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

Part II. Management of patients

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Summary

During the outbreak of Crimean-Congo haemorrhagic fever (CCHF) at Tygerberg Hospital 8 patients were diagnosed positive. CCHF was diagnosed in another patient several months later. The treatment of these 9 cases is outlined. When it became evident that CCHF could present with a spectrum of severity, treatment was adjusted according to each patient's requirements. The essential components consisted of correction of haematological abnormalities combined with hyperimmune serum; the latter is particularly important for the severely ill patient with no antibodies to CCHF. The antiviral agents ribavirin and interferon were used but evidence to substantiate their application in future cases was inconclusive. Interferon was discontinued because of severe side-effects, many of which simulated the clinical features of CCHF. Objective improvement after corticosteroid treatment was noted in only 1 patient, but some of her symptoms could have been due to a transfusion reaction. Antibiotics were not routinely used. The 2 patients who died were diagnosed late, did not receive hyperimmune serum, and eventually developed multi-organ failure. The course of CCHF can probably be modified if the diagnosis is made early, if antiserum is given, and if the haematological abnormalities are promptly corrected.

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During the outbreak of Crimean-Congo haemorrhagic fever (CCHF) at Tygerberg Hospital the staff was confronted with a disease previously unknown to them. Several factors influenced the management of these patients: (*i*) there was a delay of up to 8 days before confirmation of CCHF viraemia could be obtained, therefore patients strongly suspected of having CCHF had to be treated without diagnostic proof of the disease; (*ii*) laboratory facilities had to be improvised in the isolation ward, which limited the range of investigations; (*iii*) mass hysteria inside and outside the hospital put tremendous pressure on attending staff — in this situation there was an inclination to over-treat rather than to under-treat; and (*iv*) the scanty literature[1-4] contained no clear guidelines for treatment.

It became obvious that treatment would have to be based on sound medical principles and adjusted according to the individual's clinical condition.

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Patients and methods

Criteria were developed by which patients with highly suspicious symptoms were selected for treatment. Patients who fulfilled the following criteria were regard as potential cases of CCHF:

1. Close contact with CCHF patients or with blood products from such patients. Accidental needle inoculation or open skin wounds were specifically considered as high-risk contacts.
2. Severe influenza-like symptoms with a haemorrhagic tendency.
3. Leucopenia and/or thrombocytopenia.

Eight patients were numbered and categorized as described.[5] Cases B1, 2 and 3 fulfilled all three criteria, and cases B4 and C1 criteria 2 and 3. Case A2 did not comply with the criterion of close contact and presented with a leucocytosis. He was initially misdiagnosed. Case C2 was treated prophylactically on criterion 1 (needle inoculation) but was kept in the intensive care ward as she had rising antibody titres to CCHF. Case A1 was also initially admitted with a non-CCHF diagnosis. All 8 patients were later positively diagnosed by virological studies as having CCHF.

Treatments used included: (*i*) hyperimmune serum; (*ii*) haematological supportive measures; (*iii*) antiviral medication; (*iv*) general supportive measures; and (*v*) specific intensive care treatment for organ failure.

Hyperimmune serum

Hyperimmune serum was prepared from serum of previous patients with CCHF found to have high antibody titres after recovery; only a limited quantity was available. Five of the 8 patients received hyperimmune serum (Table I), 3 of them twice. They were infused with approximately 250 ml intravenously over 1 - 2 hours. The highest antibody titre of hyperimmune serum was 1 : 1 025.

The 2 patients who died (cases A1 and A2) received no hyperimmune serum because the diagnosis was not initially suspected. Case C1 had a mild illness and received no hyperimmune serum; case C2 received hyperimmune serum prophylactically.

Haematological supportive measures

The treatment of CCHF is essentially supportive and the most important aim is to correct haematological abnormalities (Table I). The following criteria were used:

Haemoglobin level. Fresh filtered blood (less than 5 days old) was transfused to maintain the haemoglobin level above 10 g/dl in 7 of the 8 patients.

