

Crimean-Congo Hemorrhagic Fever: Prevention and Control Limitations in a Resource-Poor Country

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In autumn 2000, an outbreak of Crimean-Congo hemorrhagic fever (CCHF) occurred in Pakistan and involved nosocomial cases due to human-to-human transmission at a tertiary care hospital in Karachi. During a hospital-based investigation, 6 serologically confirmed cases (i.e., patients seropositive for CCHF antigen or anti-CCHF immunoglobulin M antibodies by means of a capture enzyme-linked immunosorbent assay [ELISA]) and 3 clinically confirmed cases (i.e., patients with negative ELISA for CCHF but with relevant epidemiologic exposures and compatible clinical disease) of CCHF were identified. The outbreak originated in rural Balochistan, a region of known CCHF endemicity where miniepidemics regularly occur, and subsequently spread to the urban centers of Quetta and Karachi. This outbreak demonstrated the capacities and weaknesses associated with a developing country's response to hemorrhagic fever epidemics. We describe aspects of disease prevention, control challenges, and political obstacles posed by illness associated with what we refer to as the "Asian Ebola virus."

Infectious diseases remain the single greatest contributor to morbidity and mortality in the world. Diseases such as tuberculosis, malaria, lower respiratory tract infections, gastrointestinal diseases, and HIV/AIDS head the list of infections that burden humanity. Other rare infectious diseases, such as smallpox, plague, and anthrax, have come to international attention in recent years as real or potential candidate agents for biologic warfare. However, few diseases have the capacity to stimulate interest and instill concern both in the general population and the health care community as do viral hemorrhagic fevers (VHFs).

Of the major hemorrhagic fever viruses, some (Lassa, Marburg, Ebola, agents of South American VHF, Han-

taan, and Crimean-Congo) share a distinct characteristic that has important clinical and public health consequences, namely the potential for person-to-person transmission (table 1). Percutaneous or permucosal exposure to blood and other infected body fluids, especially if the fluids contain blood, can result in secondary human spread. This type of uncommon transmission takes place most often among health care workers in hospital settings [1]. These rare zoonoses pose a significant nosocomial hazard that can be minimized by proper and timely infection-control measures, careful management of infected patients, and, in some cases, administration of prophylactic therapy to health care workers after exposure [2, 3]. However, additional public health responses and community-based control measures are necessary to decrease disease transmission and prevent further spread in the community.

In autumn 2000, a serologically documented outbreak of Crimean-Congo hemorrhagic fever (CCHF) occurred in Pakistan that demonstrated the capacities and weaknesses associated with a developing country's response to hemorrhagic fever outbreaks. In this article,

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Table 1. Characteristics of some commonly recognized viral hemorrhagic fevers (VHFs).

VHF	Virus genus	Transmission	Nosocomial spread	Treatment ^a	Mortality among untreated persons, %
Yellow fever	<i>Flavivirus</i>	Mosquito	No	Supportive	25–50
Lassa fever	<i>Arenavirus</i>	Rodent	Yes	Ribavirin	30
South American hemorrhagic fever ^b	<i>Arenavirus</i>	Rodent	Uncommon	Supportive	30
Hemorrhagic fever with renal syndrome	<i>Hantavirus</i>	Rodent	Extremely rare	Ribavirin	5–15
Ebola/Marburg fevers	<i>Filovirus</i>	Primate	Yes	Supportive	50–90
Crimean-Congo hemorrhagic fever	<i>Bunyavirus</i>	Tick	Yes	Ribavirin	10–50

^a Largely based on anecdotal and small case series data rather than on randomized clinical trials.

^b Argentine VHF is caused by the Junin virus, Bolivian VHF is caused by the Machupo virus, Venezuelan VHF is caused by the Guanarito virus, and Brazilian VHF is caused by the Sabia virus.

we briefly describe the outbreak and discuss the treatment, control, and prevention aspects associated with what we refer to as the “Asian Ebola virus.”

