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Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major article

Vaccine breakthrough infections in veterans hospitalized with coronavirus infectious disease-2019: A case series



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Key Words:
COVID-19
Hospitalizations

A B S T R A C T

Background: While Severe Acute Respiratory Syndrome Coronavirus-2 vaccine breakthrough infections are expected, reporting on breakthrough infections requiring hospitalization remains limited. This observational case series report reviewed 10 individuals hospitalized with vaccine breakthrough infections to identify patient risk factors and serologic responses upon admission.

Methods: Electronic medical records of BNT162b2 (Pfizer-BioNTech) or mRNA-1732 (Moderna) vaccinated patients admitted to Veterans Affairs Ann Arbor Healthcare System with newly diagnosed Coronavirus Infectious Disease 2019 (COVID-19) between March 15, 2021 and April 15, 2021 were reviewed. Patient variables, COVID-19 lab testing including anti-S IgM, anti-N IgG antibodies, and hospital course were recorded. Based on lab testing, infections were defined as acute infection or resolving/resolved infection.

Results: Of the 10 patients admitted with breakthrough infections, all were >70 years of age with multiple comorbidities. Mean time between second vaccine dose and COVID-19 diagnosis was 49 days. In the 7 individuals with acute infection, none had observed serologic response to mRNA vaccination, 5 developed severe disease, and 1 died. Three individuals had anti-N IgG antibodies and a high polymerase chain reaction cycle threshold value, suggesting resolving/resolved infection.

Conclusions: Given the variability of vaccine breakthrough infections requiring hospitalization, serologic testing may impart clarity on timing of infection and disease prognosis. Individuals at risk of diminished response to vaccines and severe COVID-19 may also benefit from selective serologic testing after vaccination to guide risk mitigation strategies in a post-pandemic environment.

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BACKGROUND

Vaccines against Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) have been demonstrated to be highly effective in preventing symptomatic infections with Coronavirus Infectious

Disease 2019 (COVID-19).^{1,2} Despite high vaccine efficacy, a small number of breakthrough infections are to be expected. As of April 30, 2021, the Centers for Disease Control and Prevention (CDC) reported 995 acute care hospitalizations for vaccine breakthrough infections.³ However, to date there have been limited data regarding the risk factors for these patients, and no reported serologic COVID-19 testing upon hospitalization.

Between December 30, 2020 and April 1, 2021, the Veterans Affairs Ann Arbor Healthcare System (VAAAHS) vaccinated more than 25,000 Veterans, representing over 55% of its eligible patient base. In March 2021, the State of Michigan experienced a surge of COVID-19, driven largely by the novel B.1.1.7 (Alpha) variant.⁴ In this

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Conflicts of interest: All authors are employees of the US Department of Veterans Affairs. Dr Saint reports receiving grants from the Department of Veterans Affairs and personal fees from ISMIE Mutual Insurance Company, Jvion, and Doximity. Dr Gupta receives grants from the Gordon and Betty Moore Foundation. Drs Kim, Schildhouse, Bradley, Chensue, and Houchens report no additional disclosures.

observational case series report, we describe all 10 cases of SARS-CoV-2 vaccine breakthrough infections diagnosed in hospitalized patients during this time period with the goal of identifying possible patient risk factors as well as serologic responses at the time of admission.

