E-ISSN: 2791-8823

CSMJ

THE JOURNAL OF BAŞAKŞEHİR ÇAM AND SAKURA CITY HOSPITAL

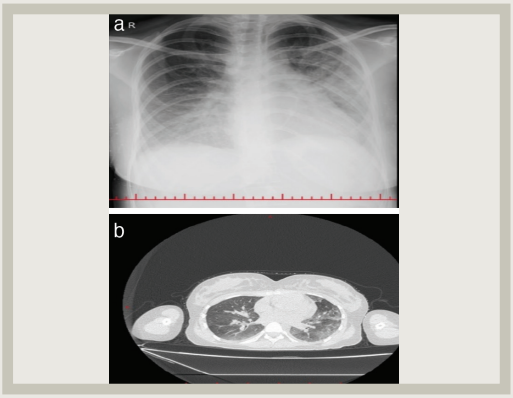

Figure 1. (a) Pulmonary X-ray showing diffuse bronchopneumonic infiltration. (b) Thorax computed tomography showing diffuse centroacinar densities at the superior lobe of the left lung representing bronchopneumonic infiltration and minimal effusion in bilateral fissures

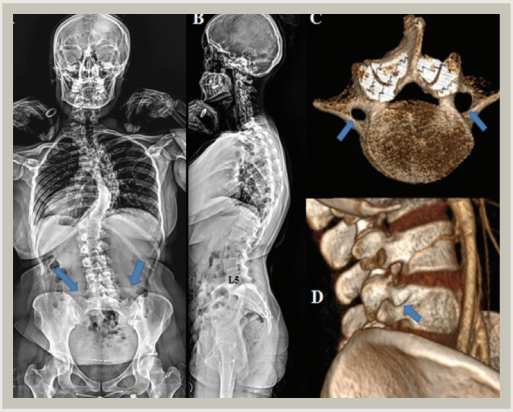

Figure 1. Radiological examinations of a 33-year-old female patient who presented to our clinic for surgical treatment. Preoperative radiological examination revealed a transverse foramen anomaly in the L5 vertebra (arrows). The spinal deformity is shown in (A) as an AP radiograph of the entire spine and in (B) as a lateral radiograph. In the (C) 3D reconstruction view, bilateral transverse foramen can be seen, which is wider on the left side. In (D), the 3D volume rendering view in the lateral plane shows that the vascular structure does not pass through the transverse foramen

AP: Anterior posterior, 3D: Three-dimensional

CAM & SAKURA MEDICAL JOURNAL

December
2023 Volume: 3 Issue: 3

www.csmedj.org

galenos Publishing House

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

CAM & SAKURA MEDICAL JOURNAL

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

galenos yayınevi

Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Printing at: Son Sürat Daktilo Dijital Baskı Merkezi Sanayi ve Ticaret Ltd. Şti.
Gayrettepe Mahallesi, Yıldızposta Caddesi, Evren Sitesi A Blok No: 32
D: 1 - D: 3 34349 Beşiktaş, İstanbul, Türkiye
Phone: +90 (212) 288 45 75 **E-mail:** info@sonsuratdaktilo.com
Printing Date: December 2023

E-ISSN: 2791-8823
International scientific journal published quarterly.

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial Board

CSMJ

Volume: 3 ▪ **Issue:** 3 ▪ December **2023**

Please refer to the journal's webpage (**https://csmedj.org/**) for "Ethical Policy", "Aims and Scope" and "Instructions to Authors".

The editorial and publication process of Cam and Sakura Medical Journal are shaped in accordance with the guidelines of the ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Cam and Sakura Medical Journal is indexed in **DOAJ, J-Gate, Türk Medline, EBSCO** and **Gale**.

The journal is published electronically.

Owner: Başakşehir Cam and Sakura City Hospital

Responsible Manager: Merih Çetinkaya

CSMJ

Volume: 3 • Issue: 3 • December 2023

Contents

CSMJ

Volume: 3 • Issue: 3 • December 2023

Editorial

Dear Colleagues,

It is my great pleasure to be with you on the last issue of CSMJ at 2023. CSMJ has been indexed in DOAJ, J-Gate, Türk Medline, EBSCO Central & Eastern European Academic Source ve Gale. This has been performed with your active support. In this last issue, you can read the review articles about both COVID-19 vaccines and also treatment of COVID-19 infections.

You can also find an original article including the evaluation of colistin performance and reliability by Phoenix M50. The second original article in this issue is about the evaluation of non-cardiac findings in children with congenital heart diseases. There are also four different case reports. You can find a case report that identified the effect of proactive malnutrition management in patients with head and neck malignancies. You will also find another case including a child with multiple sclerosis who was also on beta interferon therapy and developed active tuberculosis during this treatment. The third case report in this issue is related with the congenital scoliosis case with lomber foramen transversarium. Lastly, you can find another case report how to treat a giant right atrial mixoma by a minimally invasive resection.

I think that all the articles and case reports may provide useful insights for your routine daily practice. We want to continue to discuss different important topics in future issues of CSMJ with your support in 2024, too.

I wish all of you a happy new year.

Best regards,

On Behalf of Deputy Editors, Associate Editors, and Editorial Secretary

Merih Çetinkaya

Editor-in Chief

Cam & Sakura Medical Journal

DOI: 10.4274/csmedj.galenos.2022.2022-11-5
Cam and Sakura Med J 2023;3(3):86-90
CSMJ

COVID-19 Vaccines

Sibel Yıldız Kaya[1], Abdurrahman Kaya[2], Bilgül Mete[1]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology, İstanbul, Turkey
[2]İstanbul Training and Research Hospital, Clinic of Infectious Disease and Clinical Microbiology, İstanbul, Turkey

ABSTRACT

The novel coronavirus is an infectious disease caused by severe acute respiratory syndrome coronavirus-2. The World Health Organization declared coronavirus disease-2019 (COVID-19) outbreak is a pandemic in 2020. Many people die of acute respiratory failure both in community and hospital. Therefore, there is an urgent need for a novel effective treatment or vaccine to combat the outbreak. To develop new vaccine, a wide variety of studies have been conducted in many countries. Some vaccines are approved by the Food and Drug Administration. They were developed by a variety of techniques; mRNA, inactivated, recombinant and vector-based vaccines. Most of them are safe and effective, but some adverse reactions have been observed. COVID-19 vaccination prevented spread of the virus and halted the outbreak, by breaking the chain of the infection. Thus, the pandemic has proven again that vaccination is essential for human health. In this article, we attempted to review the commonly used ones in clinical practice.

Keywords: Coronavirus, COVID-19, pandemic, vaccines

CAM & SAKURA MEDICAL JOURNAL

Introduction

The coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The disease first appeared in China and the virus infected many people, leading to various diseases from asymptomatic to severe infection. Then it spread worldwide and the World Health Organization declared COVID-19 as a pandemic on March 11, 2020 (1). During the disease, many people developed severe pneumonia and died of the infection in the community and in the hospital due to acute respiratory failure. Therefore, there is an urgent need for a novel treatment or vaccine to combat the outbreak. To develop new vaccine, a wide variety of studies have been conducted in many countries. Some of them were approved by the Food and Drug Administration (FDA) and administered to humans with immense effort. They developed various techniques (2). They were mRNA, inactivated, recombinant and vector-based vaccines.

1. mRNA Vaccines

mRNA technology has been used for more than 20 years and displays promising potential for developing new vaccines against various diseases, including cancer and infections (3). mRNA vaccines for SARS-CoV-2 absolutely represent a novel vaccine approach. It works very differently from conventional vaccines. Conventional methods allow the body to produce antibodies by administering an antigen or a viral vector that encodes an attenuated virus or synthetic antigen (4). As their contents are prepared and generated outside the human body, it needs lots of time. Such vaccines are injected into the human body, but do not enter the human cell. However, mRNA vaccines contain

Address for Correspondence: Sibel Yıldız Kaya MD, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Infectious Disease and Clinical Microbiology, İstanbul, Turkey
Phone: +90 530 938 51 68 **E-mail:** y.sibelly@hotmail.com **ORCID ID:** orcid.org/0000-0002-6319-7889
Received: 07.11.2022 **Accepted:** 09.11.2022

synthetic mRNA molecules that encode vaccine antigens within nanoparticles (5). The mRNA sequence of the virus was directly inserted into a human cell, thereby re-programing the human cell to produce its own viral antigens. The adaptive immune system then activates, newly develops antibodies bind to the antigen and T-cells are activated. Additionally, the use of mRNA has several beneficial features compared with previous vaccines. As mRNA-based vaccine is non-infectious, there is no potential risk of infection and the other benefits are rapid, inexpensive and manufacturing (3).

There are two mRNA vaccines including BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) and mRNA-1273 (Moderna COVID-19 vaccine). Both are monovalent vaccines. The latter is approved by the FDA for individuals aged 12 years and older and for children 6 months to 11 years of age, it is available under emergency use authorization (EUA) (6). Two doses of 30 mcg are administered intramuscularly a three to eight-week interval. For immune-compromised host, a third dose is given at least 28 days after the second vaccination (7). The former is approved by the FDA for persons aged 18 years and older and is available under EUA for children 6 months to 17 years of age (8). For certain immune compromising conditions, the recommendations are the same as Pfizer-BioNTech vaccine.

In some observational and surveillance studies, both vaccines have been considered safe (9,10,11). In the phase 3 clinical trials of both vaccines, some local and systemic adverse reactions were observed. An analysis showed that both mRNA vaccines were related to the risk of myocarditis and pericarditis in people aged 18-39 years (about 22.4 and 31.2 cases per million doses, respectively) (12). Safety studies stress that the risk of myocarditis following infection is much higher than after vaccination (13). In a post-authorization study, acute allergic reactions were also seen as a potential outcome (14). In a study reviewing adverse events among healthcare workers, 98% of them had no symptoms of an allergic reaction. Compared to Pfizer-BioNTech, acute allergic reactions were mildly more frequent with the Moderna vaccine. Anaphylaxis was observed at a rate of 2.47 cases per 100.000 vaccination and the rate was similar between the two vaccines (11,15). Existing observational studies demonstrated that most reactions reported by children after receiving Pfizer-BioNTech were mild in severity. It most frequently occurs the day after vaccination and is transient (16). However, an analysis reported higher rates of myocarditis following the second dose of mRNA vaccinations among adolescent men and young adults (17). Following COVID-19 infection, these results are still much rarer among pediatric and adolescent populations (18).

The efficacy of both vaccines with two doses in preventing symptomatic COVID-19 infection in persons without previous COVID-19 has been found to be high (19,20). mRNA vaccination (>14 days after second dose) prevented hospitalization in 89%, intensive care unit admission in 90% and admission to emergency unit in 91% of the cases (21). The efficacy rate was similar to Pfizer and Moderna vaccines in these three categories and ranged from 81% to 95% in people older than 50 years (22). Among all adults, a study from Israel reported that its effectiveness for preventing death from COVID-19 was approximately 72% (23). Another study reported in early 2020 found that both mRNA COVID-19 vaccines were approximately 90% effective in preventing both symptomatic and asymptomatic infections (24). Studies conducted in the United States of America (USA) revealed that the effectiveness of the Moderna and Pfizer vaccines in preventing hospitalization was 93% and 88%, respectively (25). In another USA study evaluating BioNTech, the effectiveness in preventing infection and hospitalization was 73% and 90%, respectively. Efficiency of full vaccination against infections decreased from 88% in the first month to 47% in 5th month (26).

2. Viral Vector Vaccines

Viral vector vaccines use the viruses to transfer genes encoding vaccine antigens into body cells. Adenoviruses are the most commonly used viruses as a viral vector. The vaccine transfers the virus, which will circulate in the nucleus. The genes are expressed in the nucleus by developing the antigen, and then the induction of an immune response is commences (27). The vectors can be replicating or non-replicating. There are three viral vector vaccines, including the Johnson & Johnson/Janssen, the Oxford-AstraZeneca and Sputnik V COVID-19 vaccines.

All these vaccines are considered highly effective and appear to wane over time to mRNA vaccines. All of these are safe but rare blood clotting was observed in the first 2 vaccines (28). Another study reported an increased incidence of Guillain-Barré syndrome following vaccination with the first vaccine (29). The efficacy of the Janssen vaccine was 68% against COVID-19 infection and against COVID-19-related hospitalization was 71% in all adults (22,25). After a single dose given, the AstraZeneca vaccine demonstrated significant efficacy of 64.1% against symptomatic COVID-19 and 70.4% after two doses and the phase 3 study showed vaccine efficacy of 76% against symptomatic COVID-19 infection and 100% efficacy in preventing severe disease (30). In people receiving Sputnik V, the phase 3 results have showed 91.6% effectiveness after the first dose of vaccine and 100% effective in preventing severe COVID-19 disease (31,32).

3. Recombinant Vaccines

Protein subunits (only a selected antigenic part of virus) or virus-like particles are used for this method. Most sort of these vaccines focus on the virus's spike protein or its receptor binding domain. NVX-CoV2373 (Novavax, USA) was developed using this technology. It contains 5 µg of a recombinant full-length spike trimer as the main antigenic component and 50 µg matrix M1 adjuvant (33,34). Primary vaccination series includes two doses of vaccine with 21 days interval. The vaccine has EUA for individuals 12 years and older (33). In the phase 3 trial of Novavax, infection rates were 0.01% and 0.8% in the per-protocol group (people vaccinated with 2 doses) and placebo groups, respectively (35). All COVID-19 cases had mild infection and the vaccine was found to be 100% effective against moderate to severe infection. Most common solicited adverse events are injection site tenderness/pain, headache, myalgia, fatigue, and malaise within two days (35). In another clinical trial, ten of 7020 individuals in the per-protocol population (7 days after 2 dose vaccination with NVX-CoV2373) infected with SARS-CoV-2. None of them were hospitalized or died of COVID-19. One patient developed vaccination-related myocarditis and no anaphylaxis was observed (36).

In different studies, both local and systemic adverse reactions were seen more commonly in the vaccinated group and frequent complaints were injection site pain/tenderness, erythema, swelling, headache, muscle pain, fatigue, nausea, and vomiting. The adverse events usually were not severe (34,35,36).

4. Live Vaccines

Live vaccines use an attenuated form of the germ that leads to a disease. Since they contain all virus components, they induce both humoral and cell-mediated immunity, thereby developing a strong and long-lasting immune response.

5. Inactivated Vaccines

Inactivated vaccines are a type of conventional vaccine produced by whole virus or bacteria. A large quantity of live viruses and biosafety level-3 laboratories are required. SARS-CoV-2 viruses are inoculated into African green monkey kidney cells (Vero cell) for multiplication of virus. After yielding much viruses in culture, they are inactivated by some chemicals (37,38). All these steps take a lot of time. CoronaVac/Sinovac and Turkovac are inactivated COVID-19 vaccines. Because the vaccines contain whole virus components, immune responses can develop against viral antigens including nucleoprotein, envelope, matrix, and spike protein, thereby evoking both cellular, and humoral immunity (19). However, antibodies decrease over time, resulting in the need for booster doses (39).

Sinovac is the most widely used inactivated vaccine, developed in China. It includes an alimunium hydroxide adjuvant and is intramuscularly administered with 2 doses an interval of 2 to 4 weeks. It is also available in some other countries including Brazil, Chile, Indonesia, Mexico, and Turkey. In a phase 3 study in our country, the effectiveness of this vaccine was 83.5% (40). However, some trials from different countries reported lower efficacy (41,42). In Chile, the vaccine effectiveness was approximately 70% against SARS-CoV-2 infection and 86%-88% in preventing COVID 19-related hospitalization and death (43). A study in Brazil showed lower efficacy (47%) in the elderly (>70 years) for preventing COVID-19 infection. Its efficacy was also reported 56% and 61% for preventing hospitalization and mortal outcome, respectively (44).

Generally, this vaccine is considered as safe, but some mild and moderate adverse reactions have been observed. Injection site pain was one of the most reported reactions and fatigue was the main compliant (41,45,46,47).

ERUCoV-VAC/TURKOVAC is also inactivated vaccine developed with the support of the Health Institutes of Turkey. Vero E6 cells are used for the vaccine production. It is administered intramuscularly twice with 28 days apart. In phase 2 studies, the vaccine was evaluated on three animal models; BALB/c mice, K18-hACE2 (transgenic mice), and ferret. BALB/c mice and ferret models showed to be safety profile of the vaccine. BALB/c mice model demonstrated that the vaccine induced enhanced immunogenic response. Recently, ferret models suggested the vaccine reduces the number of upper respiratory tract infections and protects from lethal disease. The vaccine was authorized by the Turkish Medicines and Medical Devices Agency in December 2021. The phase 3 clinical trials are still in progress since June 2021.

Vaccination practice in Turkey: SARS-CoV-2 vaccination began in Turkey on January 14, 2021. The vaccines currently used are the BioNTech, Sinovac and Turkovac vaccines. A total of 151,999,998 doses of vaccine were administered in Turkey. The number of people who received 3 doses of vaccine was 28,214,781 (48). There are 3 clinical (1 phase1, 1 phase2, 1 phase3) and 6 preclinical vaccine studies are still in progress in Turkey (49).

Conclusion

Studies across the world indicated that COVID-19 vaccines are safe and effective. It is also crystal clear that vaccination

prevents the spread of the virus and halt COVID-19 outbreak, by breaking the chain of the infection. Their benefits outweigh some vaccine-related adverse reactions. Vaccines are crucial for human health and this has been proven once again by their role in controlling the pandemic.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.Y.K., A.K., B.M., Design: S.Y.K., A.K., B.M., Data Collection or Processing: S.Y.K., A.K., Analysis or Interpretation: S.Y.K., A.K., B.M., Literature Search: S.Y.K., A.K., Writing: S.Y.K., A.K., B.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. WHO Director-General's opening remarks at the media briefing on COVID19- 11 March 2020. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. (Accessed on 13 November 2020.
2. FDA Vaccines Licensed for Use in the United States. 2020. Available from :https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines:accessed 27 December 2023.
3. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov 2018;17:261-279.
4. Plotkin S. History of vaccination. Proc Natl Acad Sci U S A 2014;111:12283-12287.
5. Schlake T, Thess A, Fotin-Mleczek M, Kallen KJ. Developing mRNA-vaccine technologies. RNA Biol 2012;9:1319-1330.
6. World Health Organization. Draft landscape of COVID-19 candidate vaccines. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (Accessed on October 20, 2020).
7. US Food and Drug Administration. Pfizer-BioNTech Fact Sheets (English) and FAQs. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine#additional (Accessed on February 03, 2022).
8. US Food and Drug Administration. Spikevax and Moderna COVID-19 Vaccine. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine (Accessed on February 03, 2022).
9. Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 2021;385:1078-1090.
10. Gee J, Marquez P, Su J, et al. First month of COVID-19 vaccine safety monitoring - United States, December 14, 2020-January 13, 2021. MMWR Morb Mortal Wkly Rep 2021;70:283-288.
11. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID19 mRNA vaccination. JAMA 2021;326:1390-1399.
12. Goddard K, Lewis N, Fireman B, et al. Risk of myocarditis and pericarditis following BNT162b2 and mRNA-1273 COVID-19 vaccination. Vaccine 2022;40:5153-5159.
13. Patone M, Mei XW, Handunnetthi L, et al. Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex. Circulation 2022;146:743-754.
14. Banerji A, Wickner PG, Saff R, et al. mRNA Vaccines to Prevent COVID-19 disease and reported allergic reactions: current evidence and suggested approach. J Allergy Clin Immunol Pract 2021;9:1423-1437.
15. Blumenthal KG, Robinson LB, Camargo CA Jr, et al. Acute allergic reactions to mRNA COVID-19 vaccines. JAMA 2021;325:1562-1565.
16. John R. Adverse events among children ages 5-11 years after COVID-19 vaccination: updates from v-safe and the vaccine adverse event reporting system (VAERS). Available from: https://www.mhlw.go.jp/content/10601000/000872121.pdf (Accessed on December 13, 2021).
17. Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. JAMA 2022;327:331-340.
18. Block JP, Boehmer TK, Forrest CB, et al. Cardiac Complications After SARS-CoV-2 infection and mRNA COVID-19 vaccination - PCORnet, United States, January 2021-January 2022. MMWR Morb Mortal Wkly Rep 2022;71:517-523.
19. Krammer F. SARS-CoV-2 vaccines in development. Nature 2020;586:516-527.
20. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-2615.
21. Hahn WO, Wiley Z. COVID-19 vaccines. Infect Dis Clin North Am 2022;36:481-494.
22. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. N Engl J Med 2021;385:320-329.
23. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med 2021;384:1412-1423.

