

Severe atovaquone-resistant *Plasmodium falciparum* malaria in a Canadian traveller returned from the Indian subcontinent

THOMAS L PERRY, PRATIVA PANDEY, JENNIFER M GRANT, KEVIN C KAIN

Editor's note: Videos can be found in the online version of this article at <http://openmedicine.ca/article/view/224/221>

ABSTRACT

We report the first case of atovaquone/proguanil treatment failure in severe *Plasmodium falciparum* malaria acquired by a non-immune traveller to the Indian subcontinent. Recrudescence was complicated by neurological involvement 14 days after directly observed therapy with atovaquone/proguanil. Sequence analysis of the plasmodial cytochrome b gene confirmed a contribution of atovaquone resistance to treatment failure. The recrudescence isolate had a single mutation at position 268 (Tyr268Cys). Video recordings illustrate dramatic but ephemeral manifestations of malaria with neurological involvement.

Thomas L. Perry is a general internist/clinical pharmacologist at the Vancouver Hospital and Health Sciences Centre (VHSC) and teaches clinical pharmacology at the University of British Columbia medical school, Vancouver, Canada. **Prativa Pandey** is Medical Director of the CIWEC Clinic Travel Medicine Center in Kathmandu, Nepal. **Jennifer Grant** is a medical microbiologist in the Division of Microbiology and Infection Control, VHSC, Vancouver. **Kevin C. Kain** is Director of the Centre for Travel and Tropical Medicine at Toronto General Hospital, Toronto, Canada.

Competing interests: None declared.

Funding source: Dr. Kain's work on this report was supported by a CIHR Team Grant in Malaria, CIHR operating grant MT-13721, by Genome Canada through the Ontario Genomics Institute, and by the CIHR Canada Research Chair program.

SEVERE PLASMODIUM FALCIPARUM (PF) MALARIA can occur in non-immune travellers of all ages. Adults have a higher risk than children for renal failure and acute respiratory distress syndrome, while women are at particular risk for neurological involvement.¹ Because severe or complicated malaria is rare in developed countries, even experienced physicians can be unfamiliar with its presentation and management.^{2,3} Suggested Canadian diagnostic criteria, based upon those of the World Health Organization, include a wide spectrum of clinical, physiological and biochemical abnormalities. Any one of these findings should be considered ominous (Textbox 1).

The fixed drug combination of atovaquone/proguanil (Malarone) is approved by Health Canada for the prevention of Pf malaria and for the treatment of uncomplicated cases. Although atovaquone/proguanil remains highly effective, treatment failure has been

confirmed among travellers returning from sub-Saharan Africa and South America^{4,5} and, in 2007, from Thailand.⁶

We report the first genetically confirmed case of atovaquone-resistant falciparum malaria acquired on the Indian subcontinent. In late 2007 a Canadian traveller acquired *P. falciparum* infection in northern India or southern Nepal. She received directly observed therapy with a standard 3-day course of atovaquone/proguanil for what was thought to be uncomplicated Pf malaria; however, the infection subsequently recrudescence. At the height of her illness, the patient provided informed consent for video recording; this consent was reconfirmed in writing after her recovery. She agreed to the publication of images that include her face, under the Creative Commons License specified by *Open Medicine's* editorial policy.

Case report

A 21-year-old Canadian woman flew from Vancouver to Delhi in October 2007. Her subsequent itinerary included a river trip on the Ganges at Varanasi, India, and a 4-day jungle safari in Chitwan National Park, Nepal. She took no antimalarial chemoprophylaxis.

After travelling for 3 weeks through northern India and lowland Nepal she developed headaches, fever, and psychiatric/neurological symptoms. During a subsequent detailed neuropsychiatric interview, she described having experienced ataxia, sensory and motor problems affecting the fingers of both hands, speech difficulties, olfactory hallucinations, and perception of vivid colours.

