Cachexia in malaria and heart failure: therapeutic considerations in clinical practice

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Cachexia is an independent prognostic marker of survival in many chronic diseases including heart failure and malaria. Morbidity and mortality from malaria is high in most of the third world where it presents a very challenging public health problem. Malaria may present in the UK as fever in the returning traveller or as fever in overseas visitors. How and why cachexia develops in malaria in a manner similar to the cachexia of chronic heart failure and the treatment strategies that would alter outcomes in both diseases are discussed in this review.

Cachexia is an important feature of many chronic disorders. It occurs in infectious diseases such as malaria and tuberculosis, and in many other chronic illnesses including heart failure, liver cirrhosis, chronic obstructive pulmonary disease, cystic fibrosis, chronic renal failure, and malignancy. It is important to specifically compare cachexia in malaria and heart failure because data from research in recent years suggests that the aetiology may be similar. This may have significant clinical considerations for the specialties that are involved in the management of patients with these conditions. This comparison may explore common themes that will enable us to selectively target cachexia irrespective of its cause and modify disease prognosis. This paper aims to review the evidence for cachexia in malaria and heart failure and to highlight common denominators in aetiology, clinical manifestation, or treatment.

METHODS

Papers reviewed were identified by searching Medline (1966 to January 2004), the Cochrane Database of Systematic Reviews, EMBASE, DARE, ACP Journal Club, Excerpta Medica, the Cochrane Controlled Trials Registry, and by reviewing the bibliography of relevant articles.

MALARIA

The protozoa that cause malaria are:

- Plasmodium falciparum.
- Plasmodium malariae.
- Plasmodium vivax.
- Plasmodium ovale.

Ninety five percent of deaths occurring in malaria worldwide are due to Plasmodium falciparum. Malaria is transmitted by the bite of its insect vector, the anopheles mosquito, which also acts as a reservoir of infection. It may rarely be transmitted by blood transfusion, injection, or transplacentally. The clinical picture of Plasmodium malaria typically includes fever, malaise, joint pains, anorexia, headache, nausea and vomiting, and cough and may progress to delirium, seizures, renal failure, coma, and death. This is because falciparum malaria is a complex disease that causes multiorgan dysfunction. This is thought to occur through the excessive stimulation of inflammatory and immunological pathways mediated by proinflammatory cytokines.

The hallmark of malaria is haemolysis, which occurs when the red blood cells rupture to release schizonts. Rupture of schizonts liberates antigenic substances and toxins, which can cause widespread organ damage and failure. In falciparum malaria, red blood cells containing schizonts adhere to the lining of capillaries in brain, kidney, liver, lungs, and the gut. These vessels become congested and anoxia may develop within the organs. Repeated malaria attacks can result in long standing devitalisation that will ultimately lead to cachexia.

The interaction between malaria and cachexia is complex. Some workers have attempted to relate this interaction to socioeconomic factors and malnutrition, while others emphasise the importance of co-morbidity, and yet others stress the role of anaemia. The protective effect of intestinal helminths and chronicity is proposed to confound the malaria-cachexia interaction. Factors due to the frequency of parasite inoculation are also important. Malaria is a source of great morbidity and mortality. Immunity accrues slowly in survivors, over a period of years, and the immune response is not capable of protecting from reinfection. The most vulnerable are the individuals who lack adequate immunity: young children, pregnant women, and people with no previous exposure.

Chronic malaria

There is no agreed definition for chronic malaria. In this review, we have used the term “chronic malaria” to mean three or more acute attacks of malaria within one year in an individual with low levels of parasitaemia but not symptoms of malaria between attacks. This is different from recurrent malaria in which there is complete elimination of parasitaemia between attacks.

Abbreviations: CHF, chronic heart failure; GPI, glycosylphosphatidylinositol; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; IL, interleukin; MHCI, myosin heavy chain isoform; TNF, tumour necrosis factor; WHO, World Health Organisation.
Thus chronic malaria is a frequent feature of the indigenous population in endemic areas. It may well represent an adaptation by the host to survive repeated parasitic invasion or evolution by the parasite to exist successfully within the host.

