A nosocomial outbreak of Crimean-Congo haemorrhagic fever at Tygerberg Hospital

Part IV. Preventive and prophylactic measures

B. W. VAN DE WAL, J. R. JOUBERT, P. J. VAN EEDEN, J. B. KING

Summary

During the Crimean-Congo haemorrhagic fever (CCHF) outbreak at Tygerberg Hospital a particular problem existed: a simultaneous influenza epidemic complicated the screening of contacts because of its very similar clinical picture to that of early CCHF. The methods of identifying and screening contacts are described. Of 459 listed CCHF contacts, 7 (1.5%) developed the disease; 6 were contacts of the index case and only 1 a contact of a secondary case. Two of the 7 CCHF patients had no direct contact with the index case; this caused great concern about the dissemination, despite the otherwise full protective measures. Four of 46 blood contacts (8.7%) and 3 of 9 needle contacts (33%) developed the disease. Prophylactic interferon therapy had to be discontinued because of side-effects mimicking the symptoms of CCHF. Ribavirin was used prophylactically in 6 of the 9 inoculation contacts. One of the patients on ribavirin had a mild clinical course while 5 others who received the drug developed neither clinical CCHF nor antibodies to the virus. Two of the 3 needle contacts not treated with ribavirin had a severe clinical course. One contact with needle inoculation and 42 proven blood contacts who had not received ribavirin did not become infected. No firm conclusion can therefore be made about the protective value of prophylactic ribavirin.

During the outbreak of Crimean-Congo haemorrhagic fever (CCHF) at Tygerberg Hospital, in which 2 out of 8 patients died, serious doubt arose about the actual infectivity of CCHF.

The course of the illness in contacts made us question current beliefs about the high infectivity of blood and secretions of patients with CCHF. Two of those who contracted the disease from the initial patient had no direct contact with this patient, while numerous contacts among hospital staff and relatives of patients did not contract it.

Diagnosis was often difficult, even with a high degree of suspicion, because of a concomitant severe influenza epidemic simulating the early clinical picture. There was also an unavoidable delay of 24-36 hours for the results of CCHF antibody tests and of up to 8 days for the viral cultures to become available.

We were unprepared for this outbreak. Isolation facilities, screening procedures and prophylactic treatment had to be improvised with little available information from the literature. Staff members were put under pressure because of the unknown consequences of the outbreak and the emotions created by the media.

Our goal was to curb further spread of the disease by identifying and screening contacts, isolating them if warranted, and thus bringing the outbreak under control. Containing the outbreak would prove the correctness of the approach adopted.

Methods

Communication

A circular was distributed to the hospital staff in which available facts on CCHF, including possible infectivity and early symptoms, were described. Staff members were urged to report for examination if they thought they had suggestive symptoms. Assurance was also given that contacts would be followed up for early detection of CCHF.

The heads of all hospital departments were informed of the major symptoms and signs of CCHF and were asked to compile lists of possible, probable and definite contacts of any of the CCHF patients. Copies of these lists were sent to the Department of Comprehensive Medicine, the Medical Superintendent and all laboratories. It was compulsory for all contacts to be checked daily for early symptoms during possible incubation periods. The contacts were controlled in a pyramidal manner, with one person appointed as responsible for each group and reporting to a group higher in the pyramid. The head of a department would ultimately communicate this information to the Department of Comprehensive Medicine which informed the screening office. In this way all hospital staff could be kept under daily surveillance with a minimum delay. Routine laboratories were instructed not to process any specimen from a listed contact.

The physician in charge of contact management attended a meeting twice daily to discuss and plan strategies in accordance with new developments arising from the CCHF outbreak. A meeting was also held twice daily to monitor the clinical course of the infected patients and to plan therapy accordingly.

Ward administration

A medical ward was made available for the screening and admission of possible CCHF patients. Medical and nursing staff allocated to this ward were informed about the proper dressing procedures and the handling of secretions and laboratory specimens. The available knowledge on CCHF and the importance of strict isolation procedures for all those admitted into isolation were stressed.

