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Experiences with severe *P. falciparum* malaria in the intensive care unit

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Abstract *Objective*: To review the clinical profiles and therapies instituted for patients with severe malaria admitted to an ICU.
Design: Retrospective study.
Setting: Internal ICU of a tertiary care centre.
Patients and participants: Between January, 1992, and February, 1999, 104 patients with malaria were admitted to the General Hospital of Vienna. Sixty-nine patients suffered from *Plasmodium falciparum* malaria (66 %), seven of these were admitted to the ICU.
Measurement and results: Seven patients were admitted to the ICU, of whom three died (4 % in hospital case-fatality rate). Four patients required mechanical ventilation because of respiratory insufficiency and adult respiratory distress syndrome (ARDS), of whom three died. Three patients were treated with inhaled nitric oxide (NO) and kinetic therapy; one patient required extracorporeal veno-venous oxygenation. All patients who died required haemofiltration because of acute renal failure.
Conclusion: As *P. falciparum* is a potentially life-threatening disease, reliable criteria for ICU admission should be defined and risk factors identified. Early ICU monitoring should be attempted, especially under the following conditions: (1) lack of clinical response to anti-malarial treatment within 48 h and/or (2) any signs of neurological disturbance (hypoglycaemia excluded). Prospective multicentre trials and guidelines for supportive intensive care are urgently needed.

Key words Severe *Plasmodium falciparum* malaria · Intensive care unit (ICU) · Adult respiratory distress syndrome (ARDS) · Haemofiltration · Outcome

Introduction

About 300–500 million humans suffer from malaria annually, and 1.5–2.7 million die [1, 2, 3]. In view of the worldwide increase of malaria cases associated with travel, malaria may well become more common in developed countries, too. The treatment of *Plasmodium falciparum* infection has to be considered an emergency as it may progress towards a life-threatening disease within a few hours. In severe cases, despite some progress in intensive care management and anti-malarial treatment, mortality still remains around 20 % in developed countries and may reach 80 % in cases with adult respiratory distress syndrome (ARDS) [2]. Comprehen-

sive data on the intensive care management of malaria are currently not available because this disease usually occurs in countries that lack sufficient facilities.

The present paper aims to review the clinical profiles and therapies instituted for patients with severe malaria admitted to the intensive care unit (ICU) of a tertiary care centre.

Materials and methods

The records of all patients with severe *P. falciparum* malaria admitted to the medical ICU of the General Hospital of Vienna from January, 1992, to February, 1999, were reviewed retrospectively.

Severe and complicated malaria was defined according to 1990 World Health Organisation criteria [4]. In brief, in the presence of asexual forms of *P. falciparum* in the blood, the presence of one or more of the following features defines severe malaria: (1) cerebral malaria with deep coma (2) severe anaemia (haemoglobin < 5 g/dl) (3) oliguria (urine output < 400 ml/24 h) renal failure (serum creatinine > 265 μmol/l) (4) hypoglycaemia (blood glucose < 2.2 mmol/l) (5) acidaemia (arterial pH < 7.25) or acidosis (plasma bicarbonate concentration < 15 mmol/l) (6) circulatory collapse or shock with systolic blood pressure below 70 mmHg and persistent hypotension (systolic blood pressure < 90 mmHg despite adequate volume repletion) (7) spontaneous bleeding and/or evidence of disseminated intravascular coagulation with a prothrombin time less than 70%, a partial thromboplastin time greater than 1.2 times the upper limit of normal and a fibrinogen level lower than 2 g/l.

Acute lung injury was defined according to international criteria as the acute onset of bilateral pulmonary infiltrates with a $PaO_2/FIO_2$of less than 300 mmHg regardless of positive end-expiratory pressure (PEEP); ARDS was defined with PaO_2/FIO_2 below 150.

Treatment

All patients admitted to the ICU received parenteral quinine dihydrochloride treatment with a loading dose of 20 mg/kg body weight (in accordance with WHO criteria) [5] administered over 4 h followed by 10 mg/kg body weight every 8 h for a treatment period of 3 days, and 5 mg/kg body weight clindamycin b.i.d. for a total treatment period of 5 days.