METHODS

Electronic medical records of BNT162b2 (Pfizer-BioNTech) or mRNA-1732 (Moderna) vaccinated patients admitted to the VAAHS with newly diagnosed COVID-19 between March 15, 2021 and April 15, 2021 were reviewed. Patients were included if 2 or more weeks had elapsed since receipt of the second vaccine dose. Patient factors were collected including medical comorbidities, body mass index (BMI), immunosuppression defined as immunocompromising conditions or treatments, vaccination dates, admission date, presenting symptoms, peak supplemental oxygen requirement, highest level of hospital care needed, status at discharge (living or deceased), and COVID-19 laboratory testing including polymerase chain reaction (PCR) with cycle threshold (C_t) if known (Cepheid, Sunnyvale, CA; bioMerieux, Marcy-l'Étoile, France), SARS-CoV-2 antigen (BD Biosciences, San Jose, CA), and semiquantitative IgM anti-spike(S) and IgG anti-nucleocapsid(N) protein antibody assays (Abbot Laboratories, Abbott Park, IL). Based on COVID-19 laboratory testing, patients were determined to have acute infection or resolving/resolved infection. Acute infections were defined as positive SARS-CoV-2 PCR, with either C_t values ≤ 30 or concurrent positive SARS-CoV-2 antigen test. Resolving/resolved infections were characterized by positive PCR, C_t value >30 , and the presence of anti-N IgG antibodies. This combination of laboratory results was interpreted as consistent with resolving/resolved infection, because anti-N IgG antibodies correlate with neutralizing activity⁵ and appear approximately 10–14 days after initial infection,⁶ and C_t values inversely correlate with viral density.⁷ Presence of anti-N IgG antibodies with high C_t values suggests an expected further decrease in viral load and improvement in symptoms.⁸ Resolving/resolved infections could include COVID-19 infections greater than 10 days from initial infection, but they could also include remote COVID-19 infections with persistently positive PCR tests. In cases with indeterminate results (eg, negative anti-N IgG antibodies and a high C_t value), clinical correlation was used to define whether the case was representative of an acute or resolving/resolved infection. The administering clinic of record and staff were also noted.

RESULTS

During the study period, twenty patients were hospitalized with COVID-19, of which 10 were fully vaccinated (7 BNT162b2 and 3 mRNA-1273) (Table 1). The mean time between second vaccination dose and diagnosis of COVID-19 was 49 days. All patients with vaccine breakthrough infections were older than 70 years of age; 9 were Caucasian and 1 African American. Six had a BMI greater than 30 kg/m², all had multiple medical comorbidities, and 1 was immunosuppressed on nintedanib. Six individuals (patients 1, 2, 3, 5, 9, 10) had acute infections, of which 5 developed severe COVID-19 necessitating supplemental oxygen. Three individuals (patients 6, 7, 8) had resolving/resolved infections, of which 2 were admitted for conditions unrelated to their newly diagnosed COVID-19 infection (bacterial endocarditis, axillary abscess). The third individual (patient 6) was admitted for a concern of weakness, but never required oxygen supplementation to suggest a moderate to severe COVID-19 infection. One individual (patient 4) was indeterminate, with a positive PCR, high C_t value, negative antigen, and absent IgM and IgG antibodies. Based on clinical presentation, this was favored to represent early

acute infection rather than resolving/resolved infection without serologic response.

All individuals were vaccinated through the VAAHS, and there was no obvious relationship among vaccine breakthrough infection, vaccination location, administration date, and vaccinating personnel.

DISCUSSION

Our case series examines patients hospitalized with SARS-CoV-2 vaccine breakthrough infections, in the context of a highly vaccinated population during a COVID-19 surge in Michigan. The 10 Veterans hospitalized with vaccine breakthrough infections were elderly, had substantial comorbid conditions, and were often obese. One patient was on immunosuppressive therapy.

It is notable that, of the patients with acute infection, none had an IgM response to the spike protein. Because high levels of anti-S IgM have been found for at least 8 weeks after a second mRNA vaccine dose,⁹ there is a possibility of limited vaccine response in the individuals in this observational case series report. Genomic sequencing of these patients was not obtained; however, as the majority of infections during the surge were due to the variant Alpha strain, concern is raised for variant escape since mRNA vaccines are typically associated with high titers of neutralizing antibodies.¹⁰ Alternatively, breakthrough infection may be the result of diminished immune response due to patient specific factors. All 10 cases of vaccine breakthrough infection were in older adults, despite evidence that adults older than 65 years have similar immunogenicity to younger adults.¹¹ Emerging studies show association between risk factors such as immunosuppression¹² and hemodialysis¹³ and diminished humoral response to the SARS-CoV-2 vaccine. In addition, in de-novo COVID-19 infections, antibody responses are similarly decreased in individuals who are obese¹⁴ or diabetic.¹⁵ As these risk factors are also related to more severe COVID-19, it is important to better understand which factors lead to diminished protection following SARS-CoV-2 vaccination, and whether these patients may benefit from additional vaccine doses or preventative measures.