Department of Internal Medicine, University of Stellenbosch and Tygerberg Hospital, Parowvallei, CP

B. W. VAN DE WAL, M. MED. (INT.)
J. R. JOUBERT, M. MED. (INT.), M. D.
P. J. VAN EEDEN, M. MED. (INT.), F. C. P. (S. A.)
J. B. KING, M. MED. (INT.), PH. D.
Both the nursing and medical staff as well as the ward secretary were drawn from volunteers. This contributed much to the excellent team spirit maintained despite the high level of tension. Three interns and two physicians were needed to cope with the flow of contacts to be screened and with the routine visits to the contacts who had been admitted to this isolation ward. A 24-hour medical service was provided.

The ward was separated into three areas: a reception office, an entrance, and a screening area, and the isolation facilities. The reception office, staffed by senior nurses assisted by administrative personnel, served as the logistics centre. The senior nurses functioning as public relation officers, screened all telephone calls, and organized the transport of laboratory specimens to Johannesburg. They also double-checked all movements of people and material into and out of the ward, assisted in drawing up lists and in the daily screening of contacts and the arrangements for re-examination of suspect cases.

The larger part of the ward was intended for the admission and observation of contacts suspected of having possible early symptoms and signs of CCHF. At the back of the ward a smaller area was commissioned which could be sealed off as a high-security area. Highly suspect patients were accommodated there while waiting for serological confirmation of the diagnosis. Once this was confirmed, these patients would be transferred to the ward where the diagnosed CCHF patients were isolated.

Criteria for admission to the ward were: (i) a definitive history of contact with diagnosed CCHF patients; and (ii) where or prolonged viraemic manifestations with petechiae, a low white cell count and/or a low platelet count.

Outpatient screening

A CCHF admission sheet for both clinical and administrative use was designed. Contacts completed a questionnaire on their address, telephone numbers and possible symptoms, or mode of contact appeared. To prevent possible contamination, staff members had to dress in full theatre clothes, including masks, gowns and gloves. Suspects were thoroughly examined for signs of the disease while the exact symptoms and mode of contact were confirmed. Full haematological studies were done routinely on all contacts, while virological studies were done on those who had a positive history while virological examination for CCHF was requested on a daily basis. Biochemical analyses were done where indicated. Contacts were also brought up to date with the ward, could be discharged after thorough examination, and instructed to report back to the screening area if there were suggestive symptoms.

Contacts isolated for observation were examined 12-hourly by a physician. Haematological investigations were done twice daily while virological examination for CCHF was requested on alternate days. Biochemical analyses were done where indicated. Contacts were also brought up to date with the CHF situation and misleading media reports were corrected these visits. Attempts were made to interact socially in spite of the strict isolation procedures in order to decrease the strain caused by the isolation.

The larger part of the ward was intended for the admission and observation of contacts suspected of having possible early symptoms and signs of CCHF. At the back of the ward a smaller area was commissioned which could be sealed off as a high-security area. Highly suspect patients were accommodated there while waiting for serological confirmation of the diagnosis. Once this was confirmed, these patients would be transferred to the ward where the diagnosed CCHF patients were isolated.

Criteria for admission to the ward were: (i) a definitive history of contact with diagnosed CCHF patients; and (ii) where or prolonged viraemic manifestations with petechiae, a low white cell count and/or a low platelet count.

Outpatient screening

A CCHF admission sheet for both clinical and administrative use was designed. Contacts completed a questionnaire on their address, telephone numbers and possible symptoms, or mode of contact appeared. To prevent possible contamination, staff members had to dress in full theatre clothes, including masks, gowns and gloves. Suspects were thoroughly examined for signs of the disease while the exact symptoms and mode of contact were confirmed. Full haematological studies were done routinely on all contacts, while virological studies were done on those who had a positive history while virological examination for CCHF was requested on a daily basis. Biochemical analyses were done where indicated. Contacts were also brought up to date with the ward, could be discharged after thorough examination, and instructed to report back to the screening area if there were suggestive symptoms.

Contacts isolated for observation were examined 12-hourly by a physician. Haematological investigations were done twice daily while virological examination for CCHF was requested on alternate days. Biochemical analyses were done where indicated. Contacts were also brought up to date with the ward, could be discharged after thorough examination, and instructed to report back to the screening area if there were suggestive symptoms.

Asymptomatic contacts were discharged after the initial examination, but remained under observation by the heads of their departments for their suspected incubation period. Asymptomatic contacts were examined daily or on alternate days.