24. Thompson MG, Burgess JL, Naleway AL, et al. Interim Estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers - Eight U.S. Locations, December 2020-March 2021. MMWR Morb Mortal Wkly Rep 2021;70:495-500.
25. Self WH, Tenforde MW, Rhoads JP, et al. Comparative effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) vaccines in preventing COVID-19 hospitalizations among adults without immunocompromising conditions - United States, March-August 2021. MMWR Morb Mortal Wkly Rep 2021;70:1337-1343.
26. Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet 2021;398:1407-1416.
27. Vrba SM, Kirk NM, Brisse ME, Liang Y, Ly H. Development and applications of viral vectored vaccines to combat zoonotic and emerging public health threats. Vaccines (Basel) 2020;8:680.
28. Available from: https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia. (Accessed on May 9, 2022).
29. Hanson KE, Goddard K, Lewis N, et al. Incidence of Guillain-Barré syndrome after COVID-19 vaccination in the vaccine safety datalink. JAMA Netw Open 2022;5:e228879.
30. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99-111. Erratum in: Lancet 2021;397:98.
31. Sputnik V demonstrates 97.6% efficacy according to analysis of data from 3.8 million vaccinated persons in Russia making it the most efficient COVID-19 vaccine in the world. Sputnik V - the first registered vaccine against COVID-19. Official website vaccine against coronavirus Sputnik V. Available from: https://sputnikvaccine.com/newsroom/pressreleases/sputnik-v-demonstrates-97-6-efficacy-according-to-the-analysis-of-data-of-3-8-million-vaccinated-per/. (Accessed on June 8, 2021).
32. Tan BK, Mainbourg S, Friggeri A, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. Thorax 2021;76:970-979.
33. Emergency Use Authorization (EUA) of the Novavax COVID-19 vaccine, adjuvanted to prevent coronavirus disease 2019 (COVID-19). Available from: https://www.fda.gov/media/159897/download (Accessed on July 21, 2022).
34. Masuda T, Murakami K, Sugiura K, Sakui S, Schuring RP, Mori M. Safety and immunogenicity of NVX-CoV2373 (TAK-019) vaccine in healthy Japanese adults: interim report of a phase I/II randomized controlled trial. Vaccine 2022;40:3380-3388.
35. Dunkle LM, Kotloff KL, Gay CL, et al. Efficacy and safety of NVX-CoV2373 in adults in the United States and Mexico. N Engl J Med 2022;386:531-543.
36. Heath PT, Galiza EP, Baxter DN, et al. Safety and efficacy of NVX-CoV2373 Covid-19 vaccine. N Engl J Med 2021;385:1172-1183.
37. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369:77-81.
38. Hoenigl M, Levitz SM, Schuetz AN, Zhang SX, Cornely OA. All you need to know and more about the diagnosis and management of rare mold infections. mBio 2021;12:e02920-e0292020.
39. Zhang J, He Q, An C, et al. Boosting with heterologous vaccines effectively improves protective immune responses of the inactivated SARS-CoV-2 vaccine. Emerg Microbes Infect 2021;10:1598-1608.
40. Tanriover MD, Doğanay HL, Akova M, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. Lancet 2021;398:213-222. Erratum in: Lancet 2022;399:436.
41. Baraniuk C. What do we know about China's covid-19 vaccines? BMJ 2021;373:n912.
42. Fadlyana E, Rusmil K, Tarigan R, et al. A phase III, observer-blind, randomized, placebo-controlled study of the efficacy, safety, and immunogenicity of SARS-CoV-2 inactivated vaccine in healthy adults aged 18-59 years: An interim analysis in Indonesia. Vaccine 2021;39:6520-6528.
43. Jara A, Undurraga EA, González C, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med 2021;385:875-884.
44. Ranzani OT, Hitchings MDT, Dorion M, et al. Effectiveness of the CoronaVac vaccine in older adults during a gamma variant associated epidemic of covid-19 in Brazil: test negative case-control study. BMJ 2021;374:n2015.
45. Khoshnood S, Arshadi M, Akrami S, et al. An overview on inactivated and live-attenuated SARS-CoV-2 vaccines. J Clin Lab Anal 2022;36:e24418.
46. Karacin C, Eren T, Zeynelgil E, et al. Immunogenicity and safety of the CoronaVac vaccine in patients with cancer receiving active systemic therapy. Future Oncol 2021;17:4447-4456.
47. Zhang MX, Zhang TT, Shi GF, et al. Safety of an inactivated SARS-CoV-2 vaccine among healthcare workers in China. Expert Rev Vaccines 2021;20:891-898.
48. Available from: https://covid19asi.saglik.gov.tr/ (Accessed on 29 October 2022).
49. Available from: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines, (Access on 28 October 2022).

DOI: 10.4274/csmedj.galenos.2022.2022-12-1

Cam and Sakura Med J 2023;3(3):91-100

CSMJ

Treatment of COVID-19: Antivirals, Antibody Products, Immunomodulators, Antithrombotic Therapy, and Supplements

Asuman İnan[1], Sibel Bolukçu[2]

[1]University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

[2]Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

ABSTRACT

With the advent of the pandemic, the landscape of treatment options has undergone rapid transformations in response to evolving viral variants. Current guidelines advocate tailoring treatments based on disease severity and the distinction between outpatient and inpatient settings. Remdesivir is endorsed for hospitalized cases, whereas molnupiravir is recommended for managing mild to moderate coronavirus disease-2019 (COVID-19) in individuals at high risk of progressing to severe disease. Baricitinib holds Food and Drug Administration (FDA) approval in the United States for use in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. Furthermore, dexamethasone is indicated for severely ill COVID-19 patients who require supplemental oxygen or ventilator support. Notably, tocilizumab has demonstrated limited efficacy in reducing the risk of disease progression. The FDA has granted Emergency Use Authorization for bebtelovimab, specifically for the treatment of mild to moderate COVID-19. Tixagevimab and cilgavimab have received FDA authorization for emergency use as pre-exposure prophylaxis against COVID-19. Although there is a recommendation against the use of an intermediate dose of low-molecular-weight heparin in critically ill COVID-19 patients, supported by moderate-level evidence, this recommendation does not extend to outpatient settings. However, there is insufficient evidence to endorse or discourage the use of supplements for treating COVID-19, both in non-hospitalized and hospitalized patients.

Keywords: COVID-19, treatment, pandemic

Introduction

Coronavirus disease-2019 (COVID-19) has evolved into a pandemic characterized by a rapidly escalating incidence of infections and fatalities. Several pharmacologic interventions are currently under consideration for treatment. Acknowledging the swiftly expanding body of literature, organizations such as the Infectious Diseases Society of America (IDSA) recognize the imperative to develop dynamic, regularly updated evidence-based guidelines. These guidelines aim to provide comprehensive support to patients, clinicians, and other healthcare professionals in their strategic decision-making processes regarding the treatment and management of individuals afflicted by COVID-19.

Outlined below are the recommendations, accompanied by pertinent commentary, as delineated in the clinical practice guidelines of both the IDSA and the National Institutes of Health (NIH) for the treatment of COVID-19.

Address for Correspondence: Assoc. Prof. Asuman İnan, University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

Phone: +90 216 542 32 32 **E-mail:** asumaninan@hotmail.com **ORCID ID:** orcid.org/0000-0002-6182-1262

Received: 08.12.2023 **Accepted:** 19.12.2023

Antiviral Treatment

Remdesivir

Remdesivir is a novel nucleotide analog that is metabolized to its active metabolite, remdesivir triphosphate. Remdesivir triphosphate is a structural analog of adenosine triphosphate and competes with the natural substrate for incorporation by RNA polymerase into nascent viral RNA, which results in delayed chain termination during replication and consequently inhibits viral replication (1,2). The Food and Drug Administration (FDA) has approved remdesivir for hospitalized children aged 12 and above and adults with COVID-19, regardless of disease severity (3). One of the most recent and largest studies describing the effectiveness of remdesivir in severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection reported that despite its conditional recommendation, remdesivir may still be effective in achieving early clinical improvement. It reduces early-stage mortality and the need for high-flow oxygen supplementation and invasive mechanical ventilation among hospitalized COVID-19 patients (4). Despite the World Health Organization (WHO) reviewing its recommendation on remdesivir for hospitalized patients, guidelines from the NIH and IDSA recommend remdesivir (5,6,7).

Paxlovid (Nirmatrelvir-Ritonavir)

Nirmatrelvir inhibits the activity of the SARS-CoV-2-3CL protease, an enzyme crucial for viral replication, and co-administration with ritonavir extends the duration and increases the concentration of nirmatrelvir activity in the body (8). The FDA issued an Emergency Use Authorization (EUA) for paxlovid in December 2021 for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age). Paxlovid is available by prescription only and should be promptly initiated after the diagnosis of COVID-19 and within five days of symptom onset (9).

Several large observational studies have linked paxlovid to clinical benefits in vaccinated individuals with underlying risk factors for severe disease (10,11,12,13,14,15). For instance, a study involving 1,130 vaccinated adults who received paxlovid within five days of COVID-19 diagnosis and 1,130 controls matched for age, gender, race, and comorbidities found that paxlovid was associated with a lower rate of emergency department visits, hospitalization, and death [odds ratio (OR): 0.5, CI 0.39-0.67] (12). Notably, all 10 deaths occurred in the untreated group. These observational studies were conducted in 2022, during the predominance of Omicron subvariants, suggesting that paxlovid retains efficacy against these variants.

Molnupiravir

Molnupiravir is a pro-drug of the nucleotide analog N4-hydroxycytidine and exhibits broad-spectrum antiviral activity against RNA viruses, including influenza, Ebola, coronaviruses, and respiratory syncytial virus (14).

In a recent study involving 202 participants, a significantly lower percentage of individuals receiving an 800 mg dose of molnupiravir (1.9%) had isolatable virus on day 3 compared with the placebo group (16.7%) ($p=0.02$). By day 5, virus isolation was not possible from any participant receiving 400 or 800 mg of molnupiravir, whereas it was still evident in 11.1% of those in the placebo group ($p=0.03$). Molnupiravir was generally well tolerated, with similar adverse events observed across all groups (2).

In an international randomized controlled trial (RCT) involving 1,433 non-hospitalized, unvaccinated adults with mild to moderate COVID-19 symptoms onset within five days and at least one risk factor for severe disease, molnupiravir demonstrated an approximately 33% reduction in the risk of hospitalization or death. The combined outcome occurred in 6.8% versus 9.7% of patients compared with the placebo group, although this difference was not statistically significant (16). Among the 10 deaths reported among trial participants, one occurred in the molnupiravir group and nine occurred in the placebo group.

The FDA has approved molnupiravir for the treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19, including hospitalization or death, when alternative FDA-authorized COVID-19 treatment options are either inaccessible or clinically inappropriate (17).

Favipiravir

Favipiravir is a selective and potent inhibitor of RNA-dependent RNA polymerase, which inhibits viral genome replication. It boasts a broad antiviral spectrum, allowing its use in various infections such as influenza and Ebola. Originally synthesized in 2005, it was first approved for the treatment of influenza in Japan and later received approval in Russia for the treatment of COVID-19 (14,18).

Clinical studies on the efficacy of favipiravir for COVID-19 treatment have yielded conflicting results. In a meta-analysis, the pooled analysis of five studies indicated that favipiravir was associated with a higher clinical improvement rate than the control group, although the difference did not reach statistical significance [OR: 1.54; 95% confidence interval (CI): 0.78-3.04]. Additionally, the viral clearance rate at days 4-5, 7-8, and 10-12 did not differ between favipiravir and the comparator, and the risk of adverse events was similar between the groups

(18). However, in another recent meta-analysis of nine studies comparing the efficacy of favipiravir with that of other control groups, a significant clinical improvement was observed in the favipiravir group versus the control group during the seven days following hospitalization (RR: 1.24, 95% CI: 1.09-1.41; p=0.001). Although viral clearance was higher 14 days after hospitalization in the favipiravir group, this finding did not reach statistical significance (RR: 1.11, 95% CI: 0.98-1.25; p=0.094). The mortality rate was observed to be 30% lower in the favipiravir group, but this finding did not achieve statistical significance (19).

Lopinavir/Ritonavir

Lopinavir and ritonavir were among the first drugs investigated in clinical trials for the treatment of COVID-19. Despite showing inhibitory effects against SARS-CoV-2, three RCTs conducted among hospitalized patients with COVID-19 indicated that treatment with lopinavir/ritonavir failed to demonstrate any significant benefits in terms of mortality, the need for invasive mechanical ventilation, or 28-day hospital discharge rates (20,21,22,23). Current guidelines discourage the use of the lopinavir/ritonavir combination in hospitalized patients with COVID-19 (5,6,7,14).

Adjuvants/Supportive Treatment

Dexamethasone

Dexamethasone is a synthetic glucocorticoid, a fluorinated derivative of prednisone, known for its potent and prolonged anti-inflammatory and immunosuppressive effects. Glucocorticoids, including dexamethasone, have been investigated for their potential to modulate inflammation-mediated lung injury, thereby reducing the progression to respiratory failure and death in COVID-19 patients (15).

The primary efficacy data on glucocorticoids in COVID-19 comes from a substantial open-label trial conducted in the United Kingdom. In this study, 2104 patients with confirmed or suspected COVID-19 were randomly assigned to receive dexamethasone (administered at 6 mg orally or intravenously (IV) daily for up to 10 days), whereas 4,321 patients received usual care (24). The primary endpoint was mortality at 28 days. The results showed that 22.9% of patients in the dexamethasone group and 25.7% in the standard care group died within 28 days after randomization (age-adjusted OR: 0.83, 95% CI: 0.75-0.93; p<0.001).

Furthermore, the study demonstrated that the dexamethasone group had a lower death rate than the standard care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; RR: 0.64, 95% CI: 0.51-0.81) and those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; RR: 0.82, 95% CI: 0.72-0.94). However, no significant difference was observed among patients who did not receive respiratory support at the time of randomization (17.8% vs. 14.0%; RR: 1.19, 95% CI: 0.92-1.55).

In conclusion, the study indicated that dexamethasone treatment resulted in lower 28-day mortality in patients hospitalized for COVID-19 who were undergoing mechanical ventilation or oxygen therapy. However, it did not show a significant benefit for patients who did not receive respiratory support at the time of randomization. Consequently, dexamethasone is recommended for severely ill COVID-19 patients requiring supplemental oxygen or ventilator support.

Tocilizumab

Tocilizumab is a recombinant humanized IgG1 monoclonal antibody (mAbs) that specifically binds to both soluble and membrane-bound receptors for IL-6, thereby inhibiting this signaling pathway and reducing its pro-inflammatory effects of interleukin (IL)-6 (25).

Cumulative evidence suggests a mortality benefit associated with tocilizumab (26,27). In a meta-analysis encompassing 27 randomized trials involving over 10,000 patients hospitalized with COVID-19, all-cause mortality was lower among those receiving tocilizumab than among those receiving placebo or standard of care (OR: 0.83, 95% CI: 0.74-0.92) (26,27). The two largest trials within this analysis, conducted in patients with severe and critical COVID-19, provide support for the use of tocilizumab. However, several other trials failed to demonstrate a mortality benefit or other clear clinical advantages with these agents (28,29,30). As an example, a double-blind, randomized trial involving 243 patients with severe COVID-19, who were not intubated but showed evidence of a proinflammatory state (elevations in C-reactive protein, ferritin, D-dimer, or lactate dehydrogenase), did not reveal a significant difference in the rate of intubation or death with a single dose of tocilizumab compared with placebo (10.6% versus 12.5%, hazard ratio: 0.83, 95% CI: 0.38-1.81) (31). Tocilizumab also did not reduce the risk of disease progression.

Baricitinib

Baricitinib, a selective inhibitor of Janus activated kinase 1 (JAK1) and Janus activated kinase 2 (JAK2), serves as a modulator of signaling pathways for cytokines and growth factors that are pivotal in hematopoiesis, inflammation, and immune response (32). Beyond its immunomodulatory

effects, it is conjectured that baricitinib may exhibit antiviral properties by disrupting viral entry.

Emerging data posit a mortality advantage associated with baricitinib for patients with severe disease, even when concurrently administered with dexamethasone (33). In an expansive open-label randomized trial encompassing over 8,000 hospitalized COVID-19 patients, baricitinib demonstrated a reduction in 28-day mortality compared with standard care alone (12% vs. 14%; relative risk: 0.87, 95% CI: 0.77-0.99) (34). Noteworthy is the fact that nearly all participants (95%) were concurrently receiving glucocorticoids, with 20% on remdesivir and 23% having received tocilizumab. While these outcomes align with those of prior baricitinib trials, it is noteworthy that the relative reduction in mortality was marginally lower in this particular trial (35,36,37). In the United States, the FDA has granted approval for the use of baricitinib in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (38). Tofacitinib, another JAK inhibitor, is a potential alternative in situations where baricitinib is not readily available.

Anakinra

Anakinra inhibits the biological activity of IL-1, a proinflammatory cytokine associated with severe COVID-19. It counteracts the production of nitric oxide, prostaglandin E2, and collagenase in the synovium, fibroblasts, and chondrocytes (14,15).

A systematic review and patient-level meta-analysis conducted by Kyriazopoulou et al. (39) examined pooled data from 1,185 patients across nine studies, including individual patient data from 895 patients in six of the analyzed studies. Mortality was significantly lower in patients treated with anakinra (11%) than in those receiving standard care with or without a placebo [25%; adjusted OR: 0.32 (95% CI: 0.20-0.51)]. The use of anakinra, compared with standard care, was not associated with a significantly increased risk of secondary infections [OR: 1.35 (95% CI: 0.59-4.0)].

However, several trials of IL-1 inhibitors, including anakinra in hospitalized patients with non-severe COVID-19 and canakinumab in patients with severe COVID-19, have not demonstrated a reduction in ventilator-free or overall survival (40,41,42). Consequently, it remains uncertain whether anakinra offers advantages over other immunomodulatory agents that have demonstrated efficacy, such as IL-6 or JAK inhibitors.

Agents Supporting the Host Natural Immunity

Interferons

All viruses trigger an antiviral response that relies on the immediate production of interferon (IFN)-β in the host. The binding of IFN-β to its receptor then triggers the production of IFN-α. If the production of IFN-α/β occurs immediately and is intense enough, the infection can be stopped (14,15).

IFNs play a role in the pathogenesis of SARS-CoV-2. Low levels of IFN-I and IFN-III have been found among patients infected with SARS-CoV-2, and impaired IFN production has been associated with low viral clearance (14). Inborn errors of TLR3- and IRF7-dependent type I IFN immunity have been found to be related to life-threatening COVID-19 pneumonia (43).

In situations of an inefficient IFN response, the virus replicates, triggering a second inflammatory/immune response, which may become explosive and potentially result in a cytokine storm and acute respiratory distress syndrome.

In a meta-analysis of five RCTs regarding the effectiveness of IFN-β for the treatment of COVID-19, the average mortality rate was reported as 6.1% and 18.0% in the intervention and control groups, respectively. Likewise, the median days of hospitalization were lower in the intervention group (9 days) than in the control group (12.25 days), and IFN-β was found to increase the overall discharge rate (RR: 3.05; 95% CI: 1.09-5.01) (44).

