Management of Severe Malaria in the Intensive Care Unit

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KEYWORDS

• Severe malaria • Sepsis • Adjunctive therapy • Antimalarials • Fluid management • Respiratory failure • Acidosis

KEY POINTS

- Early recognition and diagnosis of severe malaria is vital.
- Intravenous artesunate should be used as first-line antimalarial treatment.
- The threshold for using antibiotic therapy should be low, particularly in children, in hypotensive patients, and in critically ill patients originating from endemic areas.
- Patients with severe malaria without hypotension or signs of significant volume depletion should generally receive fluids conservatively, in contrast with the recommendation for bacterial sepsis.
- There is currently insufficient evidence to recommend any specific adjunctive therapy.

BACKGROUND

Severe malaria is a medical emergency requiring early intervention to prevent death. Malaria remains one of the top 3 infectious killers in the world, alongside human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and tuberculosis, with global mortality estimates of around 1 million deaths per year.[1,2] Although most deaths occur in low-resource settings with high transmission intensity, malaria also accounts for most life-threatening illness in travelers returning from the tropics.[3]

Disclosures: C.P. Yansouni is supported by Grand Challenges Canada and the Research Institute of the McGill University Health Centre. The authors declare no conflicts of interest.
Contributors: M.P. Cheng performed literature searches and drafted several sections. C.P. Yansouni conceived the article and was responsible for the overall content.
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Crit Care Clin 29 (2013) 865–885
http://dx.doi.org/10.1016/j.ccc.2013.06.008 **criticalcare.theclinics.com**
0749-0704/13/$ – see front matter

This article highlights key aspects of the management of severe malaria syndromes, with a focus on *Plasmodium falciparum*, because it accounts for most of the deaths. Individual case management of imported malaria is emphasized, because clinicians in nonendemic settings may be less accustomed to treating severe malaria than their counterparts in high-transmission areas. However, because most data for the management of severe disease are from malaria-endemic regions, differences in management strategies between endemic and nonendemic areas and between children and adults are highlighted.

LIFE CYCLE

Malaria results from infection by *Plasmodium* parasites, of which 5 species are known to cause disease in humans: *P falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and *Plasmodium knowlesi*. Humans are the only reservoir for pathogenic species except *P knowlesi*. The principle means of transmission of *Plasmodium* parasites is via the bite of female *Anopheles* mosquitoes. The parasite's life cycle involves distinct life stages that differ with respect to pathogenic effect and susceptibility to drugs. After ingesting parasitized blood from an infected person, sporozoites develop within mosquito salivary glands. Sporozoites are subsequently transmitted to another host at the next blood meal, at which point they enter hepatocytes within approximately 30 minutes. On parasite maturation, infected hepatocytes rupture and release thousands of merozoites into the bloodstream. These organisms then infect erythrocytes and enter the intraerythrocytic lifecycle, which is responsible for disease manifestations. A minority of intraerythrocytic parasites develop by sexual reproduction into gametocytes, to be ingested eventually by another mosquito.

EPIDEMIOLOGY

Global mortality estimates for malaria range from 709,000 (95% confidence interval [CI], 554,000 to 892,000) deaths per year[1] to 1,133,000 (95% CI, 848,000 to 1,591,000) deaths in 2010.[2] Africa bears the highest burden of malaria, with 70 million reported cases in 2009, and estimates reaching 176 million (95% CI, 117 million to 241 million).[4] The incidence is thought to be decreasing in Africa, except in west and central Africa where transmission rates are the highest, with infections almost exclusively from *P falciparum*.[5,6] Most countries in southeast Asia remain endemic for the disease. It is estimated that 70% of the population is at risk for malaria, representing around 450 million people. Most cases are attributable to infection with *P falciparum*, although *P vivax* predominates in some localities.[1] *P knowlesi* is a recently emerging pathogen in this region. In the last decade, the incidence of malaria has significantly decreased in most countries in the Americas, and most now have low malaria transmission intensity. Countries in the Americas with the highest incidence of infection with *P falciparum* include Haiti, Guyana, and Suriname.[1]

Imported malaria is increasingly reported in low-incidence countries of Europe and North America. The number of imported malaria cases varies by country, with France reporting approximately 8000 cases per year,[7] the United Kingdom 1500 to 2000 cases per year,[8] the United States 1691 cases in 2010,[9] and Canada 350 to 1000 cases per year,[10] although underreporting is estimated at 30% to 50%.[11] *P falciparum* malaria accounted for 77% of potentially life-threatening tropical diseases among 82,825 ill Western travelers reported to GeoSentinel (a worldwide network of surveillance for travel-related illness) over a 15-year period.[3] Severe disease is reported in approximately 4% to 10% of imported cases.[7,9,10]