Outpatient screening

Contacts isolated for observation were examined 12-hourly by a physician. Haematological investigations were done twice daily while virological examination for CCHF was requested on alternate days. Biochemical analyses were done where indicated. Contacts were also brought up to date with the ward, could be discharged after thorough examination, and instructed to report back to the screening area if there were suggestive symptoms.

Outpatient screening

Contacts isolated for observation were examined 12-hourly by a physician. Haematological investigations were done twice daily while virological examination for CCHF was requested on alternate days. Biochemical analyses were done where indicated. Contacts were also brought up to date with the ward, could be discharged after thorough examination, and instructed to report back to the screening area if there were suggestive symptoms.

Asymptomatic contacts were discharged after the initial examination, but remained under observation by the heads of their departments for their suspected incubation period. Asymptomatic contacts were examined daily or on alternate days.

Outpatient screening

Contacts isolated for observation were examined 12-hourly by a physician. Haematological investigations were done twice daily while virological examination for CCHF was requested on alternate days. Biochemical analyses were done where indicated. Contacts were also brought up to date with the ward, could be discharged after thorough examination, and instructed to report back to the screening area if there were suggestive symptoms.

Asymptomatic contacts were discharged after the initial examination, but remained under observation by the heads of their departments for their suspected incubation period. Asymptomatic contacts were examined daily or on alternate days.

Asymptomatic contacts were discharged after the initial examination, but remained under observation by the heads of their departments for their suspected incubation period. Asymptomatic contacts were examined daily or on alternate days.
Results of prophylaxis

Within hours after the first interferon bolus dose viraemia-like symptoms (severe headache, severe myalgia, chills, prolonged rigors, malaise, nausea and low backache) were experienced by the first 3 very-high-risk contacts. Body temperature rose by between 0.8°C and 1.8°C. Although the influenza-like side-effects of interferon are well known, differentiation from possible CCHF symptoms became very difficult. We therefore discontinued the interferon therapy because apart from the above mentioned side-effects, a depressant effect on both white cells and platelets might be expected, and also because the value of interferon was unproven in any viral haemorrhagic fever.

The daily dosage of ribavirin was reduced to 30 mg/kg divided into equal 8-hourly doses after more literature had become available. Ribavirin was given to the 5 contacts for the full expected incubation period. Total quantities of ribavirin used ranged from 8200 mg over 4 days to 20000 mg over 8 days. Subjective side-effects from ribavirin were mild and were noticed after the 4th or 5th day of therapy. Mild fatigue was noted by all 5 subjects, anorexia by 4, nausea by 2 and abdominal discomfort by 1 subject.

Haemoglobin values and red cell counts dropped on the 4th day of therapy. These values were at their lowest 1 week after ribavirin had been stopped and were at pretreatment level 2 weeks later. Decreases in haemoglobin ranged from 1.1 to 3.8 g/dl, with an average of 2.32 g/dl. Decreases in red cell count ranged from 0.26 x 10^6/ml to 1.55 x 10^6/ml with a mean of 1.01 x 10^6/ml. White cell counts did not change significantly and platelet counts remained at pretreatment levels throughout the observation period. Reticulocyte counts done in 2 subjects indicated depression of red cell production, but showed a normal response 1 week after ribavirin was discontinued. Serum haptoglobin levels were determined repeatedly in the patient who had the most pronounced fall in haemoglobin, but were never decreased.

Because of initial technical problems, tests for liver function became available only several days after treatment was started. Serum transferase and protein levels remained normal in all contacts. Total bilirubin values were twice the upper limit of normal in 4 contacts, mainly because of an increase in unconjugated bilirubin. One contact's serum bilirubin level rose to more than 5 times the upper limit of normal, with over 80% of the bilirubin unconjugated. His bilirubin remained at this level for several days after ribavirin was discontinued, but was normal 1 week later. This contact was previously suspected of having Gilbert's disease. Serum urea and creatinine levels increased abnormally only in this subject and were still elevated at 1.5 times the upper limit of normal 3 weeks after ribavirin was discontinued. Fluid intake had been adequate throughout the observation period. Repeated urinalysis was negative and creatinine clearance values were normal.