She presented on 3 November 2007 to the CIWEC Clinic in Kathmandu, Nepal, complaining of fever, tiredness, headache, dizziness, "feeling strange," and "hallucinating at times" (Table 1). Her temperature was 39.5°C, blood pressure 132/70 mmHg, and heart rate 100 beats/min. Apart from pallor and icterus, the findings on physical examination were unremarkable. Laboratory values (local normal range in parentheses) included: hematocrit 38% (36%–45%), white blood cells (WBC) 2.75 giga/L (4.5–10.5), platelets 40 giga/L (150–400), total bilirubin 48 µmol/L (3.4–41.0), and a positive falciparum antigen test. Peripheral blood microscopy showed 3.4% of the red blood cells infected with *P. falciparum*. A Dengue immunoglobulin (IgM) immunochromatographic assay (Dengue Duo Cassette Kit, Panbio Diagnostics, Australia) was weakly positive.

The patient was admitted to hospital and treated with atovaquone 250 mg / proguanil 100 mg (Malarone), 4 tablets daily for 3 days, given with food after promethazine to control vomiting. Intravenous fluids were administered, as her blood pressure dropped to 80/50 mmHg on the first day. Within 12 hours of the initiation of antimalarial chemotherapy, parasitemia had declined to 2%, the hematocrit was 34%, and the platelets had increased to 90 giga/L. By day 3 of treatment, and again on day 4, parasites were no longer seen in the blood smear. Oral ciprofloxacin was added from day 2 for probable bacterial diarrhea. The patient's fever subsided and her blood pressure was 120/80 mmHg by day 5, although her heart rate was still 108. She was discharged, and appeared much improved at follow-up on 12 November. The final diagnosis was resolved Pf malaria and associated Dengue fever.

She returned to Canada on 21 November 2007 because she still felt unwell with myalgia, chills, and speech difficulties. She also reported intermittent movement disturbance, including unusual face and tongue movements, focal dystonia of her arm and neck, and gaze deviation. There was no prior psychiatric history. She reported that two physicians assessed her at walk-

in clinics, before a third recommended repeat malaria smears.

On 7 December the patient presented to hospital in Vancouver with fever and rigors. On physical examination, she was obviously unwell (temperature 39.0°C, HR = 117). Her speech was slow, stuttering and repetitive, despite normal comprehension. She provided informed written consent to videography. Laboratory abnormalities included (local reference range in parentheses): hemoglobin 60 g/L (115–155), white blood cell count 2.8 giga/L (4–11), platelets 88 giga/L (150–400), lactate dehydrogenase 437 U/L (90–210). A smear showed 2% *P. falciparum* parasitemia with delicate ring forms and gametocytes (Fig. 1). Results of a cranial computed tomography (CT) scan were unremarkable. During 3 of 4 attempted transfusions of packed red blood cells, the patient experienced chest pain and dyspnea (video clips 1–3). No evidence for acute transfusion reaction was found.

The patient was treated with conventional doses of intravenous quinine and oral doxycycline until she could take quinine reliably by mouth (Textbox 1). Clinical improvement was prompt (video clip 4). Electrocardiography and blood glucose monitoring showed no subsequent abnormality. However, on the third day in hospital, the patient noticed weakness of the left arm along with generalized motor slowing and unprovoked dystonic posturing lasting a few minutes (video clips 5, 6). Electroencephalography (EEG) performed 80 minutes later, magnetic resonance imaging, and cerebrospinal fluid analysis were all unremarkable.

Oral quinine and doxycycline were continued for 7 days, but the patient remained generally unwell (video clip 7) and parasitemic, with ring forms present up to day 6 of therapy. Gametocytes persisted for a few more days. She was discharged from hospital on day 11 and had recovered almost fully by day 35 (video clip 8). Findings of repeat serological testing for Dengue and related arboviruses were negative.

