Treating severe acute respiratory syndrome with hyperimmune globulins

To the Editor—In response to the recently published article on the use of plasma from a convalescent patient to treat severe acute respiratory syndrome (SARS),[1] Drs Burnouf and Radosevich[2] suggested that if treatment with plasma is confirmed to be helpful, a virus-inactivated, purified, and concentrated immunoglobulin (Ig) preparation obtained by the fractionation of a large pool of convalescent plasma could be developed for clinical evaluation and use for two reasons. Firstly, its use would limit the risks of exposing patients to blood-borne viral infections.[3] Secondly, pooling should enhance the polyvalency of the anti-SARS antibodies against variants of the SARS virus. Dr Chow[4] also proposed that public health authorities should store batches of hyperimmune plasma in case outbreaks of these diseases occur.

Convalescent plasma has been successfully used to treat various epidemic outbreaks. Mortality rates were reduced in the case of SARS (personal communication) and from 80.0% to 12.5% for Ebola infection.[5] We now wish to reveal for the first time that virus-inactivated, purified, and concentrated Ig preparations (SARS hyperimmune globulins) have been obtained by the fractionation of pooled plasma collected from HIV-negative and hepatitis B- and C-negative patients from Shenzhen, China, who had recovered from SARS and who produced antibodies against the SARS virus.

Two batches of SARS hyperimmune globulins have been produced from pooled convalescent plasma at a plant (with good manufacturing practice) in Shenzhen for clinical evaluation. The plasma was first treated with solvent and detergent (S/D)[6-8] to inactivate blood-borne viruses. The virus-inactivated convalescent plasma was then precipitated sequentially with different concentrations of ethanol (the modified Cohn method).[9] The SARS hyperimmune globulins were subsequently purified from the precipitate using a chromatography step licensed from Amersham Biosciences (Uppsala, Sweden). The SARS hyperimmune globulins have been examined and confirmed by the Chinese National Institute for the Control of Pharmaceutical & Biological Products, Food and Drug Administration to meet the intravenous immunoglobulins specifications required by the Chinese Pharmacopoeia, and the hyperimmune globulins have been approved for clinical evaluation. Determined by immunofluorescence assay, the SARS-specific antibody titre of SARS hyperimmune globulin is five to six times that of convalescent plasma.

The S/D method, licensed from the New York Blood Center through Amersham Biosciences, is one of the most prevalent and widely published methods of virus inactivation in use today. The majority of blood-derived products are currently manufactured using the S/D method, and more than 34 million doses of S/D-treated products have been administered to patients worldwide.[10] According to the New York Blood Center's official records, there have been no reports of hepatitis B, hepatitis C, or HIV transmission associated with the use of S/D-treated products.

In Hong Kong, we have now started to collaborate with various parties to produce more clinical batches of SARS hyperimmune globulins. It should be pointed out that the titres of antibody in plasma obtained from recovered patients are falling off rapidly. A concerted effort is urgently needed to enable this important project to be successfully accomplished so that safer and more efficient treatment alternatives can be found for SARS for future outbreaks. Once the protocol is established locally, manufacturing hyperimmune globulins will become an important task for public health authorities in the region to take up in order to face emerging viral infections—not just SARS—in the future.

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Travel-acquired infections in general

To the Editor—I am deeply impressed by the articles that appeared in the *Hong Kong Medical Journal*[1-4] and other journals on the subject of severe acute respiratory syndrome (SARS). Our front-line doctors have proven their professionalism in every respect and deserve our utmost admiration and gratitude. Now that the epidemic has subsided, at least temporarily, it might be a time to reflect on the problem of travel-acquired or 'imported' infection on a broad perspective (one might use the term 'extra-territorially acquired infection' in contrast to 'community-acquired infection'). Severe acute respiratory syndrome may return, or another infection—old or new—may be introduced to our community, especially with the intensified integration of Hong Kong into mainland China. Travel-acquired infection may be at least as important as community-acquired infection. In recent years, paragonimiasis and melioidosis have been reported to have been spread by patients who had been travelled to eastern China and Thailand, respectively.[5,6]

I reviewed the records of my hospital practice and found fives cases of travel-acquired fever in the run-up to mid-February 2003, when we recorded our first authentic case of SARS in Hong Kong. In two patients, the cause of fever was obvious. One case was due to a post-insect bite carbuncle acquired in Donguan, and the other was a case of cellulitis from a traffic injury acquired in Shenzhen. The remaining three cases deserve further discussion (Table). All three patients shared some common features. They all presented within 12 hours after the onset of fever, having been driven by the severe chills and myalgia. Their chest X-ray films all showed some bronchitic change, but no florid pneumonitis. In all patients, fever was refractory to a combination of intravenous piperacillin-tazobactam and azithromycin, but responded within 12 hours to a combination of oral ribavirin, methisoprinol, and intramuscular gammaglobulin. By day 4, all patients were afebrile. From their response to treatment, they probably had acquired some form of virus infection during their travels. In particular, one patient had remarked that nearly all fellow travellers in his boat tour of the Three Gorges came down with fever. In May, when virus testing became more available, I traced one of the two patients who had been to the Three Gorges and I tested her for coronavirus antibody; her test result was negative.

Obviously, we need more organised efforts to protect our community from travel-acquired and imported infections in terms of public education, pre-tour advisories, and (when applicable) immunisation, vigilant monitoring of returning travellers, and prompt quarantine and isolation measures whenever indicated. The same measures should also apply to visitors and immigrants. The relevant health authority should act as coordinator between established viral laboratories in the territory and the medical community at large so that sera could be promptly obtained, tests could be readily available and carried out, and the results rapidly reflected to all parties concerned.

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Table. Characteristics of three patients with travel-acquired fever

Date presented	Sex/age (years)	Temperature/ duration of fever	White blood cell count (x 10^9 /L)/lymphocytes	Site visited
14 November 2002	M/90	37.6°C, 4 days	10.1/21.4%	Zhuha
9 February 2003	M/66	38.9°C, 36 hours	7.15/9.5%	Three Gorges
20 February 2003	F/65	37.3°C, 12 hours	4.18/46.0%	Three Gorges