Imported drug-resistant severe malaria

The possibility of imported quinine-resistant malaria is low in Sri Lanka, but important to remember

The global burden caused by malarial infection is enormous. According to estimates, more than 300–500 million malaria infections occur each year affecting one-third of the world’s population [1]. The vast majority of malarial infections cause uncomplicated disease, with only about 1–2% becoming severe [2]. Severe and clinically complicated malaria, which is potentially fatal, is caused by the species *Plasmodium falciparum*. It is believed that over 3000 deaths occur daily from malaria, mostly among young children in sub-Saharan Africa [1].

Intravenous quinine is still the mainstay of treatment for severe and complicated malaria in most parts of the world [3]. It is always advisable to give quinine in the form of a rate-controlled infusion and never by bolus intravenous injection. Although there is no significant difference in mortality when quinine is used with a high initial dose versus no loading dose, the former regimen has been shown to reduce the parasite clearance time and duration of fever compared with no loading dose [4]. Hypoglycaemia is the most serious and frequent side-effect of quinine therapy. If intravenous infusion is not possible, an appropriate drug may be given intramuscularly [3]. Suppository formulations of artemisinin and its derivatives could also be used in such instances. After the administration of antimalarials it is important to monitor response by frequent clinical examination including fluid balance, temperature, pulse, respiratory rate and depth, conscious level, blood pressure, jugular venous pressure and parasitaemia every 4–6 hours for the first 48 hours [3].

Parasitaemia could remain unchanged or may even rise in the first 18–24 hours of quinine therapy, and is not a reliable indicator of drug resistance [5]. After 24 hours the counts fall in a lognormal manner and asexual parasitaemia should disappear within 5 days (gametocytes may remain) [5]. A rising or unchanging parasite count after 24 hours of quinine therapy may indicate drug resistance and warrants a change in treatment [5].

One of the most pressing issues facing the malaria endemic countries is the increase in drug resistance. Drug resistance in malaria is the ability of the parasite to survive and multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the patient [6,7]. Resistance to antimalarial drugs arises as a result of spontaneously occurring mutations that affect the structure and activity at the molecular level of the drug target in the malaria parasite or affect drug access to that target [8–10]. Mutant parasites are selected if antimalarial drug concentrations are sufficient to inhibit multiplication of susceptible parasites but are inadequate to inhibit the mutants, a phenomenon known as ‘drug selection’ [11,12]. Drug selection is
thought to be enhanced by sub-therapeutic plasma drug levels and by a flat dose-response curve to the drug. In vivo resistance has been reported to all currently available antimalarial drugs, except perhaps artemisinin [13].

An imported case of likely quinine-resistant *P. falciparum* malaria reported in this issue of *CMJ* (p.125-126) focuses our attention to a problem that is faced by all countries of the world. The ever increasing speed and volume of international travel and trade have enabled the menace of infectious diseases, including drug-resistant malaria, to cross national borders and defy traditional defences with ease. Hence it is not confined to malaria endemic parts of the world. In this case report, the persistence of asexual parasites in peripheral blood smears despite parenteral quinine therapy in recommended doses for 5 days, taken together with the persistence of fever makes the diagnosis of quinine-resistant malaria very likely. Information regarding other clinical signs, including the change in conscious level, with continued quinine therapy, adds little to this conclusion. The regular monitoring of parasite counts would have enabled the clinicians to arrive at the diagnosis of quinine resistance earlier and with more certainty.

Where there is evidence of lack of response to quinine, as in the case study described by Wijesundere and colleagues, it is justifiable to use alternative antimalarials such as artemisinin or its derivatives. When indicated it is important to use artemisinin with a second antimalarial drug (commonly mefloquine), either in combination or sequentially to reduce the risk of development of resistance to artemisinin. Parasite counts start declining 5–6 hours after starting therapy, and asexual parasitaemia generally disappears after about 72 hours [14]. Thus artemisinin derivatives appear to have a shorter parasite clearance time when compared with quinine. In Sri Lanka where there is strict control over the importation and dispensing of antimalarials, the risk of misuse of artemisinin or mefloquine is small. Together with the low and unstable transmission of malaria in the country, the threat of emergence and spread of multidrug-resistant malaria is low. Considering the risk of spread of quinine-resistant *falciparum* malaria where conditions are conducive for malaria transmission, it is of public health importance that such patients are given early and appropriate treatment. Therefore, the ready availability of alternative antimalarials when they are needed is imperative. Finally, it is important to report such cases, to ensure that doctors, both in the preventive and curative sectors, are kept well informed of the possibility of quinine-resistant *falciparum* malaria being imported to Sri Lanka.

References
The incidence of gestational trophoblastic disease (GTD) in Sri Lanka according to a hospital based study is 1 in 213 pregnancies [2] as compared to 1 in 2000 pregnancies in the USA [3]. Complete moles (CMs) are more common in Asian women [4]. The incidence of partial moles (PMs) is similar to that of CMs. PMs tend to be less often recognised clinically or pathologically, since their appearances are more subtle and easily misinterpreted as a spontaneous abortion by clinicians or as ‘products of conception’ by pathologists. Ideally, all tissue from a spontaneous abortion in the first trimester should be sent for histological examination for evidence of GTD.

Hydatidiform moles invade the myometrium (invasive mole), metastasise (metastasising mole) or become malignant (choriocarcinoma) [1].

The use of high quality ultrasound performed by transvaginal probes for prenatal obstetric dating and in patients presenting with abdominal pain or vaginal bleeding, has resulted in early identification of first trimester complications, including molar pregnancies. Abnormal pregnancies are terminated at 8–12 weeks of gestational age and these are not clinically suspected to be moles [11]. Before 1980 CMs were evacuated at a mean gestational age of 16 weeks, and currently most CMs are terminated at 8–12 weeks [3]. PMs are usually not suspected clinically but present as missed abortions with late first trimester bleeding and a small uterus for gestational age. Routine investigations should include full blood counts, liver function tests, serum β-hCG and thyroid function tests.

Macroscopically, the presence of vesicles in an abortion is highly suspicious of a molar pregnancy. In a CM, transparent grape-like vesicles measuring 1–2 cm in diameter are seen in gestations of 12 weeks or more.

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Clinical suspicion, correct histological diagnosis and follow up are mandatory

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