Mortality Associated with Severe *Plasmodium falciparum* Malaria Increases with Age

Piero Olliaro

(See the article by Dondorp et al. on pages 151–7)

Of the 4 species of human malaria parasites, *Plasmodium falciparum* is the most common cause of severe complications. Although the risk of death due to mild, uncomplicated malaria is low (<1%), infection occurring in individuals with insufficient immunity can progress to life-threatening disease when untreated or inadequately treated.

Severe malaria is proteiform; presenting signs and symptoms are diverse and may occur singly or, most often, combined in the same patient. The World Health Organization has identified the case-defining conditions [1] and the general principles for the management of severe malaria [2, 3].

Although life-threatening malaria complications can affect patients of all ages, disease presentation and mortality are intimately related to transmission intensity and age of the patient. Various studies have reported on the prevalence of the various forms of malaria, presenting conditions, and risk of death across age groups in areas with different transmission intensities, but information is difficult to summarize [4]. For the purpose of this article, the information was extracted from relevant articles, and rates with 95% CIs were recalculated; however, articles were not identified through a systematic review.

The available information indicates that severe malaria occurs in young children in areas of intense malaria transmission and in persons of all ages in areas where transmission intensity is low and that mortality differs according to the different forms of severe malaria and to the age of the patients. The underlying general principle is that when the intensity of transmission is higher, more persons are exposed to infection, exposure to infection occurs earlier, partial immunity develops earlier, and the risk of severe malaria decreases. Severe malaria may occur in areas of very low transmission. In general, the predominant forms of severe malaria are different in children and adults in different epidemiological settings, as follows: (1) severe anemia occurs in infants in areas of stable, intense transmission; (2) cerebral malaria and respiratory distress (as a consequence of metabolic acidosis) occur in young children in areas of moderate transmission; and (3) cerebral malaria, organ dysfunction (e.g., renal failure, severe jaundice, and pulmonary edema) and acidosis occur in persons of all ages in areas of low and unstable transmission.

Our knowledge of the mortality associated with severe malaria is largely based on pediatric malaria in sub-Saharan Africa (where the bulk of malaria infection and malaria-associated mortality exists); there are fewer data on adolescents and adults, and these are mostly from areas of lower transmission outside Africa. Comparisons are complicated by the different standards of care at the study sites.

The study by Dondorp et al. [5] quantified the risk of malaria with respect to the presenting symptoms and the age of the patient, using a database derived from a randomized, clinical trial comparing intravenous artesunate with quinine for the treatment of severe malaria in Southeast Asia (the SEAQUAMAT study) that was published elsewhere [6].

Previous data indicate that mortality varies with malaria presentation and age and that fatality rates are higher among adults than among children. Coma and metabolic acidosis have emerged as significant risk factors in both children and adults.

Observational studies involving children have revealed that anemia alone is associated with a low fatality rate, but the risk of death increases when multiple conditions (particularly neurological, meta-
bolic, and respiratory symptoms) coexist. Among Kenyan children (mean age, 26 months) [7], the case-fatality rate associated with severe malaria was 7.3% (95% CI, 5.53%–9.55%) overall and ranged from 1.3% among patients with severe anemia only to 34.7% among patients with simultaneous impaired consciousness, respiratory distress, and anemia. In a hospital study in Gabon [8], the overall case-fatality rate among children with severe malaria (mean age, 25.5 months) was 8.9% (95% CI, 6.77%–11.58%) and ranged from 1% among children who presented with severe anemia only to 50% among children who presented with coma, lactic acidosis, and anemia. Older children had a higher risk of death due to severe malaria. Coma, hyperlactatemia, respiratory distress, and hypoglycemia were independent predictors of fatal outcome. In Yemen [9], the case-fatality rate associated with severe malaria among children (age, 6 months to 10 years) was 3.2% (95% CI, 2.1%–4.7%) and was unrelated to age; the case-fatality rate ranged from 0% among patients with severe anemia only to 25% among patients who presented with neurological symptoms, respiratory distress, and anemia.