Discussion

During a CCHF outbreak the index case must be diagnosed early and isolated to minimize possible contacts. In our situation, where no viral haemorrhagic fever had ever been diagnosed before, large numbers of contacts could have been infected by the index case. It was impossible to isolate all 459 reported contacts. Even isolation of symptomatic and potentially high-risk contacts alone would have paralysed a large part of Tygerberg Hospital, and most medical wards would have had to be evacuated. This was impossible because no alternative patient accommodation was available. It was therefore decided that only the highly suspect contacts would be admitted for observation while waiting for virological confirmation. In the prevailing influenza epidemic only contacts with severe influenza-like symptoms associated with petechiae and a decreased platelet and white cell count could be admitted.
Two of the secondary CCHF patients had needle injuries, but 1 tertiary patient was injured during a skin biopsy procedure, and 5 asymptomatic high-risk contacts were admitted for observation during this outbreak. Several months later one of the authors had an uncomplicated deep accidental needle inoculation from a subsequent CCHF patient in a haemorrhagic state. Thus 9 very-high-risk contacts with CCHF, mostly by needle prick, were known. Six of these 9 possible direct inoculations were from index cases, the other 3 from secondary cases. Two of 6 possible inoculation contacts from index cases developed CCHF with a severe clinical illness. One of 3 inoculation contacts from secondary CCHF patients developed CCHF with a much milder clinical course. It seems thus that the morbidity from needle contact could not be higher than 3% (3 of 9).

Two of the 4 blood contacts who developed CCHF had extensive and repeated contact with the index case. Of the other 42 blood contacts who did not develop CCHF, 18 had been in extensive contact with the index case, 9 with both the index case and a secondary case, and 15 with a secondary case only. In this outbreak the infectivity rate in the haemorrhagic state of the disease may thus be calculated at 8.7% (4 of 46) of people who had extensive contact with blood. Calculating the overall infectivity rate is difficult. Based on the number of reported contacts this would be 1.5% (7 out of 459).

Not much is known about the true incidence of CCHF in South Africa. Before the Tygerberg Hospital outbreak only 8 other cases had been described in separate outbreaks. CCHF antibodies could not be detected in 98 tested veterinarians or 64 staff members of Onderstepoort Veterinary Institute. Antibodies were found in only 17 of 1108 tested sera from people living on farms in the eastern Orange Free State and northeastern Cape. Three per cent of Zambian schoolchildren were shown to have antibodies to CCHF. Infected cattle often show no signs of disease but antibodies to CCHF in cattle have been demonstrated in 3–80% of herds tested throughout South Africa. A later case of CCHF in an ostrich farmer admitted to Tygerberg Hospital in November 1984 has led to serological testing in these animals as well. Antibodies to CCHF could be demonstrated in some of them.

During the CCHF outbreak 1 patient strongly denied any contact with the index case, while another patient had only been outside the room of the index case where she was supervising the correct handling of refuse bags from the CCHF index case. This unexpected transmission of the virus resulted in a large degree of uncertainty about the need for direct contact for the CCHF to spread. The institution of measures to identify possible high-risk contacts was therefore well received.

Staff assigned to a screening ward should be volunteers and would be selected on the basis of compliance, emotional balance, and general experience. The number of staff should be adequate, because an excessive workload in such a situation has the potential for a disaster due to bad judgement. Senior medical staff should be present at all times to assist junior staff in selecting patients for admission.

In the approach to prophylaxis one should be realistic. Maximum information about efficacy, toxicity and dosage of unproven medicines must be obtained before deciding on their use. Because of the nature and results of this outbreak nothing definite could be concluded as to the efficacy of interferon and ribavirin. The severe side-effects of interferon simulating early symptoms of CCHF and the interferon-related decrease in white cells and platelets, could certainly confound the clinical picture of developing CCHF. Interferon has not been used experimentally in similar situations. The decision to use two unproven medicines at the same time could also be criticized.

Of 6 inoculation contacts from primary patients, 3 treated prophylactically with ribavirin did not develop CCHF, while 3 not treated prophylactically had severe illness. All 3 needle inoculation contacts from secondary cases were treated with prophylactic ribavirin. Only 1 of these 3, a nursing sister mentioned by Van Eeden et al. as a tertiary case, had a mild course of CCHF. It is not clear whether ribavirin did in fact protect these contacts. Of 42 non-treated blood contacts none developed CCHF. Before deciding on the use of ribavirin in future outbreaks, at least experimental proof of its efficacy would be most desirable.

REFERENCES
9. Van Eeden et al. Memorandum 12/01/65, Director of Veterinary Services, Dept of Agriculture and Fisheries, RSA, 29 April 1983.