Mechanical ventilation

Mechanical ventilation was performed using a time-cycled pressure-controlled mode with decelerating flow patterns during inspiration and expiration. PEEP levels were chosen according to oxygenation and haemodynamic interference and ranged between 5 and 15 mbar. The inspiration/expiration (I/E) ratio was 1:1 in all patients with mechanical ventilation. Peak inspiratory pressure was kept to the lowest possible level to apply sufficient tidal volumes.

Kinetic therapy and inhaled nitric oxide (NO) administration were initiated when the following criteria were fulfilled: FIO_2 of 0.6 or more; I/E ratio 1:1, PaO_2/FIO_2 below 150.

Kinetic therapy and inhaled NO administration were performed as follows: patients were put into a specially designed kinetic therapy bed (Roto Rest, KCl Mediscus, Vienna, Austria). The position was changed continuously with a maximum angle of 124°. A rotation pause of 15 s was maintained bilaterally at a maximum rotation angle. Additionally, the patients inhaled NO via the Pulmonox system (Messer Griesheim, Austria). The NO dose was increased stepwise beginning with a dose of 1 ppm and increasing according to the maximal achievable increase in arterial oxygenation saturation measured by pulse oxymetry. Response to NO therapy was defined as an increase in PaO_2/FIO_2 ratio of more than 15 and/or decrease of pulmonary shunt fraction (Q_s/Q_t) of more than 5%.

Extracorporeal membrane oxygenation (ECMO)

In one patient we used a veno-venous extracorporeal circuit. Blood was drained via one 20 gauge Wire-reinforced cannula (18 French) introduced percutaneously via the femoral vein. The oxygenated blood was returned into the superior vena cava through a 20 gauge wire-reinforced catheter (14 French) which had been advanced percutaneously via the right internal jugular vein. A femoro-jugular veno-venous bypass was established using a near occlusive roller pump (Medtronic, Minneapolis, Minnesota, USA) and a parallel configuration of two hollow fibre oxygenators. All internal surfaces of the extracorporeal system were coated by covalently bound heparin. A heat exchanger integrated in the circuit maintained the patient's temperature between 36.5 and 37.5 °C. Low dose i.v. heparin was administered by continuous infusion to achieve a partial thrombin time between 40 and 55 s. Platelets were substituted when active bleeding was present.

The extracorporeal flow rate was between 3.95 and 5.01 l/min. After initiating ECMO, ventilator settings were adjusted for the decreased pulmonary gas exchange needs and to reduce further structural damage produced by high FIO_2, large tidal volumes and high peak inspiratory pressures. Patients' lungs were ventilated with a pressure-controlled mode with a ventilatory frequency of 10, I:E ratio 4:1, peak inspiratory pressure below 31 mbar and a PEEP of 9 mbar.

On admission to the ICU all patients had blood taken for a full blood count, hepatic and renal parameters, a coagulation profile, a blood smear for parasite count and arterial blood gas and lactate estimations. All patients were monitored by continuous ECG, pulse oxymetry and an in-dwelling arterial line. APACHE III, multi-organ failure score and fluid balance were calculated using an intensive care data base (CareView, Hewlett Packard, Austria).

Results

Between January, 1992, and February, 1999, 104 patients with malaria were admitted to the General Hospital of Vienna. Sixty-nine patients suffered from *P. falciparum* malaria (66%), seven of whom were admitted to the ICU (four because of neurological disturbances, three because of respiratory failure); three patients died: one of them was transferred to our ICU from another hospital already requiring mechanical ventilation and vasopressors. The results of the autopsies are shown in Table 1. Thus, our in-hospital mortality of *P. falciparum* malaria was about 4%. In the present paper only patients admitted to the ICU were studied in detail. For patient characteristics see Table 2. Six out of seven patients came from Africa, one from India. None of the

