

were similar to those of the ancestral strain and other variants of concern (i.e., 50% inhibitory concentration values for these three agents that differed by factors of 2.5 to 4.5, 0.7 to 1.6, and 1.5 to 3.3, respectively) (Table 1).³ Clinical studies are warranted to determine whether these antiviral therapies are indeed effective against omicron/BA.2 infections. Our data indicate that some therapeutic monoclonal antibodies (REGN10987–REGN10933, COV2-2196–COV2-2130, and S309) have lower neutralizing activity against omicron/BA.2 than against earlier variant strains.

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Resistance Mutations in SARS-CoV-2 Delta Variant after Sotrovimab Use

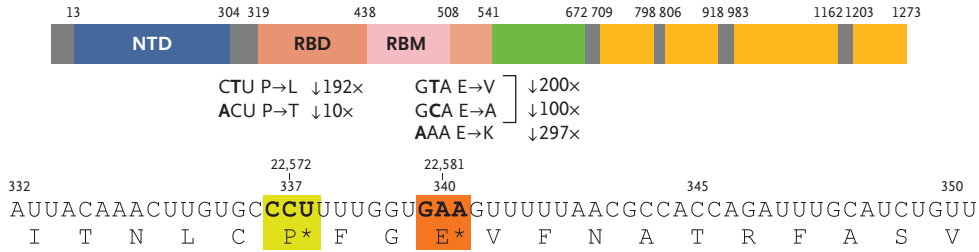
TO THE EDITOR: Sotrovimab is a monoclonal antibody that is available under emergency use authorization for the treatment of patients who are at risk for progression of coronavirus disease 2019 (Covid-19) to severe disease.¹ Sotrovimab is thought to neutralize all sarbecoviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), by binding to a highly conserved epitope within the receptor-binding domain.² However, the use of SARS-CoV-2-specific monoclonal antibodies to target a single viral epitope warrants caution because of the risk of rapid development of mutations that confer resistance after exposure to these antibodies.²⁻⁴ Mutations at positions S:E340K/A/V and S:P337L/T (Fig. 1A) have been associated with a reduction by a factor of 100 to 297 in neutralization by sotrovimab.⁵

We reviewed the first 100 consecutive patients who received sotrovimab at health care

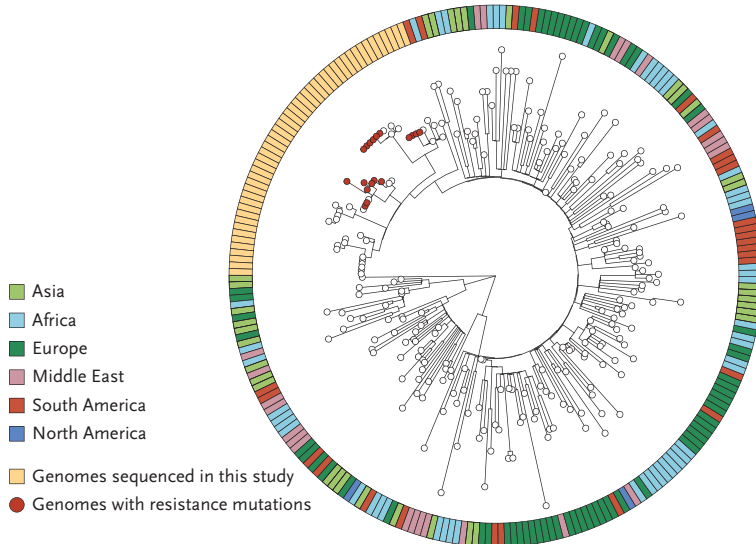
facilities in the Western Sydney Local Health District in New South Wales, Australia, during the B.1.617.2 (delta) variant outbreak between August and November 2021 (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). We identified 8 patients (Patients R001 through R008) with reverse transcriptase–polymerase-chain-reaction (RT-PCR) assays that were persistently positive for SARS-CoV-2 and for whom respiratory tract specimens obtained before and after the use of sotrovimab were available.

Genomic analysis showed that 4 of these 8 patients (Patients R001 through R004) acquired previously defined receptor-binding domain mutations within 6 to 13 days after they received sotrovimab (Fig. 1C and Table S1). Mutations in S:E340 developed in all 4 patients, findings that are concordant with those in the Covid-19 Monoclonal Antibody Efficacy Trial–