However, in the SOLIDARITY clinical trial, death occurred in 243 of 2,050 patients receiving IFN and in 216 of 2,050 receiving the control (rate ratio: 1.16; 95% CI: 0.96 to 1.39; p=0.11), and IFN did not reduce mortality, overall or in any subgroup, or reduce initiation of ventilation or hospitalization duration (23).

Consequently, IFN-β could have a role for treating COVID-19, especially if started earlier during the disease, but further RCTs, including a larger number of patients, are needed.

Anti-SARS-CoV-2 Monoclonal Antibodies

mAbs represent a focal point in ongoing investigations for the therapeutic management of COVID-19. These antibodies are typically synthesized through the identification of pathogen-specific B-cells sourced from individuals convalescing from recent infections or via the immunization of genetically modified mice possessing a humanized immune system (45).

After the identification of B-cells, the genes encoding immunoglobulin heavy and light chains are extracted, and their expression yields mAbs characterized by a specific affinity toward a predetermined target. This manufacturing methodology distinguishes itself from convalescent plasma, which comprises polyclonal antibodies obtained from individuals in the recovery phase of infection (46).

A preponderance of mAb products designed to combat SARS-CoV-2 predominantly targets the viral spike protein, which is pivotal for the virus's cellular entry mechanism, thereby obstructing viral attachment and subsequent entry into human cells. FDA-authorized formulations encompass bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovima (47,48,49,50,51).

The Omicron variant has emerged as the dominant SARS-CoV-2 variant in the United States. This variant, along with its subvariants, exhibits notable reductions in *in vitro* susceptibility to several anti-SARS-CoV-2 mAbs, particularly bamlanivimab plus etesevimab and casirivimab plus imdevimab. While sotrovimab maintains efficacy against the Omicron BA.1 and BA.1.1 subvariants, its *in vitro* neutralization activity substantially diminishes against the Omicron BA.2, BA.4, and BA.5 subvariants. Conversely, bebtelovimab retains *in vitro* neutralization activity against circulating Omicron subvariants (47,53,54).

Given the ascendancy of the Omicron variant in the United States, bebtelovimab is currently the solitary mAb recommended for the treatment of COVID-19.

At present, no specific product is designated for post-exposure prophylaxis. Nevertheless, the IDSA guideline panel suggests the post-exposure employment of casirivimab/imdevimab only under conditions where predominant regional variants exhibit susceptibility, accompanied by a conditional recommendation and low certainty of evidence. Recommendations also extend to the use of tixagevimab plus cilgavimab for pre-exposure prophylaxis (PrEP) (55). Tixagevimab/cilgavimab has received emergency authorization as PrEP against COVID-19 for immunocompromised individuals or those unable to be vaccinated or mount an effective post-vaccination immune response.

Administration of anti-SARS-CoV-2 mAbs necessitates a setting equipped to manage severe hypersensitivity reactions, including anaphylaxis. Post-injection, patients should undergo monitoring for a minimum duration of 1 hour.

Bebtelovimab

In February 2022, the FDA issued an EUA for bebtelovimab to address mild to moderate cases of COVID-19 in adults and specific pediatric patients aged 12 or above, particularly when alternative treatment options are either inaccessible or deemed clinically inappropriate (56). Bebtelovimab, classified as a neutralizing IgG1 mAbs, specifically targets the spike protein of SARS-CoV-2. Significantly, it retains binding and neutralizing efficacy against all currently identified and reported variants of concern, including Omicron and BA.2 (57).

For non-hospitalized adults aged 18 years and older presenting with mild to moderate COVID-19 and at an elevated risk of progressing to severe disease, the Panel recommends the administration of bebtelovimab as a single 175 mg IV dose at the earliest opportunity post-diagnosis and within seven days of symptom onset. Moreover, bebtelovimab is a therapeutic choice for hospitalized adults aged 18 years and older with mild to moderate COVID-19, unrelated to their hospitalization cause, provided they satisfy the FDA EUA criteria for outpatient treatment (55).

Tixagevimab Plus Cilgavimab

Tixagevimab and cilgavimab received EUA from the FDA for PrEP against COVID-19 in specific adults and pediatric patients in December 2021, with a dosing revision in February 2022. According to the IDSA guidelines, PrEP with tixagevimab/cilgavimab is recommended over tixagevimab/cilgavimab for moderately or severely immunocompromised individuals at an elevated risk of an inadequate immune response to the COVID-19 vaccine or for whom the vaccine is not recommended because of a documented serious adverse reaction, with a conditional recommendation and low certainty of evidence (58,59).

The STORM CHASER study, which focused on post-exposure prophylaxis, showed a non-significant reduction in the overall study population's risk of symptomatic COVID-19. Nevertheless, tixagevimab/cilgavimab is not authorized for post-exposure prophylaxis in individuals exposed to SARS-CoV-2 (60,61). Notably, the FDA's EUA was amended in February 2022 to increase the initial dosing of tixagevimab/cilgavimab for PrEP because of potential decreased activity (12 to 424-fold) against Omicron subvariants BA.1 and BA.1.1, while maintaining presumed neutralization efficacy against the BA.2 subvariant.

Similarly, the recommendations from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) include conditional recommendations for the use of tixagevimab-cilgavimab in high-risk, unvaccinated outpatients with mild-to-moderate COVID-19, contingent upon its activity against the infecting variant or the predominant variants based

on epidemiological data, with a moderate recommendation. There are also conditional recommendations for the use of tixagevimab-cilgavimab in high-risk outpatients at risk of vaccine failure with mild-to-moderate COVID-19, but with a very low recommendation. However, there are insufficient data to provide a recommendation for fully vaccinated patients with no risk factors for vaccine failure (62). In addition, the panel decided not to evaluate drugs currently unavailable outside the United States, such as bebtelovimab.

Sotrovimab

Data regarding sotrovimab for the treatment of COVID-19 have predominantly emanated from two clinical trials-one involving outpatients and the other focusing on hospitalized patients (53,63). In alignment with the recommendations of the ESCMID, conditional suggestions have been proposed for the application of sotrovimab in high-risk, unvaccinated outpatients exhibiting mild-to-moderate COVID-19. The stipulation for this recommendation is the confirmed activity of sotrovimab against the infecting variant, determined through individual testing, or its efficacy against the predominant variants based on epidemiological data. The quality of evidence substantiating this recommendation is moderate.

In addition, conditional suggestions are in place for the use of sotrovimab in high-risk outpatients susceptible to vaccine failure with mild-to-moderate COVID-19. Analogous to the prior scenario, confirmation of sotrovimab activity against the infecting variant through individual testing or its effectiveness against predominant variants based on epidemiological data is required. However, the quality of evidence supporting this recommendation is considered very low. Regrettably, the available data do not provide adequate information to describe a recommendation for fully vaccinated patients devoid of identified risk factors for vaccine failure.

COVID-19 Convalescent Plasma

Plasma obtained from individuals who have recovered from COVID-19 may contain antibodies against SARS-CoV-2, potentially aiding in the suppression of viral replication (64). In April 2020, the FDA established an Expanded Access Program (EAP) and an Emergency Investigational New Drug pathway, allowing individuals to access convalescent plasma. The EAP served as a primary means of obtaining convalescent plasma in the United States (65), and detailed information about both programs was made available on the FDA website.

In August 2020, the FDA issued an EUA for COVID-19 convalescent plasma (CCP) for treating hospitalized COVID-19 patients. High-titer convalescent plasma has demonstrated efficacy in reducing the risk of COVID-19-associated hospitalization. However, challenges exist in the collection, screening, and quantification of convalescent plasma antibody levels. The EUA, revised in February 2021, restricted the authorization for high-titer CCP to treat hospitalized patients with COVID-19 early in their disease course or those with impaired humoral immunity. Subsequent revisions in December 2021 limited the use of CCP to outpatients or inpatients with COVID-19 having an immunosuppressive disease or receiving immunosuppressive treatment, excluding its authorization for use in immunocompetent patients (66,67).

Given the dominance of the Omicron variant in the United States, the COVID-19 Treatment Guidelines Panel strongly advises against using CCP collected before the emergence of the Omicron variant for COVID-19 treatment. Furthermore, the Panel recommends against CCP use for treating COVID-19 in hospitalized, immunocompetent patients based on strong recommendations and evidence from one or more randomized trials without major limitations. Regarding the use of high-titer CCP collected after the emergence of Omicron for treating immunocompromised patients and non-hospitalized, immunocompetent patients with COVID-19, there is insufficient evidence for a definitive recommendation. *In vitro* data suggest neutralizing activity against the Omicron variant but do not provide conclusive evidence of clinical efficacy in the current context (68,69,70,71).

The IDSA guidelines align with these recommendations, strongly advising against the use of CCP for hospitalized patients with COVID-19 based on moderate certainty of evidence. The FDA recommends administering 1 unit of convalescent plasma (approximately 200 mL), with an additional unit being considered based on clinical judgment. High-titer CCP is preferred, especially when administered early in the disease course (preferably within 3 days of diagnosis). However, predicting the antibody titer in plasma is challenging, and measurement before use is recommended when feasible. The FDA defines “high-titer” convalescent plasma on the basis of neutralizing antibody titers in specific assays (72).

The safety and efficacy of CCP during pregnancy and in pediatric patients have not been systematically evaluated in clinical trials. Published data are limited to case reports and case series, suggesting that the use of CCP in these populations should be considered on a case-by-case basis, adhering to EUA criteria. Adverse effects associated with CCP administration include transfusion-transmitted infections (e.g., HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile non-hemolytic reactions, transfusion-related acute

lung injury, transfusion-associated circulatory overload, hemolytic reactions, hypothermia, metabolic complications, and post-transfusion purpura.

Anticoagulant and Antiplatelet Therapy

It is recommended that patients with COVID-19 who are undergoing anticoagulant or antiplatelet therapies for underlying conditions should continue these medications, unless significant bleeding develops or other contraindications are present (73). For hospitalized patients with COVID-19 experiencing rapid deterioration of pulmonary, cardiac, or neurological function or sudden, localized loss of peripheral perfusion, it is recommended to evaluate the patients for thromboembolic disease (70). In hospitalized patients, low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) is preferred over oral anticoagulants because of their shorter half-lives, quick reversibility, ability for IV or subcutaneous administration, and fewer drug-drug interactions. When heparin is used, LMWH is preferred over UFH.

In non-hospitalized patients with COVID-19, the use of anticoagulants and antiplatelet therapy for the prevention of venous thromboembolism or arterial thrombosis is not recommended, except in a clinical trial. This recommendation does not apply to patients with other indications for antithrombotic therapy.

The COVID-19 treatment guidelines of the NIH recommend against routinely continuing venous thromboembolism prophylaxis after hospital discharge for patients with COVID-19, unless they have another indication or are participating in a clinical trial. For patients discharged after COVID-19-related hospitalization who are at high risk of venous thromboembolism and at low risk of bleeding, there is insufficient evidence for the Panel to recommend either for or against continuing anticoagulation unless another indication for VTE prophylaxis exists (70). The ESCMID guidelines recommend against the use of an intermediate dose of LMWH in critically ill patients with COVID-19 at a moderate evidence level. However, the use of intermediate or therapeutic doses of LMWH in non-critically ill patients with COVID-19 is recommended only in the context of a clinical trial at the moderate evidence level (62).

Supplements

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin that has been investigated for potential therapeutic effects in individuals with varying degrees of illness severity. Functioning as an antioxidant and free radical scavenger, it exhibits anti-inflammatory properties, influences cellular immunity and vascular integrity, serves as a cofactor in endogenous catecholamine generation, and has been scrutinized in numerous disease states, including COVID-19 (74,75). However, most studies on COVID-19 suffer from significant limitations, such as small sample sizes, a lack of randomization or blinding, divergent doses or formulations of vitamin C, disparate outcome measures, and heterogeneous study populations comprising patients with varying concomitant medications and COVID-19 disease severity.

To offer more definitive guidance on the role of vitamin C in the prevention and treatment of COVID-19, it is imperative to conduct adequately powered, well-designed, and meticulously executed clinical trials. At present, there is insufficient evidence to either recommend or discourage the use of vitamin C for treating COVID-19 in both non-hospitalized and hospitalized patients (70).

Vitamin D

Vitamin D plays a crucial role in bone and mineral metabolism. The expression of the vitamin D receptor in immune cells, including B-cells, T-cells, and antigen-presenting cells, coupled with the ability of these cells to synthesize the active vitamin D metabolite, suggests that vitamin D can modulate both innate and adaptive immune responses (76). This immunomodulatory capacity raises the possibility that vitamin D could offer protection against SARS-CoV-2 infection or mitigate the severity of COVID-19. Notably, vitamin D deficiency is more prevalent among older individuals and those with obesity and hypertension, conditions that have been correlated with poorer outcomes in COVID-19 patients (77). Consequently, there is currently insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19 (70). Further research is needed to establish clearer guidelines regarding the role of vitamin D in COVID-19.

Zinc

Elevated intracellular concentrations of zinc have demonstrated effective inhibition of the replication processes of various RNA viruses (78). The correlation between zinc and COVID-19, exploring the impact of zinc deficiency on the severity of COVID-19 and the potential improvement of clinical outcomes through zinc supplementation, is currently a subject of investigation. Accurately measuring zinc levels proves challenging because of its distribution as a component of diverse proteins and nucleic acids (79). To provide

comprehensive guidance on the role of zinc in preventing and treating COVID-19, there is an urgent need for adequately powered, well-designed, and rigorously conducted clinical trials.

The present lack of sufficient evidence has led the NIH Panel to refrain from making a definitive recommendation either for or against the use of zinc in treating COVID-19. The panel advises against employing zinc supplementation beyond the recommended dietary allowance (i.e., 11 mg of zinc daily for men, 8 mg for non-pregnant women) for preventing COVID-19, except within the context of a clinical trial. This stance is based on a moderate recommendation and expert opinion (70).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.İ., S.B., Concept: A.İ., S.B., Design: A.İ., S.B., Data Collection or Processing: A.İ., S.B., Analysis or Interpretation: A.İ., S.B., Literature Search: A.İ., S.B., Writing: A.İ., S.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Singh AK, Singh A, Singh R, Misra A. Remdesivir in COVID-19: a critical review of pharmacology, pre-clinical and clinical studies. Diabetes Metab Syndr 2020;14:641-648.
2. Fischer W, Eron JJ, Holman W, et al. Molnupiravir, an oral antiviral treatment for COVID-19. medRxiv [Preprint].
3. Veklury. US FDA approved product information; Foster City, CA: Bristol Gilead Sciences, Inc; October 2020. Accessed November 22, 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf
4. Angamo MT, Mohammed MA, Peterson GM. Efficacy and safety of remdesivir in hospitalised COVID-19 patients: a systematic review and meta-analysis. Infection 2022;50:27-41.
5. Agarwal A, Hunt B, Stegemann M, et al. A living WHO guideline on drugs for COVID-19. BMJ 2020;370:m3379. Update in: BMJ. 2020;371:m4475. Update in: BMJ 2021;372:n860. Update in: BMJ 2021;374:n1703. Update in: BMJ 2021;374:n2219. Erratum in: BMJ 2022;377:o1045.
6. National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Accessed September 08, 2022. Available from: https://covid19treatmentguidelines.nih.gov/
7. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Accessed September 30, 2021. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
8. Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe Covid-19 outcomes during the omicron surge. N Engl J Med 2022;387:790-798.
9. Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19. Accessed November 08, 2022. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
10. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients. Clin Infect Dis 2023;76:e342-e349. Erratum in: Clin Infect Dis 2023;76:1158-1159.
11. Epic Research. Paxlovid significantly reduces COVID-19 hospitalizations and deaths. Accessed September 29, 2022. Available from: https://www.epicresearch.org/articles/paxlovid-significantly-reduces-covid-19-hospitalizations-and-deaths
12. Ganatra S, Dani SS, Ahmad J, et al. Oral nirmatrelvir and ritonavir in nonhospitalized vaccinated patients with coronavirus disease 2019. Clin Infect Dis 2023;76:563-572.
13. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. Lancet 2022;400:1213-1222.
14. Şimşek-Yavuz S, Komsuoğlu Çelikyurt FI. An update of anti-viral treatment of COVID-19. Turk J Med Sci 2021;51:3372-3390.
15. Drożdżal S, Rosik J, Lechowicz K, et al. An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment. Drug Resist Updat 2021;59:100794.
16. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2022;386:509-520.
17. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. Accessed September 29, 2022. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
18. Chen PJ, Chao CM, Lai CC. Clinical efficacy and safety of favipiravir in the treatment of COVID-19 patients. J Infect 2021;82:186-230.
19. Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. Sci Rep 2021;11:11022. Erratum in: Sci Rep 2022;12:1996.
20. Choy KT, Wong AY, Kaewpreedee P, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Res 2020;178:104786.

21. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787-1799.
22. Recovery Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2020;396:1345-1352.
23. WHO Solidarity Trial Consortium; Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. N Engl J Med 2021;384:497-511.
24. RECOVERY Collaborative Group; Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.
25. Sebba A. Tocilizumab: the first interleukin-6-receptor inhibitor. Am J Health Syst Pharm 2008;65:1413-1418.
26. Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev 2021;3:CD013881.
27. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Shankar-Hari M, Vale CL, et al. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. JAMA 2021;326:499-518.
28. Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. Accessed August 04, 2020. Available from: https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00
29. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med 2021;384:1503-1516.
30. Reuters. Roche rheumatoid arthritis drug fails to help COVID-19 patients in Italian study. Accessed August 04, 2020. Available from: https://www.reuters.com/article/us-health-coronavirus-roche-hldg/roche-rheumatoid-arthritis-drug-fails-to-help-covid-19-patients-in-italian-study-idUSKBN23O3GG
31. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020;383:2333-2344.
32. Stebbing J, Krishnan V, de Bono S, et al. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. echanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO Mol Med 2020;12:e12697.
33. Kramer A, Prinz C, Fichtner F, et al. Janus kinase inhibitors for the treatment of COVID-19. Cochrane Database Syst Rev 2022;6:CD015209.
34. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. Lancet 2022;400:359-368. Erratum in: Lancet 2022;400:1102.
35. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021;9:1407-1418.
36. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. N Engl J Med 2021;384:795-807.
37. Stebbing J, Sánchez Nievas G, Falcone M, et al. JAK inhibition reduces SARS-CoV-2 liver infectivity and modulates inflammatory responses to reduce morbidity and mortality. Sci Adv 2021;7:eabe4724.
38. US Food and Drug Administration. Accessed November 18, 2022). Available from: https://www.fda.gov/media/143822/download
39. Kyriazopoulou E, Huet T, Cavalli G, et al. Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis. Lancet Rheumatol 2021;3:e690-e697.
40. CORIMUNO-19 Collaborative group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respir Med 2021;9:295-304.
41. Davidson M, Menon S, Chaimani A, et al. Interleukin-1 blocking agents for treating COVID-19. Cochrane Database Syst Rev 2022;1:CD015308.
42. Caricchio R, Abbate A, Gordeev I, et al. Effect of canakinumab vs placebo on survival without invasive mechanical ventilation in patients hospitalized with severe COVID-19: a randomized clinical trial. JAMA 2021;326:230-239.
43. Zhang Q, Bastard P, Liu Z, et al. Inborn errors of type I IFN immunity in patients with lifethreatening COVID-19. Science 2020;370:eabd4570.
44. Nakhlband A, Fakhari A, Azizi H. Interferon-beta offers promising avenues to COVID-19 treatment: a systematic review and meta-analysis of clinical trial studies. Naunyn Schmiedebergs Arch Pharmacol 2021;394:829-838.
45. Marovich M, Mascola JR, Cohen MS. Monoclonal antibodies for prevention and treatment of COVID-19. JAMA 2020;324:131-132.
46. Marston HD, Paules CI, Fauci AS. Monoclonal antibodies for emerging infectious diseases - borrowing from history. N Engl J Med 2018;378:1469-1472.
47. Madhi SA, Baillie V, Cutland CL, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. N Engl J Med 2021;384:1885-1898.
48. US Food and Drug Administration. Fact sheet for health care providers: Emergency Use Authorization (EUA) of bamlanivimab and etesevimab. Accessed May 20, 2021. Available from: https://www.fda.gov/media/145802/download
49. US Food and Drug Administration. Fact sheet for health care providers: Emergency Use Authorization (EUA) of REGEN-COV (casirivimab with imdevimab). Accessed May 20, 2021. Available from: https://www.fda.gov/media/145611/download
50. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021;325:632-644.
51. Huang DT, McCreary EK, Bariola JR, et al. Effectiveness of casirivimab-imdevimab and sotrovimab during a SARS-CoV-2 delta variant surge: a cohort study and randomized comparative effectiveness trial. JAMA Netw Open 2022;5:e2220957.