Prothrombin ratio. Fresh frozen plasma was given when the prothrombin time ratio rose above 1,3 (normal 1,0 - 1,3). Alternatively, factor IX complex was given if the patient had a fluid overload. Two patients (cases A1 and 2) received fresh frozen plasma and factor IX complex.

Fibrinogen. Diffuse intravascular coagulation (DIC) was suspected when the fibrinogen level dropped below 150 mg/dl. Cryoprecipitate was used as a source of fibrinogen and 1 000 U were given when indicated. The fibrinogen level was monitored regularly in all patients, and heparin 5 000 U 12-hourly intravenously by infusion pump was started if the level fell below 150 mg/dl. All 8 patients received heparin and the response was monitored by the partial thromboplastin time (PTT). Care was taken not to exceed an activated PTT of 2 - 3 times normal value. Heparin was discontinued as soon as the coagulation profile normalized.

Platelets were transfused to maintain the count above 100 x 10^9/l; this was necessary in 7 of the 8 patients (an average of 7 mega-units per patient).

Leucocytes were transfused when the patients were febrile and a granulocyte count of less than 0,5 x 10^9/l was recorded (4 of 8 patients: average 2 units per patient). Proven bacterial infection not responding to antibiotics was not found in any of the patients.

Antiviral medication

Interferon was given intravenously to 6 patients but had to be discontinued because of side-effects. A regimen of interferon 18 million U intravenously every second day was used for the first week in 6 cases (B1, 2, 3, 4, C1 and 2).

Sufficient ribavirin was not available at the onset of the outbreak and only case C2 received it prophylactically. She received a total of 10,5 g, an initial dosage of 500 mg intravenously followed by 4 doses of 1 g 6-hourly and 12 doses of 500 mg 6-hourly.

General supportive measures

Prophylactic antibiotics were not given routinely. They were given in case B2 for an *Escherichia coli* urinary tract infection. The 2 patients who died received broad-spectrum antibiotic coverage as septicaemia was a major consideration; CCHF was initially not suspected in these 2 cases. Corticosteroids were given to 5 patients because of the possibility of immune complex-induced vessel damage and subsequent haemorrhage. Case A1 received 4 doses of methylprednisone 30 mg/kg. Cases A2, B1, 2 and 3 received hydrocortisone 100 mg 6-hourly intravenously in a reducing dosage over 3 - 4 days. Cases B4, C1 and 2 did not receive any corticosteroids. Indomethacin suppositories were used for symptomatic relief. Lorazepam, a short-acting tranquillizer, was chosen for sedation.

Specific intensive care treatment for organ failure

The 2 patients who died (cases A1 and 2) were admitted for organ support to two different intensive care units as CCHF was not primarily considered. Serial haemodynamic studies were done on case A2 (Table II).

Results

Hyperimmune serum

Symptomatic improvement was observed in cases B1, 2, 3 and 4 after receiving hyperimmune serum. This effect lasted for at least 12 hours before symptoms recurred. A temporary improvement was again observed after the second administration of hyperimmune serum.

Haematological supportive measures

Patients received blood products as indicated in Table I. Control of the bleeding tendency was possible in all 8 patients. Large quantities of blood and blood products were administered to the 2 patients who died. The bleeding tendency was successfully controlled with this active approach. Death was due to multiple organ failure.

Antiviral medication

No beneficial effects were observed from interferon treatment. It was impossible to distinguish between symptoms caused by interferon and those caused by CCHF, and interferon

TABLE I. HYPERIMMUNE SERUM AND HAEMATOLOGICAL SUPPORTIVE MEASURES (UNITS)

	Hyperimmune serum	Blood	Leucocytes	Platelets*	Cryoprecipitate /FFP	Factor IX complex
Surviving cases						
Case B1	2	1	5	16	—	—
Case B2	2	3	4	6	3 000	—
Case B3	2	2	1	6	3 000	—
Case B4	1	—	—	6	—	—
Case C1	1	1	1	6	2 000	
Case on prophylactic treatment						
Case C2	1	2	—	—	—	—
Deaths						
Case A1	—	40	—	5	10 000; 15	15 x 10 ml
Case A2	—	31	—	6	3 000; 28	15 x 10 ml

*Mega-unit = 4 x 10^{11} platelets.
FFP = fresh-frozen plasma.