ILLUSTRATIVE DISEASE OUTBREAK

Between 3 September and 5 December 2000, 29 patients with clinical illness suggesting CCHF were admitted to the Aga Khan University Hospital in Karachi, Pakistan, a 647-bed private, tertiary care, academic teaching hospital that serves the residents of Karachi (population, ~8–12 million inhabitants), and the surrounding Sindh province. The outbreak was first identified after the death of a hospital health care worker involved in the care of a 40-year-old butcher admitted to the hospital with gastrointestinal bleeding. Subsequently, a working case definition was developed to guide the use of strict isolation precautions and antiviral prophylaxis. Suspected cases involved patients admitted with fever and thrombocytopenia but without splenomegaly, thus excluding common febrile diseases such as malaria and enteric fever [3]. During the ensuing hospital-based investigation, 6 serologically confirmed cases (i.e., patients who were seropositive for CCHF antigen or anti-CCHF IgM antibodies by means of capture ELISA) and 3 clinically confirmed cases (i.e., patients with serological tests negative for CCHF but with relevant epidemiologic exposures and compatible clinical disease) of CCHF were identified. The outbreak originated in rural Balochistan, a region of known CCHF endemicity where miniepidemics regularly occur, and subsequently spread to the urban centers of Quetta and Karachi. Seven cases were in various areas within Karachi and 2 were in Quetta (tables 2 and 3). Two cases occurred among butchers who were likely exposed to infected animals during slaughtering. There were 3 cases of human-to-human transmission, including 2 nosocomial cases in nursing staff and 1 of 2 infected boys from a local orphanage.

At the outset of this hospital-based CCHF outbreak, serological testing of patients with suspected cases was not available. The National Institute of Health in the capital city, Islamabad,

had a CCHF antibody assay several years earlier, but it had not been available for routine use for some time. Accordingly, serological confirmation of all our cases came from the US Centers for Disease Control and Prevention (CDC) in Atlanta; serum samples obtained from patients with suspected cases were frozen and sent to the CDC for testing in weekly batches. In light of CCHF endemicity in Pakistan (figure 1) [4–6], the hospital’s clinical microbiology laboratory subsequently obtained a serological assay that allowed in-house diagnosis of cases, and this was used to successfully detect a case of CCHF in a patient from Quetta hospitalized in May 2001.

Early diagnosis and strict blood and body fluid infection-control precautions were deemed to be essential to limit exposure to caregivers. Relevant hospital control measures included formulation of a hospital management policy for suspected CCHF cases (i.e., case identification, strict isolation, and contact tracing of exposed individuals), creation of a CCHF task force, expanding knowledge and improving skills of health care workers (i.e., on the proper use and role of universal precautions and barrier nursing techniques; notification of needlestick injuries and other blood and body fluid exposures; timely reporting of suspected cases; instructions for proper phlebotomy techniques; appropriate handling, disinfection, decontamination, and/or disposal of all contaminated specimens, items, and hospital environmental surfaces), and enhancing communication (within the hospital and with the media). Concurrent disinfection of equipment and environments contaminated with blood discharges was accomplished with heat or chlorine disinfectants.

In view of the potential for secondary transmission of CCHF to family members during burial preparation, relatives were not allowed to handle, in the usual culturo-religious manner, the bodies of those who died with confirmed or suspected CCHF. Instead, the bodies were washed in the hospital by trained nursing staff and taken for burial in an impervious polyethylene bag. No one was allowed to directly touch the body at the time of burial. Concomitant community infection-control measures

Table 2. Serological and epidemiologic characteristics of patients who reported to the emergency department and were admitted with suspicion of Crimean-Congo hemorrhagic fever (CCHF), September–November 2000.