The patient returned to our emergency department 81 days later, after developing subtle and intermittent stuttering and involuntary facial twitching. This had progressed over 2 weeks after a presumed viral gastroenteritis to involuntary writhing movements of her entire body. Vital signs, including temperature, were normal. The admitting physicians hypothesized that anxiety related to a written examination exacerbated the abnormal movements that precipitated her repeat presentation. The neurology service observed pouting, eye closing, tongue and mouth contractions, episodes of limb flexion with truncal torsion, and bilateral writhing movements. (No video recording was obtained.) All laboratory studies, including repeat EEG, were normal. Physicians unfamiliar with this patient's prior acute malarial illness requested psychiatric consultation and neuropsychiatric testing to evaluate the hypothesis of a

Textbox 1: Suggested Canadian criteria for the diagnosis of severe falciparum malaria*

EITHER

History of recent possible exposure and no other recognized pathology

OR

Asexual forms of *P. falciparum* on blood smear

AND

Any one or more of the following 11 features:

1. Impaired consciousness or coma
2. Severe normocytic anemia
3. Renal failure
4. Pulmonary edema or adult respiratory distress syndrome
5. Hypoglycemia
6. Circulatory collapse, shock
7. Spontaneous bleeding / disseminated intravascular coagulation
8. Repeated generalized convulsions
9. Acidemia / acidosis
10. Hemoglobinuria
11. Parasitemia of < 5% (>250 000 mL in non-immune individuals)

*These criteria, adapted from the WHO management guidelines available at www.who.int/malaria/docs/hbsm.pdf, are reproduced from Health Canada (2004)¹⁴

Textbox 2: Chemotherapy of severe or complicated *Plasmodium falciparum* malaria*

NOTE: A switch to oral therapy should be made as soon as possible.

A. If an infusion pump is available:

Quinine^a (base) 5.8 mg/kg loading dose (quinine dihydrochloride^b [salt] 7 mg/kg) intravenously by infusion pump over 30 minutes followed immediately by 8.3 mg base/kg (quinine dihydrochloride [salt] 10 mg/kg) diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours (maintenance dose), repeated 8 hourly^c until the patient can swallow, then quinine tablets to complete 3 to 7 days of treatment (7 days for Southeast Asia).

B. Without an infusion pump:

Quinine^a(base) 16.7 mg/kg loading dose, (quinine dihydrochloride^b [salt] 20 mg/kg), by intravenous infusion over 4 hours, then 8.3 mg base/kg (quinine dihydrochloride [salt] 10 mg/kg) diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours (maintenance dose), repeated 8 hourly^c until the patient can swallow, then quinine tablets to complete 3 to 7 days of treatment (7 days for Southeast Asia).

PLUS

(either concurrently with quinine or immediately after)

1. Doxycycline: 100 mg orally twice daily for 7 days; pediatric dose = 2 mg/kg (to a maximum of 100 mg) twice daily; contraindicated: pregnancy, breastfeeding or if age < 8 years.

OR

2. Atovaquone/proguanil: 4 tablets once daily for 3 days (adjust for pediatric dosage – see Table 8 of original document¹⁴).

OR

3. Clindamycin: 10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is clear of sexual parasites (Note: Should be used only if patient is unable to take doxycycline or atovaquone/proguanil).

Note: Parenteral quinidine should be used only if parenteral quinine is unavailable. Because of increased risk of cardiac toxic effects with quinidine, cardiac monitoring is required.

^a Loading dose should not be used if patient received quinine, quinidine, or mefloquine within the preceding 24 hours.

^b Parenteral quinine dihydrochloride may be obtained through the Canadian Malaria Network (see original document¹⁴ and website http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/04vol30/30s1/appendix6_e.html for contact information).