Public health challenge
About 100 million people worldwide are subject to malaria infection annually, of whom 1% will die during the acute illness. About 90% of the worldwide malaria burden is borne by sub-Saharan Africa, and lately, the disease has reappeared in previously malaria-free areas as a result of epidemics, the decline in public health systems, and drug resistance. The World Health Organisation (WHO) report of 1997 states that about 40% of the world’s population is at risk of malaria. This percentage at risk may increase if the disease continues to spread at the present rate. Specifically, about 25–30 million people from non-tropical countries will visit areas in which malaria is endemic yearly. Out of this number, about 10 000 to 30 000 will become infected.

Molecular basis of the pathogenesis of falciparum malaria
It was the Italian physician Camillo Golgi who first hypothesised in 1886 that the cause of the febrile paroxysm in malaria was the release of a toxin of parasite origin. Maegraith in 1948 posited that the various pathological processes in malaria were the results of the induction of endogenous mediators of host origin. There is now evidence to suggest that host cells, acting under the influence of the parasite P falciparum, trigger the release of pro-inflammatory cytokines, which then provokes their onset. There are studies showing a close correlation between disease severity and circulating levels of tumour necrosis factor (TNF) in both children and adults. These cytokines can generate the inducible form of nitric oxide synthase and thus produce a continuous large supply of nitric oxide in tissues and cause cerebral symptoms, immune suppression, and weight loss.

CD4+ T-cells in malaria
CD4+ T-cells are thought to have a role in immunity to the blood stages of malaria, and cytokines associated with monocyte and T-cell activation have been implicated in the disease. Similar cytokines are known to occur in the pathogenesis of cachexia in heart failure.

Glycosylphosphatidylinositol (GPI)
GPI produced by P falciparum is a parasite toxin inducing the production of TNF and interleukin (IL)-1 by host macrophages. This exerts its effect by the activation of a two component signalling pathway within the host cells. GPI causes TNF-mediated weight loss in mice.

Overlap of symptomatology: algid malaria
Algid malaria is a shock-like syndrome. Most patients with severe falciparum malaria exhibit a raised cardiac index (>5 l/min/m²), which can be traced to pyrogen-mediated vasodilatation with low systemic vascular resistance and low or normal pulmonary arterial wedge pressures. The WHO report on falciparum malaria in 2000 states that the clinical picture produced in algid malaria is similar to Gram negative septicemia. Endotoxaemia also occurs in patients with falciparum malaria. An agonal fall in cardiac index secondary to metabolic acidosis, hypoxaemia, and septicemia may occur. This is similar to what is observed in the final stages of heart failure from non-cardiac causes, especially that associated with end stage renal disease and sepsis. Malaria may thus be viewed as a collection of overlapping syndromes acting through different organ systems with several mechanisms.

Immunity to falciparum malaria
Plasmodium falciparum is one of the most virulent human pathogens. The factors that determine its virulence are poorly defined, although the adhesion of infected red blood cells to the vascular endothelium has been associated with some of the syndromes of severe disease. Immune responses cannot prevent repeated attacks of malaria. Specific immunity has been attributed either to the presence of cytotoxic lymphocytes that act against the parasite’s liver stage of infection or to antibodies that react against blood stage antigens. Antigenic diversity, clonal antigenic variation and T-cell antagonism may contribute to the parasite’s evasion of the protective and parasiticidal host responses. It is proposed that an understanding of immunity in the setting of malaria may be the link to understanding how cachexia develops in chronic heart failure (CHF) with a known similar cytokine profile.

