

Exchange Transfusion in Severe Falciparum Malaria

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Abstract

Malaria associated with complications or a fatal outcome is caused by *Plasmodium falciparum*. The mortality due to this disease is parallel to the degree of parasitemia. Successful use of exchange blood transfusion as a therapeutic adjunct for this infection was reported. The rationale for this form of therapy is based on (1) rapid reduction in parasite load by exchange transfusion, (2) removal of toxic substances and (3) reducing microcirculatory sludging. We describe here thirteen cases of severe falciparum malaria treated with infusion of quinine dihydrochloride and exchange transfusion 2,320 - 8,000 ml of whole blood. We observed that the greatest reduction in the average circulating infected red blood cells, from 20.7 per cent to 9.3 per cent, seemed to occur early in the first 2,000 ml of blood exchange and the parasitemia often reduced to 5.1 per cent in patients who had 4,000 ml of blood exchange. In order to reduce the initial parasitemia to 5 per cent by exchange transfusion, we suggest the volume of exchange transfusion should be 2,000 ml for average parasitemia 10 per cent, 4,000 ml for parasitemia > 20 per cent and 2,000 - 4,000 ml for parasitemia 10 - 20 per cent.

Key word : Severe Falciparum Malaria - Exchange Transfusion

A marked increase in the incidence of malaria caused by *Plasmodium falciparum* has been observed⁽¹⁾. Delays in diagnosis and beginning of appropriate chemotherapy are common features of complicated or fatal cases and are particularly likely to result in severe parasitemia especially in non-immune hosts⁽²⁾. Chances of survival may be reduced if therapy is delayed by 12 hours⁽³⁾.

The complications of infection due to falciparum malaria may include cerebral malaria, renal failure, adult respiratory distress syndrome (ARDS) or iatrogenic pulmonary edema, hematologic complications such as severe intravascular hemolysis and disseminated intravascular coagulation (DIC) with profound thrombocytopenia^(4,5), hepatic dysfunction and hypoglycemia. The mortality is

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directly proportional to the degree of parasitemia⁽⁶⁾ and to the development of complications. It appears that prompt reduction in the level of parasitemia is essential to improve survival. Significant mortality occurs with marked parasitemia (>5%) despite parenteral antimalarial therapy and general symptomatic and supportive care⁽⁷⁾. Several reports over the past 20 years⁽⁸⁻¹⁶⁾ and the study of Miller⁽¹⁷⁾ based on a series of 11 patients have described the use of exchange transfusion as adjunctive therapy for severe falciparum malaria. We report herein the volume of blood that should be exchanged in 13 severe falciparum malaria and the precipitous fall in the level of parasitemia associated with marked clinical improvement was observed during the procedure.

PATIENTS AND METHOD

Thirteen cases of severe malaria with more than 5 per cent of infected erythrocytes and complications such as coma, jaundice, hypotension, pulmonary edema or ARDS and hematologic disorder, were admitted to the intensive care unit at Siriraj Hospital. Twelve patients had acquired infection by going to and staying in the endemic areas of malaria (West and Southeast of Thailand), only one had acquired his infection in a referral hospital by blood transfusion for treatment of anemia from acute lymphocytic leukemia. On admission eleven of the thirteen patients had evidence of encephalopathy (cerebral malaria) with other complications; vomiting 9 cases, hypotension 2 cases, jaundice 8 cases, shock 3 cases, renal failure 6 cases, diarrhea 3 cases, coagulopathy 5 cases and ARDS 2 cases. Another two cases had no cerebral complications but one had high parasitemia, hypotension, marked jaundice and severe vomiting, and the other one who suffered from acute lymphocytic leukemia was treated with immunosuppressive drugs and had a very high parasitemia, marked anemia and also jaundice (Table 1).

Clinical findings on admission

Data were collected on 13 patients, 9 males and 4 females (Table 1). All the patients were judged to have severe complicated *P. falciparum* infections at the time of enrollment. The initial parasite density of three patients was 5-10 per cent and 10 patients had a parasite density of 10-60 per cent. Eleven of these patients had evidence of

encephalopathy at admission and 2 had abnormal test results according to the World Health Organisation's definition of severe or complicated malaria.