Characteristic	City of residence, no. of patients (n = 29)			
	Karachi	Quetta	Hyderabad	Gilgit
CCHF illness				
Serologically confirmed	4	2	0	0
Clinically confirmed ^a	3	0	0	0
Non-CCHF illness				
Seronegative for CCHF	7	1	1	1
Serologically confirmed dengue fever ^b	3	0	0	0
Diagnosis of CCHF clinically excluded ^c	5	2	0	0
Total	22	5	1	1

^a All 3 patients had relevant epidemiologic exposures; 2 were seronegative for CCHF, and 1 did not undergo serological testing.

^b All 3 patients were seronegative for CCHF.

^c No patients underwent serological testing.

were also undertaken by the epidemiologists of the Department of Community Health Sciences (Karachi), in conjunction with the local health department, and involved active community surveillance and contact tracing and provided community-based health education and educational materials. Administration of prophylaxis with oral ribavirin after exposure was offered to anyone at high-risk for exposure, such as those who were directly exposed to the blood of CCHF patients through contact or needlestick injury. Although all 9 patients with CCHF were treated with ribavirin, 5 (56%) died.

DISCUSSION

The Pakistani outbreak described here, which was eventually contained by a successful multidisciplinary collaboration between the hospital's infection-control team, clinical microbiologists, hospital administrators, and university epidemiologists, confirmed the vulnerability and limitations of the health care system in a resource-poor country that are associated with bloodborne and other occupationally related pathogens. This epidemic acutely demonstrated the lack of clear understanding of the basic concepts and principles of infection control among both health care personnel and hospital administrators.

Ignorance of and indifference to necessary precautions, as well as an insufficient number of isolation rooms, contribute to nosocomial disease outbreaks. Furthermore, although hospitals in an Islamic country such as Pakistan do not have the same problem with HIV/AIDS as do those in most developing nations, both hepatitis C and hepatitis B virus are hyperendemic in Pakistan and pose significant threats to health care workers [7]. Yet, nurses and house officers regularly perform phlebotomies, insert intravascular catheters, and perform other diag-

nostic and therapeutic procedures without the use of appropriate barrier precautions.

Analysis of the recent CCHF epidemic in Pakistan also highlights another important feature of inadequate yet frequent infection-control practices at many hospitals in resource-poor countries: an overemphasis on cost containment. Individual personnel and entire medical wards in hospitals may be rewarded for limiting use—and thus reducing costs—of items, such as hand soap and disinfectants, paper towels for hand washing, gloves, masks, and gowns. The principle of universal infection-control precautions becomes supplanted by the overriding, short-sighted focus on saving money, despite the significant costs that are associated with failing to protect health care workers in developing countries [7].

The involvement and expertise of clinicians, microbiologists, and public health practitioners are essential for the early detection and management of naturally occurring disease epidemics, as well as those that might follow covert acts of bioterrorism. However, the investigation and containment of an infectious disease epidemic is only as good as its weakest link. An essential step in outbreak investigations of communicable disease is surveillance to define the geographic extent of human transmission by tracking suspected cases and obtaining appropriate laboratory specimens. During our CCHF outbreak, which spanned 3 months, the government was very slow in becoming actively involved. In the months before the outbreak spread to Karachi, >15 reports of CCHF occurring in Balochistan had appeared in the lay press. However, despite these reports, no case had been microbiologically confirmed, and regional and national health officials had paid little if any heed to their occurrence. The first serologically documented case of CCHF came from our university, yet despite the heightened

Table 3. Characteristics of patients with confirmed Crimean-Congo hemorrhagic fever (CCHF), September–November 2000.