Table 1: Case chronology

Date	Event	Remarks
mid-Oct 2007	Travels to Delhi, Varanasi (India), Chitwan, Kathmandu (Nepal)	Exposed to mosquitoes at Varanasi, possibly Chitwan National Park
Nov 3, 2007	Presents to clinic in Kathmandu with fever, pallor, icterus, visual/olfactory hallucinations; later describes altered speech, gait	3.4% Pf parasitemia; platelets 40 giga/L; IgM test positive for dengue; treatment with atovaquone/proguanil (Malarone) x 3 days
Nov 8, 2007	Discharged improved; apparently better at follow-up Nov 12	Patient later describes persistent speech, gait disturbance
Nov 21, 2007	Returns to Canada, unwell	2 doctors in walk-in clinics subsequently miss diagnosis of recrudescence falciparum malaria
Dec 7, 2007	Presents to Vancouver General Hospital: unwell, anemia, fever, speech disturbance and movement disorder, hallucinations and altered perceptions (video clips 1–4)	Pf parasitemia 2% (Fig. 1), Hb 60 g/L, platelets 88 giga/L; conventional treatment started with intravenous quinine and oral doxycycline; RBC transfusions associated with dyspnea and chest pain; rapid general improvement
Dec 10, 2007	General improvement (video clip 5) interrupted by intermittent violent movement disorder (video clip 6)	Cranial CT, MRI, EEG findings all “normal;” CSF studies normal. Movements ephemeral, not universally recognized as abnormal.
Dec 14, 2007	Greatly improved, but gait disturbance, fatigue, and slow speech persist (video clip 7)	Self-perpetuating asexual forms of Pf persists to Day 6 of therapy. Gametocytemia persists for a few more days.
Jan 10, 2008	Virtually complete clinical resolution (video clip 8)	No drug therapy. Patient still notes some difficulties with concentration and balance/coordination.
Mar 31, 2008	Return of intermittent and ephemeral neurological symptoms and signs; patient presents again to hospital	Abnormal stuttering, pouting, facial and eye movements, truncal torsion, limb flexion observed, apparently associated with stress of writing an examination. Spontaneous resolution with no further episodes in subsequent 9 months.

Pf = *Plasmodium falciparum*; IgM = immunoglobulin; Hb = hemoglobin; RBC = red blood cell; CT = computed tomography; MRI = magnetic resonance imaging; EEG = electroencephalography; CSF = cerebrospinal fluid

“conversion disorder.” The neuropsychologist found “no obvious psychiatric overlay to her current presentation.” The abnormal movements subsided spontaneously, but isolated facial twitching recurred briefly after use of alcohol, 5 months later. One year after the definitive treatment in Vancouver, the patient was healthy and free of neurological sequelae.

This patient’s recrudescence of *P. falciparum* parasitemia at least 2 weeks after initial parasite clearance indicated late treatment failure, suggesting the possibility of acquired atovaquone resistance. DNA was extracted from the 7 December 2007 blood sample obtained in Vancouver using QIAGEN columns (QIAGEN, Chatsworth, CA) and the cytochrome b gene was amplified and sequenced to detect mutations as described.^{5,7,8} The patient’s isolate possessed a Tyr268Cys mutation previously associated with atovaquone/proguanil treatment failure and with in vitro atovaquone resistance, with a 9000-fold increase in the 50% minimal inhibitory concentration.^{4,5}

Discussion

Clinical encounters with travellers offer important opportunities to detect emerging drug-resistant malaria.⁹ Here we report the first known case of atovaquone/proguanil-resistant *P. falciparum* malaria acquired by a short-term traveller to the Indian subcontinent. Atovaquone binds to the parasite’s mitochondrial cytochrome bc1 complex, inhibiting electron transport and collapsing mitochondrial membrane potential.¹⁰ Resistance has been linked to mutations in the plasmodial cytochrome b gene.¹¹

This patient likely acquired Pf malaria during a river trip at Varanasi, during which she slept outdoors and was aware of exposure to mosquitoes. Malaria risk among travellers to Nepal, including Chitwan National Park, is very low. During a recent outbreak of febrile illness that affected 6000 residents of the Chitwan district, no malaria was detected.^{12,13}

