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COMMENTARY

SARS-CoV-2 vaccination in pediatric patients with immune thrombocytopenia

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1 | INTRODUCTION

As SARS-CoV-2 vaccines become available to the pediatric population, vaccination safety in pediatric patients with immune thrombocytopenia (ITP) is an important consideration. The Pfizer-BioNTech SARS-CoV-2 vaccine is currently authorized for children ≥5 years of age.[1] High profile reports of new-onset ITP following vaccination in adults revealed ITP as a potential complication, and exacerbation of pre-existing ITP is also a concern.[2–5] However, no pediatric data are published, restricting guidance for patients and healthcare providers. Historically, studies reported an increased risk of new-onset ITP following measles-mumps-rubella (MMR) vaccine in children, but this has not been reproduced with other vaccinations.[6–8] Vaccination is imperative as COVID-19 infection has significant implications. Over 12 million pediatric COVID-19 cases have been reported with 0.1%–1.5% of cases requiring hospitalization and 316 per 1,000,000 cases of the severe post-COVID-19 complication of multisystem inflammatory syndrome in children (MIS-C).[9,10] COVID-19 infection itself also carries a risk of thrombocytopenia.[11,12] Here, we review the literature describing the risks of SARS-CoV-2 vaccination in patients with ITP and make recommendations for healthcare providers caring for pediatric patients with ITP.

2 | EXISTING EVIDENCE IN ADULTS

Initially, a case series of 20 adult patients was published reporting mostly new-onset thrombocytopenia within 2 weeks of vaccination. The index patient, initially reported in *The New York Times*, died from cerebral hemorrhage, while all others responded to typical ITP treatment (corticosteroids [CS], intravenous immunoglobulin [IVIG]). The rate of new-onset ITP was similar to expected new cases of ITP per year (2–6/100,000 adults).[13–15]

Following this initial study, several retrospective studies investigated the risk of exacerbation in pre-existing ITP with a reported incidence of 12%–20% (Table 1).[5,16–22] A single-center study of 34 adult patients with persistent or chronic ITP showed that half had a ≥20% decrease in platelet count with only six requiring intervention.[23] In a multicenter study of 218 adult patients with ITP in the Netherlands, 13.8% (n = 30) had an exacerbation (defined as ≥50% decline in platelet count, >20% decline and nadir <30 × 10^9/L, or requiring rescue medication). Risk factors included baseline platelet count <50 × 10^9/L, ITP treatment at onset of vaccination, and younger age. Fifteen patients (6.9%) required rescue medications after vaccination and most responded well; 2.2% had WHO grade 2–4 bleeding.[17] In another 10-center study, there were 33 ITP exacerbations in 117 patients with pre-existing ITP. Nineteen exacerbations followed vaccine dose 1 with seven patients requiring rescue treatment, while 14 exacerbations followed dose 2 with nine patients requiring rescue treatment; all responded. Most required only first-line treatment with

TABLE 1 List of published cases of immune thrombocytopenia (ITP) after SARS-CoV-2 vaccination

Author, year, number of patients	Type of study	New-onset or existing ITP	Vaccine manufacturer
Fueyo-Rodriguez, 2021 ($n = 1$)	Case report	New	Pfizer
Portuguese, 2021 ($n = 1$)	Case report	Existing	Moderna
Collins, 2021 ($n = 2$)	Case series	New	Pfizer
Welsh, 2021 ($n = 28$)	Case series	New and existing	Pfizer, Moderna
Lee, 2021 ($n = 91$)	Case series	New and existing	Pfizer, Moderna, Oxford-AstraZeneca, Johnson and Johnson
Lee, 2021 ($n = 20$)	Case series	New and existing	Pfizer, Moderna
Crickx, 2021 ($n = 3$)	Case series	Existing	Comirnaty BNT162b2, Vaxzevria ChadOx1n-CoV-19, SpikeVax mRNA-1273
Shah, 2021 ($n = 3$)	Case series	New and existing	Pfizer, Johnson and Johnson
Jiang, 2021 ($n = 34$)	Case series	Existing	Pfizer, Moderna
Visser, 2021 ($n = 30$)	Prospective case–control	Existing	Pfizer, SpikeVax mRNA-1273, Vaxzevria ChAdOx1-S
Fatizzo, 2021 ($n = 4$)	Prospective	Existing	Pfizer, Moderna, Astra-Zeneca
Kuter, 2021 ($n = 6$)	Prospective	Existing	Pfizer, Moderna, Johnson and Johnson

CS and/or IVIG and no major bleeding occurred. Prior splenectomy and treatment with more than or equal to five previous lines of therapy had a significantly higher risk of exacerbation after dose 1, while only more than or equal to five lines of therapy remained significant for dose 2. Age, gender, vaccine type, and concurrent autoimmune disease were not significant. Most patients with stable or increased platelet counts after dose 1 had similar stability or higher counts following dose 2. For patients whose platelet counts decreased by >20% after dose 1, 44% had a >20% decrease after dose 2. One of five patients who needed rescue therapy after dose 1 required rescue therapy after dose 2.[5]

