELSO Guidance Document: ECMO for COVID-19 Patients with Severe Cardiopulmonary Failure. *ASAIO J.* 2020;66(5):472–474. PMID: 32243267 https://doi.org/10.1097/MAT.0000000000001173
4. Badulak J, Antonini MV, Stead CM, Shekerdemian L, Raman L, Paden ML, ECMO for COVID-19: Updated 2021 Guidelines from the Extracorporeal Life Support Organization (ELSO). *ASAIO* J. 2021 Feb 26. PMID: 33657573 https://doi.org/10.1097/MAT.0000000000001422. Online ahead of print.
5. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* . 2020;191:145–147. PMID: 32291094 https://doi.org/10.1016/j.thromres.2020.04.013
6. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood* . 2020;136(4):489–500. PMID: 32492712 https://doi.org/10.1182/blood.2020006520
7. Chang J.C. Thrombocytopenia in critically ill patients due to vascular microthrombotic disease: Pathogenesis based on "two activation theory of the endothelium". *Vascul Dis Ther* . 2017;2(5):1–7. https://doi.org/10.15761/VDT.1000132
8. Pravda NS, Pravda MS, Kornowski R, Orvin K. Extracorporeal membrane oxygenation therapy in the COVID-19 pandemic. *Future Cardiol* . 2020;16(6):543–546. PMID: 32301347 https://doi.org/10.2217/fca-2020-0040
9. Smereka J, Puslecki M, Ruetzler K, Filipiak KJ, Jaguszewski M, Ladny JR, et al. Extracorporeal membrane oxygenation in COVID-19. *Cardiol J.* 2020;27(2):216–217. PMID: 32285929 https://doi.org/10.5603/CJ.a2020.0053
10. Jacobs JP, Stammers AH, St Louis J, Hayanga JWA, Firstenberg MS, Mongero LB, et al. Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in Coronavirus Disease 2019: Experience with 32 Patients. *ASAIO J.* 2020;66(7):722–730. PMID: 32317557 https://doi.org/10.1097/MAT.0000000000001185
11. Ziats NP, Pankowsky DA, Tierney BP, Ratnoff OD, Anderson JM. Adsorption of Hageman factor (factor XII) and other human plasma proteins to biomedical polymers. *J Lab Clin Med.* 1990;116(5):687–696. PMID: 2146350
12. Despotis GJ, Avidan MS, Hogue CW Jr. Mechanisms and attenuation of hemostatic activation during extracorporeal circulation. *Ann Thorac Surg* . 2001;72(5):S1821–1831. PMID: 11722116 https://doi.org/10.1016/s0003-4975(01)03211-8
13. Tsujimoto H, Tsujimoto Y, Nakata Y, Fujii T, Takahashi S, Akazawa M, et al. Pharmacological interventions for preventing clotting of extracorporeal circuits during continuous renal replacement therapy. *Cochrane Database Syst Rev* . 2020; 3(3):CD012467. PMID: 32164041 https://doi.org/10.1002/14651858.CD012467.pub2
14. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost* . 2020;18(7):1559–1561. PMID: 32302453 https://doi.org/10.1111/jth.14849
15. Ranucci M, Ballotta A, Di Dedda U, Bayshnikova E, Dei Poli M, Resta M, et al. The procoagulant pattern of patients with COVID-19 acute respiratory distress syndrome. *J Thromb Haemost* . 2020;18(7):1747–1751. PMID: 32302448 https://doi.org/10.1111/jth.14854
16. Mulder M, Fawzy I, Lance M. ECMO and anticoagulation: a comprehensive review. *Neth J Crit Care* . 2018;26(1):6–13.
17. Protti A, Iapichino GE, Di Nardo M, Panigada M, Gattinoni L. Anticoagulation Management and Antithrombin Supplementation Practice during Veno-venous Extracorporeal Membrane Oxygenation: A Worldwide Survey. *Anesthesiology* . 2020;132(3):562–570. PMID: 31764152 https://doi.org/10.1097/ALN.0000000000003044
18. Levine MN, Hirsh J, Gent M, Turpie AG, Cruickshank M, Weitz J, et al. A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med* . 1994;154(1):49–56. PMID: 8267489
19. Thota R, Ganti AK, Subbiah S. Apparent heparin resistance in a patient with infective endocarditis secondary to elevated factor VIII levels. *J Thromb Thrombolysis* . 2012;34(1):132–134. PMID: 22302637 https://doi.org/10.1007/s11239-012-0692-z
20. Downie I, Liederman Z, Thiyagarajah K, Selby R, Lin Y. Pseudo heparin resistance caused by elevated factor VIII in a critically ill patient. *Can J Anaesth* . 2019;66(8):995–996. PMID: 31076959 https://doi.org/10.1007/s12630-019-01391-y
21. Durrani J, Malik F, Ali N, Jafri SIM. To be or not to be a case of heparin resistance. *J Community Hosp Intern Med Perspect* . 2018;8(3):145–148. PMID: 29915655 https://doi.org/10.1080/20009666.2018.1466599
22. Iapichino GE, Protti A, Andreis DT, Panigada M, Artoni A, Novembrino C, et al. Antithrombin during extracorporeal membrane oxygenation in adults: National survey and retrospective analysis. *ASAIO* J. 2019;65(3):257–263. PMID: 29746315 https://doi.org/10.1097/MAT.0000000000000806
23. Wong TE, Nguyen T, Shah SS, Brogan TV, Witmer CM. Antithrombin concentrate use in pediatric extracorporeal membrane oxygenation: A multicenter cohort study. *Pediatric Crit Care Med.* 2016;17(12):1170–1178. PMID: 27662567 https://doi.org/10.1097/PCC.0000000000000955
24. Makdisi G, Wang I. Extra Corporeal Membrane Oxygenation (ECMO) review of a lifesaving technology. *J Thorac Dis* . 2015;7(7):E166–E176. PMID: 26380745 https://doi.org/10.3978/j.issn.2072-1439.2015.07.17
25. Morales-Quinteros L, Del Sorbo L, Artigas A. Extracorporeal carbon dioxide removal for acute hypercapnic respiratory failure. *Ann Intensive Care* . 2019;9(1):79. PMID: 31267300 https://doi.org/10.1186/s13613-019-0551-6
26. Bilen O, Loftis L, Teruya J. Severe thrombotic and bleeding complications in a baby with heterozygous factor V Leiden and acquired von Willebrand disease on ECMO. *J Extra Corpor Technol.* 2011;43(2):64–69. PMID: 21848174
27. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. *J Am Call Cardiol* . 2020;75(23):2950–2973. PMID: https://doi.org/10.1016/j.jacc.2020.04.031
28. Levy JH, Sniecinski RM, Welsby IJ, Levi M. Antithrombin: anti-inflammatory properties and clinical applications. *Thromb haemostasis* . 2016;115(4):712–728. PMID: 26676884 https://doi.org/10.1160/TH15-08-0687

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