Mortality has been relatively similar across various hospital-based trials regarding severe malaria, despite differences in inclusion criteria, patterns of presenting conditions, and standard of care. A meta-analysis of randomized, controlled trials of intravenous quinine versus intramuscular artemether included 1925 severe malaria cases from 7 studies (3 trials involved non-African adults) [10]. Mortality among 958 quinine-treated patients was 17.2% (95% CI, 14.89%–19.77%) overall and was similar among children (16.7% [95% CI, 13.79%–20.06%]; 96 of 574 children died) and adults (17.5% [95% CI, 13.90%–21.76%]; 67 of 383 adults died). Interestingly, mortality was higher among the 378 children enrolled in the 2 studies (from Malawi and The Gambia) that included only patients with cerebral malaria who were treated with quinine (20.6%; 95% CI, 16.71%–25.10%) and among the patients in studies in Vietnam, Thailand, and Papua New Guinea that enrolled adults with any World Health Organization–defined criterion indicating severe malaria (19.5% [range, 16.7%–34.0%]; 95% CI, 15.53%–24.17%). A meta-analysis of mortality among Asian patients treated in randomized, controlled trials comparing intravenous quinine with artesunate was recorded in addition to the results of the SEAQUAMAT trial. Mortality among the 1789 patients who received quinine ranged from 14% to 34% and was 23% in the SEAQUAMAT study. In India, mortality was 16.0% (95% CI, 11.47%–21.79%; 34 of 212 patients died) among adults, compared with 2.9% (95% CI, 0.17%–16.38%; 1 of 36 patients died) among children; cerebral malaria, severe anemia, renal failure, and respiratory distress were highly statistically significantly related to fatal outcome in the regression analysis, and age was less statistically significantly related to fatal outcome [11].

There are few data on non-Asian adults. In Tanzania, mortality was 24% (95% CI, 17.95%–16.38%; 14 of 171 adult patients with severe malaria died). Unconsciousness, renal failure, and pulmonary edema had a high prognostic value for fatal outcome; mortality ranged from 2% among patients with none of these conditions to 100% among patients with all 3 conditions. The risk of death was independent of age [12]. Mortality was 10.8% (95% CI, 5.74%–19.61%); 10 patients died) among 93 travelers returning to Europe [13]. Coma, pulmonary edema, shock, and metabolic acidosis were statistically significantly associated with a fatal outcome. The lower fatality rate in this series is ascribed to the high standard of care.

With regard to the study by Dorndorp et al. [5], the original study enrolled 1461 patients in 4 countries (Bangladesh, India, Indonesia, and Myanmar) [6]; 1050 (72%) of these patients fulfilled the strict World Health Organization criteria for severe malaria and were analyzed. These are countries with low-to-moderate malaria transmission and where both mild and severe malaria can occur at all ages, although with intercountry variations in transmission intensity and age distribution. On the whole, this database had few children and no infants. More than one-half of the patients (53%) were aged 21–50 years, with few in the extreme age categories (there were no infants, 6% were <5 years of age, and 9% were ≥50 years of age). The overall mortality was 24% and varied on the basis of the site (9%–28%) and treatment (15% in the artesunate group vs. 22% in the quinine group; P < .001).

When the presenting conditions were considered individually in the univariate analysis, coma and metabolic acidosis were associated with a higher risk of death than were the other conditions among all of the age groups. Hyperparasitemia and renal impairment were also significant factors on aggregate but were not particularly significant in the group of patients aged >50 years (possibly because, although these symptoms were the most prevalent among older patients, this age group was comparatively small).

The risk of death was related to age and severity of presenting conditions. Mortality increased steadily from 6% among the patients aged <10 years to 36.5% among the patients aged >50 years and from 9.5% among patients with 1 severity criterion to 50% among patients with ≥5 criteria. To predict mortality on the basis of patient age and presenting clinical conditions, Dondorp et al. [5] used a logistic regression model that began with the entire set of independent variables (saturated model) and tested the fit of the model after progressively deleting variables (backward stepwise regression). At the same time, coefficients were also tested for statistical significance, for inclusion or exclusion (goodness-of-fit test). By proceeding this way, age was isolated as the remaining explanatory variable; to our knowledge, this is the first time such a finding has been reported. This does not mean that other variables are not important but that they were dropped earlier in the iterations of
the model. Importantly, despite the diverse presenting syndromes across the different age groups, depth of coma and severity of acidosis were the most important prognostic factors, independent of age. As an aside, it is worthwhile to note the concordance between standard base excess (a choice of Dondorp et al. [5]) and plasma bicarbonate concentration (a World Health Organization criterion) to express metabolic acidosis.

The study by Dondorp et al. [5] and similar studies are important because they identify the risk factors and help target patients at special risk, so that these patients can receive the appropriate interventions. The availability of individual patient data from relevant studies for a meta-analysis would allow for the confirmation of the broader applicability of the results presented here, particularly if the studies included more patients at the extremes of the age distribution, notably the very young and patients aged >50 years. Other large trials of pediatric severe malaria in Africa that are currently under way are expected to contribute further data to our understanding of the critical conditions associated with the mortality associated with severe P. falciparum malaria.

Acknowledgments

Potential conflicts of interest. P.O.: no conflicts.

References