Evidence for cachexia in malaria
The studies that provide the evidence for the occurrence of cachexia in chronic malaria are summarised in table 1. Various workers have studied the relationship between malarial immunity and nutritional status. In Tanzania, no correlation was found between malaria antibody titres and indices of malnutrition. In Kenya, a variant surface antigen specific IgG in chronic pregnancy associated malaria was found to protect against low birth weight. In Colombia, mean antibody titres to P falciparum were lower in malnourished children than in well nourished ones. P vivax antibody titres were higher in malnourished children. There is evidence from observational cohorts that malnutrition decreases the susceptibility to malaria and that this may be due to an interaction with host immunity. There is also evidence that malnutrition worsens the prognosis in malaria. The level at which malnutrition ceases to become protective and becomes an adverse prognostic indicator is not clear. The host immunity described is related to “stunting” and “wasting” rather than malnutrition. Stunting has been shown to be protective in malaria. Thus, it has been proposed that the improved ability of malnourished children to produce certain cytokines in response to stimulation by specific malarial antigens may be the key. Tanner et al reported that malaria was the main contributory factor to growth retardation in children in a hyperendemic rural community of Tanzania. Mbago et al determined that malaria was a significant predictor of weight for height measurements in underweight children living in holoendemic areas of urban Tanzania. We have not found any studies that addressed directly the issue of the response of cachexia to treatment interventions in malaria and how this might affect prognosis. However, a small study by Van Den Broeck et al in 1993 found an association between nutritional status and mortality risk and extreme malnutrition in holoendemic areas of Zaire.

HEART FAILURE
“Heart failure is a fascinating cluster of syndromes, full of paradoxes, defies simple definition yet is common and deadly”. The 2001 guidelines issued by the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the

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European Society of Cardiology states that heart failure is a syndrome containing certain key features typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling plus an objective evidence of cardiac dysfunction at rest. That a clinical response to treatment directed at heart failure should demonstrate some improvement in symptoms and/or signs.27

Cachexia in CHF
Cachexia is an adverse prognosticator in heart failure.28 There is considerable disagreement in the question of the percentage of heart failure patients who develop cachexia and how this should be defined and measured. Carr et al reported that up to 50% of patients with CHF suffered from some form of malnutrition.29 Anker and Coats published that up to 15% of patients attending their CHF clinic developed cachexia during the clinical course of CHF.30 Roubenoff et al observed that loss of more than 40% of lean body tissue would cause death.31 Several studies show that CHF is characterised by persistent immune activation in vivo. This is reflected in the increased levels of inflammatory cytokines TNF, IL-1β, and IL-6; and chemokines monocyte chemoattractant protein-1 and IL-8 within the blood and the enhanced expression of various inflammatory mediators within the failing myocardium.

Competing theories
There are several theories for the causes of cachexia in CHF. Figure 1 shows the factors that are known to affect the development of cachexia in chronic diseases like CHF and the relationship between these factors. We point out, however, that it would be difficult to propose a specific hypothesis regarding molecular mechanisms of cachexia as the different mechanisms and pathways proposed have not been fully defined.

Physical inactivity and muscle atrophy
Widespread abnormalities of skeletal muscle bulk, function, and metabolism is a recognised consequence of CHF. Around 400 BC, a syndrome of “heart failure” in which the “shoulders, clavicles, chest and thighs melt away” was described by a scholar from the school of Hippocrates.32 William Withering in 1795 wrote of a patient with heart failure as someone “whose body was greatly emaciated.”33 There is recent evidence to support this.34 35 Physical inactivity and deconditioning may play a part in the muscle atrophy seen in many chronic disease states, although in CHF this atrophy is significantly different from that observed in physical inactivity.

Table 1: Studies on weight loss in malaria

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Region/country</th>
<th>Parameters studied</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanner et al</td>
<td>1987</td>
<td>Tanzania</td>
<td>Stunting/wasting</td>
<td>3%–20% wasting, 35%–71% stunting</td>
</tr>
<tr>
<td>Dominguez-Vazquez et al</td>
<td>1990</td>
<td>Colombia</td>
<td>Malnutrition using the Gomez classification</td>
<td>49% mild, 14% moderate, 2% severe</td>
</tr>
<tr>
<td>Mbago and Namfua</td>
<td>1991</td>
<td>Tanzania</td>
<td>Weight for height, weight for age, wasting underweight</td>
<td>Male sex, better; mother’s age and education, better; immunisation status; number of children under 5 21.6% low MUAC</td>
</tr>
<tr>
<td>Kikafunda et al</td>
<td>1998</td>
<td>Uganda</td>
<td>Mid-upper arm circumference, Weight, Supine length, Stunting</td>
<td>24.1% underweight, 23.8% short for age, 6.9%</td>
</tr>
<tr>
<td>Genton et al</td>
<td>1998</td>
<td>Papua New Guinea</td>
<td>Stunting/wasting, height for age score, weight for height, wasting underweight</td>
<td>21% stunted, 10% wasted, 5% both</td>
</tr>
<tr>
<td>Nacher et al</td>
<td>2001</td>
<td>Thailand</td>
<td>Body mass index, Height for age score, stunting</td>
<td>51% stunted, 38% not stunted</td>
</tr>
<tr>
<td>Deen et al</td>
<td>2002</td>
<td>Gambia</td>
<td>VSA specific IgG, resistance to PAM, birth weight, maternal anaemia</td>
<td>Chronic PAM and low or absent VSA specific IgG causes low birth weight babies, maternal anaemia</td>
</tr>
<tr>
<td>Staalsoe et al</td>
<td>2004</td>
<td>Kenya</td>
<td>VSA specific IgG, resistance to PAM, birth weight, maternal anaemia</td>
<td>Chronic PAM and low or absent VSA specific IgG causes low birth weight babies, maternal anaemia</td>
</tr>
</tbody>
</table>