Treatment

Eight patients received quinine dihydrochloride 10 mg/kg and 5 severely complicated high parasitemia patients received an initial loading dose of quinine dihydrochloride (20 mg/kg) diluted with 5 per cent dextrose in normal saline 200 - 500 ml intravenously dripped within 2 - 4 hours every 8 hours until the patients could swallow without vomiting then quinine dihydrochloride was replaced by quinine sulphate 600 mg orally every 8 hours and continued to complete 7 days. After quinine therapy, tetracycline or erythromycin 250 mg every 6 hours or doxycycline 200 mg/day for 7 days was followed.

Exchange transfusion

Exchange transfusion was done early in the course of therapy during or between intermittent doses of quinine dihydrochloride infusion. Expected volume of whole blood for exchange transfusion was 1-1.5 times of total blood volume in each patient. Individual total blood volume was estimated as 70 ml/kg body weight. Exchange transfusion was done continuously and completed of when the expected blood volume for exchange was reached. During exchange transfusion procedure, volume of removed blood was sequentially numbered and parasites were counted.

RESULTS

Quinine dihydrochloride infusion and response to therapy

All of the patients received quinine dihydrochloride infusion and also received exchange transfusion. Quinine dihydrochloride was replaced by oral quinine sulphate in 11 patients when they could take it by mouth. Two of the thirteen patients died before the change of treatment. In the remaining 11 patients, 10 cases had no parasites in the blood within 3 - 7 days and in the other patient who had underlying acute lymphocytic leukemia, no parasite was found after 11 days. No serious toxicity was observed except cinchonism (tinnitus and vomiting) which the patients could tolerate until the end of the treatment and this symptom was resolved.

Table 1. *Falciparum malaria treated with drugs and exchange transfusion.*

Case No.	Age (yr)/sex	Clinical presentation	Complications	Drug therapy	Volume and duration of exchange transfusion	Parasitemia level (%) at start	Outcome
1	24/F	Fever, vomiting, diarrhoea, lethargy, hepatomegaly, papilloedema, jaundice	Anemia, renal failure, coma, coagulopathy, hypoglycemia	Q + T	W.B. 4,500 ml. 3 h	10.7	0.5 survived
2	19/M	Fever, vomiting, hepatomegaly, coma, jaundice	Pulmonary edema, hypoglycemia	Q + E	W.B. 5,000 ml. 3 h	38.2	8.8 survived
3	6.3/M	Fever, marked anemia, hepatomegaly, underlying acute lymphocytic leukemia and diabetes	Renal failure	Q + D	W.B. 6,015 ml. 3 h	61.5	2.6 survived
4	16/F	Fever, vomiting, hepatomegaly, jaundice	Coagulopathy, shock, hypoglycemia, marked anemia	QL + E	W.B. 5,455 ml. 3 h	28.6	1.3 survived
5	19/M	Fever, coma, jaundice vomiting	Shock	QL + E	W.B. 5,000 ml. 3 h	28.6	6.1 survived
6	19/M	Fever, hepatosplenomegaly, lethargy	Pulmonary edema, hypokalemia, hypoglycemia	QL + E	W.B. 5,000 ml. 3 h	10.6	0.9 survived
7	27/M	Fever, vomiting, hepatomegaly, seizure	Coma, pulmonary edema, hypoglycemia, hypotension	QL + E	W.B. 3,000 ml. + PRC 1000 3 h	7.2	1.1 survived
8	38/M	Fever, vomiting, hepatomegaly, perichioral, coma	Seizure, ARDS, brain edema, renal failure, with renal calculi both kidneys, thrombocytopenia, with bleeding	Q	W.B. 5,090 ml. 2 h 15 mins.	5	0.2 dead (5 days)
9	45/M	Fever, vomiting, coma, jaundice	Seizure, paralysis, brain stem infarct, pneumonia	Q + T	W.B. 7000 ml. 3 1/2 h	11.6	0.7 survived
10	45/F	Fever, hepatomegaly, coma, underlying diabetes	Coma, seizure, ARDS, renal failure, coagulopathy, shock	QL	W.B. 5,140 ml. 2 1/2 h	14.2	0.8 dead (2 days)
11	20/M	Fever, vomiting, diarrhoea, hepatomegaly, jaundice, coma	Hypotension, hypoglycemia	Q + T	W.B. 3,380 ml. 2 h	30.0	2.8 survived
12	40/M	Fever, hepatomegaly, jaundice, coma	Renal failure, shock, diarrhoea, coagulopathy, respiratory infection	Q + E	W.B. 6,000 ml. 2 h	11.8	1.4 survived
13	22/M	Fever, vomiting, hepatomegaly, jaundice, coma	Marked anemia, coagulopathy, hypoglycemia, renal failure	Q + E	W.B. 2,320 ml. 4 h	34	< 1 survived
Q	=	infusion of quinine dihydrochloride 10 mg/kg q 8 h 7 days:	QL	=	initial quinine loading dose 20 mg/kg then followed by 10 mg/kg q 8 h for 7 days		
T	=	Tetracycline 250 mg q 6 h for 7 days	E	=	Erythromycin 250 mg q 6 h for 7 days		
D	=	Doxycycline 200 mg/day for 7 days	W.B.	=	whole blood		
PRC	=	packed red cell	ARDS	=	adult respiratory distress syndrome		
h	=	hour	(.....)	=	time from the beginning of therapy until death.		