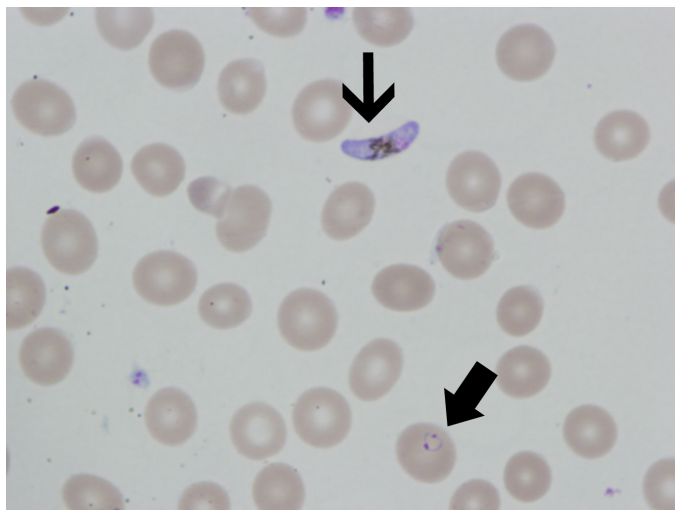


Figure 1. Blood film showing *P. falciparum* during acute blood-stage infection. Thick arrow: ring-stage parasite (early asexual stage responsible for blood-stage infection of red blood cells and clinical manifestations of malaria). Thin arrow: gametocyte (sexual stage, infective to mosquitoes and responsible for disease transmission, but not causing clinical symptoms). Gametocytes may persist after effective treatment and clearance of asexual parasites

Malaria in travellers is almost completely preventable with precautions such as the use of bed nets, insect repellents and prophylactic medications when indicated. Health Canada¹⁴ and the United States Centers for Disease Control and Prevention¹⁵ recommend malaria prophylaxis for travel to most of India. Atovaquone/proguanil is a commonly prescribed first-line drug because of its efficacy and tolerability.¹⁶ However, increasing resistance may threaten the effectiveness of this safe and well-tolerated agent.

For our patient, initial treatment may have been suboptimal, insofar as atovaquone/proguanil is recommended only for the treatment of uncomplicated falciparum malaria.⁴ The neuropsychiatric symptoms noted at her initial presentation in Kathmandu may have been attributed to her febrile and dehydrated condition, in the context of suspected dual infections with Pf malaria and Dengue, since the Dengue rapid IgM test was positive. Dengue IgM tests are known to yield frequent false positive results, especially in the equivocal range.¹⁷ In retrospect, there may have been cerebral involvement by Pf at clinical onset, a criterion for more aggressive therapy (Textbox 2). The relatively high parasitemia of 3.4% at presentation may have contributed to the emergence of atovaquone resistance and recrudescent infection, given that higher parasite burdens are associated with higher risk of treatment failure.

Health care workers in non-endemic areas may not recognize the symptoms and seriousness of severe mal-

aria (Textbox 1). Falciparum malaria has a 1% overall mortality, but up to 22% of severe cases end in death, even with appropriate treatment.¹⁸ It can also cause a spectrum of neurological abnormalities extending well beyond the established but narrow World Health Organization definition of “cerebral malaria” as “unrousable coma not attributable to any other cause.”¹⁹ Some symptoms or signs reflecting central nervous system involvement may be subtle, or missed by a physician not previously familiar with the patient.

The pathophysiology of cerebral malaria involves a poorly understood multi-system disorder resulting from a dynamic interplay between the host immune response and determinants of parasite virulence. Activation of cytokines, chemokines and complement cascades contributes to the metabolic derangement and tissue injury that characterize severe malaria. Pf-infected red blood cells sequester in the microvasculature of vital organs of all infected individuals, but only occasionally induce overt neurological symptoms or sequelae.²⁰

Physicians with experience involving more than 9000 neurologically affected Kenyan children recently proposed the term “malaria with neurological involvement” to describe the large majority of patients who presented with neurological illness attributable to malaria but did not fulfill the official WHO definition of “cerebral malaria.” They emphasize that “the public health importance of such neurological involvement is enormous,” not only for acute treatment costs but also because long-term neurological and cognitive impairments have been described in 24% of children with a history of cerebral malaria or of malaria with multiple seizures. Children also suffer an increased risk for sequelar epilepsy.²¹