MUAC, mid upper arm circumference; PAM, pregnancy associated malaria; VSA, variant surface antigen.

Figure 1 Interplay between chronic disorders and cachexia (BMR, basal metabolic rate; NO/INOS, nitric oxide/inducible form of nitric oxide synthetase; TNF, tumour necrosis factor).
Muscle hypothesis
Coats et al postulated that haemodynamic alterations trigger the development of complex peripheral alterations which contribute to sympathetic excitation during exercise and symptom generation and degeneration.\(^3\)\(^4\)\(^5\) Regular exercise increases skeletal muscle bulk and improves survival in CHF.

Chronic low frequency electrical stimulation
A small clinical trial by Nuhr et al reported that four hours a day of chronic low frequency stimulation for 10 weeks improved exercise performance and significantly increased peak oxygen uptake.\(^9\) These changes were associated with changes in the profiles of the enzymes citrate synthase and glyceraldehydephosphate dehydrogenase, and the myosin heavy chain isoforms (MHCIs) were shifted in the slow direction. The increases in the MHC slow isoform was at the expense of the MHCIId/x fast isoform suggesting an increase in lean muscle mass and improvement in deconditioning due to CHF.\(^3\)

Neurohormonal hypothesis
Merrill et al reported an increased concentration of renin in the blood of patients with CHF.\(^6\) Subsequently the mechanism for salt and water retention in CHF was described.\(^7\) The concept that neuroendocrine activation is central to the pathogenesis and prognosis of heart failure is well established.\(^8\)\(^9\) Packer used the neurohormonal hypothesis to postulate that CHF progresses because activated endogenous neurohormonal systems are deleterious to the heart and cardiovascular system.\(^8\) Thus catecholamines are now accepted to be raised in cachexia because of heart failure.\(^10\)

Cytokines in CHF
Levine et al observed that patients with severe CHF had raised circulating levels of TNF.\(^1\) This was followed by reports of increased concentrations of TNF in patients with cardiac cachexia. The clinical significance of these observations is that TNF elevation in CHF is associated with marked activation of the renin-angiotensin system, cachexia, advanced disease, and an adverse prognosis.\(^10\) It has also been observed that the TNF receptor family (Fas) transduces the apoptotic signal into cells. And there are reports of the occurrence of apoptosis with abnormal consequences in the human heart.\(^11\) TNF is now thought to play a significant part in left ventricular remodelling.

Insulin resistance
Insulin resistance and the development of the metabolic syndrome have been implicated as a contributing cause of cachexia in CHF.\(^12\) In infectious diseases, hyperinsulinaemia and insulin resistance are commonly associated with hypoglycaemia. In malaria, insulin resistance may also occur in association with hypoglycaemia.\(^13\) It may be due to parasitaemia or treatment with quinine.

Dehydroepiandrosterone/cortisol ratio, growth hormone, and basal metabolic rate
The role of hormonal changes, dehydroepiandrosterone/cortisol ratio, growth hormone, and insulin-like growth factor as underlying the severe metabolic and endocrine abnormalities in these diseases was described by Anker et al.\(^14\) An increase in basal metabolic rate is thought to be central to this.

