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REVIEWS/FOCUS ON

Defining SARS-CoV-2 breakthrough infection needing hospitalization in mass vaccination era: from disease-centered to patient-centered care

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Abstract.

After the implementation of mass vaccination campaigns, breakthrough infections by SARS-CoV-2 are being increasingly observed worldwide, due to high pervasiveness of viral spread, emergence of novel variants, progressive ease of restrictive measures and waning protection against infection. Although breakthrough infections have generally lower clinical severity than COVID-19 in unvaccinated subjects, a consistent number of patients may still require hospitalization. These patients are generally old, frail and with a high number of comorbidities. Despite COVID-19-related symptoms are generally milder, they may still exhibit complicated clinical course for their intrinsic clinical complexity. The abrupt emergence of the SARS-CoV-2 omicron variant in the final weeks of 2021 could also contribute to increase the burden of breakthrough infection needing hospitalization, due to its extremely high infectiousness and the serious concerns over failure of immune response induced by available vaccines. The organization of hospital care should thus consider the changing epidemiology of patients admitted with SARS-CoV-2 infection in the post-vaccine era, to improve the quality and appropriateness of care and specifically address the needs of each patient.

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Introduction

The epidemiological context

In the second half of 2021, the trend of the COVID-19 pandemic across different countries can be viewed as the result of a complex and fragile equilibrium between, on one side, the diffusion of highly-transmissible SARS-CoV-2 variants, seasonal trends in the spread of coronaviruses and relaxation of restrictive measures, and, on the other side, mass vaccination campaigns (1). Current vaccines exhibit high effectiveness against SARS-CoV-2 transmission and development of severe forms of COVID-19 (2), that seems to be only mildly affected by the worldwide spread of the delta variant (3). However, the extremely high pervasiveness of viral spread across the world, the reprise

of international travels and the progressive ease of universal masking and social distancing make the occurrence of SARS-CoV-2 infection frequent also in those who have completed vaccine schedules (4,5).

Furthermore, concerns over waning immunity have also been recently raised, basing on real-world data of subjects vaccinated at the beginning of the campaign (6,7). This phenomenon may be emphasized in older and frail subjects, due to immunosenescence and immune depression, and represents the rationale for the recent recommendation of a “booster” vaccine dose (6,7). In fact, anti-SARS-CoV-2 vaccine registration trials were not focused on older frail populations, and were not designed to measure the extent and duration of protective response in these subjects (8).

SARS-CoV-2 breakthrough infections in hospital

The epidemiological context after the implementation of mass vaccination campaigns has deep implications for hospital care of COVID-19 patients. From summer 2021 onwards, the number of patients with SARS-CoV-2 breakthrough infection needing hospital admission has been increasing (4,5). This phenomenon should not be attributed uniquely to vaccine failure, spread of novel SARS-CoV-2 variants and waning immunity, but is also the result of the massive viral spread and infective capacity.

Patients with breakthrough infections generally have milder clinical courses and different care needs than their unvaccinated counterparts, who display the typical clinical presentation of severe COVID-19, with rapidly progressive respiratory failure due to interstitial pneumonia (9,10).

Epidemiological data suggest that vaccines are able to modify the natural history of SARS-CoV-2 infection, implying lower risks of Intensive Care Unit (ICU) admission and mortality (9-10).

However, few studies have defined the clinical characteristics and care needs of patients hospitalized with SARS-CoV-2 breakthrough infection to date.

A large multicenter study from the United States has recently highlighted that vaccinated patients needing hospital admission for COVID-19 were older and with a higher number of comorbidities than unvaccinated patients (10). Furthermore, the highest level of respiratory illness during hospital stay was significantly lower in vaccinated patients, who also experienced shorter duration of stay and higher frequency of recovery (10). These results match those previously obtained by Juthani et al. (5), who showed that 46% of patients who needed hospital admission for SARS-CoV-2 breakthrough infection had no respiratory symptoms, and the positive Polymerase-Chain Reaction (PCR) test for SARS-CoV-2 was an incidental finding. Juthani et al. also detected a significant burden of comorbidities, including overweight, cardiovascular disease, cancer and diabetes, in those patients admitted with SARS-CoV-2 breakthrough infection (5).