A Protein Sequence and Coordinates of Mutations



B Phylogeny of the Delta Variant



C Read Frequency and Viral Load

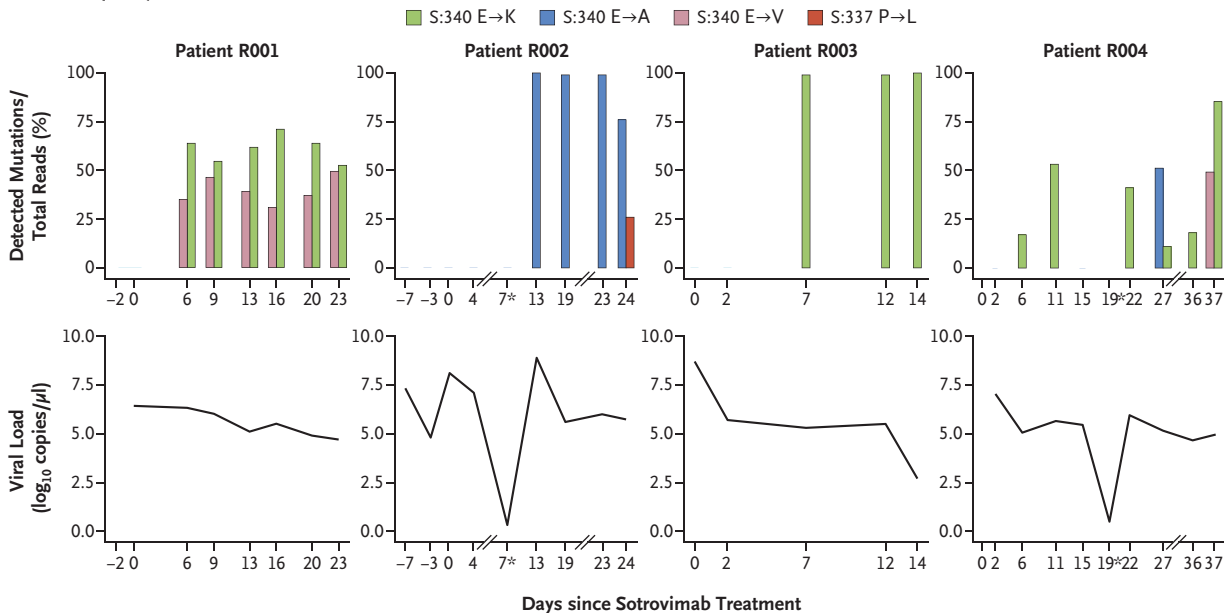


Figure 1 (facing page). SARS-CoV-2 Viral-Load Dynamics and Acquisition of Resistance Mutations after Sotrovimab Treatment.

The acquisition of mutations conferring a high level of resistance to sotrovimab and the dynamics of the viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are shown. Panel A shows the N-terminal domain (NTD), receptor-binding domain (RBD), and receptor-binding motif (RBM) of the SARS-CoV-2 spike protein and the protein sequence and coordinates of mutations that were acquired in the RBD of the spike protein after sotrovimab treatment. We found five mutations (S:E340K/A/V and S:P337L/T) that have been reported to reduce susceptibility to sotrovimab by factors of 297, 100, 200, 192, and 10, respectively.^{1,5} Panel B shows the global phylogeny of subsampled isolates of the SARS-CoV-2 delta variant, a variant of concern, with the geographic region of sequences indicated in the outer ring. Panel C shows the findings in four patients with SARS-CoV-2 infection who received sotrovimab. The acquisition and read frequency of mutations conferring high levels of resistance to sotrovimab and the SARS-CoV-2 load at each sampling point are shown. The asterisks indicate two sampling time points in which a high-quality SARS-CoV-2 genome could not be recovered (in Patient R002 on day 7 and in Patient R004 on day 19) and potential resistance mutations could not be revealed. All the patients in whom resistance mutations developed (Patients R001 through R004) were hospitalized during the sampling periods.

Intent to Care Early (COMET-ICE).² Cultures obtained from these patients remained positive for 23, 24, 12, and 15 days, respectively, after they received sotrovimab (Table S2). Read frequencies of S:E340K/A/V mutations increased over the course of infection; the proportion of the viral population carrying S:E340K/A/V exceeded 75% by day 7 in Patient R002, by day 13 in Patient R003, and by day 37 in Patient R004 (Fig. 1C and Table S2). In addition, a minority variant developed in Patient R002 at position P337L after fixation of the S:E340K mutation. A retrospective review of 11,841 SARS-CoV-2 genomes in the Global Initiative on Sharing All Influenza Data database (a site for compiling sequence data on viruses) (Table S3) and reported in New South Wales, Australia, identified 4 additional patients with S:E340 mutations. In 1 patient, the SARS-CoV-2 genome was detected 5 days after sotrovimab treatment, and in another it was detected 11 days after treatment.

These data show the persistence of viable SARS-CoV-2 in patients after sotrovimab infusions and the rapid development of spike gene mutations associated with high-level sotrovimab resistance in vitro. These findings underscore the importance of stewardship of monoclonal antibodies, particularly because sotrovimab is one of the few monoclonal antibodies with retained activity against the B.1.1.529 (omicron) variant.¹ Postmarketing genomic surveillance of patients who receive monoclonal antibodies for the treatment of SARS-CoV-2 infection is prudent in order to minimize the risk of both treatment failure and the transmission of potentially resistant SARS-CoV-2 variants in health care settings and the community, given that SARS-CoV-2 may be isolated up to 24 days after sotrovimab treatment.

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Early Treatment with Sotrovimab for Covid-19

TO THE EDITOR: Three issues are major drawbacks in the trial conducted by Gupta et al. (Nov. 18 issue)¹ on the administration of the SARS-CoV-2 neutralizing antibody sotrovimab to prevent the progression of Covid-19. First, the definition of “high risk” was based on arbitrary factors, as reflected by the low 29-day case fatality rate in the overall trial population (0.2%; 1 of 583 patients) and the low percentage of patients who were admitted to the intensive care unit (0.9%; 5 patients); these data are not representative of a high-risk population.² Second, patients with immunocompromise, who constitute an important high-risk population, especially in the era of vaccination, were excluded by the protocol from enrollment in the trial.^{3,4} Third, neutralizing antibody titers were not obtained before the intervention, and the effect of emerging autologous immunity remains obscure.⁵ We thus conclude, on the basis of a low case fatality rate, the exclusion of patients with immunocompromise, and missing data regarding preexisting autologous immunity, that caution should be exercised in transferring these preliminary results to clinical practice.

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TO THE EDITOR: Gupta et al. describe in the Methods section of their article that the patients who underwent screening for eligibility were those at high risk for progression either owing to older age or because they presented with at least one risk factor, such as obesity (defined as a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of >30). In the Supplementary Appendix (available with the full text of their article at NEJM.org), a change in eligibility criteria is noted: the obesity criterion was raised to a BMI of more than 35.