Severe malaria is clinically similar to other severe febrile illnesses. However, in endemic areas, parasitological confirmation of parasitemia is often unavailable or unreliable. False-positive malaria microscopy is common. The most important consequence of treating only for malaria when no parasitemia exists is failure to address other life-threatening conditions. Invasive bacterial infections are detected in up to one third of children with clinical features of severe malaria but a slide with results negative for malaria. Even among genuinely parasitized children, severe illness is not always due to malaria in endemic areas. We believe that routine use of parenteral antibiotics among children with a slide that indicates malaria and life-threatening disease is warranted because invasive bacterial infections are likely to be under-ascertained and are associated with increased mortality. Published data on co-morbidity with HIV infection and malnutrition are reviewed. A structured approach to assessment and care is essential, and is largely independent of underlying etiology.