TABLE II. SERIAL HAEMODYNAMICS IN CASE A2

	15 September 1984				16 September 1984	
	13h00	15h00	21h00	23h45	04h00	08h00
Temperature (°C)	35,4	35,0	34,5	34,0	34,8	33,9
Haemoglobin (g/dl)	4,0	6,2	11,6	13,7	11,7	10,2
pH (arterial)	7,23	7,25	7,38	7,44	7,62	7,44
$CaCO_2$ (mmol/l)	13,4	12,4	25,6	27,0	33,3	26,1
CI (l/min/m²)	6,4	5,1	4,6	3,2	2,1	1,2
BP (m) (mmHg)	76,7	58,7	110	110,3	68,3	77,7
CVP (cm H_2O)	11	20	21	18	18	9
Wedge pressure (mmHg)	13	16	25	20	16	10
$S\bar{v}o_2$ (%)	63,9	61,4	49	78,7	60,5	42,7
SVR (dyne.s/cm⁵)	424,3	304,2	842,8	1 210,4	1 029,7	2 404
$\dot{V}$ (o_2) (ml/min)	247,3 (pred 277,7)	331,2	395,4	119,6	198	168,7
COD	2,9 (pred 4,1)	2,7 (pred 3,4)	2,9 (pred 3,0)	5,6 (pred 4,7)	3,1 (pred 4,8)	1,9 (pred 5,4)

CI = cardiac index (normal 2,5 - 3,5); SVR = systemic vascular resistance (normal 900 - 1 500); COD = coefficient of oxygen delivery; $\dot{V}$ (o_2) = oxygen consumption; $S\bar{v}o_2$ = mixed venous saturation; BP (m) = mean arterial blood pressure; CVP = central venous pressure; pred = predicted; $CaCO_2$ = carbon dioxide content — arterial blood.

was therefore discontinued in the CCHF-proven patients.[6] Ribavirin was administered only to patient C2, who manifested an attenuated form of CCHF. Case C2 was however a tertiary case and a milder picture of CCHF might probably be expected. She complained of nausea, headache and malaise. Ribavirin was discontinued when this patient's bilirubin level rose to 36 mmol/l (20 mmol/l unconjugated). Serum γ-glutamyl transferase values increased from 24 to 61 U/l, and haemoglobin dropped from 13,8 g/dl to 9,2 g/dl. It was, however, difficult to ascertain which of the above abnormalities were caused by ribavirin and which by the actual illness itself.

General supportive measures

Objective improvement on corticosteroids was observed only in case B3. This patient's maculopapular rash and fever subsided within 24 hours of starting corticosteroids. The rash and fever could have been due to the administration of blood products and not necessarily to CCHF. Indomethacin suppositories gave the most relief and were superior to mefenamic acid or paracetamol for relieving the CCHF symptoms.

Specific intensive care treatment for organ failure

Both patients who died developed multiple organ failure, which initially included liver, cerebral and renal failure but later also cardiac and pulmonary insufficiency. Ventilation was started in both patients because of cerebral depression in the presence of multiple organ failure and not because of gas exchange problems. General oedema and large pleural effusions that needed drainage developed in both patients without clinical or radiological evidence of cardiac failure. Severe metabolic acidosis developed terminally.

Haemodynamic studies in case A2 revealed the following: an initial low systemic vascular resistance of 424,3 dyne.s/cm⁵ (normal 900 dyne.s/cm⁵) supported the admission diagnosis of septicaemia. Notwithstanding an initial cardiac index (CI) of 6,4 with good ventricular filling pressures, an insufficient coefficient of oxygen delivery (COD) of 2,9 (predicted 4,1) and oxygen saturation of the pulmonary artery (Svo_2) of 63,9% suggested myocardial suppression. This suspicion was confirmed when the CI fell progressively with a decreasing COD and the Svo_2 afterload rise.