The presence of comorbidities and residence in nursing homes represent significant risk factors for hospital admission due to SARS-CoV-2 breakthrough infection also in large population-based studies even after the administration of a vaccine booster dose (4,7).

Overall, these findings suggest that the clinical characteristics of patients needing hospitalization for COVID-19 have been substantially modified by mass vaccination campaigns. Before these campaigns, almost all patients hospitalized with COVID-19 had severe respiratory failure, irrespective of the presence of comorbidities (11). This clinical picture is still dominant in unvaccinated patients who are currently admitted to hospital. However, a substantial part of COVID-19-related admissions nowadays involves subjects with breakthrough infection, who generally have milder respiratory involvement and complex clinical pictures due to the presence of multiple comorbidities. Significant respiratory involvement may anyway be present also in those patients who have completed the original two-dose vaccinal schedule more than three months before infection with SARS-CoV-2, and have not received the booster dose yet (12).

A classification of breakthrough infections in hospital

In Table 1, we propose a real-world classification of patients needing hospitalization for COVID-19 in the post-vaccination era. Each category of patients may correspond to a different pathway of care, involving wards with different care intensity and specialist know-how. Community facilities or hospital-at-home programs consisting in multidisciplinary mobile units may be even involved for milder cases (13).

Table 1. Characteristics of patients hospitalized with positive COVID-19 molecular tests in the mass vaccination era and proposal of their best setting of care.

Type of patient	Characteristics	Best setting of care
Unvaccinated	Fever, respiratory failure, chest imaging evidence of interstitial pneumonia	Pneumology Infectivology Internal medicine ICU or subintensive care
Breakthrough infection, asymptomatic	Admitted for reasons unrelated to COVID-19, unexpected positivity on RT-PCR testing for SARS-CoV-2	Internal medicine Other specialty according to the index clinical picture
Breakthrough infection, paucisymptomatic	Complex clinical presentation exhibiting some features (fever, dyspnea) compatible with both COVID-19 and other pre-existing diseases, chest imaging negative or undetermined for interstitial pneumonia, presence of multimorbidity and/or frailty. COVID-19 is not the index disease but simply one condition with the same or lower priority than other conditions	Internal medicine Geriatrics Community facilities (milder cases) Hospital-at-home programs (milder cases)
Breakthrough infection, symptomatic	Fever, respiratory failure, chest imaging evidence of interstitial pneumonia, usually with reduced severity and potential of	Pneumology Infectivology Internal medicine or geriatrics

	<p>evolution towards severe forms.</p> <p>Comorbidities may be present, but COVID-19 holds the highest priority in care.</p>	<p>ICU or subintensive care</p>
<p>Long-term positivity (vaccinated or not)</p>	<p>Documented previous episode of COVID-19, admitted for reasons unrelated to COVID-19 or for complex cardiorespiratory symptoms not certainly related to acute interstitial pneumonia, possible long-COVID features, persistent viral shedding from upper airway mucosa</p>	<p>Internal medicine</p> <p>Geriatrics</p> <p>Community facilities (milder cases)</p> <p>Hospital-at-home programs (milder cases)</p>

In fact, in the post-vaccine era, hospitalization in patients with SARS-CoV-2 breakthrough infection may occur for clinical reasons unrelated to COVID-19, and the finding of positive molecular testing on admission may even be unexpected. In other cases, generally regarding older patients with multimorbidity and frailty who received vaccination in the early phases of the campaign, COVID-19 may represent just one of multiple clinical conditions, and sometimes has even a lower clinical priority than another index disease. In these patients the occurrence of respiratory failure, if present, cannot be uniquely attributed to COVID-19, but can also be related to pre-existing cardiorespiratory conditions. Some of these patients may also have experienced previous SARS-CoV-2 infections, so that it is difficult to determine whether the occurrence of a novel positive molecular test represents reinfection or long-term positivity due to persistent viral shedding.

