



KARDIOLOGIA POLSKA

Polish Heart Journal
The Official Peer-reviewed Journal
of the Polish Cardiac Society
since 1957

Online first

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ISSN 0022-9032

e-ISSN 1897-4279

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Article type: Letter to the editor

Received: April 22, 2023

Accepted: April 27, 2023

Early publication date: May 2, 2023

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The course and treatment of COVID-19 in heart transplant recipients

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We read with interest a paper by Nowak et al. [1] presenting the results of a case series study of heart transplant recipients infected with SARS-CoV-2. Although the study group consisted of only 5 patients, so that conclusions should be drawn with caution, there is an undeniable trend towards a decrease in complications of COVID-19 in the era of predominance of Delta and Omicron variants, vaccination and antiviral treatment [1] compared to the first phase of the pandemic in Poland [2]. All patients presented [1] were hospitalized, but none required mechanical ventilation or ICU admission, and the only death was related to septic shock, not COVID-19 per se. In contrast, a recent study by Hazan et al. [3] demonstrated that of 57 hospitalized cases (of which 51 were confirmed to be infected with either Delta or Omicron variants), 53% required ICU admission, 38% required mechanical ventilation and/or ECMO, and 38% died, with a higher rate of complications in Omicron-infected patients, although 75% of them were fully vaccinated. However, Hazan [3] reported that only 4% of patients received antiviral treatment. In this context, we agree with Nowak et al. that there is still a need for rapid diagnosis of COVID-19 and early initiation of antiviral treatment in immunocompromised patients.

What caught our attention in the paper by Nowak et al. [1] was that 2 out of 5 patients had pulmonary aspergillosis. The authors did not explain whether aspergillosis was diagnosed in the course of COVID-19 or whether it was a pre-existing condition. van Grootveld et al. [4] recently showed that the incidence of COVID-19 associated pulmonary aspergillosis reached

up to 15% of patients admitted to the ICU but data on the coexistence of COVID-19 and pulmonary aspergillosis in stable hospitalized patients are scarce. Therefore we are curious about the prevalence of pulmonary aspergillosis among heart transplant recipients hospitalized at the Authors' center during the study period. Furthermore, given our own experience with difficulties in diagnosing fungal infections, we would like to ask how the diagnosis of aspergillosis was confirmed. Antifungal treatment with triazole derivatives causes fluctuations in immunosuppression due to interactions with calcineurin inhibitors. This leads to another question: what were the tacrolimus concentrations at the time of COVID-19 diagnosis (in the aspergillosis group versus other patients)?

Since COVID-19 was mostly diagnosed in the first year after transplantation or shortly after acute rejection, it is likely to be associated with extensive immunosuppression. Balancing the risk of acute organ rejection with the risk of infectious complications needs a careful adjustment of immunosuppression regimens. Kolonko et al. [2] reported that in one-third of heart transplant recipients, the dose of immunosuppressants was reduced after diagnosis of COVID-19, except for the dose of calcineurin inhibitors which remained unchanged. Did Nowak and colleagues follow any rules, or was the immunosuppressive treatment adjusted only on a case-by-case basis? Furthermore, an interesting fact has been observed previously [2]: in kidney transplant recipients a significant increase in median tacrolimus levels was noted during the first weeks of COVID-19 when compared to the mean values before infection. Do the Authors have similar observations?

At the end of the discussion of immunosuppressive therapy during COVID-19 treatment, we would like to mention a ritonavir-boosted nirmatrelvir, another drug approved and now available for the early treatment of mild to moderate COVID-19. Due to the ritonavir component of the combination, a strong cytochrome P450 (CYP) 3A4 inhibitor and a P-glycoprotein inhibitor, many significant drug-drug interactions could be expected. In general, it is recommended to temporarily withhold certain immunosuppressants (e.g., tacrolimus, everolimus, sirolimus) and to reduce the dose of the others (e.g. cyclosporine) during ritonavir-boosted nirmatrelvir administration [5].

Article information

Conflict of interest: None declared.

Funding: None.

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