52. Fact Sheet For Healthcare Providers: Emergency Use Authorization For Bebtelovimab Avaliable from: https://www.fda.gov/media/156152/download
53. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2022;327:1236-1246.
54. Yu J, Collier AY, Rowe M, et al. Comparable neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 Variants. medRxiv [Preprint]. 2022.
55. Infectious Diseases Society of America guideline. Avaliable from: https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/monoclonal-antibodies/
56. Coronavirus (COVID-19) Update: FDA Authorizes New Monoclonal Antibody for Treatment of COVID-19 that Retains Activity Against Omicron Variant. Avaliable from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains
57. Westendorf K, Žentelis S, Wang L, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. bioRxiv. 2022. [Preprint].
58. IDSA Guidelines on the Treatment and Management of Patients with COVID-19. Avaliable from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-14
59. T-cells C. AZD7442 PROVENT Phase III prophylaxis trial met primary endpoint in preventing COVID-19.
60. Mode D, Stockholm LC. AstraZeneca: AZD7442 reduced risk of developing severe COVID-19 or death in TACKLE Phase III outpatient treatment trial.
61. CHASER S. Update on AZD7442 STORM CHASER trial in post-exposure prevention of symptomatic COVID-19 (Form 6-K). Available from: https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html#
62. Bartoletti M, Azap O, Barac A, et al. European society of clinical microbiology and infectious diseases guidelines for coronavirus disease 2019: an update on treatment of patients with mild/moderate disease. Clin Microbiol Infect 2022;28:1578-1590.
63. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. Lancet Infect Dis 2022;22:622-635.
64. Writing Committee for the REMAP-CAP Investigators; Estcourt LJ, Turgeon AF, et al. Effect of convalescent plasma on organ support-free days in critically Ill patients with COVID-19: a randomized clinical trial. JAMA 2021;326:1690-1702.
65. Convalescent plasma therapy. Available from: https://www.mayoclinic.org/tests-procedures/convalescent-plasma-therapy/about/pac-20486440
66. US Food and Drug Administration. Convalescent plasma: EUA letter of authorization. Accessed June 27, 2022. Available from: https://www.fda.gov/media/141477/download
67. Bégin P, Callum J, Jamula E, et al. Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial. Nat Med 2021;27:2012-24.
68. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021;397:2049-2059.
69. Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med 2021;384:610-618.
70. COVID-19 Treatment Guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/
71. Emergency Use Authorızatıon (EUA) of Covid-19 Convalescent Plasma for Treatment of Coronavırus Disease 2019 (COVID-19). Available from: https://www.fda.gov/media/141478/download
72. Clinical Memorandum. Available from: https://www.fda.gov/media/141480/download
73. Cuker A, Tseng EK, Nieuwlaat R, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. Blood Adv 2021;5:872-888.
74. Wei XB, Wang ZH, Liao XL, et al. Efficacy of vitamin C in patients with sepsis: an updated meta-analysis. Eur J Pharmacol 2020;868:172889.
75. Fisher BJ, Seropian IM, Kraskauskas D, et al. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. Crit Care Med 2011;39:1454-1460. Erratum in: Crit Care Med 2011;39:2022.
76. Aranow C. Vitamin D and the immune system. J Investig Med 2011;59:881-886.
77. People with Certain Medical Conditions. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
78. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6:e1001176.
79. Hambridge K. The management of lipohypertrophy in diabetes care. Br J Nurs 2007;16:520-524.

DOI: 10.4274/csmedj.galenos.2023.2023-4-4

ORIGINAL ARTICLE

101

Cam and Sakura Med J 2023;3(3):101-106

CSMJ

Evaluation of Colistin Performance of Phoenix M50 with Sensititre FRCOL in Clinical Isolates

Ayşe Nur Ceylan, Selda Kömeç, Abdurrahman Gülmez, Beyza Öncel

University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Medical Microbiology, İstanbul, Turkey

What is known on this subject?

The Clinical Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing, Polymyxin Breakpoints Working Group published a report in 2016 indicating that the colistin susceptibility test should only be performed with the broth microdilution method, in accordance with the rules set in International Organization for Standardization. Users of semi-automated devices should apply rigorous quality control and check with the manufacturer whether or not they are confident that their method for colistin antibiotic susceptibility test gives correct results.

What this study adds?

In this study, we compared the colistin susceptibility results of gram- negative bacteria isolated between June 2021 and June 2022, studied with Sensititre FRCOL and Phoenix M50. Thus, we aimed to determine the reliability of Phoenix M50 for reporting colistin results.

ABSTRACT

Objective: In the report published by the Clinical Laboratory Standards Institute-European Committee on Antimicrobial Susceptibility Testing (EUCAST), Polymyxin Breakpoints Working Group, they recommended that laboratories using semi-automatic devices take into account the manufacturer's recommendations and implement strict quality control (QC) studies when reporting the colistin result. In this study, we compared the one-year colistin susceptibility results with those of Sensititre FRCOL and Phoenix M50. Thus, we aimed to determine the reliability of Phoenix M50 for reporting colistin results.

Material and Methods: Extensively drug-resistant Gram-negative bacteria grown from clinical samples that arrived at the laboratory between June 2021 and June 2022 were included. MALDI-TOF Microflex LT/SH Smart MS was used for bacterial identification, and Phoenix M50 and Sensititre FRCOL were used for colistin antibiotic susceptibility testing, according to the manufacturer's recommendations. The results obtained were evaluated in line with the EUCAST criteria. QC was performed using *Escherichia coli* ATCC 25922 and NCTC 13846 strains in accordance with EUCAST recommendations.

Results: We studied 782 strains of *K. pneumoniae* (n=175), *P. aeruginosa* (n=99), and *A. baumannii* (n=508). Categorical agreements were 90.3%, 93.9%, and 94.5%. Thevery major error rate (VME) of Phoenix M50 was found to be 40.4%. Considering the VME for *K. pneumoniae, A. baumannii,* and *P. aeruginosa*, 17.7%, 75.0%, and 100.0% were found, respectively. The ME rates of *K. pneumoniae, A. baumannii, and P. aeruginosa* were 5.3%, 0.8%, and 1.1%, respectively.

Conclusion: The susceptible colistin results of these bacteria by Phoenix M50 should be confirmed by broth microdilution as the VME is above acceptable values. While the results of colistin detection resistant by Phoenix M50 could be reported for *P. aeruginosa* and *A. baumannii*,it needs to be confirmed with broth microdilution for *K. pneumoniae*.

Keywords: Colistin susceptibility test, broth microdilution, Phoenix M50, *K. pneumoniae*, *A.baumannii*

Address for Correspondence: Ayşe Nur Ceylan MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Medical Microbiology, İstanbul, Turkey

Phone: +90 506 761 57 71 **E-mail:** aysenurceylan1011@gmail.com **ORCID ID:** orcid.org/0000-0002-0049-6873

Received: 27.04.2023 **Accepted:** 28.11.2023

Introduction

Colistin, initially isolated from the soil bacterium *Paenibacillus polymyxa* subsp. *colistinus* in 1947, is a polypeptide antibiotic effective against Gram-negative bacteria (1). Although colistin was used for years after its discovery, because of its high toxicity, it was replaced with other less toxic antibiotic groups in the 1970s. The rapid increase in multidrug-resistant Gram-negative bacteria recently has again led colistin to come into question as a treatment option (2).

While determining the harm- benefit balance of this highly toxic drug, the sensitivity result from the laboratory is critical in terms of guiding clinicians. In addition, the Clinical Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) Polymyxin Breakpoints Working Group published a report in 2016 indicating that the colistin susceptibility test should only be performed with broth microdilution method, in accordance with the rules set in International Organization for Standardization (ISO) standards, and other methods, including agar dilution, disc diffusion, and gradient strip test, should not be used (3). Although the recommendations favor using the microdilution method, its use is limited as it is time-consuming and expensive, and the results are dependent on the experience of the laboratory staff.

Finally, this report was updated in May 2020 and includes the following statement: "we could not systematically evaluate semi-automated colistin methods, but by sending isolates with minimum inhibitory concentration (MIC) values in the non-susceptible range to colleagues around the world, we have disclosed the frequent occurrence of very major errors." Users of semi-automated devices should apply rigorous quality control (QC) and check with the manufacturer whether or not they are confident that their method for colistin AST gives correct results. QC of colistin must be performed with both a susceptible QC strain (*Escherichia coli* ATCC 25922 or *Pseudomonas aeruginosa* ATCC 27853) and the colistin-resistant *E. coli* NCTC 13846 (*mcr-1* positive). For *E. coli* NCTC 13846, the colistin MIC target value is 4 mg/L and should only occasionally be 2 or 8 mg/L (4). When the 2023 guidelines of these two organizations are examined, EUCAST states that the only method that can be used for colistin is the broth microdilution method, and CLSI states that broth microdilution, agar dilution, and disk elution methods can be used for colistin (5,6).

Our institution is a large hospital with a capacity of 2,700 beds, serving national and international patients. Extensive drug-resistant Gram-negative bacteria grow, especially in samples taken from hospitalized patients, and the use of colistin for treating these microorganisms is inevitable. Phoenix M50 (semi- automated system) is used for antibiotic susceptibility tests in our laboratory. Colistin susceptibility tests for extensively drug-resistant Gram-negative bacteria are reported with the results of Sensititre FRCOL. In this study, we compared the susceptibility results of colistin in Gram-negative bacteria isolated between June 2021 and June 2022, which were studied with Sensititre FRCOL (commercial broth microdilution system) and Phoenix M50. Thus, we aimed to determine the reliability of Phoenix M50 in reporting colistin susceptibility test results.

Material and Methods

In this study, extensively drug-resistant *K. pneumoniae, A. baumannii, and P. aeruginosa* isolates grown from clinical samples that arrived at the laboratory between June 2021 and June 2022 were included. MALDI-TOF Microflex LT/SH Smart MS (Bruker Daltonics, Germany) was used for bacterial identification, and Phoenix M50 (BD Diagnostics, USA) and Sensititre FRCOL (Thermo Scientific, West Sussex, UK) were used for colistin antibiotic susceptibility testing, according to the manufacturer's recommendations. The results obtained were evaluated in line with the EUCAST criteria (7,8,9). The study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (decision no: 2022-138, date: 27.04.2022).

According to EUCAST version 12.0 recommendations, MIC breakpoints of colistin ≤2 mg/L for *Klebsiella pneumoniae* and *Acinetobacter baumannii*; ≤4 mg/L for *P. aeruginosa* considered susceptible and >2 mg/L for *K. pneumoniae* and *A. baumannii;* >4 mg/L *P. aeruginosa* considered resistant. QC studies for Phoenix M50 and Sensititre FRCOL were regularly performed with *E. coli* ATCC 25922 and *E. coli* NCTC 13846 strains (4).

The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of the Phoenix M50 were evaluated based on the sensitivity FRCOL. Results were evaluated according to the ISO criteria. Categorical aggrement (aggrement of sensitive and resistant results of the two systems), major error (ME) (susceptible by Sensititre FRCOL, but resistant by the Phoenix M50), and very major error (VME) (resistant by Sensititre FRCOL, but susceptible by the Phoenix M50) of the Phoenix M50 were calculated according to the Sensititre FRCOL [categorical agreement (CA) >90%; ME and VME <3%] (10).

Statistical Analysis

Statistical analyses were conducted with using "IBM SPSS Statistics" (version 26.0, Chicago) statistical software. The agreements between the Phoenix M50 and sensitivity were evaluated using Cohen's Kappa (κ) analysis. A κ value above 0.80 was interpreted as excellent, between 0.60 and ≥0.80 as good, between 0.60 and ≥0.40 as moderate, and between 0.40 and ≥0.20 as low moderate agreement.

Results

The susceptibility results of all isolates studied with Phoenix M50 and sensitivity FRCOL are shown in Tables 1 and 2.

Susceptibility test results in *K. pneumoniae* isolates revealed a significant correlation between Sensititre and Phoenix M50 (κ: 0.784, p<0.001; Figure 1A). Moreover, susceptibility results in *P. aeruginosa* revealed a low correlation between Sensititre and Phoenix M50 (κ: 0.004, p=0.883; Figure 1B). The susceptibility results in *A. baumannii* revealed a low-significant correlation between Sensititre and Phoenix M50 (κ: 0.149, p<0.001; Figure 1C).

The sensitivity of Phoenix M50 was 94.38% [confidence interval (CI): 92.43%-95.96%], specificity was 84.29% (CI: 73.62%-91.89%), PPV was 98.39% (CI: 97.26%-99.06%), and NPV was 59.60% (CI: 51.78%-66.96%) in all strains (Table 3).

For *K. pneumoniae*, the sensitivity of Phoenix M50 was 90.68% (CI: 83.93%-95.25%), specificity was 89.47% (CI: 78.48%-96.04%), PPV was 94.69% (CI: 89.30%-97.44%), and NPV was 82.26% (CI: 72.40%-89.13%) (Table 4).

For *P. aeruginosa*, the sensitivity of Phoenix M50 was 94.90% (CI: 88.49%-98.32%), specificity was 0.00% (CI: 0.0%-97.50%), PPV was 98.94% (CI: 98.89%-98.98%), and NPV was 0% (CI: -) (Table 4).

For *A. baumannii*, the sensitivity of Phoenix M50 was 99.16% (CI: 97.86%-99.77%), specificity was 25.0% (CI: 11.46%-43.40%), PPV was 95.16% (CI: 94.15%-96.00%), and NPV was 66.67% (CI: 38.88%-86.28%) (Table 4).

When the susceptibility test results of 782 isolates were analyzed, the CA was 93.5%. Among 782 isolates, *A. baumannii* (508), *K. pneumoniae* (175), and *P. aeruginosa* (99) were analyzed separately and CA was 94.5%, 90.3%, and 93.9%, respectively. Essential agreement could not be calculated because the Phoenix M50 device had few colistin wells.

The percentages of VME for *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* were 17.7%,100.0% and 75.0%, respectively. In contrast, the percentages of ME for *K. pneumoniae*, *P. aeruginosa* and *A. baumannii* were 5.3%, 1.1% and 0.8%, respectively.

Table 1. **MIC values of all isolates by sensitivity Sensititre FRCOL**

Organism	0.25	0.5	1	2	4	8	16	32	64	≥128	Total	Susceptibility
Acinetobacter baumannii	1	108	316	51	11	7	8	4	0	2	**508**	93.7%
Klebsiella pneumoniae	5	66	19	23	15	7	16	15	6	3	**175**	64.5%
Pseudomonas aeruginosa	1	5	23	61	4	3	1	0	1	0	**99**	94.9%

MIC: Minimum inhibitory concentration

Table 2. **MIC values of all isolates by Phoenix M50**

Organism	≤1	2	4	>4	Total	Susceptibility
Acinetobacter baumannii	494	2	2	10	**508**	97.6%
Klebsiella pneumoniae	118	0	0	57	**175**	67.4%
Pseudomonas aeruginosa	98	0	0	1	**99**	98.9%

MIC: Minimum inhibitory concentration

Table 3. **Comparison of antibiotic sensitivity results of Phoenix M50 with sensitivity FRCOL**

		Phoenix M50		
		Susceptible (n)	Resistant (n)	Total (n)
Sensititre	Susceptible	672	11	683
	Resistant	40	59	99
	Total	712	70	782

MIC results of colistin-susceptible *E. coli* ATCC 25922 and colistin-resistant *E. coli* NCTC 13846 were <1 mg/L and 4 mg/L, respectively.

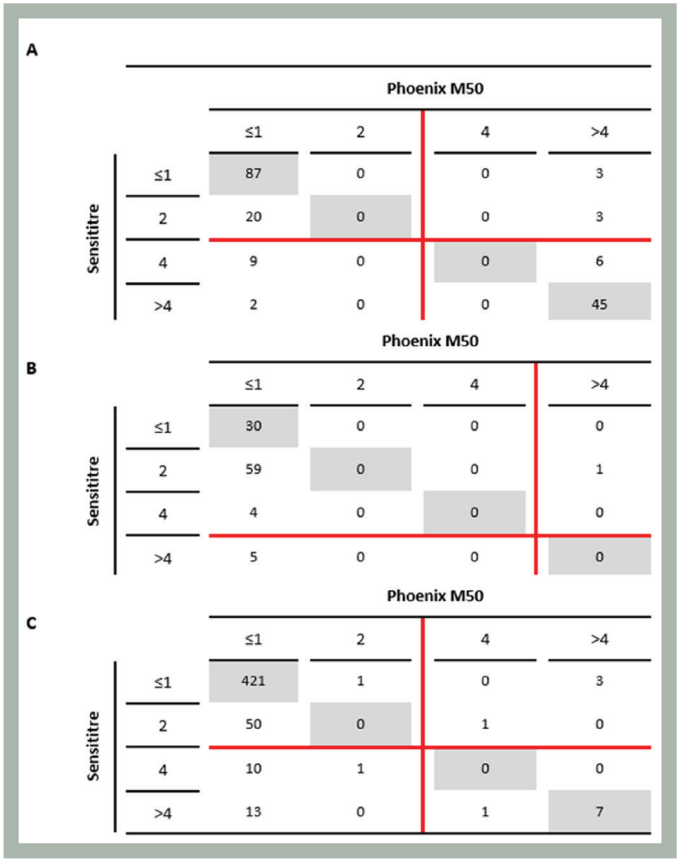

Figure 1. Distribution of MIC values for *K. pneumoniae* (A), *P. aeruginosa* (B), and *A. baumannii* (C) determined using Sensititre FRCOL and Phoenix M50

MIC: Minimum inhibitory concentration

Discussion

Colistin is one of the last-choice drugs that is preferred for treating extensively drug- resistant and pan-drug-resistant Gram-negative bacteria, including *P. aeruginosa, A. baumannii, and K. pneumoniae* infections (7). Therefore, determining colistin sensitivity with accurate and reliable tests is very important considering the benefit it will provide for the patient's treatment. In 2017, the CLSI and EUCAST working group recommended (9) applying the reference BMD test using a polystyrene microplate and colistin sulfate salt according to the recommendations of the ISO-20776-1 to determine colistin susceptibility (10). The EUCAST development laboratory has published these results by comparing various commercial broth microdilution systems, including the sensititre, with the reference method. Sensititre stated that the commercial broth microdilution system can be used to test the susceptibility of colistin (7). According to this study, essential agrement for sensitivity was 96% and CA was 95%. No VME was found among the 75 isolates; only 4 isolates had ME. In different studies, commercial broth microdilution systems and reference methods were compared, and it was determined that colistin sensitivity could be studied with commercial broth microdilution systems (7,11,12). The CLSI and EUCAST working group reported, which was updated in 2020; "Users of semi-automated devices should apply rigorous QC and check with the manufacturer whether or not they are confident that their method for colistin AST gives correct results. QC of colistin must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa*

Table 4. Comparison of antibiotic sensitivity results of Phoenix M50 with sensitivity FRCOL for *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*

			Phoenix M50		
K. pneumonia	**Sensititre**		**Susceptible (n)**	**Resistant (n)**	**Total (n)**
		Susceptible (n)	107	6	113
		Resistant (n)	11	51	62
		Total (n)	118	57	175
P. aeruginosa	**Sensititre**		**Susceptible (n)**	**Resistant (n)**	**Total (n)**
		Susceptible (n)	93	1	94
		Resistant (n)	5	0	5
		Total (n)	98	1	99
A. baumannii	**Sensititre**		**Susceptible (n)**	**Resistant (n)**	**Total (n)**
		Susceptible (n)	472	4	476
		Resistant (n)	24	8	32
		Total (n)	496	12	508

ATCC 27853) and colistin-resistant *E. coli* NCTC 13846 (*mcr-1* positive). For *E. coli* NCTC 13846, the colistin MIC target value is 4 mg/L and should only occasionally be 2 or 8 mg/L." as proposal (4). In our laboratory, Phoenix M50 is routinely used for antibiotic susceptibility testing, and a Sensititre™ FRCOL (commercial BMD) is used for colistin susceptibility testing in line with the recommendations of EUCAST. For both systems, QC strains (*E. coli* ATCC 25922 and *E. coli* NCTC 13846) were tested weekly. Since the QC results for colistin with Phoenix M50 were within the recommended mean limits without exception, we thought that we could report the colistin susceptibility with Phoenix M50, instead of the more expensive and difficult to implement BMD. Based on this thought, we aimed to retrospectively evaluate our one-year data and compare the results of colistin using Phoenix M50 and Sensititre FRCOL, according to the ISO criteria (10).