Some patients needing hospitalization for SARS-CoV-2 breakthrough infection may also present with the typical COVID-19 picture: fever, progressive respiratory failure, chest imaging compatible with interstitial pneumonia. These patients generally have received their last dose of anti-COVID-19 vaccine a longer time before other patients with breakthrough infection (generally more than three months), or have a substantial burden of frailty and multimorbidity, representing significant

risk factors for both severe outcomes of COVID-19 and vaccine failure. Furthermore, the occurrence of such cases could be more frequent during winter and early spring, when the seasonal spread of SARS-CoV-2 is generally higher and associated with more severe clinical pictures (11). The care needs of these patients are similar to unvaccinated counterparts, although the prognosis is more favorable in terms of risk of ICU admission and mortality. A high degree of inter-individual variability in the clinical course and prognosis of the disease is however present, so that unfavorable outcomes cannot unfortunately be ruled out also in patients who completed their vaccinal schedule. Medical history, with particular focus on vaccine timing, and chest imaging, particularly involving computed tomography or ultrasound (14), could represent the main parameters for classifying patients with breakthrough infection upon admission.

Such classification could be useful not only for epidemiological and research purposes, but also for organizing hospital care. In fact, unvaccinated patients and patients with symptomatic breakthrough infection may be best managed in specialist wards dedicated to COVID-19 with priority access to ICU and subintensive care. Conversely, patients belonging to the “asymptomatic”, “paucisymptomatic” and “persistent positivity” groups may be best managed in internal medicine and geriatrics COVID-19 wards, where clinicians have the know-how for managing complex pictures characterized by frailty and multimorbidity (15-17).

The organization of hospital care, which has been disrupted by the sudden emergence of COVID-19 pandemic in 2020, should in fact be adapted to the changing epidemiology and needs of patients admitted with positive PCR tests for SARS-CoV-2 (18). Before the pandemic, organization of medical wards by care intensity has prompted significant advantages in terms of appropriateness, quality and safety of care, particularly for older patients with multiple chronic conditions and frailty (19,20). The changes in COVID-19 epidemiology driven by mass vaccination campaigns should thus induce a paradigm change also in hospital organization, from a disease-centered model, to a

patient-centered model considering that nowadays patients needing hospital admission for COVID-19 do not always have the same clinical picture and thus have different care needs.

The omicron threat

The abrupt emergence of the SARS-CoV-2 omicron variant in the last weeks of 2021 represents a serious threat for public health and functioning of healthcare systems (21-22). The omicron variant, first described in South Africa in November 2021, is characterized by an unprecedented infectiousness, with doubling times of cases esteemed in less than three days (21-22). Furthermore, molecular investigations suggest that the protection conferred by the current vaccines against SARS-CoV-2 is significantly lower for this variant than for other variants that have caused outbreaks earlier in 2021 (23).

Preliminary data from clinical investigations suggest that the omicron variant is associated with milder disease and substantially reduced risk of hospital admission than the delta variant (24-27). However, from a public health perspective, it is unclear whether this advantage balances the extremely high infectiousness and rapidity of spread among the population. In fact, there are substantial concerns that the omicron variant can cause an extremely high number of hospital admissions, even involving vaccinated patients. This circumstance could lead to hospital overcrowding and substantial difficulties in delivering care for clinical conditions unrelated to COVID-19 (28).

In this scenario, hospitalization of patients with SARS-CoV-2 breakthrough infection is more and more probable in the near future. Unfortunately, solid data on the clinical pictures caused by the omicron variant in patients needing hospital admission are lacking at the time of writing. However, prompt recognition of the severity of respiratory involvement and its clinical priority with respect of other coexisting conditions remains of utmost importance for delivering the best care in the most appropriate clinical setting. The high diffusion of omicron infections makes it also fundamental to

avoid hospitalization whenever possible. Hospital-at-home services specifically dedicated to COVID-19 patients could be thus implemented to relieve the overcrowding of acute-care wards (13, 29).

Conclusions

Mass vaccination campaigns and the emergence of novel viral variants have substantially modified the epidemiology of COVID-19 also from a hospital perspective. Despite the increasing frequency of SARS-CoV-2 breakthrough infections, to date few studies have focused on the clinical characteristics and care needs of patients who need hospital admission for SARS-CoV-2 infection after completion of the vaccination schedule, and none of them concerned the omicron variant. A consistent fraction of these patients have only mild or moderate respiratory involvement, but a high degree of clinical complexity due to older age, frailty and comorbidities. Hospital care should be organized in accordance with the needs of this novel category of COVID-19 patients, with tailored clinical pathways.

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