Both patients needed inotropic support to maintain an acceptable cardiac output. A significant pulmonary shunt (mean 37,5%) in the presence of acceptable left ventricular filling pressures suggested a preterminal pulmonary capillary leak.

Discussion

The outbreak of CCHF at Tygerberg Hospital provided a unique opportunity for observation and treatment of patients with divergent manifestations of the disease, ranging from critical illness to an attenuated and mild form.

The limited previous therapeutic experiences with CCHF were based on uncontrolled results only,[1-3] and our results were also uncontrolled. The prognostic spectrum of disease confronting us, the available laboratory facilities to monitor patient response, and the administration of antiviral agents were unique features.

Hyperimmune serum treatment provided temporary symptomatic improvement. It was not given to the 2 patients who died; only small amounts were available and continuous infusion was not possible. Clinical improvement was observed in patients when they developed rising antibody titres in spite of not receiving additional hyperimmune serum. The absence of antibody response in the patients who died suggests that administration of hyperimmune serum is of the utmost importance in patients whose own antibody production is ineffective, especially when they are critically ill.

In retrospect, transfusion of small quantities of hyperimmune serum to patients with a good endogenous antibody response served no purpose. The major indications for hyperimmune serum would be the following: (*i*) during the early period of influenza-like symptoms and on the 1st or 2nd day after appearance of haemorrhagic manifestations in patients with a history of exposure to diagnosed cases; (*ii*) in patients who are very ill, specifically after a tick bite or potential exposure to ticks where a tendency to major haemorrhage is present and tick-bite fever has been excluded; and (*iii*) when there is clinical and haematological evidence of CCHF as described by several groups and in this study.

Administration of hyperimmune serum should in all cases be preceded and followed by determination of the patient's own capacity for antibody production. It remains uncertain, however, whether transfusions of small amounts of hyperimmune serum would have any therapeutic effect in such cases. Transfusion in our patients had a temporary clinical effect, as evidenced by a short-lived sense of well-being which lasted 12 hours in the 4 patients. We would suggest that massive and continuous infusion of hyperimmune serum over

a period of 48 - 72 hours is more likely to influence the course of the disease. Experience during an outbreak of CCHF at Rashid Hospital in Dubai[1] suggested that hyperimmune serum given to 1 patient shortened the protracted convalescence seen in other patients.

Haematological support constituted the most important part of the treatment. Control of haemorrhage was possible in all patients, and was achieved by platelet transfusions to obtain a minimum platelet count of 100 x 10^9/l. Such high platelet requirements may have been caused by small-vessel damage or by a functional platelet defect.[4] Both patients who died had used salicylates, which inhibit aggregation of platelets and might have aggravated haemostatic abnormalities already present. Endothelial damage is also a factor as suggested by our electron microscopy data.[7]

Heparin was used in all 8 patients without any hard evidence that it prevented the development of DIC. In the first case described in South Africa heparin was in fact discontinued.[3] It was suggested that the primary haemostatic abnormality is not a DIC but that DIC is an occasional late complicating manifestation.[4]

Anaemia was not a major problem in 6 of the 8 cases. Filtered red blood cells should be used to reduce white cell reactions. Fibrinogen levels were well controlled by giving cryoprecipitate. If available, fibrinogen may also be used in doses of 2 - 4 g.

Corticosteroid treatment gave objective improvement only in case B3, but her maculopapular rash and fever could have been due to transfusion of blood products. Evidence for immune complex involvement was found in only 1 patient and is not an indication for corticosteroid administration. Corticosteroids were used in the Dubai outbreak on the assumption that this would be beneficial for the thrombocytopenia,[1] but no objective proof is available to recommend their routine use.