Given that high risk individuals are more likely to have a diminished humoral response to the SARS-CoV-2 vaccine and subsequently an elevated risk of severe COVID-19 infection, might post-vaccination antibody testing be used in this population to determine those with diminished vaccination response so that they could be encouraged to continue precautions? Currently the Food and Drug Administration recommends against routine antibody testing to assess immunity after SARS-CoV-2 vaccination.¹⁶ However, without a better understanding of vaccine response, many high risk individuals could be at even greater risk as mitigation measures are relaxed (eg, mandatory masking) for the fully vaccinated. For high risk individuals, the selective use of antibody testing for anti-S IgM and IgG may be useful to identify those that would benefit from enhanced precautions to SARS-CoV-2 exposure.

Five of the 7 patients with acute breakthrough infection in this case series had severe COVID-19 symptoms necessitating supplemental oxygen or ventilatory support. While the CDC reported that fully vaccinated adults 65 years and older are 94% less likely to be hospitalized with COVID-19,¹⁷ it is noteworthy that only 1 individual was hospitalized in their study. While patients with breakthrough infections may tend to have milder symptoms, some will still develop severe symptoms that necessitate hospitalization. Our experience with Michigan Veteran patients demonstrates that despite higher than average vaccination rates within this population, surging case counts within the community will lead to an increase in breakthrough infections and hospitalizations. As the Delta strain and other highly virulent strains become more prevalent, this report reinforces the need to not only rapidly vaccinate entire communities, but also

Table 1
Summary of 10 fully vaccinated veterans hospitalized with COVID-19

Patient number	Age (y)	Body Mass Index (kg/m ²)	Medical comorbidities	Immune system suppression	Presenting symptoms	Vaccine series received	Days between second vaccine dose and hospitalization	COVID-19 laboratory testing				Peak suppoxygen need (L/min)	Peak hospital level of care	Status at hospital discharge	
								PCR [§] status (C _t)	Antigen status	Anti-S IgM [¶] (nl, 0-0.99)	Anti-N IgG [¶] (nl, 0-1.39)				Results interpretation
1*	78	33	CHF, cirrhosis, CKD	N	Dyspnea, LE swelling	Pfizer	66	Positive (22.4)	Negative	0.53	0.67	Acute infection	4	General	Living
2*	71	32	CHF, COPD, DM, IPF	Y [‡]	Dyspnea, LE swelling	Pfizer	63	Positive (-)	Positive	0.13	0.11	Acute infection	Mech Vent	ICU	Deceased
3*	91	32	Afib, HTN, CVA, AI	N	Cough, N/V/D	Pfizer	60	Positive (13.1)	Positive	0.26	0.03	Acute infection	6	General	Living
4*	80	18	CHF, Dementia, CVA	N	Weakness, lethargy	Pfizer	54	Positive (34.7)	Negative	0.19	0.03	Acute infection	-	General	Living
5*	88	41	COPD, OSA, DM	N	Dyspnea, cough	Moderna	63	Positive (13.6)	Positive	0.14	0.03	Acute infection	2	General	Living
6	82	19	COPD, ESRD on HD, HTN	N	Dyspnea, weakness	Moderna	21	Positive (32.3)	Negative	5.79	6.23	Resolving/ Resolved infection	-	ICU	Living
7* [†]	73	26	CAD, HTN,	N	Fever, bacterial endocarditis	Pfizer	38	Positive (37.3)	Negative	0.87	3.55	Resolving/ Resolved infection	-	General	Living
8	88	33	CAD, DM, CKD	N	Axillary abscess	Moderna	50	Positive (44.5)	Negative	2.62	2.20	Resolving/ Resolved infection	-	General	Living
9*	83	32	COPD, DM, CKD	N	COVID-19 positive on SNF testing	Pfizer	42	Positive (-)	Positive	0.28	0.52	Acute infection	-	General	Living
10*	78	45	CHF, COPD, DM, CKD	N	Dyspnea, fever	Pfizer	40	Positive (19.2)	Positive	0.94	0.02	Acute infection	2	General	Living