In a study conducted in Greece in 2017, the colistin susceptibility of 117 *A. baumannii* strains was compared with the semi-automatic systems and reference method, according to ISO criteria (10). The CA of Vitek 2 and Phoenix 100 was found to be 89.7% and 88.9%, respectively, and VME rates of 37.9% and 41.4%, respectively (13). In another study, CA for Vitek 2 was 88.2%, and the ME was 36.0% (12). According to the study by Carretto et al. (14), comparing the reference method and the Phoenix 100, the CA was found to be 96.8%, while the ME was 10%. In another study (15), the performance of Phoenix M50 was evaluated using 533 Gram-negative clinical isolates, and BMD was used as the reference method for colistin performance. In the same study, CA was found for 131 Gram-negative bacteria, 96 of which were colistin-resistant, with a VME of 0% and a ME of 1.5% (15). A study conducted in India in 2021 included 25 clinical isolates (14 *E. coli* and 11 *K. pneumoniae*) and compared the colistin susceptibility performance of the Phoenix M50 system with the Mikrolatest MIC colistin susceptibility testing kit as a reference method. The ratio of VME and ME for colistin in the Phoenix M50 system was 0% (16). We compared Phoenix M50 and Sensititre FRCOL, a commercial BMD test that EUCAST indicated can be used for colistin sensitivit. When we examined the susceptibility results of 782 isolates, the CA was found to be 93.5%. *A. baumannii* (n=508)*, K. pneumoniae* (n=175) *and P. aeruginosa* (n=99) were analyzed separately, and the CA was calculated as 94.5%, 90.3%, and 93.9%, respectively.

Although the CA rates seem high (>90%), when the incompatible results are examined in detail, the percentages of VME for *K. pneumoniae, P. aeruginosa,* and *A. baumannii* were 17.7%, 100.0% and 75.0%, respectively. In contrast, the percentages of ME for *K. pneumoniae, P. aeruginosa,* and *A. baumannii* were 5.3%, 1.1%, and 0.8%, respectively.

Based on these percentages, it appears that Phoenix M50 "susceptible" results for colistin shouldnot be reported for these bacteria. The ME rates for *A. baumannii, K. pneumoniae,* and *P. aeruginosa* isolates were 0.8%, 5.3%, and 1.1%, respectively. When compared with Sensititre, it is seen that "resistant" results gained from Phoenix M50 could be reported for *A. baumannii* and *P. aeruginosa*, but should not be reported for *K. pneumoniae* (17).

Broth microdilution is one of the most reliable methods for reporting colistin susceptibility. However, in addition to the difficulties and cost in implementation, there are procedures that must be applied in the study to ensure accurate results. As possible contamination may give erroneous results, the test should be studied in a biosafety cabinet and must be performed with a single experienced person to ensure a standardization. In our study, as a final control, we also inoculated the suspension on 5% sheep blood agar after BMD procedures to check whether it is pure or not.

Semi-automated systems are frequently used in clinical microbiology laboratories to study susceptibility testing because they reduce workload, perform data management with expert system analysis software, and provide results in a shorter time than conventional methods (18).

Conclusion

As a result, it has been seen that susceptible colistin results on the Phoenix M50 for *K. pneumoniae*, *P. aeruginosa,* and *A. baumannii* should be validated by broth microdilution, since the ME rates are above acceptable values. While the results of colistin detection resistant by Phoenix M50 could be reported for *P. aeruginosa* and *A. baumannii*, it needs to be confirmed with broth microdilution for *K. pneumoniae*. Most of the isolates in our study were susceptible. Studies with larger sample sizes are required, including more colistin-resistant isolates.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (decision no: 2022-138, date: 27.04.2022).

Informed Consent: Not necessary.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.N.C., S.K., A.G., Design: A.N.C., A.G., Data Collection or Processing: A.N.C., S.K., A.G., B.Ö., Analysis or Interpretation: A.N.C., A.G., Literature Search: A.N.C., S.K., A.G., B.Ö., Writing: A.N.C., S.K., A.G., B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Ainsworth GC, Brown AM, Brownlee G. Aerosporin, an antibiotic produced by *Bacillus aerosporus* Greer. Nature 1947;159:263.
2. Poirel L, Jayol A, Nordmann P. Polymyxins: antibacterial activity, susceptibility testing, and resistance mechanisms encoded by plasmids or chromosomes. Clin Microbiol Rev 2017;30:557-596.
3. Bakthavatchalam YD, Veeraraghavan B. Challenges, issues and warnings from CLSI and EUCAST Working Group on polymyxin susceptibility testing. J Clin Diagn Res 2017;11:DL03-DL04.
4. EUCAST. Antimicrobial susceptibility testing of colistin-problems detected with several commercially available products. EUCAST warnings concerning antimicrobial susceptibility testing products or procedures. 2020.
5. CLSI. Performance standards for antimicrobial susceptibility testing. 33rd ed. CLSI supplement M100. Clinical and Laboratory Standards Institute. 2023.
6. EUCAST. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. 2023.
7. Matuschek E, Åhman J, Webster C, Kahlmeter G. Antimicrobial susceptibility testing of colistin - evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Acinetobacter* spp. Clin Microbiol Infect 2018;24:865-870.
8. Andrews JM. Determination of minimum inhibitory concentrations. J Antimicrob Chemother 2001;48(Suppl 1):5-16.
9. EUCAST. Recommendations for MIC determination of colistin (polymyxin E) As recommended by the joint CLSI-EUCAST Polymyxin Breakpoints Working Group; 2016.
10. ISO 20776-2:2021. Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices - Part 1: Broth microdilution reference method for testing the *in vitro* activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases ISO; 2021.
11. Kansak N, Aslan M, Adaleti R, Aksaray S. Evaluation of the two commercial methods based on broth microdilution against reference microdilution method for *Klebsiella pneumoniae* isolates. Mikrobiyol Bul 2020;54:606-612.
12. Chew KL, La MV, Lin RTP, Teo JWP. Colistin and polymyxin B susceptibility testing for carbapenem-resistant and *mcr*-positive Enterobacteriaceae: comparison of sensititre, MicroScan, Vitek 2, and etest with broth microdilution. J Clin Microbiol 2017;55:2609-2616.
13. Vourli S, Dafopoulou K, Vrioni G, Tsakris A, Pournaras S. Evaluation of two automated systems for colistin susceptibility testing of carbapenem-resistant *Acinetobacter baumannii* clinical isolates. J Antimicrob Chemother 2017;72:2528-2530.
14. Carretto E, Brovarone F, Russello G, et al. Clinical validation of sensi test colistin, a broth microdilution-based method to evaluate colistin MICs. J Clin Microbiol 2018;56:e01523-e01517.
15. Hong JS, Kim D, Kang DY, et al. Evaluation of the BD Phoenix M50 Automated microbiology system for antimicrobial susceptibility testing with clinical isolates in Korea. Microb Drug Resist 2019;25:1142-1148.
16. Bhatia M, Singh RI, Rani D, et al. Comparative evaluation of two automated ID/AST systems and mikrolatest kit in assessing the *in vitro* colistin susceptibility of carbapenem-resistant Enterobacteriaceae isolates: a single-center exploratory study from North India. J Pharm Bioallied Sci 2022;14:52-55.
17. Humphries RM, Ambler J, Mitchell SL, et al. CLSI methods development and standardization working group best practices for evaluation of antimicrobial susceptibility tests. J Clin Microbiol 2018 56:e01934-e01917.
18. Karlowsky JA, Richter SS. Antimicrobial susceptibility testing systems. Manual of Clinical Microbiology 2015;1274-1285.

DOI: 10.4274/csmedj.galenos.2023.2023-10-2

ORIGINAL ARTICLE

107

Cam and Sakura Med J 2023;3(3):107-112

CSMJ

Investigation of Non-cardiac Findings in Conotruncal Heart Diseases in Children

Gülce Gökmen*, Halise Zeynep Genç, İbrahim Cansaran Tanıdır, Erkut Öztürk*

University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Cardiology, İstanbul, Turkey

*Contributed equally to the study.

What is known on this subject?

Conotruncal heart diseases are a group of cardiac malformations heterogeneous from an anatomic standpoint but with a common embryologic origin: abnormal rotation of the outflow tract.

What this study adds?

In children with conotruncal heart defects, routine extracardiac evaluation is beneficial and assists in improving surgical outcomes.

ABSTRACT

Objective: Individuals with conotruncal heart disease (CHD) often exhibit a range of associated anomalies. Our study aimed to investigate the frequency of non-cardiac comorbidities in patients with CHD.

Material and Methods: Our study was a hospital-based, single-center, retrospective, observational study conducted at our clinic between August 1, 2020, and November 1, 2022. The study included 179 cases, both male and female, aged between 0 day and 6 months, with CHDs diagnosed. Data from each patient, including gender, complete blood count, biochemical and coagulation tests, abdominal ultrasound (USG), cranial USG, and serum immune globulin levels, were evaluated.

Results: In 14.5% of the 179 patients included in the study, abnormal renal function test results were detected. In 18.4% of the cases, abnormal liver function test results were detected. When evaluated according to the diagnosis group, among the 21 patients diagnosed with interrupted aortic arch (IAA), 7 (33.3%) had abnormal liver function test results. In 25.7% of the cases, the leukocyte count was abnormal. In 12.8% of the cases, the platelet count in the complete blood count was abnormal. In 10.6% of the cases, abnormal results were found in the coagulation tests. In 21.2% of the cases, abnormal results were found in the serum immunoglobulin (Ig) and Ig subgroups. When evaluated according to the diagnosis group, among the 21 patients diagnosed with IAA, 10 (47.6%) had abnormal results. In 19% of the cases, abdominal USG results were pathological, and in 9.5% of the cases, cranial USG results were pathological.

Conclusion: CHD in children may be accompanied by non-cardiac problems that cause hemodynamic and systemic problems and affect organ systems. Routine liver function tests, renal function tests, coagulation, complete blood count, immune screening, and abdominal USG evaluation may be useful to improve the quality of life of patients and reduce morbidity and mortality while waiting for necessary surgical interventions.

Keywords: Child, conotruncal heart diseases, extracardiac manifestations

Address for Correspondence: Gülce Gökmen MD, Erkut Öztürk MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatric Cardiology, İstanbul, Turkey

Phone: +90 212 909 60 00 **E-mail:** drgulcegkmn@gmail.com, erkut_ozturk@yahoo.com

ORCID ID: G.G. - orcid.org/0009-0004-9820-1050, E.Ö. - orcid.org/0000-0002-1762-3269

Received: 31.10.2023 **Accepted:** 27.12.2023

Introduction

Congenital heart defects are the most common type of birth defect and one of the major causes of perinatal mortality, with a worldwide prevalence of 1 per 100 births (1). Because of the heterogeneity within the group of Conotruncal heart diseases (CHDs), epidemiologic studies often focus on subgroups of conditions, such as conotruncal heart defects (CTDs). Conotruncal defects are a subset of serious and relatively common CHDs, defined as defects of the cardiac outflow tracts of the great arteries.

This class of defects includes transposition of the great arteries (TGA), tetralogy of Fallot (TOF), double outlet right ventricle (DORV), ventricular septal defect with pulmonary atresia (VSD-PA), interrupted aortic arch (IAA), double outlet left ventricle (DOLV), and truncus arteriosus (TA). The manifestations and prognoses of CHD in children vary significantly. In addition to these diseases, non-cardiac problems that cause serious hemodynamic and systemic issues and affect organ systems can also occur (2,3).

Patients with CTDs often require early surgical treatment and have high mortality and morbidity (4).

These findings can impact the diagnosis and treatment processes of patients. Our study aimed to investigate the frequency of extracardiac manifestations in patients with CHD.

Material and Methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Başaksehir Çam and Sakura City Hospital Local Ethics Committee (decision no: 2022.04.130).

Our study was a hospital-based, single-center, retrospective, observational study conducted at the Department of Pediatric Cardiology, Child Health and Diseases Division, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, between August 1, 2020, and November 1, 2022. The study included 179 cases, both male and female, aged between 0 day and 6 months, diagnosed with CHD such as TGA, TOF, DORV, VSD-PA, IAA, and TA. Data from each patient, including gender, complete blood count, biochemical and coagulation tests, abdominal ultrasound (USG), cranial USG, and serum immunoglobulin levels (IgA, IgG, IgM, and IgG subclasses: IgG1, IgG2, IgG3, IgG4), were evaluated.

In the blood tests obtained from patients, parameters such as white blood cell count, platelet count, and biochemical factors including renal function tests [urea, creatinine (Cr)] and liver function tests (alanine transaminase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, albumin), as well as coagulation tests (prothrombin time, activated partial thromboplastin time, fibrinogen), and serum immune globulin levels were compared to age-appropriate reference ranges, and values falling outside these ranges were considered abnormal.

The USG results were evaluated by the radiology department of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital.

Statistical Analysis

Statistical analyses were performed using SPSS 25 program (SPSS Inc., Chicago, IL, USA). Frequencies and percentages are presented for categorical data. Median values and interquartile ranges were used for variables with non-normal distributions, whereas those with normal distributions were described using the mean and standard deviation.

Results

The primary diagnosis of patients is shown in Table 1. Extracardiac findings of patients are shown in Table 2. In 14.5% of the 179 patients included in the study, abnormal renal function test results were detected. When evaluated according to the diagnosis groups, among the 55 patients diagnosed with TGA, 17 (30.9%) had abnormal renal function test results. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 21 patients diagnosed with IAA, 2 (9.5%) had abnormal results. Among the 13 patients diagnosed with TA, 1 (7.7%) had abnormal results. Among the 15 patients diagnosed with DORV, 1 (6.1%) had abnormal results. Among the 49 patients diagnosed with TOF,

Table 1. Gender and diagnosis of patients

		n	%
Total		179	100.0
	Female	76	42.5
	Male	103	57.5
TGA		55	30.7
TOF		49	27.4
DORV		15	8.4
VSD-PA		19	10.6
IAA		21	11.7
DOLV		7	3.9
TA		13	7.3

TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, VSD-PA: Ventricular septal defect with pulmonary atresia, IAA: Interrupted aortic arch, DOLV: Double outlet left ventricle, TA: Truncus arteriosus

3 (6.1%) had abnormal results. No abnormalities were found in the renal function test results of the 19 patients diagnosed with VSD-PA. There was a statistically significant difference among the parameters when evaluating renal function tests according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.02).

In 18.4% of the cases, abnormal liver function test results were detected. When evaluated according to the diagnosis groups, among the 21 patients diagnosed with IAA, 7 (33.3%) had abnormal liver function test results. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 55 patients diagnosed with TGA, 15 (27.3%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 4 (21.1%) had abnormal results. Among the 15 patients diagnosed with DORV, 2 (13.3%) had abnormal results. Among the 13 patients diagnosed with TA, 1 (7.7%) had abnormal results. Among the 49 patients diagnosed with TOF, 2 (4.1%) had abnormal renal function test results. There was a statistically significant difference among the parameters when evaluating liver function tests according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.025).

Table 2. Evaluation of blood tests in conotruncal diseases

	Normal test result n (%)	Anormal test result n (%)
Renal function test	153 (85.5)	26 (14.5)
Liver function test	146 (81.6)	33 (18.4)
Leukocyte counts	133 (74.3)	46 (25.7)
Platelet counts	156 (87.2)	23 (12.8)
Coagulation test	160 (89.4)	19 (10.6)
Immune function test	141 (78.8)	38 (21.2)

In 25.7% of the cases, the leukocyte count was abnormal. When evaluated according to the diagnosis groups, among the 55 patients diagnosed with TGA, 26 (47.3%) had abnormal leukocyte counts. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 4 (21.1%) had abnormal results. Among the 15 patients diagnosed with DORV, 3 (20%) had abnormal results. Among the 21 patients diagnosed with IAA, 4 (19%) had abnormal results. Among the 49 patients diagnosed with TOF, 17 (14.3%) had abnormal leukocyte counts. There was a statistically significant difference among the parameters when evaluating leukocyte counts according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.01).

In 12.8% of the cases, the platelet count in the complete blood count was abnormal. In the complete blood count, the platelet count was abnormal in 18.2% of the patients diagnosed with TGA, 14.3% of the patients diagnosed with IAA and DOLV, 10.5% of the patients diagnosed with VSD-PA, 10.2% of the patients diagnosed with TOF, and 7.7% of the patients diagnosed with TA. There was no statistically significant difference among the parameters when evaluating platelet counts according to the diagnoses (p=0.894).

Table 3 summarizes the results of coagulation parameters according to diagnoses. In 10.6% of the cases, abnormal results were found in coagulation tests. When evaluated according to the diagnosis groups, among the 55 patients diagnosed with TGA, 12 (21.8%) had abnormal coagulation test results. Among the 7 patients diagnosed with DOLV, 1 (14.3%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 2 (10.5%) had abnormal results. Among the 21 patients diagnosed with IAA, 2 (9.5%) had abnormal results. Among the 15 patients diagnosed with DORV, 1 (6.7%) had abnormal

Table 3. Evaluation of coagulation tests according to diagnoses in conotruncal heart diseases

Diagnosis	Total number of patients	Normal value			Non-reference value (abnormal)			p value
		Number	Original diagnosis %	Total patient %	Number	Original diagnosis %	Total patient %	
TGA	55	43	78.2	24	12	21.8	6.7	
TOF	49	48	98	26.8	1	2	0.6	
DORV	15	14	93.3	7.8	1	6.7	0.6	
VSD-PA	19	17	89.5	9.5	2	10.5	1.1	**0.043**
IAA	21	19	90.5	10.6	2	9.5	1.1	
DOLV	7	6	85.7	3.4	1	14.3	0.6	
TA	13	13	100	7.3	-	-	-	

TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, VSD-PA: Ventricular septal defect with pulmonary atresia, IAA: Interrupted aortic arch, DOLV: Double outlet left ventricle, TA: Truncus arteriosus

results. Among the 49 patients diagnosed with TOF, 1 (2%) had abnormal coagulation test results. There was a statistically significant difference among the parameters when evaluating coagulation tests according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.043).