Exchange transfusion, parasitologic and consciousness responses

Thirteen patients underwent exchange transfusion early in the course of therapy during or between intermittent doses of quinine dihydrochloride. The average duration of exchange transfusion in 13 cases was 3 hours and 52 minutes (range from 2 to 4 hours) as shown in Table 1. Volume of blood used for exchange transfusion was 2,320 to 8,000 ml. Duration of exchange transfusion depended on the patient's hemodynamics and volume of blood exchange. The number of parasitemia ranged from 5 per cent to 61.5 per cent. Only 11 patients with complete parasite counts during the procedure are shown in Fig. 1 and 2. Individual parasitemia of 11 patients and volume for blood exchange are illus-

trated in Fig. 1. Mean percentage of 11 parasitemia is shown in Fig. 2. The parasite counts fell dramatically over time, with the steepest decline occurring early in the procedure. Within the first 2000 ml of blood exchange, the average circulating parasitemia in all 11 cases was reduced from 20.7 per cent to 9.3 per cent, approximately one half of the baseline (Fig. 2). After 4000 ml of blood exchange was complete, parasitemia could be reduced from 9.3 per cent to 5.1 per cent, approximately a quarter of the baseline. Over 4000 ml of blood exchange could lower the parasites very little. Consciousness of the 11 comatose patients also dramatically recovered just after continuous exchange transfusion was completed in this study.