In our patient, diverse and ephemeral symptoms and signs reflected diffuse but temporally variable encephalopathy resulting from a life-threatening Pf infection. Her clinical instability confused experienced physicians, leading some to hypothesize a “functional” (psychiatric) cause for a clinical presentation rarely seen in Nepal or Canada. Her initial syndrome presumably reflected dynamic microvascular and biochemical changes in cerebral, cardiopulmonary and, perhaps, other circulations, in the absence of abnormalities detectable by conventional diagnostic imaging and tests. Attempted transfusion of packed red cells correlated with onset of chest pain and shortness of breath, which was likely another manifestation of her diffuse but rapidly changing intravascular pathophysiology. Transfusion may have been unwise, since even in more severe malaria there is no clear evidence that transfusion improves outcome.²²

Reflection on the complex pathophysiology of Pf malaria suggests a novel answer to the classic neurological question: “Where is the lesion?” In severe mal-

aria, the apparent “lesion” (video clips 1–7) may vary within minutes from “nowhere” to “everywhere” in the body, including the brain. Our patient’s recapitulation of neurological symptoms and signs more than 3 months after resolution of her severe malaria may have reflected a lingering brain injury that was better appreciated by the patient and her family than by clinical observers unfamiliar with her normal appearance and personality (video clip 8).

For physicians working in nontropical regions, improved understanding of the gravity and variety of clinical presentations of severe malaria could reduce delay in diagnosis and encourage attention to optimal treatment. It is obviously preferable to arrest Pf infection before “malaria with neurological involvement” proceeds to prostration, frank coma, or death and qualifies the patient for the traditional WHO definition of “cerebral malaria.” Accepting the expanded definition proposed by Kenyan investigators could help emphasize the crucial importance of early and aggressive treatment of this disease.²¹

Acknowledgments: We thank our patient for her altruism in sharing videographic images of her experience with others who can learn from it. Dr. Diane Roscoe of the Vancouver Hospital and Health Science Centre assisted with specimen handling, and Mr. Chris Stephenson of the University of British Columbia and Dr. Tarek Loubani provided invaluable technical assistance with the video images.