In Table 4, Ig levels are shown according to the diagnoses. In 21.2% of the cases, abnormal results were found in the serum Ig and Ig subgroups. When evaluated according to the diagnosis groups, among the 21 patients diagnosed with IAA, 10 (47.6%) had abnormal results. Among the 13 patients diagnosed with TA, 6 (46.2%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 6 (31.6%) had abnormal results. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 49 patients diagnosed with TOF, 10 (20.4%) had abnormal results. Among the 15 patients diagnosed with DORV, 3 (20%) had abnormal results. Among the 55 patients diagnosed with TGA, 1 (1.8%) had abnormal results in serum Ig and Ig subgroups, indicating immunodeficiency. There was a statistically significant difference among the parameters when evaluating Ig tests according to the diagnoses, and the likelihood of pathological results was significantly increased (p<0.001).

In 19% of the cases, abdominal USG results were pathological, and in 9.5% of the cases, cranial USG results were pathological. Among abdominal USG pathologies, 70% were related to the kidneys (increased renal parenchymal echogenicity in 10 patients, renal pelvis dilation in 8 patients, horseshoe kidney in 4 patients, and one patient with dysplastic kidney). The remaining 30% involved liver and biliary tract pathology (increased liver echogenicity in 7 patients, increased gallbladder wall thickness, and dilation in 4 patients). When evaluated according to the diagnosis groups, among the 15 patients diagnosed with DORV, 7 (46.7%) had pathological abdominal USG results. Among the 55 patients diagnosed with TOF, 13 (23.6%) had pathological findings. Among the 19 patients diagnosed with VSD-PA, 4 (21.1%) had pathological findings. Among the 21 patients diagnosed with IAA, 4 (19%) had pathological findings. Among the 13 patients diagnosed with TA, 2 (15.4%) had pathological findings. Among the 49 patients diagnosed with TOF, 4 (8.2%) had pathological results in abdominal USG. No pathological abdominal USG results were found in the 7 patients diagnosed with DOLV. There was a statistically significant difference among the parameters when evaluating abdominal USG results (p=0.032). Cranial USG evaluation showed pathological results in 17 (9.5%) of all conotruncal patients. the cranial pathologies detected in USG were as follows: 8 cases of corpus callosum abnormalities, 5 cases of hydrocephalus, 2 cases of cerebellar atrophy, and 2 cases of choroid plexus cyst. Among these patients, 4 had TGA (2.2%), 5 had TOF (2.8%), 3 had PA-VSD (1.7%), 3 had IAA (1.7%), and 2 had DOLV (1.1%). There was no statistically significant difference among the parameters when evaluating cranial USG results according to the diagnoses (p>0.05).

Discussion

In this study, we investigated abnormal laboratory results in children with CHD and explored extracardiac manifestations. The number of studies conducted in this field is limited. Our study suggests the need for better risk classification and improved resource allocation for future patients.

Regarding white blood cell counts, 25.7% of cases had abnormal results. Patients diagnosed with TOF exhibited a higher frequency of abnormal white blood cell counts (47.4%, p=0.01) compared with other diagnoses, whereas TGA cases did not show abnormal counts. Among specific diagnoses, DOLV had a frequency of 28.6%, VSD-PA had 21.1%, DORV had 20%, IAA had 19%, and Fallot tetralogy (FT) had 14.3%

Table 4. Evaluation of immune function tests according to diagnoses in conotruncal heart diseases

Diagnosis	Total number of patients	Normal value			Non-reference value (abnormal)			p value
		Number	Original diagnosis %	Total patient %	Number	Original diagnosis %	Total patient %	
TGA	55	54	98.2	30.2	1	1.8	0.6	
TOF	49	39	79.6	21.8	10	20.4	5.6	
DORV	15	12	80	6.7	3	20	1.7	
VSD-PA	19	13	68.4	7.3	6	31.6	3.4	**<0.001**
IAA	21	11	52.4	6.1	10	47.6	5.6	
DOLV	7	5	71.4	2.8	2	28.6	1.1	
TA	13	7	53.8	3.9	6	46.2	3.4	

TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, VSD-PA: Ventricular septal defect with pulmonary atresia, IAA: Interrupted aortic arch, DOLV: Double outlet left ventricle, TA: Truncus arteriosus

abnormal white blood cell count frequencies (p=0.01). However, it is worth noting that a limited number of studies have been conducted in this area.

Trombocytopenia is a common finding in patients with 22q11.2 deletion syndrome. Lawrence et al. (5) found that approximately 70% of patients exhibited thrombocytopenia when compared with control subjects. Our study yielded incongruent results with these data. No statistically significant differences were observed in thrombocyte counts between different diagnoses (p>0.05).

In our study, 14.5% of cases had abnormal blood urea nitrogen, Cr, and kidney function test (KFT) results. Among the specific diagnoses, TGA and DOLV cases showed the highest rates of abnormalities (30.9% and 28.6%, respectively). No abnormalities were found in the KFT results of VSD-PA cases. The evaluation of KFT results based on diagnoses revealed statistically significant differences between parameters (p=0.02), indicating the need for close monitoring of KFT tests.

For liver function tests, 18.4% of cases yielded abnormal results. Evaluating results according to diagnoses, 33.3% of IAA cases, 28.6% of DOLV cases, 27.3% of TOF cases, 21.1% of VSD-PA cases, and 13.3% of DORV cases showed abnormalities. The rates were lower in TA and FT cases (7.7% and 4.1% respectively, p=0.025). Close monitoring of LFT tests is recommended in CHDs.

Majiyagbe et al. (6) found a prevalence of 37.1% for coagulation abnormalities in children with congenital heart diseases and 7.1% in control groups. They also reported a significantly higher prevalence of coagulation abnormalities in cyanotic CHD patients compared to acyanotic ones (57.1% vs. 17.1%). They found significant associations between oxygen saturation levels, coagulation abnormalities, and cyanotic CTDs. Detection of coagulation anomalies is crucial for improving the quality of life and reducing morbidity and mortality in cyanotic children with CTDs. Our study identified abnormal coagulation test results in 10.6% of the cases. This prevalence was highest in TGA cases (21.8%). No abnormalities were found in the coagulation tests of TA cases. Despite cyanotic heart defects being the predominant cause, the prevalence of abnormal coagulation tests in FT cases was relatively low. Therefore, routine coagulation screening is recommended to enhance the quality of life and reduce morbidity and mortality while awaiting corrective surgeries.

Diller et al. (7) discovered that 27.5% of cases exhibited immunodeficiency among 54,449 patients with congenital heart diseases. They noted that this condition increased hospitalization rates. In our study, 21.2% of the cases exhibited out-of-range serum Ig and Ig subclasses test results, indicating immunodeficiency (p<0.001). This prevalence was highest in IAA and TA cases (47.6% and 46.2%, respectively). Only 1.8% of the TGA cases had immunodeficiency. The evaluation of immunodeficiency based on diagnoses revealed statistically significant differences between parameters (p<0.001), which could impact hospitalization rates and durations.

In our study, 19% of cases yielded pathological abdominal USG results. Evaluating results based on diagnoses, 46.7% of DORV cases had pathological abdominal USG results, whereas no DOLV cases showed pathological abdominal USG results. Pathological results were observed in 23.6% of TGA cases, 21.1% of VSD-PA cases, and 19% of IAA cases (p=0.0329. In our study, the frequency of pathological results in cranial USG did not exhibit statistically significant differences (p=0.262).

Study Limitations

This study was conducted in a single center with a limited number of patients and was retrospective.

Conclusion

Children with CHD can experience non-cardiac issues that contribute to hemodynamic and systemic challenges, affecting various organ systems. Employing a comprehensive approach that involves regular assessments of liver and renal functions, coagulation profiles, complete blood counts, immune function, and abdominal USG can prove beneficial. These measures aim to enhance patients' quality of life, mitigate morbidity and mortality, and provide essential insights while awaiting crucial surgical interventions.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Başaksehir Çam and Sakura City Hospital Local Ethics Committee (decision no: 2022.04.130).

Informed Consent: An informed consent form was signed by each subject included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.G., Concept: G.G., H.Z.G., İ.C.T., Design: G.G., H.Z.G., İ.C.T., Data Collection or Processing: G.G., İ.C.T., E.Ö., Analysis or Interpretation: G.G., H.Z.G., İ.C.T., E.Ö., Literature Search: G.G., İ.C.T., E.Ö., Writing: G.G., H.Z.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Long J, Ramadhani T, Mitchell LE. Epidemiology of nonsyndromic conotruncal heart defects in Texas, 1999-2004. Birth Defects Res A Clin Mol Teratol 2010;88:971-979.
2. Sivanandam S, Glickstein JS, Printz BF, et al. Prenatal diagnosis of conotruncal malformations: diagnostic accuracy, outcome, chromosomal abnormalities, and extracardiac anomalies. Am J Perinatol 2006;23:241-245.
3. Hutson MR, Kirby ML. Model systems for the study of heart development and disease. Cardiac neural crest and conotruncal malformations. Semin Cell Dev Biol 2007;18:101-110.
4. Chen R, Yang L, Wu X, Ma M, Zhao B. A preliminary study on the prenatal diagnosis of fetal conotruncal defects using intelligent navigation echocardiography. Int J Gynaecol Obstet 2021;153:138-145.
5. Lawrence S, McDonald-McGinn DM, Zackai E, Sullivan KE. Thrombocytopenia in patients with chromosome 22q11.2 deletion syndrome. J Pediatr 2003;143:277-278.
6. Majiyagbe OO, Akinsete AM, Adeyemo TA, Salako AO, Ekure EN, Okoromah CAN. Coagulation abnormalities in children with uncorrected congenital heart defects seen at a teaching hospital in a developing country. PLoS One 2022;17:e0263948.
7. Diller GP, Lammers AE, Fischer A, et al. Immunodeficiency is prevalent in congenital heart disease and associated with increased risk of emergency admissions and death. Eur Heart J 2023;44:3250-3260.

DOI: 10.4274/csmedj.galenos.2023.2023-1-4

CASE REPORT 113

Cam and Sakura Med J 2023;3(3):113-115

CSMJ

The Effect of Proactive Approach to Malnutrition and its Impact on Quality of Life in Patients with Head and Neck Malignities: A Case Example

Sibel Baktır Altuntaş, Başak Korkmazer, Hilal Özkaya, Kübra Perişan Eker, Arif Eker

University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Family Medicine, İstanbul, Turkey

What is known on this subject?

Chemotherapy and radiotherapy used in the treatment of nasopharyngeal cancer may cause mucositis. Mucositis-related swallowing difficulty is an important contributor to the development of malnutrition and requires early intervention for nutritional status management using a multidisciplinary approach.

What this case report adds?

By identifying the risk of malnutrition at an early stage in patients with malignancy, a proactive approach to nutrition may contribute to the patient's recovery in a short time and to the success of the treatment.

ABSTRACT

Head and neck cancers may lead to malnutrition in patients because of the natural course of the disease and treatment-related complications. A 36-year-old patient who experienced pain and nutritional difficulties due to mucositis after combined chemoradiotherapy for nasopharyngeal cancer was found to be at risk for malnutrition. To prevent the development of malnutrition, it was decided to feed him through a percutaneous endoscopic gastrostomy (PEG) tube, and sufficient calorie intake was provided. The PEG tube was removed after alleviation of symptoms and achieving adequate nutritional performance that could meet all calorie needs with oral nutrition. It should be kept in mind that early recognition of the malnutrition risk in patients with malignancy and a proactive approach to nutrition will contribute to the regression of existing complaints in a short time and the patients' regaining their former performance.

Keywords: Comprehensive health care, dysphagia, malnutrition, palliative care, percutaneous endoscopic gastrostomy

Introduction

Nasopharyngeal cancer is a malignant tumor that originates from the nasopharyngeal epithelium. Its etiology may be influenced by various factors, including genetic factors, environmental factors, and viral agents, especially Epstein-Barr virus. Undesirable conditions such as mucositis, xerostomia, and dysphagia in the oral cavity may develop in patients with nasopharyngeal cancer because of both treatment-related side effects and the natural course of the disease, and these may lead to nutritional problems (1).

Enteral nutrition and eligible calorie intake should be provided to patients with insufficient oral food intake due to various underlying benign and malignant diseases and complications associated with their treatment (2).

This case report aims to highlight the impact of early percutaneous endoscopic gastrostomy (PEG) and nutritional palliation

Address for Correspondence: Sibel Baktır Altuntaş MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Family Medicine, İstanbul, Turkey

Phone: +90 505 745 14 39 **E-mail:** drsibell@gmail.com **ORCID ID:** orcid.org/0000-0003-1392-9014

Received: 25.01.2023 **Accepted:** 20.04.2023

on disease course and quality of life in a patient with nasopharyngeal cancer who experienced rapid weight loss and was at risk for malnutrition.

Case Report

A 36-year-old male patient was referred to the family medicine outpatient clinic with complaints of difficulty and pain while swallowingsolid foods. It was learned that the complaints worsened following 32 doses of chemotherapy (CT) and 2 doses of radiotherapy (RT) administered for nasopharyngeal carcinoma, which was diagnosed 4 months ago. Despite using antiseptic oral solution 4 times daily and paracetamol 2x500 mg/day, it was noted that his complaints did not regress. It was also revealed that the patient had a weight loss of more than 7% during the last three months.

Physical examination did not reveal any significant finding other than oral mucositis. The patient was evaluated clinically and found to have a body mass index of 24.5 kg/m^2, a Nutrition Risk Score-2002 (NRS) score of 3:3, and a visual analogue scale (VAS) score of 6. The albumin level was 4.6 g/L, the prealbumin level was 17 g/L, the C-reactive protein level was 47 mg/L, and the hemoglobin level was 11.5 g/dL, according to the findings of the laboratory tests. In the patient who was admitted to our palliative care service for nutrition and pain relief, the paracetamol dose was changed to 3x500 mg/day. Moreover, 1x100 mg/day tramadol was added for the management of pain, and the VAS decreased to 3.

The daily calorie requirement of the patient, who was deemed to be at risk of nutritional deficiency, was estimated and oral nutritional support products were initiated; however, it was determined that the daily calorie intake did not meet the need due to dysphagia. To determine the etiology of dysphagia, it was decided to control the nasopharyngeal passage opening, and an opinion was obtained from the department of otorhinolaryngology. Upon the detection of obliteration in the nasopharynx, the patient was fed a glutamine-supplemented nutritional support product through the nasogastric tube. Considering the age and general condition of the patient, we concluded that the continuation of feeding through a nasogastric tube would not be appropriate in terms of patient comfort and quality of life. It was decided that the patient who will continue to receive RT should be fed a PEG tube. PEG placement was performed after a decision was made with the gastroenterology team. No complications developed during or after the procedure.

Following PEG placement, a nutrition plan was made according to the daily calorie and protein needs of the patient together with the palliative care dietitian. He was planned to be fed a nutritional support product containing 1.2 calories/mL and a daily calorie intake of 1900 calories. At the 24th hour following the PEG placement, he was started to be fed with 20 cc/h nutritional supplement and 10 cc/h water. The total daily calories needed by the patient were reached on the fourth day with a gradual increase in dose. The patient, without tolerance problems during his hospitalization in the palliative care unit, was discharged with recommendations one week after PEG placement, with appropriate training on nutrition and maintenance of the PEG tube.

After 15 days, the patient's outpatient control was found to be suitable, and it was observed that the complaints of mucositis and dysphagia regressed.

In the control examination 4 weeks after discharge, the patient's complaints completely disappeared, and accordingly, it was observed that the patient's oral intake also increased, and he gained 9 kg in 30 days, and the NRS-2002 score was 1. The prealbumin value increased from 17 to 25 g/L, the hemoglobin value increased from 11.5 to 13.4 g/dL, and the albumin value increased to 4.7 g/L. With the approval of the gastroenterology clinic, the patient's PEG tube was removed, and he was interned to the palliative care service. Oral intake was stopped for 3 days, and the patient was fed with total parenteral nutrition. At the end of day 3, complete closure of the gastrostomy incision line was observed with inspection, and 10 cc diluted methylene blue was administered with a nasogastric tube, and no leakage was detected at the PEG incision site. Oral feeding was initiated with regimen 1 liquid diet. In the follow-up clinical examinations, by gradually revising his diet, the daily calorie requirement was fulfilled with the regimen 3 oral diet. The patient, who completed RT, was discharged with a VAS score of 1.

Discussion

Palliative care comprises a multidisciplinary treatment approach that aims to improve the quality of life of patients with chronic diseases and to prevent or lessen the symptoms associated with terminal illness and the side effects of the treatments.

Palliative care aims to alleviate physical and emotional symptoms, especially pain, and to evaluate and support nutrition when necessary (3). The main objective of palliative care regarding malnutrition is to assess the risk, prevent it from developing, andprovide nutritional supportif necessary.

Head and neck malignancies may negatively impact nutrition, even in the early stages of the disease. Dysphagia is common in patients with head and neck cancer, particularly

in those receiving RT (1). It has been revealed that the presence of dysphagia increases the risk of malnutrition 2.4 times (4).

Following a multidisciplinary evaluation with gastroenterology and otorhinolaryngology regarding a patient who was at risk for malnutrition because of head and neck cancer, PEG was inserted in the early period before the patient's performance was affected by malnutrition, preventing the patient from reaching premorbid nutritional status in a short time. In a study by Wiggenraad et al. (5) evaluating the effect of prophylactic nutrition with PEG on weight loss in patients with head and neck cancer receiving CT, switching to enteral nutrition in the early period reduces weight loss. In another trial comparing the outcomes of reactive and prophylactic PEG tube placement in patients with locally advanced head and neck malignancies treated with CT, a decrease in the rates of hospitalization, aspiration, and stricture development was observed with PEG feeding (6).

A proactive approach, which includes nutritional support by reconfiguring the risk of malnutrition in the early period of malignancy, can contribute to the patient's recovery in a short time. In this patient, with a holistic and proactive approach, the patient's quality of life was improved and he was supported to return to his previous life as soon as possible.

Ethics

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.B.A., H.Ö., Design: S.B.A., B.K., Data Collection or Processing: B.K., K.P.E., A.E., Analysis or Interpretation: S.B.A., H.Ö., K.P.E., Literature Search: A.E., Writing: S.B.A., B.K., H.Ö., K.P.E., A.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Li H, Li L, Huang X, et al. Radiotherapy-induced dysphagia and its impact on quality of life in patients with nasopharyngeal carcinoma. Strahlenther Onkol 2019;195:457-467.
2. Xu Y, Guo Q, Lin J, et al. Benefit of percutaneous endoscopic gastrostomy in patients undergoing definitive chemoradiotherapy for locally advanced nasopharyngeal carcinoma. Onco Targets Ther 2016;9:6835-6841.
3. World Health Organization (WHO) definition of palliative care. Available from: https://www.who.int/news-room/fact-sheets/detail/palliative-care (Access on 20 June 2022)
4. Foley NC, Martin RE, Salter KL, Teasell RW. A review of the relationship between dysphagia and malnutrition following stroke. J Rehabil Med 2009;41:707-713.
5. Wiggenraad RG, Flierman L, Goossens A, et al. Prophylactic gastrostomy placement and early tube feeding may limit loss of weight during chemoradiotherapy for advanced head and neck cancer, a preliminary study. Clin Otolaryngol 2007;32:384-390.
6. Baschnagel AM, Yadav S, Marina O, et al. Toxicities and costs of placing prophylactic and reactive percutaneous gastrostomy tubes in patients with locally advanced head and neck cancers treated with chemoradiotherapy. Head Neck 2014;36:1155-1161.

DOI: 10.4274/csmedj.galenos.2023.2023-5-2
Cam and Sakura Med J 2023;3(3):116-119

CSMJ

Active Pulmonary Tuberculosis During Interferon Beta-1a Therapy in a Child with Multiple Sclerosis: A Case Report

Pakize Cennetoğlu[1], Zeynep Öz[1], Canan Caymaz[2], Peren Perk Yücel[1], Pınar Arıcan[1], İhsan Kafadar[1]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatrics, Division of Pediatric Neurology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediactrics, Division of Pediatric Infectious Diseases, İstanbul, Turkey

What is known on this subject?