Leptin
Leptin may also play a part in cachexia. Like cytokines, leptin serves as a peripheral messenger to convey signals to the brain. Expression of leptin is stimulated by glucocorticoids, endotoxins, and cytokines and its actions include inhibition of the hypothalamo-pituitary-adrenal axis. Indeed leptin exerts a direct, dose dependent inhibition of stimulated cortisol secretion by normal human and rat adrenal cells in vitro.\(^15\) Adipocytes are implicated in the cachexia seen in malaria.\(^16\) The evidence is not clear.\(^17\)

Malnutrition/malabsorption
Malnutrition and malabsorption are well known causes of cachexia in chronic diseases. Losses of nutrients through the gastrointestinal and urinary tracts are other mechanisms proposed as possible causes. In CHF increased right atrial pressure and tricuspid regurgitation is associated with whole body protein turnover and cachexia.\(^18\)\(^19\) What is not so clear is whether this is a cause or effect.

<table>
<thead>
<tr>
<th>Table 2: Comparison between cachexia in CHF and cachexia in malaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>HLA association not known</td>
</tr>
<tr>
<td>Genotypes not known to ameliorate disease severity</td>
</tr>
<tr>
<td>Associated with malnutrition</td>
</tr>
<tr>
<td>Skinfold thickness associated with prognosis</td>
</tr>
<tr>
<td>Respiratory distress and pulmonary oedema frequently present</td>
</tr>
<tr>
<td>Nitric oxide implicated in the pathogenesis</td>
</tr>
<tr>
<td>Prostaglandins D(_2), E(_2) production increased</td>
</tr>
<tr>
<td>Multiorgan failure a feature of the terminal stages of CHF</td>
</tr>
<tr>
<td>High blood levels of TNF present</td>
</tr>
<tr>
<td>Increased production of IL-6, IL-1</td>
</tr>
<tr>
<td>Decreased production of anti-inflammatory cytokine IL-10, IL-12 in severe malaria</td>
</tr>
<tr>
<td>High serum uric acid is a marker of systemic inflammation</td>
</tr>
<tr>
<td>High blood levels of cholesterol beneficial</td>
</tr>
<tr>
<td>Increased gastrointestinal permeability associated with endotoxin levels</td>
</tr>
<tr>
<td>Bacterial lipopolysaccharide triggers release of proinflammatory cytokines</td>
</tr>
<tr>
<td>Hypoinsulinaemia associated with insulin resistance and the onset of the metabolic syndrome</td>
</tr>
<tr>
<td>Growth hormone and insulin-like growth factor implicated in pathogenesis of disease</td>
</tr>
</tbody>
</table>

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common to those with chronic malaria and CHF. Table 2 provides a list of the key features. How useful is this background knowledge? We recognise some of these features may not apply in routine clinical settings, because they are still experimental. We have nonetheless provided them because there are on-going efforts by researchers to make some of them the routine therapeutic considerations of the future.

**CYTOKINES IN MALARIA**

Malaria infected individuals produce large amounts of proinflammatory cytokines. This cytokine response is responsible for the high levels of fever that occur within a few days of the inoculation of non-immune individuals with *Plasmodium* spp. The idea that cachexia in malaria is mediated by TNF was first mooted by Hotez et al. Animal models have shown that weight loss in malaria is influenced by TNF. Blocking TNF in mice that received parasite specific T-cells prolongs survival. In human studies the production of proinflammatory cytokines like IL-1, IL-6, and TNF have been shown to mediate the clinical progress of fever, anorexia, and weight loss. TNF as noted in CHF above, acts by inducing the synthesis of IL-6, and by the induction of nitric oxide synthesis. Details of various studies of cytokines in malaria are summarised in table 3. TNF is down-regulated by IL-10 in children living in malaria holoendemic areas of Kenya and appears to inhibit the production of erythropoietin. Raised serum concentrations of TNF have been reported in malaria, and high concentrations correlate with increasing disease severity. IL-10 is also increased in malaria, and has been shown to down-regulate TNF. Severe anaemia has been associated with severe malaria in Ghanaian children with defective IL-10 production. Previously, it was shown that IL-10 gene knockout mice develop more severe disease and experienced higher mortality rates than normal mice, prompting the suggestion that children with *P. falciparum* infection who produce balanced levels of IL-10 to regulate excessive TNF are better able to control severe anaemia, and the observation that severe anaemia may be a further consequence of the deranged immunology seen in malaria. It has thus been proposed that the balance between IL-10 and TNF may modulate the severity of anaemia in children.