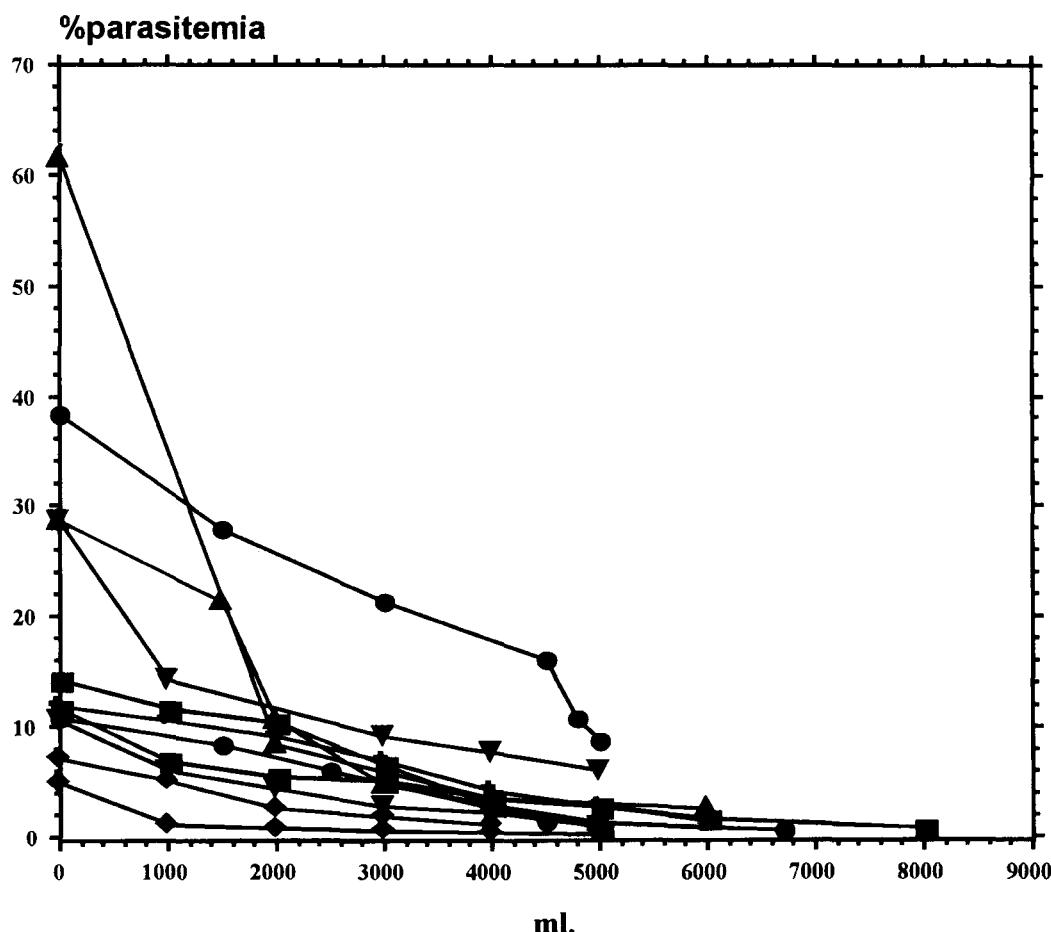


Fig. 1. Relationship between percentage of parasitemia and volume of whole blood exchange transfusion in 11 patients.

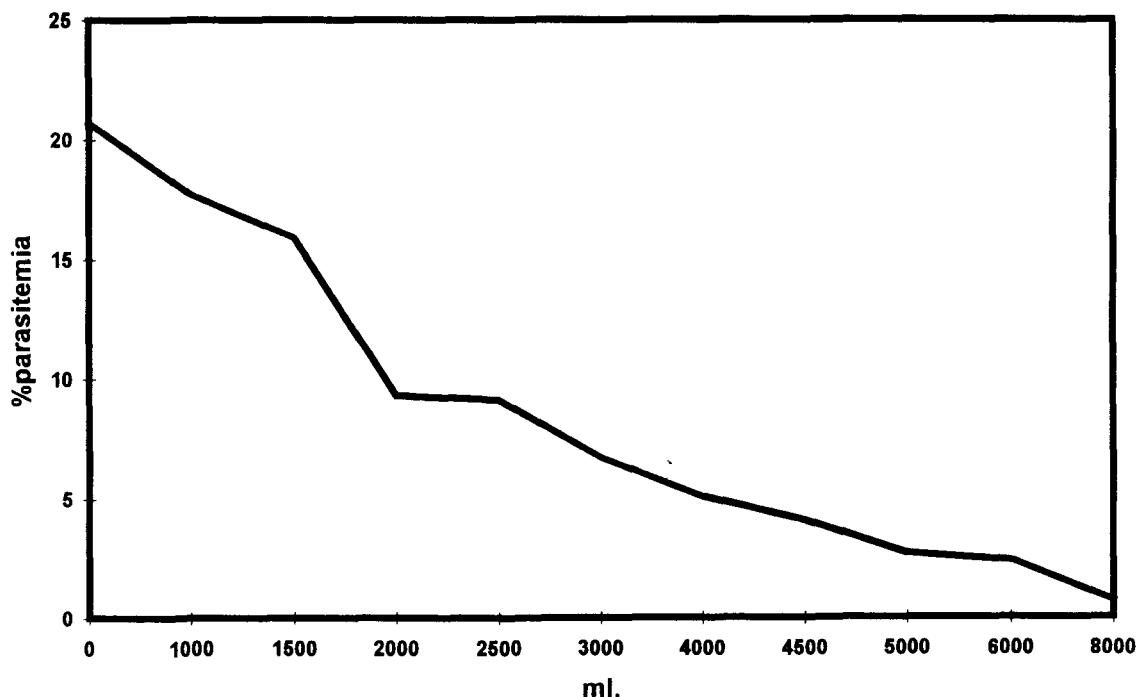


Fig. 2. Mean percentage of parasitemia in 11 patients after blood exchange transfusion.