Beta interferons are the first class of disease-modifying therapies, and their immunomodulatory effects are achieved by inhibiting T-cell activation and proliferation. However, modulation and interference with the patient's immune system may lead to adverse effects, such as increased susceptibility to infections.

What this case report adds?

This is the first case of pulmonary tuberculosis in a pediatric patient with multiple sclerosis treated with interferon beta-1a, and effective treatment of serious infectious side effects was described.

ABSTRACT

Interferon (IFN) beta (β) is a potent anti-inflammatory and immunomodulatory agent that is used for treating patients with multiple sclerosis (MS). In this study, we present the case of a 15-year-old female patient diagnosed with MS and treated with IFN β-1a for six months who was referred to the emergency department with complaints of fatigue, fever, and coughing. She was diagnosed with pulmonary tuberculosis (TB). IFN β-1a therapy was stopped and anti-TB treatment was initiated. After nine months of therapy, she recovered from TB. This case presented with a rare side effect during the treatment of pediatric-onset MS with immunomodulatory drugs, demonstrating the importance of screening and close follow-up of patients with TB.

Keywords: Case report, interferon beta, multiple sclerosis, pediatric neurology, tuberculosis

Introduction

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory, and neurodegenerative disease of the central nervous system (CNS) (1). Pediatric-onset MS is used to describe patients who develop symptoms before 16 years of age (2). Immunomodulatory drugs are widely used for treating patients with MS to alleviate and prevent the accumulation of neurological deficits, and their safety and tolerability are well established in adults; however, the available literature for pediatric-onset MS is limited (3). Beta-interferons (β-IFNs) are the first class of disease-modifying immunomodulatory agents used for treating pediatric-onset MS; however, modulation and interference with the patient's immune system may cause adverse effects, such as increased susceptibility

Address for Correspondence: Pakize Cennetoğlu MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Pediatrics, Division of Pediatric Neurology, İstanbul, Turkey
E-mail: pakize.c@gmail.com **ORCID ID:** orcid.org/0000-0001-8963-68-70
Received: 23.05.2023 **Accepted:** 27.07.2023

to infections (4,5). In immunosuppressed patients, one of the most significant infections is tuberculosis (TB), but currently, there is limited information about the probability of latent TB in patients with MS (6,7). TB reactivation can occur because of the impact of immunosuppressive treatments on cellular immunity and depends on host susceptibility during exposure (8,9). Only 4 MS cases treated with IFN β-1b (10) and diagnosed with TB have been reported, and we did not find any reported active TB in pediatric MS patients treated with IFN β-1a. In this study, we present a case of active pulmonary TB in a pediatric MS patient treated with IFN β-1a. Informed consent was obtained from the patient's relatives.

Case Report

A 15-year-old female patient had been referred to our hospital two years ago with fatigue, headache, and difficulty walking complaints. She did not have any degenerative or neurological disorder in her medical and family history. In her physical examination, muscle strength in the lower extremities was 2/5, reflexes were normoactive, and there was no loss of sensation. Laboratory findings and CNS evaluation were normal. The immunoglobulin G index and oligoclonal band were negative. Magnetic resonance imaging (MRI) revealed bilateral diffuse nodular lesions in the left cerebellar peduncle, right cerebellar vermis, cerebral peduncle, and anterior pons. Based on clinical findings and MRI imaging, the patient was diagnosed with MS and treated with 1000 mg prednisone for 5 days, and the dose was tapered over 20 days. She was followed up without medication during remission. After eight months, she was referred to the emergency department because of recurring complaints of fatigue, weakness, and inability to walk. She was treated with prednisone at the same dose again because of her second attack. Her symptoms were alleviated, but her walking disability continued. After pulse steroid therapy, weekly intramuscular IFN β-1a therapy was initiated because of progressive relapsing attacks. After ruling out acute infection, the tuberculin skin test (TST) was negative and the pulmonary X-ray was reported as normal. While she was treated with IFN β-1a therapy, she experienced symptoms including fatigue, fever, coughing, and vomiting during the sixth month of IFN-β therapy after she had received two pulse steroid therapies eight months before. Physical examination revealed crepitant rales at 1/3 basal levels of the lungs. Pulmonary X-ray showed diffuse bronchopneumonic infiltration, and thoracic computed tomography showed diffuse centroacinar densities at the superior lobe of the left lung and minimal effusion in bilateral fissures (see Figure 1a, b). Sputum culture could not be obtained because of a lack of patient cooperation. *Mycobacterium tuberculosis* polymerase chain reaction was positive in two consecutive gastric aspirates. The TST was anergic. Complications related to susceptibility to infection developed in the patient who had a history of pulse steroid therapy and was currently undergoing IFN-β therapy. The patient was diagnosed with TB. Her IFN-β therapy was stopped, and anti-TB treatment was initiated with ethambutol 1.5 g/day, pyrazinamide 2 g/day, isoniazide 300 mg/day, and rifampicin 600 mg/day. Antibiogram confirmed *M. tuberculosis* susceptibility to all first-line drugs. After nine months of anti-TB therapy, she was free of TB, and during the anti-TB treatment period, the patient did not experience a relapse of MS.

Discussion

In this article, we present the case of a pediatric-onset MS patient who was diagnosed with TB while receiving IFN therapy. We found that no similar pediatric case has been reported in the literature. The treatment of the patient was organized on the basis of the recommendations of the International Pediatric MS Study Group suggesting early disease-modifying treatment for pediatric patients with

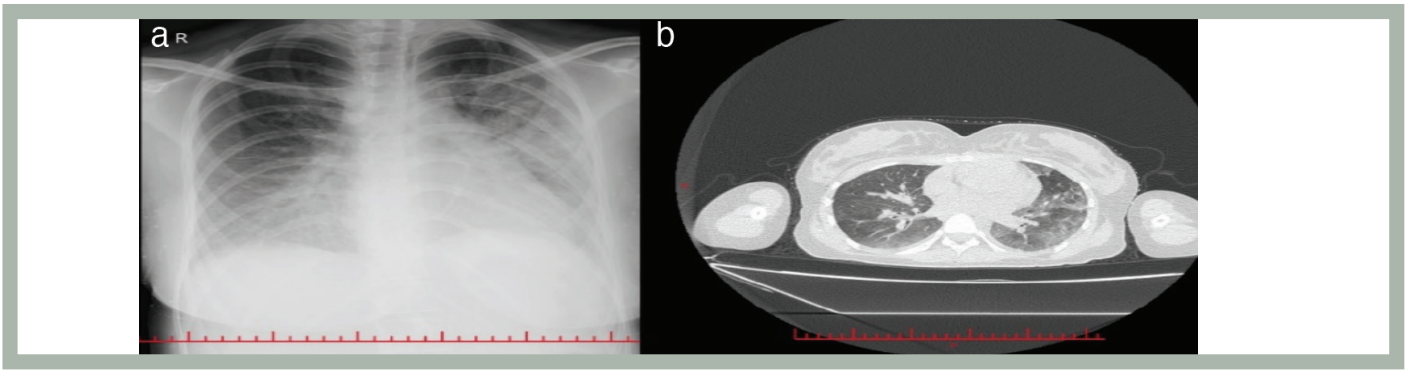

Figure 1. (a) Pulmonary X-ray showing diffuse bronchopneumonic infiltration. (b) Thorax computed tomography showing diffuse centroacinar densities at the superior lobe of the left lung representing bronchopneumonic infiltration and minimal effusion in bilateral fissures

relapsing-remitting MS due to the benefits seen in adults. We were aware of the importance of long-term follow-up in this treatment, particularly in terms of side effects, such as activation or reactivation of latent infection, which are potentially most probably associated with drugs affecting cell-mediated immunity (8,11,12).

We diagnosed our patient with pulmonary TB, and when we reviewed the literature, we found that TB cases have been reported while treated with immunomodulatory drugs, including teriflunomide, cladribine, and alemtuzumab (13,14,15). Cohen et al. (16) reported two TB cases in >900 individuals treated with alemtuzumab in clinical trials. At the same time, they reported that none of the nearly 400 control patients treated with IFN developed TB (16).

The effects of IFN-β were evaluated, and the reported side effects were flu-like syndrome and mild transient leucopenia (17). Gärtner et al. (18) reported a severe adverse effect rate of 11.9% (12 events), including benign intracranial hypertension, depression, and nephrotic syndrome, and all patients recovered.

TB cases under IFN β-1a among other therapies had not been reported in the literature until Sirbu et al. (10) described 4 cases of active pulmonary TC triggered by IFN β-1b therapy of MS. The onset of active TB was 28, 49, 35, and 46 years old, and the time between IFN-1b treatment initiation and TB was 12, 48, 36, and 84 months, respectively. IFN β-1b treatment was discontinued when active TBC was confirmed and was resumed immediately after the cessation of TB treatment. One patient was diagnosed with TB again after 14 years (10). We diagnosed TB six months after the initiation of IFN therapy and discontinued it while she was receiving anti-TB therapy. After nine months of treatment, she was TB-free. Our limitations were that our case was a single case and our observation time was limited. When pediatric MS patients treated with IFN-β were evaluated, we did not encounter any reported TB cases, and there were many publications reporting that relapse rates were reduced in pediatric MS cases with the use of IFN-β. Taking into consideration these benefits, we planned to reinitiate therapy.

There is no definitive cure for pediatric-onset MS, but appropriate treatment should be initiated as soon as possible to slow disability and disease progression. Patients should also be monitored for drug-related side effects. This case report presents the effective treatment of TB diagnosed after the use of IFN-β in a pediatric MS patient. Considering the favorable outcome of the use of IFN-β therapy for treating patients diagnosed with pediatric MS, it is appropriate to control the patients for respiratory complaints, screening for latent TB, and follow-up for infectious pathologies.

Acknowledgement

We used the CARE checklist when writing our report (19).

Ethics

Informed Consent: Obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: P.C., Z.Ö., P.P.Y., C.C., P.A., İ.K., Concept: P.C., Z.Ö., P.P.Y., C.C., P.A., İ.K., Design: P.C., Z.Ö., P.P.Y., C.C., P.A., İ.K., Data Collection or Processing: P.C., İ.K., Analysis or Interpretation: P.C., İ.K., Literature Search: P.C., İ.K., Writing: P.C., İ.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Rodríguez Murúa S, Farez MF, Quintana FJ. The ımmune response in multiple sclerosis. Annu Rev Pathol 2022;17:121-139.
2. de Chalus A, Taveira M, Deiva K. Pediatric onset multiple sclerosis: future challenge for early diagnosis and treatment. Presse Med 2021;50:104069.
3. Waubant E, Banwell B, Wassmer E, et al. Clinical trials of disease-modifying agents in pediatric MS: opportunities, challenges, and recommendations from the IPMSSG. Neurology 2019;92:e2538-e2549.
4. Dhib-Jalbut S, Marks S. Interferon-beta mechanisms of action in multiple sclerosis. Neurology 2010;74(Suppl 1):S17-S24.
5. Luna G, Alping P, Burman J, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol 2020;77:184-191. Erratum in: JAMA Neurol 2021.
6. Pai M, Behr MA, Dowdy D, et al. Tuberculosis. Nat Rev Dis Primers 2016;2:16076.
7. Machuca I, Vidal E, de la Torre-Cisneros J, Rivero-Román A. Tuberculosis en pacientes inmunodeprimidosTuberculosis in immunosuppressed patients Enfermedades Infecciosas y Microbiología Clínica 2018;36:366-374.
8. Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect Dis 2018;5:ofy174.
9. Fragoso YD, Adoni T, Anacleto A, et al. How do we manage and treat a patient with multiple sclerosis at risk of tuberculosis? Expert Rev Neurother 2014;14:1251-1260.
10. Sirbu CA, Dantes E, Plesa CF, Docu Axelerad A, Ghinescu MC. Active pulmonary tuberculosis triggered by interferon beta-1b therapy of multiple sclerosis: four case reports and a literature review. Medicina (Kaunas) 2020;56:202.
11. Miller AE. Oral teriflunomide in the treatment of relapsing forms of multiple sclerosis: clinical evidence and long-term experience. Ther Adv Neurol Disord 2017;10:381-396.
12. Rommer PS, Milo R, Han MH, et al. Immunological aspects of approved MS therapeutics. Front Immunol 2019;10:1564.
13. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011;365:1293-1303.
14. Gözübatık-Çelik RG, Öztürk M. A case of multiple sclerosis diagnosed with tuberculosis during teriflunomide therapy. J Surg Med 2022;6:535-536.
15. Rammohan K, Coyle PK, Sylvester E, et al. The development of cladribine tablets for the treatment of multiple sclerosis: a comprehensive review. Drugs 2020;80:1901-1928.
16. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 2012;380:1819-1828.
17. Basiri K, Etemadifar M, Derakhshan F, et al. Interferon-beta in pediatric multiple sclerosis patients: safety in short-term prescription. Acta Med Iran 2012;50:97-100.
18. Gärtner J, Brück W, Weddige A, et al. Interferon beta-1b in treatment-naïve paediatric patients with relapsing-remitting multiple sclerosis: two-year results from the BETAPAEDIC study. Mult Scler J Exp Transl Clin 2017;3:2055217317747623.
19. Gagnier JJ, Kienle G, Altman DG, et al. The CARE Guidelines: consensus-based clinical case reporting guideline development. Glob Adv Health Med 2013;2:38-43.

DOI: 10.4274/csmedj.galenos.2023.2023-5-4
Cam and Sakura Med J 2023;3(3):120-122

CSMJ

Congenital Scoliosis with Bilateral Foramen Transversarium in the Fifth Lumbar Vertebra

Yiğit Önaloğlu[1], Kadir Abul[1], Ali Kürşad Ganiyusufoğlu[2], Ali Volkan Özlük[1], Mehmet Bülent Balioğlu[1]

[1]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Radiology, İstanbul, Turkey

What is known on this subject?

In typical human anatomy, the cervical vertebrae differ from the thoracic and lumbar vertebrae in the presence of a pair of foramen transversarium (FT).

What this case report adds?

To date, there has been no reported lumbar FT in a case diagnosed with congenital scoliosis. In particular, when using pedicle or lateral mass screws for the cervical spine, the FT and the possibly accompanying vascular structures may be at risk. It should be noted that this situation may also occur in congenital scoliosis in the trajectory of the transpedicular pedicle screws. In any case of suspected congenital scoliosis in which surgical intervention is planned, a sensitive evaluation with computed tomography angiography is recommended to rule out any unexpected anatomic variations.

ABSTRACT

The foramen transversarium (FT) is frequently mentioned in the cervical spine, and the possibility of injury to the vertebral artery and vein passing through this structure is noted, particularly during surgical procedures. In this report, we present an atypically located FT at the level of the L5 vertebra, which was identified during the pre-operative three-dimensional computed tomography (CT) evaluation of a patient with congenital scoliosis in our clinic. A 33-year-old female patient with congenital scoliosis was admitted to our clinic because of cosmetic deformities and spinal pain. CT showed multiple bone formation abnormalities in the thoracic region and surprisingly, bilateral FT at the level of the L5 vertebra in the lumbar region of the spine with no accompanying vascular structures on digital CT angiography. The literature defining lumbar FT is sparse. We believe that knowledge of this rare variant can add to the relevant literature and that it is important to consider this variant in radiological imaging and surgical procedures in this region.

Keywords: Anatomical variation, congenital scoliosis, lumbar foramen transversarium, neurosurgery

Introduction

Congenital scoliosis occurs worldwide with a frequency of 0.5-1/1000 births, and 50% of cases require treatment. Congenital scoliosis is a three-dimensional (3D) deformity of the spine characterized by different formation and segmentation abnormalities. Surgical need depends on the type of anomaly, its location, and the general growth potential of the individual (1).

Address for Correspondence: Yiğit Önaloğlu MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Orthopedics and Traumatology, İstanbul, Turkey
Phone: +90 505 269 61 08 **E-mail:** yonaloglu@gmail.com **ORCID ID:** orcid.org/0000-0002-3893-797X

Received: 30.05.2023 **Accepted:** 18.12.2023

The literature frequently mentions the foramen transversarium (FT) and its variations in the cervical spine and refers to the possibility of injury to the vertebral artery and vein passing through this structure, especially during surgical procedures (2,3).

The cervical vertebrae differ from the thoracic and lumbar vertebrae in the presence of a pair of FTs. However, there are a few reports in the literature in which FT appears as an anatomical variation in the lumbar region homologous to the foramen processus transversi of the cervical vertebrae (4). While recognition of lumbar FT can be ignored in cases that do not require invasive procedures, it is essential to consider such anatomic differences in cases where surgical treatment is planned.

Case Report

We present the anatomical alteration of the FT of the L5 vertebra found during the pre-operative examination of a 33-year-old female patient with congenital scoliosis who presented to our clinic. She was admitted for pain and cosmetic deformities with a Cobb curvature of 71 degrees in the main thoracic region and 47 degrees in the thoracolumbar region. The patient's spine has the following congenital anomalies: T2 non-segmented hemivertebra, T2 butterfly vertebra, T7 butterfly vertebra, T8-9 right semi-segmented accessory hemivertebra, T9-10 right semi-segmented accessory hemivertebra, T11-12 fusion, and T11-12 left non-segmented hemivertebra. We observed 13 ribs on the left side and 12 on the right side. Cervical, thoracic, and lumbar spinal magnetic resonance imaging scans did not reveal any intraspinal pathology, and there were no abnormalities at the craniocervical junction. Posterior instrumented fusion surgery with multiple osteotomies is recommended. The surgical fusion level planning did not cover the L5 lumbar vertebra.

The radiology department was contacted after a routine preoperative 3D computed tomography (CT) scan revealed several cervical and thoracic bone abnormalities as well as a bilateral FT in the L5 vertebra. CT angiography was recommended by the relevant department. On detailed examination of the butterfly-shaped lumbar L5 vertebra, bilateral, well-formed FTs were detected. The FTs were wider on the left and connected the corpus and pedicle to the two transverse processes. As depicted in Figure 1, no vascular structures were found in the foramen.

