ptive against puncture. The concentration expected from a lumbar centrations in ventricles, compared with resulting from compression of the fourth homogeneous distribution of voriconazole re-reported data from Lutsar et al. [1], mor, we noticed in the previously re-measured CSF concentrations. Further-more, we noticed in the previously re-measured CSF concentrations. Further-more. We can assess that the liver graft was not involved in these low concentrations of voriconazole, because it exhibited normal function. The sampling procedure can perhaps explain the low results. The CSF specimen was collected during 2 h through the intraventricular catheter. Therefore, the in vitro instability of voriconazole and/or adsorption of voriconazole on the lines and collection materials of the intraventricular derivation are able to decrease measured CSF concentrations. Furthermore, we noticed in the previously re-port ed data from Lutsar et al. [1] that, among samples that yielded the 7 lowest concentrations found (which were similar to ours), 4 samples were obtained through an intraventricular catheter. A nonhomogeneous distribution of voriconazole resulting from compression of the fourth ventricle could also explain the lower concentra-tions in ventricles, compared with the concentration expected from a lumbar puncture.

In conclusion, voriconazole is highly active against Aspergillus species, but additional studies are needed to confirm that our low drug concentrations result from the method of sampling and not from poor efficacy of this molecule in the CSF.

Acknowledgment

Conflict of interest. All authors: No conflict.

E. Denes,1 N. Pichon,2 M. Debette-Gratien,3 B. Bouteille,4 and J. M. Gaulier2
1Infectious Diseases Department, 2Intensive Care Unit, 3Hepatology Department, 4Laboratory of Mycology and Parasitology, and 5Department of Pharmacology and Toxicology, Centre Hospitalier Universitaire Dupuytren, Limoges, France

References

1. Lutsar I, Roffey S, Troke P. Voriconazole concentra-tions in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. Clin Infect Dis 2003; 37:728–32.

2. Espinel-Ingroff A, Chaturvedi V, Fothergill A, Rinaldi MG. Optimal testing conditions for de-termining MICs and minimum fungicidal concentra-tions of new and established antifungal agents for uncommon molds: NCCLS collabor-ative study. J Clin Microbiol 2002; 40:3776–81.

3. Schwartz S, Milatovic D, Thiel E. Successful treatment of cerebral aspergillosis with a novel triazole (voriconazole) in a patient with acute leukaemia. Br J Haematol 1997; 97:663–5.

4. Venkataramanan R, Zang S, Gayowski T, Singh N. Voriconazole inhibition of the metabolism of tacrolimus in a liver transplant recipient and in human liver microsomes. Antimicrob Agents Chemother 2002; 46:3091–3.

Use of Clinical Criteria and Molecular Diagnosis to More Effectively Monitor Patients Recovering after Severe Acute Respiratory Syndrome Coronavirus Infection

In early 2003, a novel severe acute respiratory syndrome (SARS) coronavirus (CoV) [1] spread around the world; ultimately, more than 8000 patients in 32 countries contracted SARS, many of whom died. Although gold standard methods, such as viral culture, can help diagnose SARS, these methods are by no means as efficient and rapid as PCR-based diagnostic tests. The speed and sensitivity of molecular diagnostic tests for SARS is often considerably greater than than that of serological and viral culture methods [2]. Our reported enhanced real-time PCR (ERT) method [3, 4] is $\geq$100-fold more sensitive than conventional real-time PCR. The higher sensitivity of this method may reveal potential SARS CoV carriers who have SARS CoV levels that are undetectable by other methods, and the sensitivity of the ERT method may be particularly important for ensuring that patients who have had SARS are not infectious before discharge from the hospital [5].

In collaboration with Princess Margaret Hospital (PMH; Hong Kong), samples obtained from 3 patients during recovery after SARS were analyzed (table 1). Six to nine weeks after the onset of infection, SARS CoV could still be detected by ERT in certain samples (table 1), indicating that, although clinical signs and symptoms had subsided and a host immune response had been mounted, viral clearance was not complete. Patient 1 was transferred on 17 June 2003 to the Wong Tai Sin Hospital (WTSH; Hong Kong), which was con-ver ted into a specialized center for convalescent care of patients with SARS during the epidemic, but he was returned to PMH because of recurrent pneumonia, indicated by chest radiography on 18 June. The ERT method clearly demonstrated the presence of SARS CoV in all samples obtained from the patient on 16 June (table 1), which was 1 day before his transfer to WTSH. The possible relapse of infection in patient 1 after his transfer to another hospital indeed raises the question of how patients with SARS who have PCR results negative for SARS CoV should be handled [5]. Standardization of clinical criteria and PCR-based methods should be emphasized to ensure accurate diagnosis of SARS after hospital admission and prior to hospital discharge. More studies will be neces-sary to determine the infectivity status of patients who have ERT results positive.
Table 1. Summary of demographic characteristics, clinical history, and laboratory results for patients recovering after severe acute respiratory syndrome (SARS) coronavirus (CoV) infection in Hong Kong, 2003.