Coagulopathy

There were 5 in 13 cases with coagulopathy on the first day of admission (Table 1). Case number 1, 4, 10 and 12 without anysite of bleeding were survived. Case number 13 with only ecchymosis on the skin was dead from acute renal failure and ARDS after 5 days of admission. Coagulopathy was completely corrected before or during the blood exchange procedure with fresh frozen plasma or fresh whole blood.

Fatal cases

Two of the 13 patients died. Patient No. 8 was noted to have a level of *P. falciparum* parasitemia of 5 per cent. He had a history of travelling to Southeast Thailand, an endemic area of malaria. At admission he developed tonic convulsion, petechial hemorrhage in both arms and abdominal wall, moderate jaundice and hematuria. Renal calculi were found in both kidneys by plain film of the urinary system. He was treated with quinine dihydrochloride 10 mg/kg infusion every 8 hours and

an exchange transfusion 5,090 ml of whole blood within 2 hours and 15 minutes after which his parasitemia level decreased to 0.2 per cent. He recovered consciousness and he could talk. After 2 days of admission he developed acute renal failure, coagulopathy followed by ARDS. Despite the intensive treatment for acute renal failure by dialysis and mechanical ventilation with end expiratory positive pressure breathing, his condition deteriorated and he died after 5 days of admission.

Patient No. 10 presented at the hospital with a seven days' history of fever after staying in an endemic area of malaria with impairment of consciousness and clonic convulsion. She also had diabetes mellitus. The examination of a thin film blood smear revealed that approximately 14.2 per cent of her erythrocytes were infected with *P. falciparum*. She was treated with an initial loading dose of quinine dihydrochloride (20 mg/kg) infusion and an exchange transfusion, after which her parasitemia level was 0.8 per cent and she gained consciousness. On her second day in the hospital she

worsened with acute renal failure, adult respiratory distress syndrome and coagulopathy. The patient died of respiratory failure on the third day in the hospital.

DISCUSSION

The pathophysiology of severe *P. falciparum* malaria is characterized by the sequestration and sludging of erythrocytes that contain the parasites in vascular beds and lead to mechanical circulatory obstruction, local metabolic derangement, the accumulation of parasites and host-derived toxins, and finally end-organ dysfunction(18). It has been shown that the prognosis in severe malaria is strongly related to the density of parasite infection of the erythrocyte at the time of diagnosis(19). The goal of initial therapy is to improve the prognosis by lowering the level of parasitemia as rapidly as possible(20). Our experience indicates that the rapid therapy with exchange transfusion in complicated malaria cases with more than 5 per cent of infected erythrocytes is a reasonable approach to achieve this goal.

Because of its rapid schizonticidal activity, parenteral quinine dihydrochloride has been the mainstay of initial therapy(5,21). Delay in the initiation of chemotherapy has been shown to increase the probability of death(22). We must give a loading dose of parenteral quinine dihydrochloride to severe cases who have high parasitemia (>10%) and severe complications such as in case No. 10. The reason is the minimal inhibitory concentration (MIC) for malaria of the normal dose of quinine (10 mg/kg) given every 8 hours will take 1.5 days but only 4 hours in the loading dose(23). The two patients who died had presented with multiple characteristics associated with poor prognosis including underlying diseases. Case No. 8 had underlying renal calculi in both kidneys and developed progressive renal failure and no response to dialysis and he also had respiratory failure from ARDS, coagulopathy with bleeding and cerebral edema. Case No. 10 had untreated diabetes mellitus and developed acute renal failure, ARDS, shock, seizure and coagulopathy.

An exchange transfusion exerts its effect by removing parasitized erythrocytes and red cell debris that contribute to sequestration and sludging of erythrocytes and lead to mechanical circulatory obstruction. It has also been suggested the process