Discussion

In typical human anatomy, the vertebral artery, vein, and accompanying sympathetic plexus pass through the FT,

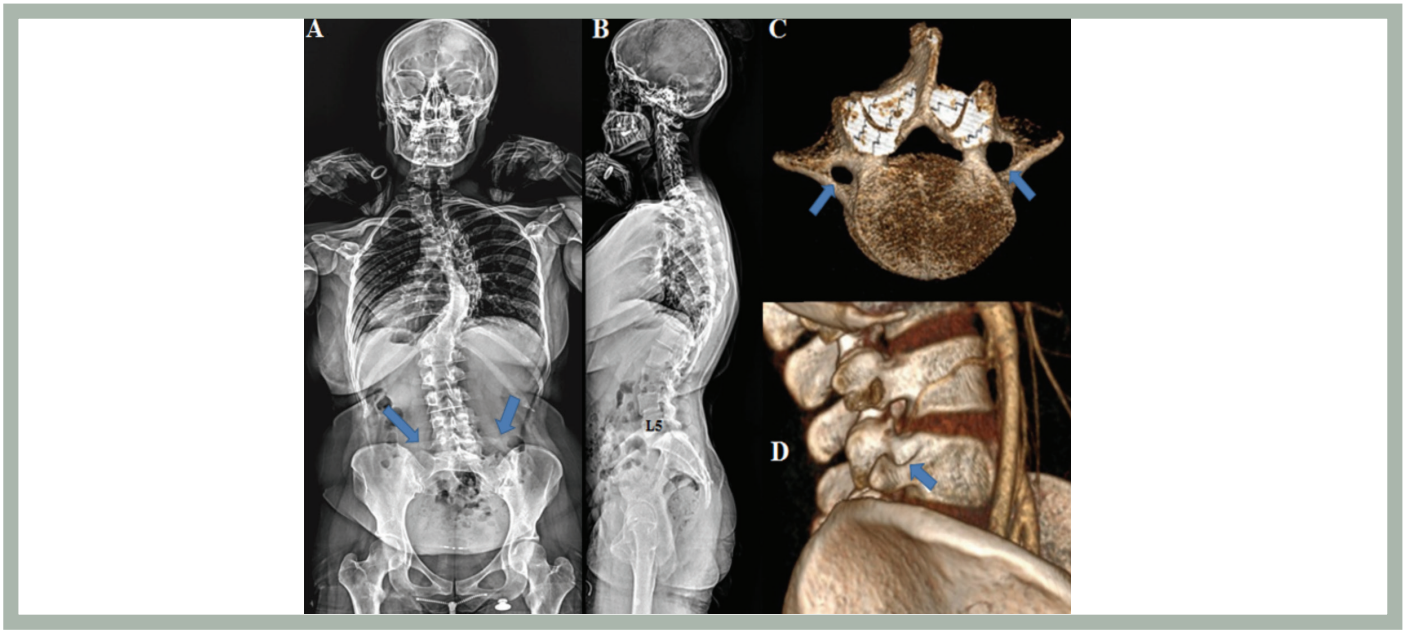

Figure 1. Radiological examinations of a 33-year-old female patient who presented to our clinic for surgical treatment. Preoperative radiological examination revealed a transverse foramen anomaly in the L5 vertebra (arrows). The spinal deformity is shown in (A) as an AP radiograph of the entire spine and in (B) as a lateral radiograph. In the (C) 3D reconstruction view, bilateral transverse foramen can be seen, which is wider on the left side. In (D), the 3D volume rendering view in the lateral plane shows that the vascular structure does not pass through the transverse foramen

AP: Anterior posterior, 3D: Three-dimensional

which is normally located in the processus transversus of all cervical vertebrae. While the vertebral artery ascends through the FT of the sixth cervical vertebra, only the vertebral vein(s) are located in the seventh cervical foramen. The 6th cervical vertebra is the most common entry point of the vertebral artery to the FT, but some studies have reported that the C4, C5, and C7 cervical vertebrae can also be the entry point of the vertebral artery (5,6). In the present case, no vascular structures were observed in the FT of L5 on CT angiography imaging and 3D volume rendering reformats.

FT can be encountered in the lumbar region, especially in L1 and L5 (7). Beers et al. (4) reported four cases with a diagnosis of possible spinal stenosis or disk herniation in routine computed tomography of the lower lumbar spine. The authors stated that these foramina probably developed when the costotransverse elements between the mammillary and accessory processes failed to unite at the site of the anastomotic vessels during the embryological period (4). To date, there have been no reports of lumbar FT in a case diagnosed with congenital scoliosis.

Especially when using pedicle or lateral mass screws for the cervical spine, the FT and the possibly accompanying vascular structures may be at risk (8). It should be noted that this situation may also occur in congenital scoliosis in the trajectory of the transpedicular pedicle screws. In any case of suspected congenital scoliosis in which surgical intervention is planned, a sensitive evaluation with CT angiography is recommended to rule out any unexpected anatomic variations.

Ethics

Informed Consent: Obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.A., A.V.Ö., Concept: K.A., M.B.B., Design: K.A., M.B.B., Data Collection or Processing: A.K.G., Analysis or Interpretation: Y.Ö., K.A., M.B.B., Literature Search: Y.Ö., K.A., Writing: Y.Ö., K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Sebaaly A, Daher M, Salameh B, Ghoul A, George S, Roukoz S. Congenital scoliosis: a narrative review and proposal of a treatment algorithm. EFORT Open Rev 2022;7:318-327.
2. Zibis AH, Mitrousias V, Baxevanidou K, Hantes M, Karachalios T, Arvanitis D. Anatomical variations of the foramen transversarium in cervical vertebrae: findings, review of the literature, and clinical significance during cervical spine surgery. Eur Spine J 2016;25:4132-4139.
3. Dickerman RD, Reynolds A, East JW. The vertebral artery: know the high risk patients. Surg Radiol Anat 2006;28:539-540.
4. Beers GJ, Carter AP, McNary WF. Vertical foramina in the lumbosacral region: CT appearance. AJR Am J Roentgenol 1984;143:1027-1029.
5. Wakao N, Takeuchi M, Kamiya M, et al. Variance of cervical vertebral artery measured by CT angiography and its influence on C7 pedicle anatomy. Spine (Phila Pa 1976) 2014;39:228-232.
6. Kim JT, Lee HJ, Kim JH, Hong JT. Quantitative analysis of unusual entrance of the vertebral artery into the cervical foramen (V2 segment) and its clinical implications. Eur Spine J 2016;25:4188-4194.
7. Tubbs RS, Shoja MM, Loukas M. Bergman's Comprehensive Encyclopedia of Human Anatomic Variation. Tubbs RS, Shoja MM, Loukas M, ed. Wiley; 2016.
8. Zibis A, Mitrousias V, Galanakis N, Chalampalaki N, Arvanitis D, Karantanas A. Variations of transverse foramina in cervical vertebrae: what happens to the vertebral artery? Eur Spine J 2018;27:1278-1285.

DOI: 10.4274/csmedj.galenos.2023.2022-11-12

Cam and Sakura Med J 2023;3(3):123-125

CSMJ

Minimally Invasive Resection of a Giant Right Atrial Myxoma: A Case Report

Emre Boysan[1], Osman Fehmi Beyazal[2], Renda Cırcı[1], Erol Şener[1]

[1]Medicana International Ankara Hospital, Clinic of of Cardiovascular Surgery, Ankara, Turkey

[2]University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Cardiovascular Surgery, İstanbul, Turkey

What is known on this subject?

Myxomas are common in the left atrium. Myxomas can be excised using minimally invasive methods.

What this case report adds?

In patients with giant myxoma in the right atrium, surgery can be performed safely and effectively with minimally invasive methods instead of conventional median sternotomy, with appropriate localization and dimensions. With this method, hospital and intensive care hospital stays can be reduced and better cosmetic results can be achieved.

ABSTRACT

Heart tumors can be divided into primary and secondary tumors. Secondary tumors are more common than primary tumors. The majority of primary tumors are benign, and the most common type is myxoma. Myxomas are most commonly seen in the left atrium and rarely in the right atrium or ventricles. Surgical excision can be performed with conventional median sternotomy in giant myxomas, whereas minimally invasive methods are preferred in tumors of appropriate size and localization. In this article, we report the successful operation of a giant cardiac myxoma in the right atrium with minimally invasive surgery.

Keywords: Myxoma, giant right atrium tumor, minimally invasive surgery

Introduction

The estimated prevalence of primary heart tumors is 1:2000 at autopsy, with approximately 90% benign (mostly myxoma), whereas secondary tumors are approximately 20 times more common than primary tumors (1). Myxomas are usually seen in the atrial fossa ovalis region, 75% in the left atrium, 10-15% in the right atrium, and rarely in the ventricle or heart valve (2). They are usually asymptomatic and detected by imaging methods performed for other reasons. In symptomatic cases, the triad of embolism, intracardiac obstruction, and structural findings is characteristic.

Case Report

A 40-year-old male patient was admitted with complaints of shortness of breath for six months. His vital signs were stable, his heart rate was normal and rhythmic, no pathological sound or murmur was detected, hepatomegaly and pretibial edema were not observed, and he had no other disease in his history. Transthoracic echocardiography (TTE) revealed an ejection fraction (EF): 55% and a pedicled myxoma of 7 cm in diameter in the interatrial septum of the right atrium. Subsequently, transesophageal echocardiography (TEE) revealed a

Address for Correspondence: Osman Fehmi Beyazal MD, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, Clinic of Cardiovascular Surgery, İstanbul, Turkey

Phone: +90 212 909 60 00 **E-mail:** osmanfehmibeyazal@gmail.com **ORCID ID:** orcid.org//0000-0001-6211-0676

Received: 24.11.2022 **Accepted:** 18.06.2023

CAM & SAKURA MEDICAL JOURNAL

6.3 x 4.8 cm diameter, multilobular, heterogeneous mass that was adhered to the base of the inferior right atrium wall, partially compatible with mobile myxoma, prolapsed into the tricuspid valve and right ventricle in the right atrium, and formed relative tricuspid valve stenosis. In addition, the tricuspid annulus was 42 mm, mild tricuspid valve regurgitation was detected, and no thrombus was detected in the left atrium. No pathology was observed in the coronary arteries on coronary angiography. Surgery was planned for the patient using a minimally invasive method. The right jugular vein, right femoral vein, and right femoral artery were cannulated. Then, a 5 cm incision was made from the right fourth intercostal space, and the right atrium was reached under direct vision (Figure 1). Cardiac arrest was achieved with antegrade single-dose Del Nido cardioplegia. After right atriotomy, the mass adhered to the right atrium free wall with a stalk. The entire mass was excised together with the right atrial free wall. Afterwards, tricuspid ring annuloplasty was performed using a size 34 Edwards Lifesciences ring. The right atrium was closed with 3.0 prolene without using a patch. Cardiopulmonary bypass time was 120 min and cross-clamp time was 60 min. No blood products were used during or after the operation. The postoperative pathology report was compatible with myxoma. The patient, who was taken to the intensive care unit after the operation, was extubate at the fourth hour. He was taken to the hospital on the first postoperative day. He was discharged on the 4th postoperative day because he had no problem.

Discussion

Myxomas, the most common benign cardiac tumor, arise from multipotent mesenchymal cells in the endocardium and can be round, oval, polypoid, pedunculated, or sessile (3). They typically occur in middle age and affect women more often than men. They are often found in the left atrium and are attached to the fossa ovalis by a stalk. Most myxomas occur sporadically but can sometimes be associated with a syndrome called the "Carney complex", an autosomal dominant condition characterized by endocrinopathy and skin pigmentation. Myxomas in the Carney complex are usually multicentric, atypically localized, occur at younger ages, and recurrence is more common after surgery (2).

Patients may be asymptomatic and diagnosed incidentally using other imaging methods. Symptoms vary according to tumor location, size, and mobility. Stroke, mesenteric ischemia, spleen or kidney infarction, acute extremity

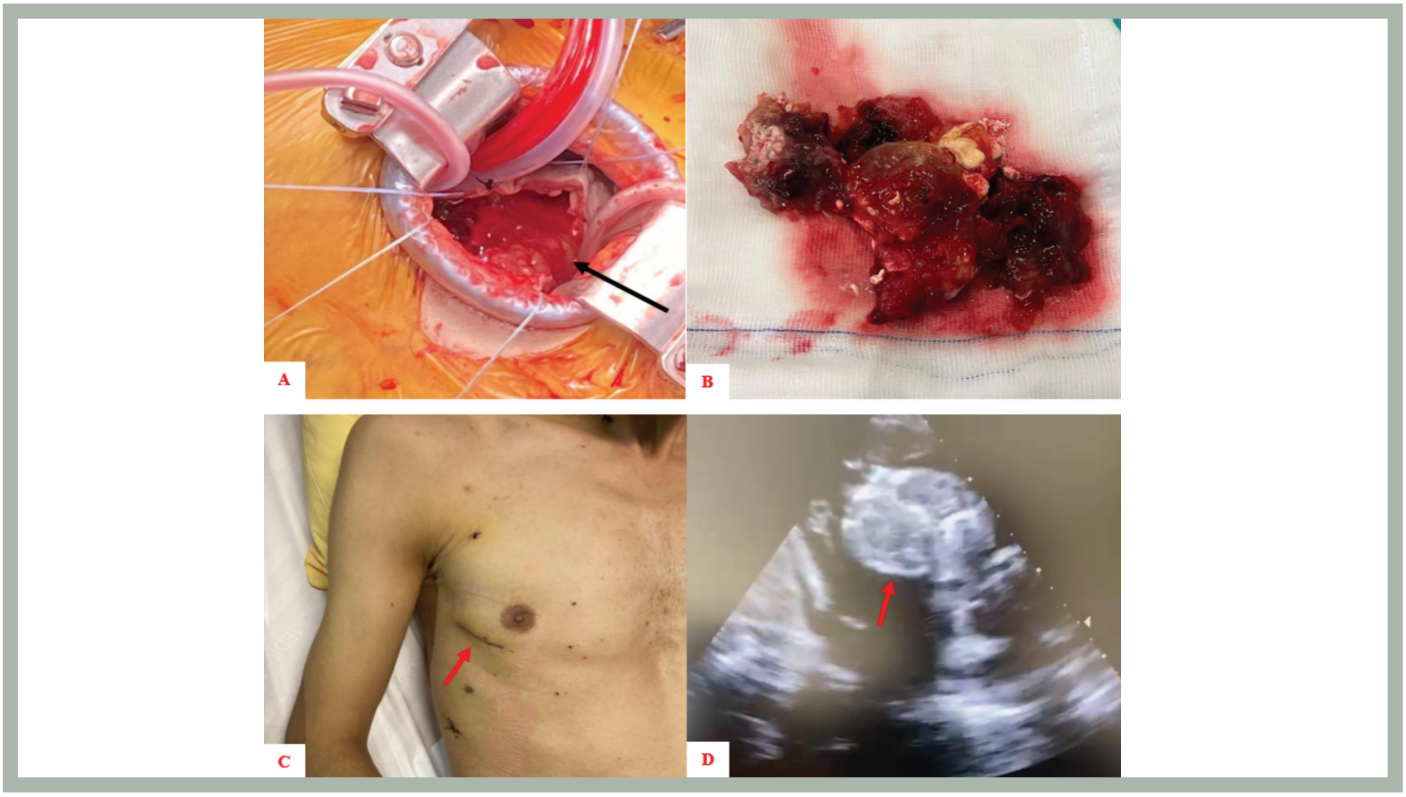

Figure 1. (A) Incision made in the right fourth intercostal space and giant right atrial myxoma seen with black arrow inside. (B) Appearance after surgical excision (could not be removed in one piece due to giant myxoma and small incision). (C) Postoperative view of the incision site. (D) Echocardiographic view of a right atrial myxoma with prolapsed right ventricle

ischemia, and pulmonary embolism may occur because of distal embolization of the tumor or its thrombus. It can mimic the signs of other valvular diseases and cause obstruction in any heart chamber or valve, causing symptoms of right or left heart failure. Any arrhythmia, including atrial fibrillation, ventricular tachycardia, and ventricular fibrillation, may occur because of disruption of the normal myocardium, and sudden death may develop. Patients may also present with non-specific symptoms such as fatigue, cough, fever, arthralgia, myalgia, weight loss, and erythematous rash.

Diagnosis can be made with TTE, which is generally accepted as the gold standard, whereas TEE can be useful when the findings are unclear. Complete surgical resection of cardiac myxoma provides the best clinical outcome. The surgical strategy for myxomas varies according to the location and size of the mass. Although it can be performed with the conventional method, median sternotomy, the operation can also be performed with minimally invasive methods in cases where the tumor is in the appropriate localization. Along with video-assisted port-access and endoscopic port-access methods, robotically assisted endoscopic methods have also been used. Kadiroğulları et al. (4) showed that myxoma excision can be performed safely and effectively with robotic-assisted endoscopic surgery. Catheter-based strategies are not recommended in cases of myxoma because of potential embolization.

In this case report, we report a rare case of giant right atrial myxoma, which was admitted with mild tricuspid valve regurgitation and shortness of breath and surgically removed using minimally invasive methods. Using this method, the patient could be discharged without using any blood products, with a shorter intensive care unit and hospital stay compared with sternotomy. In addition, patient satisfaction was achieved in terms of cosmetics. In the literature, Naser et al. (5) reported a case of giant myxoma (9.8 x 7.8 cm) in the right atrium with signs of right heart failure. However, in this case, it was performed with a median sternotomy, and a pericardial patch was used (5). Beiras-Fernandez et al. (6) reported a case of giant myxoma (9 x 7 cm) in the right atrium that caused cardiovascular collapse and in which sternotomy was preferred. On the other hand, Gaisendrees et al. (7) reported a case of giant left atrial myxoma (5 x 7 cm), which was removed by minimally invasive surgery by making an 8 cm right anterior thoracotomy incision.

In patients with giant myxoma in the right atrium, surgery can be performed safely and effectively with minimally invasive methods instead of conventional median sternotomy, with appropriate localization and dimensions. With this method, hospital and intensive care hospital stays can be reduced and better cosmetic results can be achieved.

Ethics

Informed Consent: Obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.B., O.F.B., Design: E.B., O.F.B., R.C., E.Ş., Data Collection or Processing: E.B., O.F.B., R.C., Analysis or Interpretation: E.B., O.F.B., E.Ş., Literature Search: E.B., O.F.B., R.C., Writing: E.B., O.F.B., E.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Bussani R, Castrichini M, Restivo L, et al. Cardiac tumors: diagnosis, prognosis, and treatment. Curr Cardiol Rep 2020;22:169.
2. Poterucha TJ, Kochav J, O'Connor DS, Rosner GF. Cardiac tumors: clinical presentation, diagnosis, and management. Curr Treat Options Oncol 2019;20:66.
3. Raicea VC, Suciu H, Raicea AD, Macarie GC, Mezei T, Maier MS. Giant left atrial myxoma - literature review and case presentation. Rom J Morphol Embryol 2021;62:361-368.
4. Kadiroğulları E, Onan B, Aydın Ü, Başgöze S, Şen O. A comparison of robotically-assisted endoscopic versus sternotomy approach for myxoma excision: a single-center experience. Turk Gogus Kalp Damar Cerrahisi Derg 2020;28:450-459.
5. Naser N, Hadziomerovic N, Bahram D, Kacila M, Pandur S. Giant right atrial myxoma with symptoms of right heart failure. Med Arch 2021;75:66-68.
6. Beiras-Fernandez A, Kornberger A, El-Beyrouti H, Vahl CF. Giant right atrial myxoma: a rare cause of cardiovascular collapse. SAGE Open Med Case Rep 2019;7:2050313X19841461.
7. Gaisendrees C, Mader N, Sabashnikov A, Schlachtenberger G, Suhr L, Wahlers T. Minimally invasive resection of a giant left atrial myxoma: a case report. Perfusion 2020;35:263-266.

2023 Referee Index

Abdullah Özkök
Ali Öner
Arda Özyüksel
Atakan Tanaçan
Ayşe Bahadır
Ayşe Filiz Yetimakman
Ayşegül İnci Sezen
Balkan Şahin
Birsen Pınar Yıldız
Burak Onan
Bülent Güçlü
Canan Caymaz
Çiğdem Aydoğmuş
Emine Ömür
Erman Çilsal
Esra Gürkaş
Feyza Karagöz Güzey
Filiz Ormancı
Furkan Bahadır Alptekin
Gökhan Eyüpoğlu
Gülhan Tunca Şahin
Güzin Zeren Öztürk
Hakan Aykan
Hakan Temiz
Halil Cebeci
Hasan Sivrikaya
Hüseyin Şehit Burhan
Işık kaban
İlhan Yılmaz
İsa Özyılmaz
İstemi Han Çelik
Mehmet Emirhan Işık
Meliha Meriç Koç
Melike Ersoy
Mustafa Ali Akın
Nihal Akçay
Okcan Basat
Osman Çimen
Özgür Taşkapılıoğlu
Ramazan Güven
Ramazan Korkusuz
Rıza Adaleti
Selman Gökalp
Semih Korkut
Sevda Şener Cömert
Sibel Bolukçu
Şerife Yılmaz
Tuğçe Aksu Uzunhan
Yusuf Ünal Sarıkabadayı
Zuhal Yeşilbağ
Zülal Çelik

2023 Author Index

2023 Subject Index

2023 Subject Index