Table 1 Autopsy records of 3 patients with severe P. falciparum malaria

	Patient 2	Patient 3	Patient 4
Cause of Death	ARDS Dilatation of the right heart	Edema of the brain Brainstem herniation	ARDS Dilatation of the right heart
Pathological anatomical Diagnoses:	Malaria pigment in liver, spleen, lymph nodes Edema of the brain Hepatosplenomegalia Multiple infarctions of the spleen Intrahepatic cholestasis Multiple renal infarctions Ascites ARDS Edema of the lungs Hypertrophy of the left heart Dilation of the right heart Multiple gastric erosiones	Ikterus Edema of the brain Petechial bleeding in the brainstem Cerebellar herniation ARDS Hypertrophy of the left heart Dilation of the right heart Congestions of organs	Intrahepatic Cholestastasis Edema of the brain ARDS Dilatation of the right heart Hemorrhagic pericarditis Hemorrhagic ascites
Histology	Spleen: malaria pigments, spleen infarctions Liver: malaria pigment, intrahepatic cholestasis Fatty degeneration of the liver Kidney: multiple kidney infarctions Femoral bone marrow: Malaria pigments Brain: diffuse edema of the brain, vascular stasis, petechial bleeding	Brain: diffuse edema of the brain Multiple petechial bleeding within corpus callosum and capsula interna cerebri	Spleen: autolytic Liver: intrahepatic cholestasis Kidney: acute impairment of the tubuli Lung: diffuse alveolar damage Brain: diffuse edema Myocard: lympho-mononuclear myocarditis

Table 2 Severe malaria at the ICU: patients' characteristics

Patient	age	sex	Country	Prophylaxis	Days at the ICU
1	36	m	Gambia	n	4
2	57	m	Kenia	n	3
3	56	m	Nigeria	n	6
4	36	f	Kenia	n	6
5	44	f	India	n	11
6	59	m	Malawi	n	2
7	63	m	Namibia	n	4

patients was on anti-malarial chemoprophylaxis (see Table 2). Four patients required mechanical ventilation because of respiratory insufficiency and finally ARDS. Three of them died (75 %, see Table 3). All patients who died required haemofiltration because of acute renal failure (ARF; see Table 4). Three of the four patients requiring mechanical ventilation were also treated with inhaled NO and kinetic therapy using a kinetic bed as described above (see Table 4). One of the ventilated patients required extracorporeal veno-venous oxygenation because of an inability to maintain sufficient arterial oxygenation by conventional mechanical ventilation (see Table 4). For laboratory and biological parameters see Table 5; the time course of central venous pressure and fluid balances are shown in Table 6.

Discussion

It is estimated that more than 30,000 American and European travellers develop malaria each year. The case-fatality rate of falciparum malaria varies in the literature between 1.2 % in Singapore [6], 3 % in Germany [7] and 4 % in the United States [8]. Severe malaria in returning travellers commonly results from delays in diagnosis, which subsequently necessitates optimal supportive therapy in addition to effective anti-malarial treatment. However, there is no consensus about the intensive care management of severe malaria cases in view of the lack of data. Most published reports rely on the retrospective description of only a few patients [2, 9, 10]. Nevertheless, these reports provide valuable information about ICU management and possible prognostic factors.

Four out of seven patients with severe malaria were transferred to our ICU because of cerebral symptoms. Cerebral manifestations are common complications of severe malaria in returning travellers and include coma, confusion and fitting. Cerebral malaria is associated with a high mortality (10–59 %) [2, 11, 12, 13]. The widely accepted classification of cerebral malaria by Warrell et al. [14] depends upon the presence of deep coma. However, there is some debate about the clear criteria of cerebral malaria and, according to Blumberg [1], a broader definition including disturbed conscious-

Table 3 Severe malaria at the ICU: clinical data

Patient	APA-CHE 3	MOF	Hepatic Impair-ment	Acute renal failure	Mechanical Ventilation	Hematol. disorder	Cerebral malaria	Outcome
1	19	3	N	n	n	y	y	cured
2	63	11	Y	y	y	y	n	dead
3	69	11	Y	y	y	y	y	dead
4	30	5	Y	y	y	y	y	dead
5	67	10	Y	y	y	y	y	cured
6	19	1	N	n	n	y	y	cured
7	30	1	N	y	n	y	y	cured

Table 4 Severe malaria at the ICU: ICU treatment

Patient	Mechanical Ventilation	Kinetic therapy	Inhalative NO (max ppm)	ECMO	hemofil-tration	vasopres-sors
1	n	n	n	n	n	n
2	y	y	Y (15)	n	y	y
3	y	y	Y (15)	n	y	y
4	y	y	Y (10)	y	y	y
5	y	n	n	n	n	y
6	n	n	n	n	n	n
7	n	n	n	n	y	n

ness, confusion or convulsion not explained by hypoglycaemic or other metabolic abnormality may be warranted. In addition to the four patients admitted to the ICU because of cerebral symptoms, a further two patients developed cerebral involvement. It has been suggested that early admittance to the ICU whenever cerebral symptoms are present might improve outcome. This is especially true as cerebral symptoms often precede the failure of other organ systems. It appears plausible that such patients benefit most from early supportive intensive care.