removes circulating toxic factors and harmful metabolites(5). For these reasons, the exchange of both red cells and plasma components of whole blood may provide more benefit than the exchange of red cells alone. The appropriate total volume of the exchange has not been defined. Preliminary data suggested as few as four units may be beneficial(24). In our study, the thirteen adults with *P. falciparum* malaria had 2320 to 8000 ml of blood exchanged. Although, the parasitologic response was somewhat variable, the greatest reduction in the circulating infected red cells seemed to occur early in the first 2000 ml. In our experience the parasitemia often reduced to 5 per cent or less in adults with hyperparasitemia who had 4000 ml of blood exchange as shown in Fig. 2. Careful monitoring of the patient's parasitemia level until it reaches such an end point rather than the exchange of a predetermined volume will in many cases reduce the number of units of blood products to which the patient is exposed and thereby reduce the possibility of transfusion associated complications such as blood transfusion-related human immunodeficiency virus (HIV) infection and hepatitis virus. Miller(17) suggested that the exchange transfusion should be continued until the level of parasitemia is less than 5 per cent. We suggest 2000 ml of exchange blood transfusion for average parasitemia 10 per cent, 4000 ml for parasitemia > 20 per cent and 2000-4000 ml for parasitemia 10-20 per cent. Both patients died despite the parasitemia being reduced to one per cent after exchange transfusion because they had underlying diseases and severe complications. Although, there is still no general agreement about the indications for exchange transfusion, it should be considered as a useful adjunct to chemotherapy in patients with parasitemia greater than 10 per cent or particularly in > 5 per cent with acute renal failure, coma, disseminated intravascular coagulation or adult respiratory distress syndrome(17, 25). Exchange transfusion accelerates the reduction of the parasite load, but its effect on removing toxic factors remains hypothetical. The reported observations suggest that exchange transfusion has no immediate influence on the reduction of the blood concentration of tumor necrosis factor (TNF) and that quinine alone reduces TNF blood levels(26). To what extent high TNF levels cause or anticipate the clinical severity of the disease remains unclear.

However, the close correlation between the level of parasitemia and mortality despite appropriate antimalaria chemotherapy has provided the reason for using exchange transfusion to rapidly reduce the number of circulating parasitized erythrocytes. Exchange transfusion appears to be a valuable adjunct to chemotherapy.

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การเปลี่ยนถ่ายเลือดในผู้ป่วยพัลซิปาร์มมาลาเรียขั้นรุนแรง

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มาลาเรียที่มีอาการแทรกซ้อนรุนแรงจะเกิดจากพลาสไมเดียม พัลซิปาร์มสมอ อัตราตายของผู้ป่วยจะเป็นไปตามจำนวนของมาลาเรียในเลือดได้มีรายงานการรักษาที่ได้ผลโดยการเปลี่ยนถ่ายเลือดร่วมกับการรักษาเฉพาะโรค เหตุผลในการรักษาโดยวิธีนี้คือ (1) จะลดจำนวนมาลาเรียในเลือดได้อย่างรวดเร็ว (2) กำจัดสารพิษต่าง ๆ (3) ลดการกดตีก่อนของเลือดที่ให้หลวในหลอดเลือดเล็ก ๆ รายงานนี้จะรายงานผลของการเปลี่ยนถ่ายเลือดในผู้ป่วยมาลาเรียพัลซิปาร์มที่มีอาการแทรกซ้อนที่รุนแรง 13 ราย โดยเปลี่ยนถ่ายเลือด 2,320-8,000 มลลิลิตร ร่วมกับการรักษาด้วยคิวินิน ได้โดยครอโนร์ต ผลปรากฏว่า จำนวนมาลาเรียเฉลี่ยลดลงจาก 20.7 เปอร์เซ็นต์ เหลือ 9.3 เปอร์เซ็นต์ เมื่อเปลี่ยนถ่ายเลือด 2,000 มลลิลิตร และถ้าเปลี่ยนถ่ายเลือดต่อไปถึง 4,000 มลลิลิตร จะลดจำนวนมาลาเรียเหลือเพียง 5.1 เปอร์เซ็นต์เท่านั้น ดังนั้นถ้าต้องการลดจำนวนมาลาเรียเริ่มต้นให้ลดลงเหลือ 5 เปอร์เซ็นต์ โดยการเปลี่ยนถ่ายเลือดรายงานนี้ขอแนะนำให้เปลี่ยนถ่ายเลือด 2,000 มลลิลิตร สำหรับผู้ป่วยที่มีมาลาเรีย 10 เปอร์เซ็นต์ 4,000 มลลิลิตร สำหรับผู้ป่วยที่มีมาลาเรีย 20 เปอร์เซ็นต์ และ 2,000 - 4,000 มลลิลิตร สำหรับผู้ป่วยที่มีมาลาเรีย 10 - 20 เปอร์เซ็นต์

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