**CYTOKINES IN CHF**

TNF, IL-1β, and IL-6 are known to have important pathogenic roles in CHF, and may contribute to cachexia associated with CHF.

**COMPARISON OF PLASMA TNF IN CHF AND MALARIA**

Figure 2 was derived from the data published by Kurtzhals et al and Cicoira et al. It shows plasma levels of TNF in a normal population, CHF patients, and malaria patients. They provide no direct comparison and should be interpreted with caution. The methodologies employed in assaying and analysing the samples are not the same, and the Kurtzhals group did not screen for chronic malaria. However, the trend is that TNF levels are highly raised in the acute event like malaria and increased to a lesser amount in CHF. Whether an acute event with highly raised TNF levels occurs before the onset of CHF is not yet known. Clearly more studies are needed to confirm absolute TNF and endotoxin levels in all stages of both diseases before postulating a common denominator.

**GENETIC REGULATION OF TNF EXPRESSION**

TNF-α related cachexia in malaria might be influenced by the genetic make-up of individuals and populations. TNF-α has two subtypes (TNF-α1/TNF-α2) and severe malaria is found significantly more frequently in heterozygotes. Rates of TNF-α subtypes vary between populations and may influence susceptibility to severe malaria and cachexia.

**THERAPEUTIC AND PROGNOSTIC IMPLICATIONS**

Cachexia complicating any chronic disease state is associated with an increased risk of death during the course of that disease. Anker et al have suggested that the loss of more than

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**Table 3** Summary of data on cytokines in malaria

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Region/country</th>
<th>Cytokine studied</th>
<th>No of patients</th>
<th>Blood level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allan et al</td>
<td>Gambia</td>
<td>TNF-α</td>
<td>34 children with cerebral malaria</td>
<td>56–91 pg/ml, 95% CI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41 to 1.54</td>
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<td></td>
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<td></td>
<td></td>
<td>70–618 pg/ml, 95% CI</td>
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<td></td>
<td></td>
<td>42 to 2033</td>
</tr>
<tr>
<td>Kurzhal et al</td>
<td>Ghana</td>
<td>TNF-α</td>
<td>68 children with uncomplicated</td>
<td>110–200 pg/ml (TNF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>malaria</td>
<td>640–1400 pg/ml (IL-10)</td>
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<td></td>
<td></td>
<td></td>
<td>80–140 pg/ml (TNF)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-10</td>
<td>41 children with cerebral malaria</td>
<td>400–1200 (IL-10)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>915 pg/ml (falciparum)</td>
</tr>
<tr>
<td>Singh et al</td>
<td>India</td>
<td>TNF-α</td>
<td>26 children with uncomplicated</td>
<td>280–6 pg/ml (vivax)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>malaria</td>
<td></td>
</tr>
<tr>
<td>Migot-Nabias et al</td>
<td>Gabon</td>
<td>IL-10</td>
<td>39 adults with uncomplicated</td>
<td>15 adults with cerebral malaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>malaria</td>
<td>3.5–7 pg/ml range</td>
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<td>1–157.5</td>
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<td>2.4 pg/ml range</td>
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<td></td>
<td></td>
<td>0–161.7</td>
</tr>
<tr>
<td>Nussenblatt et al</td>
<td>Cameroon</td>
<td>IL-10</td>
<td>273 children with uncomplicated</td>
<td>5–25 pg/ml (range:</td>
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<td></td>
<td></td>
<td></td>
<td>malaria</td>
<td>28–1380)</td>
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<td>63–426 pg/ml (range:</td>
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<td></td>
<td></td>
<td></td>
<td>28–1380)</td>
</tr>
<tr>
<td>Jason et al</td>
<td>Malawi</td>
<td>IL-10</td>
<td>32 children with uncomplicated</td>
<td>4–28 pg/ml (range:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>malaria</td>
<td>8–23000)</td>
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<td></td>
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<td>IL-6</td>
<td></td>
<td>337–430 pg/ml (range:</td>
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<td>9–124300)</td>
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<td>16 pg/ml range</td>
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<td>&lt;16 pg/ml range</td>
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<td></td>
<td>&lt;16–1280</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IFN-γ</td>
<td>186 children with uncomplicated</td>
<td>26 pg/ml range</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>malaria</td>
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CI, confidence interval; IFN-γ, interferon gamma.
6% of the pre-morbid body weight or the presence of a body mass index <15 in an adult being treated for a chronic disease should prompt heightened therapeutic consideration. This may include:

- Nutritional support.
- Exercise training.
- Periodic weighing or a carefully documented weight history.
- Modification of lipid profile.
- Anticytokine therapy.
- Intravenous immunoglobulin.
- Administration of anti-inflammatory cytokines.
- More regular follow up.

Table 4 lists the various points in the pathophysiology of these two diseases where it is theoretically possible for new intervention strategies to be applied.

**Modification of lipid profile**
Cytokines and endotoxin are known to stimulate triglycerides and cholesterol synthesis. Dyslipidaemia is a feature of severe malaria. Recent studies suggest that the inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase can interfere with the activation of anti-inflammatory pathways in the body causing down-regulation of cytokine and chemokine production. This enzyme is raised in CHF and in malaria. Thus, there arises the question of whether the low blood levels of cholesterol seen in severe cachexia complicating chronic malaria should be viewed as an adverse prognostic marker and subject to the same therapeutic considerations as blood cholesterol levels in CHF. In CHF high and moderately raised levels of blood cholesterol would be treated with statins. Perhaps, the enhancement of the immunomodulatory effects of statins may see a novel role for HMG CoA reductase inhibitors in malaria. In contrast, cholesterol-rich serum lipoproteins are able to modulate the inflammatory immune response because they bind to, and detoxify, bacterial lipopolysaccharide whose production is increased in CHF and many chronic diseases.

**Anticytokine drugs**
There are many probable therapeutic interventions that may modify the profiles of cytokines in chronic disease states. A summary is given below:

1. Anti-inflammatory cytokines such as IL-10, IL-12, IL-18, and interferon suppress the inflammation and may play a part in therapeutic interventions.
2. The inhibition of cytokine synthesis using drugs such as glucocorticoids, cyclosporine A, Th2 selective inhibitors, myophenolate, and tacrolimus may modify cachexia.
3. The administration of soluble cytokine receptors to mop up secreted cytokines.
4. The use of humanised blocking antibodies to cytokines or their receptors.
5. The use of drugs that block the signal transduction pathways activated by cytokines.

Serum levels of uric acid are high and correlate with systemic inflammation in severe malaria and CHF. Anticytokine therapy using agents like pentoxifylline may be another ground common to both diseases. Two large clinical trials using etanercept, a TNF receptor analogue that blocks the effect of TNF, the RENAISANCE and RECOVER, were stopped early in 2001 because they failed to demonstrate a benefit in patients with CHF. However, the addition of pentoxifylline to standard antimalarial treatment is known to decrease the duration of coma and mortality in patients with *P falciparum* cerebral malaria as shown by Di Perri et al. This better outcome was associated with a decrease in serum TNF levels. Addition of pentoxifylline to treatment with standard heart failure drugs in patients with dilated cardiomyopathy may be associated with a significant improvement in left ventricular ejection fraction and symptoms.

**Intravenous immunoglobulins**
Recent evidence suggests that there may be a survival advantage in using intravenous immunoglobulins in peripartum cardiomyopathy, CHF, and malaria. The approach may be
similar to the strategy in other chronic diseases like Kawasaki disease, dermatomyositis, and multiple sclerosis.

CONCLUSION

Many advances were made in our understanding of the pathogenesis of severe malaria and its sequelae in the second half of the last century. During the same period, notable advances were made in the management of CHF. Despite this, morbidity and mortality related to both diseases remain poor, and malaria is re-emerging in areas once suffering, enriching humanity. In the future, we will require continued efforts to prevent and control measures against intestinal parasites. Additionally, research into the pathophysiology of falciparum malaria will continue to be crucial.

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