| Variable                  | Patient 1                  | Patient 2                  | Patient 3                  |
|---------------------------|----------------------------|----------------------------|----------------------------|
| Sex                       | M                          | M                          | F                          |
| Age, years                | 49                         | 86                         | 87                         |
| Date of hospital admission| 29 Mar                     | 22 Mar                     | 1 Apr                      |
| Symptoms                  | Allergy to penicillin and tetracycline; low-grade fever; sputum | Right MCA infarction; gouty attack; high-grade fever | Left corona radiata infarction; fever |
| Serological test result for SARS CoV | Positive                      | Positive                      | Positive                      |
| Radiographic findings     | Bilateral infiltrates       | RLZ haz processing to both lungs | Multiple patchy consolidations in both lungs |
| Date SARS confirmed       | 29 Mar                     | 28 Apr                     | 1 Jun                      |
| ERT results, by sample and date obtained | NS                           | OS                          | Urine                       |
|                           | 16 Jun                     | 16 Jun                     | 16 Jun                     |
|                           | Positive                   | Positive                   | Positive                   |
|                           | Negative                   | Negative                   | Negative                   |
|                           | 24 Jun                     | 24 Jun                     | 24 Jun                     |
|                           | Positive                   | Positive                   | Positive                   |
|                           | Negative                   | Negative                   | Negative                   |
|                           | 27 Jun                     | 27 Jun                     | 27 Jun                     |
|                           | Negative                   | Negative                   | Negative                   |
|                           | 02 Jul                     | 02 Jul                     | 02 Jul                     |
|                           | Negative                   | Negative                   | Negative                   |
|                           | 16 Jun                     | 24 Jun                     | 27 Jun                     |
|                           | Positive                   | Positive                   | Negative                   |
|                           | Negative                   | Negative                   | Negative                   |
|                           | 02 Jul                     | 27 Jun                     | 02 Jul                     |
|                           | Negative                   | Negative                   | Negative                   |

NOTE. MCA, middle cerebral artery; NS, nasopharyngeal swab sample; OS, oral swab sample; RLZ hazz, right lower zone hazziness.

for SARS CoV. The data suggest that medical professionals should verify whether residual viral particles in recovering patients remain infectious and whether they may constitute the source of possible future outbreaks of infection.

Because SARS is a newly emerging disease that causes serious consequences, many countries have formulated contingency plans for possible future SARS outbreaks. One of the containment activities currently undertaken by the World Health Organization to prevent SARS from repeatedly becoming a widely established threat is to develop a robust and reliable diagnostic test [6], which will probably rely on PCR-based technology. Use of a highly sensitive method, such as the ERT method [3, 4] and a similar method that was reported recently [7], will be the first step toward more accurate screening of suspected SARS carriers and will minimize the occurrence of false-negative cases. Patients with false-positive cases can always be quarantined while awaiting further reconfirmation of infection. But patients with false-negative cases could be discharged into the community and pose a dangerous SARS threat to the public [8]. Therefore, stringent clinical criteria and use of the ERT method might effectively monitor patients recovering after SARS.

Acknowledgments

We thank Sino-i.com, Dr. Cecilia W. B. Pang (Biotechnology Director, Information Technology and Broadcasting Branch, Commerce, Industry and Technology Bureau, Hong Kong Special Administrative Region), and Fung-Kwok Ma (New Century Forum), for facilitating this study.

Financial support. The Philip K. H. Wong Foundation, Kennedy Y. H. Wong, Pun-Hoi Yu, and the New Century Forum Foundation. C.G.W. is the principal investigator of the National Emergency Action on SARS Research (Beijing Group), supported by the Ministry of Public Health and the Ministry of Science and Technology of China.

Conflict of interest. All authors: No conflict.

References

1. Ksiazek TG, Erdman D, Goldsmith CS, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003; 348:1953–66.
2. World Health Organization. Severe acute respiratory syndrome (SARS): laboratory diagnostic tests. 29 April 2003. Available at: http://www.who.int/csr/sars/diagnostictests/en/print.html. Accessed 2 April 2004.
3. Lau LT, Fung YW, Wong PF, et al. A real-time PCR for SARS-coronavirus incorporating target gene pre-amplification. Biochem Biophys Res Commun 2003; 312:1290–6.
4. Yu ACH, Lau LT, Fung YW. Boosting the sensitivity of real-time PCR SARS detection by simultaneous reverse transcription and target gene pre-amplification. N Engl J Med 2004; 350:1577–9.
5. Tsang OT-Y, Chau T-N, Choi K-W, et al. Severe acute respiratory syndrome: relapse? Hospital infection? Emerg Infect Dis 2003; 9:1180–1.
6. World Health Organization. Severe acute respiratory syndrome (SARS): status of the outbreak and lessons for the immediate future. 20 May 2003. Available at: http://www.who.int/csr/media/sars_wha.pdf. Accessed 2 April 2004.
7. Jiang SS, Chen T-C, Yang J-Y, et al. Sensitive and quantitative detection of severe acute re-
spiratory syndrome coronavirus infection by real-time nested polymerase chain reaction. Clin Infect Dis 2004; 38:293–6.

8. Yu AC. The difficulties of testing for SARS. Science 2004; 303:469–71.

Reprints or correspondence: Dr. Albert Cheung-Hoi Yu, Neuroscience Research Institute, Key Laboratory of Neuroscience, Peking University and Dept. of Neurobiology, Peking University Health Science Ctr., Ministry of Education, 38 Xue Yuan Rd., Beijing 100083, China (achy@dnachip.com.hk).

Clinical Infectious Diseases 2004; 39:604–6
© 2004 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2004/3904-0039$15.00