Interferon and ribavirin were used in the suspected and CCHF patients. Interferon and CCHF both cause severe influenza-like symptoms as well as suppression of white cell and platelet counts. These side-effects might complicate the clinical picture where life-threatening leucopenia and thrombocytopenia are due to the disease. Due to the bleeding tendency in the CCHF patients in this study intramuscular interferon to reduce the side-effects was contraindicated.

Ribavirin was given to patient C2. The mild clinical picture could have been due to the fact that she was a tertiary contact. She developed an increase in mainly unconjugated bilirubin and liver enzymes as well as a drop in haemoglobin level. These changes could have been due to ribavirin therapy or to the actual illness. The side-effects of ribavirin therapy have been well documented.[8] The increase in mainly unconjugated bilirubin previously recorded has not been explained.[8] Changes in haemoglobin and red cell counts are mostly dose-related and reversible, except with very high dosages.[8] A carefully conducted study by Jahrling *et al.*[9] showed that combined treatment of ribavirin with Lassa virus-immune monkey serum resulted in improved survival in monkeys experimentally infected with Lassa fever. This treatment was more successful than hyperimmune serum or ribavirin alone.

A 9th case of CCHF was diagnosed at Tygerberg Hospital in the 6-month period subsequent to the CCHF outbreak. This patient received only haematological supportive treatment and hyperimmune serum. No antiviral agents were administered and he recovered uneventfully.

Secondary bacterial infection was present in only 1 patient despite leucopenia in 5 of the 8 patients. The 2 patients who died received antibiotics as septicaemia was considered in the differential diagnosis. Only case B1 had proven *E. coli* urinary tract infection. Routine antibiotic administration as suggested by Suleiman *et al.*[1] is not justified. Indomethacin suppositories were superior to mefenamic acid or paracetamol for symptomatic relief. This effect may be due to the marked anti-prostaglandin action of indomethacin.

Two previously unrecorded manifestations were found in the haemodynamic studies of case A2: (*i*) the myocardial depression might be explained by diffuse capillary damage with tissue hypoxia and subsequent necrosis or by a viral myocarditis; and (*ii*) non-cardiogenic pulmonary capillary leak seemed to be a late manifestation in cases A1 and A2.

We advocate early inotropic myocardial support and positive end-expiratory pressure in these critically ill patients. Unexplained blood loss without external evidence may be a diagnostic and therapeutic problem. In case A2 the haemoglobin level fell from 17 to 4 g/dl without external signs of bleeding. Retroperitoneal bleeding was suspected because of the severe abdominal distension without free fluid or blood in the peritoneal cavity.

It is advisable to have an indwelling arterial line to obtain blood for regular arterial blood gas determinations and for other special investigations in order to adjust therapy. The alternative of multiple arterial punctures can cause Volkmann's ischaemic contracture, which necessitated an emergency fasciotomy in patient A2 to relieve the pressure. A central venous catheter is preferable to a peripheral venous line as these patients often need massive transfusions. Catheters should be inserted by an open surgical procedure under adequate clotting coverage. Treatment of the 2 patients who died was carried out in a restricted environment and involved several invasive procedures.

Blood aerosols during ventilation and suction as well as the handling of needles constitute a real threat to intensive care nursing staff. The use of a Vickers medical respirator may be essential in this specific situation to protect nursing staff. Special care should be taken to minimize needle inoculation, an important mode of dissemination of the disease (3 proven cases of CCHF and 2 prophylactic treatment cases).

Conclusion

CCHF is a spectrum of disease ranging from critical illness and death despite intensive supportive treatment to a mild influenza-like illness with recovery after minimal support. CCHF is curable when diagnosed and treated early. The major important therapeutic contributions are hyperimmune serum administration to selected patients and correction of haematological abnormalities. Recognition of poor prognostic symptoms and signs with early active multi-organ support in addition to high dosages of hyperimmune serum may substantially influence the prognosis in critically ill CCHF patients.

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