Patient no. ^a	Age in years	Admission date	Outcome	Exposure			
				Animal	Person with CCHF	Occupation	Area of residence
1	18	Sep 17	Died	None	None	Laborer	Quetta
2	40	Oct 12	Died	Cattle, sheep	None	Butcher	Karachi
3	31	Oct 22	Died	None	Yes	Nurse assistant	Karachi
4	48	Oct 22	Recovered	None	None	Office worker	Karachi
5	28	Nov 21	Recovered	None	Yes	Nurse	Karachi
6	16	Nov 3	Died	Chickens, goats, pet pigeons	None	Student	Karachi
7	19	Nov 15	Died	House rats	None	Student	Karachi (orphanage)
8	15	Nov 16	Recovered	House rats	Yes	Student	Karachi (orphanage)
9	28	Nov 18	Recovered	Cattle, sheep	None	Butcher	Quetta

^a Patients 2, 5, and 7 had clinically confirmed cases (all were either seronegative for CCHF or did not undergo serological testing); the remaining cases were serologically confirmed.

media attention and demand for up-to-date information, the government still chose not to initiate any formal epidemiologic investigation until late in the outbreak, and it fell on the academic medical center to do so. Not a single case of CCHF was reported from any other hospital in Karachi, including the 3 large government teaching hospitals, and it seemed as if neither private nor public hospitals wanted the publicity associated with a case of CCHF. Accordingly, human, animal, and insect surveillance was extremely limited, and vector control measures to reduce exposure to infected ticks (e.g., use of diethyltoluamide-containing repellents, administration of vaccine to animals, and dipping of domestic livestock in 2% sodium hypochlorite) were not appropriately undertaken.

The viruses that cause hemorrhagic fever syndromes, especially those documented to be associated with human-to-human transmission (such as CCHF), are potential candidates for agents of bioterrorism. In a recent invited article on confronting biological weapons, Fine and Layton [8] outlined recommendations for improving the capacity of public health administrations to respond to bioterrorism. These include enhancing awareness and training of clinicians and other health care workers, increasing public health resources and expertise, improving communication between human and animal health authorities, strengthening laboratory capacity, and preparing comprehensive public education and media outreach programs. The CCHF experience in Karachi provides practical lessons in



Figure 1. Geographic distribution (shaded areas) of Crimean-Congo hemorrhagic fever

outbreak detection, laboratory diagnosis, investigation, and response that can influence planning for future naturally occurring or bioterrorism-associated infectious disease epidemics.

Careful management of fluid and electrolyte levels is the cornerstone of therapy for CCHF. In an outbreak in the former U.S.S.R., Soviet physicians found little clinical benefit associated with the administration of convalescent-phase immune plasma, although plasma with high neutralizing antibody titers has been reported as being potentially useful [3]. The CCHF virus is susceptible *in vitro* to ribavirin, but controlled clinical trials have not established the efficacy of this drug. When administered either parenterally or orally, ribavirin has been reported to have some anecdotal benefit in uncontrolled studies involving both sporadic and outbreak cases of CCHF, Lassa fever, Bolivian hemorrhagic fever, and hemorrhagic fever with renal syndrome caused by Hantaan virus [9–11]. In a 1994 outbreak, 3 Pakistani health care workers with a 90% risk of mortality were provided oral ribavirin, and all recovered quickly without sequelae soon after the drug was initiated [10]. All patients seen in the 2000 outbreak described in this article received ribavirin, with only a 44% response rate.

In summary, the hospitalization of persons with a highly communicable or highly fatal infectious disease, such as meningococcal meningitis, rabies, or VHF (including that due to Ebola and CCHF viruses) predictably generates anxiety, confusion, and fear among hospital staff with patient-care responsibilities. Armed with a modicum of knowledge about CCHF, and with meticulous attention to relevant infection-control and standard barrier precautions, health care personnel can feel confident in protecting themselves against this disease. Nevertheless, other ingredients are required to successfully address CCHF, including political will. Although the health care community may at times lament the role of the media in sensationalizing certain disease occurrences, in the case of fever due to Ebola virus, the generated notoriety may have substantially affected political visibility and research priority, leading to a

new investigational vaccine for this rare but deadly infection. CCHF, although much more widely distributed geographically than Ebola virus, has not enjoyed the same global publicity. We may do well to portray it as the “Asian Ebola virus” that it seems to be, with the hope of further stimulating national, international, and scientific attention that may enhance future preventive and control efforts.

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