In prospective studies monitoring pre- and post-vaccination platelet counts, adult patients with ITP overall did well. Ten percent (4/38) of patients had a clinically significant reduction in platelets and required escalation of current ITP therapy after vaccination in one study.[24] In another study of 52 adults with chronic ITP, 12% ($n = 6$) experienced exacerbations 2–5 days after vaccination (median = 2). Five of these patients responded to CS±IVIG.[18]

Healthy patients without ITP also experience thrombocytopenia after vaccination. The incidence of decreased platelet count in the control group of healthy volunteers in the Netherlands study was 63% (vs. 50% in the ITP cohort). Platelet count reduction might be associated with the immune response to SARS-CoV-2 vaccination and not specific to patients with ITP.[17,25] A nested case–control study in Hong Kong demonstrated no increased risk of thrombocytopenia above background after vaccination, with the incidence of thrombocytopenia after vaccination lower than after COVID-19 infection. The incidence of thrombocytopenia after vaccination was 1.29–2.51/10,000 versus 1254/10,000 COVID-19 cases.[26] This study did not differentiate post-infection ITP from infection-associated thrombocytopenia. The rate of ITP associated with SARS-CoV-2 infection overall is unknown and limited to case reports/series.[27,28]

3 | PROPOSED APPROACH TO VACCINATION IN PEDIATRIC PATIENTS WITH ITP

There are no published data on the experience of SARS-CoV-2 vaccination in pediatric patients with ITP, thus these recommendations are based on the adult data.

Vaccination against SARS-CoV-2 is crucial as a public health measure to control the pandemic. The risk of significant morbidity and mortality from COVID-19 infection in pediatric patients is less than in adults but remain considerable. Current data for adults with and without ITP suggest that the vaccine is safe in this population (detailed above).

Recommendations must be individualized and consider patient and physician factors, including ease of lab monitoring, current ITP status and therapies, and risk of severe COVID-19 infection. We recommend considering a platelet count the week before vaccination for current active ITP patients, followed by a post-vaccination platelet count the week following vaccination, and as needed if symptoms arise. In a study of pediatric patients who developed ITP after initial MMR vaccination, zero patients (total = 65) developed recurrent ITP after the second dose.[29] The MMR experience combined with adult SARS-CoV-2 data suggest that a second dose should still be given even with exacerbation or de novo ITP after the first dose.

At this time, given the importance of vaccine antibody response, anti-CD20 treatment should be avoided in the setting of ITP exacerbation unless there are limited other treatment options. Available monoclonal antibodies for both pre-exposure prophylaxis and potential early therapy of acute infection for older children and adolescents should be considered for patients receiving immunosuppressive therapy for ITP. However, access to therapy, as well as efficacy of antibodies against current and future variants may limit this therapy option.

Further data on vaccination safety in pediatric patients with ITP is crucial to provide robust recommendations. Future studies should address this issue, including risk factors for ITP exacerbation, safety of a second dose for patients with exacerbation after dose 1, and bleeding rates and treatment during exacerbations. One effort is the Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion-Autoimmune Cytopenia Registry. Pediatric providers complete a REDCap form for any patients with autoimmune cytopenia and documented COVID-19 infection or post vaccination (https://www.research.chop.edu/secure-aic). This website, like COVID-19 registries for other diseases, stores de-identified data and therefore is IRB exempt under 45 CFR 46.104(d) 4(ii) and compliant under HIPAA Safe Harbor De-identification standards.

4 | CONCLUSION

Based on the current research in adults with ITP, SARS-CoV-2 vaccination appears overall safe, with a low risk of ITP exacerbation. Reassuringly, in patients with symptomatic exacerbations, almost all patients responded quickly to first-line therapy without significant bleeding complications. The combination of apparent ITP risk with natural infection, the risk of severe disease and MIS-C post-infection in some patients, coupled with the ongoing public health benefit of SARS-CoV-2 vaccination, lead us to recommend SARS-CoV-2 vaccination for most pediatric patients with ITP. These recommendations are based on expert opinion due to the limited available data for children, and thus more research is needed.