It has previously been reported that the three most common complications leading to death in adults with severe malaria are pulmonary oedema, ARF and sepsis [3]. Respiratory failure resulting from pulmonary oedema and/or ARDS has an extremely high mortality, as also shown in the present study [2, 7, 9, 15, 16]. Four out of seven patients developed ARDS, three of them died (75 %). Mortality rates of up to 80 % have been reported in the literature. The pathophysiology of malarial ARDS is still not well understood. The hypothesis for pulmonary oedema in severe malaria is an abnormally high vascular permeability secondary to pulmonary microvascular dysfunction. Volume overload and hypoalbuminaemia may increase pulmonary capillary leakage [2]. Both normal and low pulmonary artery wedge pressures (PAWP) have been found, yet iatrogenic fluid overload appears to be a major risk factor [15, 17]. In all our patients who developed ARDS positive fluid balances were necessary to achieve haemodynamic stability before admission to the ICU (patient 4: + 5600 ml) or during the first 24 h of ICU stay (see Table 6). This might also have contributed to the development of pulmonary oedema. Strict control of fluid balance and, if possible, invasive haemodynamic measurement should be carried out in these patients. Our experiences are in accordance with those of Blumberg et al. [1], who suggested that patients would benefit from fluid restriction in order to avoid the development of ARDS. Possible consecutive problems of fluid restriction, like ARF, are easier to handle and obviously less life-threatening when temporary renal replacement is properly instituted. Instead of excessive hydration [18], early use of inotropic agents should be initiated in cases of haemodynamic instability.

As shown in our patients, kinetic therapy and inhaled NO administration did not improve the outcome of patients with ARDS, however the number of patients was too small to draw final conclusions. It has previously been shown that NO inhalation in patients with ARDS induces redistribution of pulmonary perfusion in favour of ventilated areas without a significant change of cardiac output. It is associated with a decreased PAP, a reduced intrapulmonary right-to-left shunt, and an improvement of PaO_2, probably because the inhaled NO predominantly dilates vessels of ventilated areas [19]. However, a recently published study in ARDS patients shows that inhaled NO may improve gas exchange but does not affect mortality [20]. In our study one patient was treated with extracorporeal veno-venous membrane oxygenation because of an inability to obtain sufficient oxygenation by conventional mechanical ventilation, instead of using kinetic therapy and NO inhalation. The pulmonal function improved initially, however the

Table 5 Severe malaria at the ICU: parasitological and chemical data

Patient	Parasitemia (%)	Platelets (10^9/L)	Hb (g/L)	Alat (UI/l)	Asat (UI/l)	Lactate (mmol/L)	Bilirubin (μmol/L)	Creatinine (μmol/L)	pH (units)
1	10	56	114	20	18	2.4	50.7	74.3	7.47
2	5	113	75	24	29	11.3	119.9	336.8	7.16
3	12	39	93	208	523	10.1	163.5	281.1	6.89
4	15	22	115	173	183	5.3	68.6	197.1	7.3
5	5	56	71	93	52	4.1	57.6	213.9	7.41
6	13	35	123	33	38	2	16.8	86.6	7.52
7	9	51	111	31	25	0.9	13.3	503.9	7.35

Table 6 Central venous pressure (CVP, cm H_2O) and fluid balance (FB, ml) over a maximal observation period of 5 days

Patient	CVP/FB d0	CVP/FB d1	CVP/FB d2	CVP/FB d3	CVP/FB d4	CVP/FB d5
1	4/+ 891	4/+ 1296	–	–	–	–
2	8/+ 8031	14/+ 832	18/+ 672	–	–	–
3	8/+ 4575	10/+ 7432	13/+ 2612	16/– 1245	13/+ 2050	16/+ 4520
4	3/– 796	9/– 945	14/+ 735	16/+ 4510	–	–
5	4/+ 4870	8/+ 4880	11/+ 2613	12/+ 1549	13/+ 2069	–
6	8/+ 846	12	–	–	–	–
7	16/+ 118	17/– 1086	14/+ 1082	10	–	–

patient finally died because of electromechanical dissociation.