Afib, Atrial fibrillation; AI, Aortic insufficiency; CHF, Congestive heart failure; CKD, Chronic kidney disease; COPD, Chronic obstructive pulmonary disease; C_t, Cycle threshold (if known); CVA, Cerebrovascular accident; DM, Diabetes mellitus; ESRD on HD, End-stage renal disease on hemodialysis; HTN, Hypertension; ICU, intensive care unit; IPF, Idiopathic pulmonary fibrosis; LE, lower extremity; Mech Vent, mechanical ventilation; nl, normal limit; N/V/D, nausea, vomiting, diarrhea; OSA, Obstructive sleep apnea; SNF, skilled nursing facility.

*Considered vaccination failure.

[†]Transferred from another acute care hospital.

[‡]Receiving nintedanib therapy.

[§]PCR assay (Cepheid, Sunnyvale, CA, bioMerieux, Marcy-l'Étoile, France).

^{||}SARS-CoV-2 antigen test (BD Biosciences San Jose, CA).

[¶]Serology Anti-S IgM and Anti-N IgG (Abbott Laboratories, Lake Forest, IL).

practice other risk mitigation strategies if local COVID-19 case volumes are high.

In our observational case series report, 3 individuals (30%) had resolving/resolved infections and were admitted for reasons other than moderate to severe COVID-19. These data are consistent with CDC studies demonstrating that 29% of patients hospitalized with a diagnosis of post-vaccination breakthrough infections were asymptomatic or primarily hospitalized for reasons other than COVID-19.³ Given that SARS-CoV-2 PCR can remain positive in asymptomatic individuals for extended periods,¹⁸ our report suggests that a subset of hospitalizations with COVID-19 breakthrough infections likely represent new diagnoses of resolving/resolved infections. For newly diagnosed COVID-19 infections, CDC recommends isolation precautions for 10 days after first positive viral test.¹⁹ However, for these asymptomatic SARS-CoV-2 breakthrough infections in the hospital, serologic testing may impart clarity on the timing of infection and could aid infectious disease consultants in designing patient-specific infection control processes.

This report has several strengths. Staff administering vaccines underwent the same training, vaccines were stored and handled meticulously, and needle length was adjusted to patient BMI. The lack of relationship between vaccine breakthrough infection and vaccination clinic, date, or vaccination personnel suggests associations observed were more likely related to the vaccine or the recipient rather than the vaccination process.

There are also limitations to this case series, such as the lack of genomic sequencing to detect variants. Laboratory testing included anti-S IgM and anti-N IgG antibodies, but not anti-S IgG antibodies, which would have helped better define humoral response to the vaccine, given limited knowledge of IgM antibody persistence beyond 8 weeks. Serial serologic testing was not done to determine the trajectory of an individual's antibody response. This may have helped to further characterize certain cases such as patient 7 who had a resolving/resolved infection but a negative anti-S IgM antibody. Immune protection also involves both serologic and cellular mechanisms, and further research is required to better understand the importance of either.

In summary, we report 10 patients with SARS-CoV-2 vaccine breakthrough infections requiring hospitalization, including those with acute infection but without observed serologic response, a majority of whom developed severe disease. Our experience suggests that even as vaccination rates climb nationwide, breakthrough infections may continue to occur, especially amidst variant strains and new COVID-19 surges. Additional understanding of factors leading to vaccine breakthrough infection is critical to guide risk mitigation strategies and to help care for those who require acute care hospitalization. Finally, the potential role of serologic antibody testing to identify high risk individuals or to tailor hospital infection control policies should be explored.

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