REFERENCES

- Mühlberger N, Jelinek T, Behrens RH, Gjørup I, Coulaud JP, Clerinx J, et al. Surveillance importierter Infektionen in Deutschland Surveillance Networks. Age as a risk factor for severe manifestations and fatal outcome of falciparum malaria in European patients: observations from TropNetEurop and SIMPID Surveillance Data. *Clin Infect Dis*. 2003;36(8):990–995.
- Kain KC, Harrington MA, Tennyson S, Keystone JS. Imported malaria: prospective analysis of problems in diagnosis and management. *Clin Infect Dis*. 1998;27(1):142–149.
- Kain KC, MacPherson DW, Kelton T, Keystone JS, Mendelson J, MacLean JD. Malaria deaths in visitors to Canada and in Canadian travellers: a case series. *CMAJ*. 2001;164(5):654–9.
- Boggild AK, Parise ME, Lewis LS, Kain KC. Atovaquone-proguanil: Report from the CDC expert meeting on malaria chemoprophylaxis (II). *Am J Trop Med Hyg*. 2007;76(2):208–23.
- Rose GW, Suh KN, Kain KC, Le Saux N, McCarthy AE. Atovaquone-proguanil resistance in imported falciparum malaria in a young child. *Pediatr Infect Dis J*. 2008;27(6):567–569.
- Krudsood S, Patel SN, Tangpukdee N, Thanachartwet W, Leowattana W, Pornpininworakij K, et al. Efficacy of atovaquone-proguanil for treatment of acute multidrug-resistant Plasmodium falciparum malaria in Thailand. *Am J Trop Med Hyg*. 2007;76(4):655–8.
- Schwartz E, Bujanover S, Kain KC. Genetic confirmation of atovaquone-proguanil-resistant Plasmodium falciparum malaria acquired by a nonimmune traveler to East Africa. *Clin Infect Dis*. 2003;37(3):450–451.
- Kuhn S, Gill MJ, Kain KC. Emergence of atovaquone-proguanil resistance during treatment of Plasmodium falciparum malaria acquired by a non-immune north American traveller to west Africa. *Am J Trop Med Hyg*. 2005;72(4):407–9.
- Labbé A, Patel S, Crandall I, Kain KC. A molecular surveillance system for global patterns of drug resistance in imported malaria. *Emerg Infect Dis*. 2003;9(1):33–6.
- Srivastava IK, Rottenberg H, Vaidya AB. Atovaquone, a broad spectrum antiparasitic drug, collapses mitochondrial membrane potential in a malarial parasite. *J Biol Chem*. 1997;272(7):3961–3966.
- Korsinczyk M, Chen N, Kotecka B, Saul A, Rieckmann K, Cheng Q. Mutations in Plasmodium falciparum cytochrome b that are associated with atovaquone resistance are located at a putative drug-binding site. *Antimicrob Agents Chemother*. 2000;44(8):2100–2108.
- Cave W, Pandey P, Osrin D, Shlim DR. Chemoprophylaxis use and the risk of malaria in travelers to Nepal. *J Travel Med*. 2003;10(2):100–5.
- Lewis MD, Serichantalergs O, Pitarangsi C, Chuanak N, Mason CJ, Regmi LR, et al. Typhoid fever: a massive, single-point source, multidrug-resistant outbreak in Nepal. *Clin Infect Dis*. 2005;40(4):554–61.
- Health Canada. Canadian recommendations for the prevention and treatment of malaria among international travellers. *Canadian Communicable Disease Report*. 2004;30S1
- Centers for Disease Control and Prevention. Malaria. Arguin PM, Kozarsky PE, Reed C (editors). *Health Information for International Travel 2008*. Atlanta: US Department of Health and Human Services, Public Health Service: 2007.
- Looareesuwan S, Viravan C, Webster HK, Kyle DE, Hutchinson DB, Canfield CJ. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. *Am J Trop Med Hyg*. 1996;54(1):62–6.
- Gubler DJ. Dengue and Dengue hemorrhagic fever. *Clin Microbiol Rev*. 1998;11(3):480–96.
- Dondorp A, Nosten F, Stepniewska K, Day N, White N. South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. 2005;366(9487):717–725.
- Severe malaria: A practical handbook*. Geneva: World Health Organization: 2008.
- Mackintosh CL, Beeson JG, Marsh K. Clinical features and pathogenesis of severe malaria. *Trends in Parasitology*. 2004;20(12):597–603.
- Idro R, Ndiritu M, Ogutu B, Mithwani S, Maitland K, Berkley J, et al. Burden, features, and outcome of neurological involvement in acute falciparum malaria in Kenyan children. *JAMA*. 2007;297(20):2232–2240.
- Meremikwu M, Smith HJ. Blood transfusion for treating malarial anaemia. *Cochrane Database of Systematic Reviews*. 1999;(Issue 4).

Citation: Perry TL, Pandey P, Grant JM, Kain KC. Severe atovaquone-resistant *Plasmodium falciparum* malaria in a Canadian traveller returned from the Indian subcontinent *Open Med* 2009;3(1):10-16

Published: 20 January 2009

Copyright: Open Medicine applies the Creative Commons Attribution Share Alike License, which means that anyone is able to freely copy, download, reprint, reuse, distribute, display or perform this work and that authors retain copyright of their work. Any derivative use of this work must be distributed only under a license identical to this one and must be attributed to the authors. Any of these conditions can be waived with permission from the copyright holder. These conditions do not negate or supersede Fair Use laws in any country.