There is evidence of renal impairment in approximately 50 % of adults admitted with severe malaria [3, 21]. Since ARF frequently predisposes patients to pulmonary oedema and sepsis, it is critical that it be promptly recognised and aggressively treated by extracorporeal renal replacement techniques such as haemofiltration/dialysis. Dialysis appears to be beneficial for ARF associated with malaria, particularly when started early in the course of the illness [3]. However, it should be noted that most patients with severe falciparum malaria do not require dialysis/haemofiltration as moderate renal impairment is usually transient and reversible following rehydration and anti-malarial treatment. However, as mentioned above, there is a only narrow pathway between benign and deleterious fluid replacement in patients with severe *P. falciparum* malaria. Yet despite early institution of continuous haemofiltration only one out of four patients with ARF survived. The pathogenesis of renal failure is related to acute tubular necrosis and dehydration [2, 21]. Our autopsy reports showed tubular necrosis in one patient, while another had multiple renal infarctions (see Table 1).

The strong association between acid base status and disease severity has previously been noted [22]. Accordingly, the highest arterial lactate concentrations were associated with poor prognosis in our patients. Jaundice and deranged liver function tests are common findings in patients with severe malaria [2]. Autopsy showed intrahepatic cholestasis in all patients. ALT and ASAT were increased in four patients. Although disseminated intravascular coagulation (DIC) is reported in less than 10 % [2] of patients with severe malaria, it was found in all our patients who died (3/7, 42 %), thus it was strongly related with a poor outcome. It could be shown previously that procoagulant alterations in falciparum malaria correlate with parasitaemia, serum levels of TNF alpha and clinical severity [23]. However, low dose heparin had no influence on parasitaemia or haemostatic parameters in human falciparum malaria [23]. Hemmer et al. [23] recommended avoiding heparin in falciparum malaria because of possible side effects. In addition, there is no consensus for the use of anticoagulants in patients with DIC. Although a recent review on behalf of the International Society of Thrombosis and Haemostasis recommends the use of heparin for the majority of DIC patients [24].

In recent years several studies have been undertaken to investigate pentoxifylline, an inhibitor of tumour necrosis factor, as a supportive treatment in *Plasmodium falciparum* malaria [25, 26], but no clinical benefit could be observed. None of our patients received pentoxifylline.

With regard to autopsy, two out of three patients died because of ARDS and consequent dilatation of the right heart, one patient died due to brain stem herniation. The diffuse cerebral oedema found in all our dead patients most likely reflects a well known post-mortem phenomenon, as earlier studies have disclosed the formation of significant oedema during the course of cerebral malaria [8].

Patients suffering from severe *P. falciparum* malaria in Austria are usually non-immune travellers. It has to

be noted that all our patients admitted to the ICU took no chemoprophylaxis against malaria. Obviously there is a delay between the first clinical symptoms and adequate treatment [8, 18].

In summary, we conclude that despite improvements in intensive care management, the mortality of severe *P. falciparum* malaria in the ICU remains high. ARDS causing irreversible and untreatable respiratory failure is probably the most important cause of death in our patients. Cerebral complications were the major reasons for admittance to the ICU. The overall mortality of *P. falciparum* malaria in our hospital was 4% and in the ICU 40%. [2, 8].

Success in the management of severe falciparum malaria depends on early diagnosis, the use of effective anti-malarial treatment and the immediate application of supportive measures such as mechanical ventilation, haemodynamic monitoring and haemodialysis. Treatment should be guided by the clinical presentation. Since *P. falciparum* malaria is a medical emergency, treatment should be undertaken by experienced physicians. Established WHO criteria of complicated malaria [4] could serve as a possible guideline for ICU admission. As recommended by Lichtman et al., criteria for ICU admission should be based on organ failure. They state that patients with three or more organ failures, as well as patients with either renal or respiratory failure, should have high priority for intensive care. With regard to our observations, the following should be stated:

1. Early ICU monitoring should be attempted, especially under the following conditions: (1) lack of clinical response to anti-malarial treatment within 48 h and/or (2) any signs of neurological disturbance (hypoglycaemia excluded)
2. In order to avoid acute lung failure, a restrictive fluid balance is warranted. Invasive haemodynamic monitoring might be a useful adjunct.
3. In cases of haemodynamic deterioration, vasopressors rather than excessive fluid rescue should be employed.
4. Extracorporeal renal replacement therapy should be initiated prior to end-stage renal failure.

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