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CONFLICT OF INTEREST

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REFERENCES

1. FDA. *FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Children 5 through 11 Years of Age*. FDA; 2021. https://www.fda.gov/news-events/press-announcements/fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use-children-5-through-11-years-age. Accessed February 7, 2022.
2. Grady D, Mazzei P. Doctor's death after COVID vaccine is being investigated. The New York Times. January 12, 2021. https://www.ncbi.nlm.nih.gov/search/research-news/12431/. Accessed February 7, 2022.
3. Collins EC, Carr MJ, Kim JS, et al. Immune thrombocytopenia in 2 healthy young women after the Pfizer-BioNTech BNT16B2b2 messenger RNA coronavirus disease 2019 vaccination. *J Am Coll Emerg Physicians Open*. 2021;2(5):e12531.
4. Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2021;39(25):3329-3332.
5. Lee EJ, Beltrami-Moreira M, Al-Samkari H, et al. SARS-CoV-2 vaccination and immune thrombocytopenia in de novo and pre-existing ITP patients. *Blood*. 2022;139(10):1564-1574.
6. France EK, Glanz J, Xu S, et al. Risk of immune thrombocytopenic purpura after measles-mumps-rubella immunization in children. *Pediatrics*. 2008;121(3):e687-e692.
7. Mantadakis E, Farmaki E, Buchanan GR. Thrombocytopenic purpura after measles-mumps-rubella vaccination: a systematic review of the literature and guidance for management. *J Pediatr*. 2010;156(4):623-628.
8. David P, Shoenfeld Y. ITP following vaccination. *Int J Infect Dis*. 2020;99:243-244.
9. Payne AB, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. *JAMA Netw Open*. 2021;4(6):e2116420.
10. Children and COVID-19: state-level data report. American Academy of Pediatrics; 2022. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ Accessed February 7, 2022.
11. Bomhof G, Mutsaers PGNJ, Leebeek FWG, et al. COVID-19-associated immune thrombocytopenia. *Br J Haematol*. 2020;190(2):e61-e64.
12. David P, Dotan A, Mahroum N, et al. Immune thrombocytopenic purpura (ITP) triggered by COVID-19 infection and vaccination. *Isr Med Assoc J*. 2021;23(6):378-380.
13. Fogarty PF. Chronic immune thrombocytopenia in adults: epidemiology and clinical presentation. *Hematol Oncol Clin North Am*. 2009;23(6):1213-1221.
14. Schoonen WM, Kucera G, Coalson J, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. *Br J Haematol*. 2009;145(2):235-244.
15. Moulis G, Palmaro A, Montastruc JL, et al. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. *Blood*. 2014;124(22):3308-3315.
16. Lee EJ, Cines DB, Gernsheimer T, et al. Thrombocytopenia following Pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol*. 2021;96(5):534-537.
17. Visser C, Swinkels M, van Werkhoven E, et al. COVID-19 vaccination in patients with immune thrombocytopenia. *Blood Adv*. 2022;6(6):1637-1644.
18. Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. *Br J Haematol*. 2021;195(3):365-370.
19. Crickx E, Moulis G, Ebbo M, et al. Safety of anti-SARS-CoV-2 vaccination for patients with immune thrombocytopenia. *Br J Haematol*. 2021;195(5):703-705.

20. Shah SRA, Dolkar S, Mathew J, et al. COVID-19 vaccination associated severe immune thrombocytopenia. *Exp Hematol Oncol*. 2021;10(1):42.
21. Fueyo-Rodriguez O, Valente-Acosta B, Jimenez-Soto R, et al. Secondary immune thrombocytopenia supposedly attributable to COVID-19 vaccination. *BMJ Case Rep*. 2021;14(5):e242220.
22. Portuguese AJ, Sunga C, Kruse-Jarres R, et al. Autoimmune- and complement-mediated hematologic condition recrudescence following SARS-CoV-2 vaccination. *Blood Adv*. 2021;5(13):2794-2798.
23. Jiang D, Portuguese AJ, Weatherford A, et al. Platelet trends after COVID-19 vaccination in patients with chronic or persistent immune thrombocytopenia. *Am J Hematol*. 2021;96(12):E472-E474.
24. Fattizzo B, Giannotta JA, Cecchi N, et al. SARS-CoV-2 vaccination in patients with autoimmune cytopenias: the experience of a reference center. *Am J Hematol*. 2021;96(11):E413-E416.
25. Flego D, Cesaroni S, Romiti GF, et al. Platelet and immune signature associated with a rapid response to the BNT162b2 mRNA COVID-19 vaccine. *J Thromb Haemost*. 2022;20(4):961-974.
26. Sing CW, Tang CTL, Chui CSL, et al. COVID-19 vaccines and risks of hematological abnormalities: nested case-control and self-controlled case series study. *Am J Hematol*. 2022;97(4):470-480.
27. Bhattacharjee S, Banerjee M. Immune thrombocytopenia secondary to COVID-19: a systematic review. *SN Compr Clin Med*. 2020;2(11):2048-2058.
28. Mahevas M, Moulis G, Andres E, et al. Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: a French multicentre series. *Br J Haematol*. 2020;190(4):e224-e229.
29. Stowe J, Kafatos G, Andrews N, et al. Idiopathic thrombocytopenic purpura and the second dose of MMR. *Arch Dis Child*. 2008;93(2):182-183.

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