Clinical Microbiology and Infection 30 (2024) 59–65

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Systematic review

Physiopathology and clinical management of blackwater fever: a scoping review

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ARTICLE INFO

Article history:
Received 11 July 2023
Received in revised form
8 September 2023
Accepted 14 September 2023
Available online 20 September 2023

Editor: E. Bottieau

Keywords:
Blackwater fever
Clinical management
Clinical presentation
Malaria
Physiopathology
Scoping review
Trigger

ABSTRACT

Background: Blackwater fever (BWF) is a severe syndrome occurring in patients with malaria upon antimalarial treatment, characterized by massive intravascular haemolysis and haemoglobinuria. BWF is a neglected condition and management recommendations are unavailable.
Objectives: We performed a scoping review to appraise available data on clinical picture, treatment and physiopathology of BWF, which could guide rationally its clinical management.
Methods: MEDLINE, EMBASE, LILACS, Web of Science, and Scopus databases, and the reference list of relevant publications, were searched. Papers reporting original data on BWF cases or investigating the physiopathology of BWF were eligible. Data regarding case characteristics, trigger event, clinical management and outcome were extracted. For papers investigating the physiopathology of BWF, study design and principal findings were extracted. No quality assessment was performed. Data are presented as numbers and percentages, and summary of findings, grouped by paper focus (clinical description or physiopathology).
Results: 101 papers were included. The majority of BWF cases were observed in autochthonous children (75.7%) and adults (15.3%), in contrast with historical perception that BWF patients were typically expatriates. Clinical management was described for 794 cases; corticosteroids were used in 23. Outcome was reported for 535 patients, with 18.1% mortality. The trigger was reported for 552 (47.5%) cases; in 70.4% identified as quinine. However, two RCT comparing artesunate and quinine for falciparum malaria treatment did not find significant difference in BWF occurrence after their administration. Two case-control studies did not find significant difference in G6PDH deficiency between malaria patients with and without BWF.
Conclusions: The physiopathology and optimal treatment of BWF remain similarly unknown as they were over a century ago. Empirical supporting treatment approach seems reasonable, while change of antimalarial drug and use of corticosteroids remain object of debate. **Paola Rodari, Clin Microbiol Infect 2024;30:59**

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Introduction

Blackwater fever (BWF) is a severe febrile syndrome occurring in patients with malaria, characterized by massive intravascular haemolysis and haemoglobinuria with intermittent passage of dark-coloured urine, anaemia, and possible development of acute renal failure. Although some authors attributed the description of BWF as far in time as Hippocrates, most likely BWF started to be observed at the beginning of the 19th century, coincidentally with the more widespread use of quinine [1,2]. Incidence was described around 0.5–2% of malaria cases and mortality around 20–35% [1–3].

At the turn of 19th–20th century, four main theories on the cause of BWF were discussed: (a) intoxication by quinine; (b) malaria itself; (c) consequence of previous malaria infections; and (d) an agent different from malaria [1,4].

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https://doi.org/10.1016/j.cmi.2023.09.009
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That malaria was an essential condition preceding BWF became soon clear [4–8] based on geographical coincidence [5–7,9], and constant demonstration of malaria plasmodia when parasitaemia was assessed before the attack [10,11]. Cases of BWF were also described during the so-called 'malaria therapy', used a century ago to treat neurosyphilis [12]. Although mainly observed with 'malignant tertian' malaria, BWF occurred also with non-falciparum species and was independent from the severity of the disease and level of parasitaemia [4,13–17]. However, malaria alone could not induce BWF, as shown in some now despicable experiments, in which *Plasmodium falciparum* was inoculated in psychiatric patients [18–21].

The physiopathology of BWF was still largely obscure when apparently it virtually disappeared around the Second World War, notably when antimalarial drugs other than quinine, such as mepacrine or chloroquine, became available [2]. This was illustrated by the epidemiology of malaria in military personnel in West Africa [6,7] and South-West Pacific [22], or in the case of the malaria epidemic of 1942 in Greece [3]. However, when, in the 1980s, chloroquine resistance begun to increase and quinine resumed its role in the treatment of severe malaria, cases of BWF re-emerged [23], at least, apparently, until the introduction of artemisinin derivatives at the beginning of 2000s.

The possible role of quinine as a trigger for BWF was recognized since the mid-19th century [8], although still questioned at the beginning of the 20th century [24]. Besides the epidemiological correlation, a constant temporal relation of a few hours between quinine intake for malaria fever and onset of BWF was described [3,15]. Although a direct toxicity of quinine seemed to be excluded as the haemolytic mechanism [4], the erratic occurrence of BWF induced the hypothesis that some sort of acquired 'individual sensibility' to quinine existed [3,4,13,25–27]. The frequent observation that BWF occurred especially in 'partially immune' subjects who took quinine in an erratic manner for malaria prophylaxis or treatment [1,3–5,13,28] opened the hypothesis that haemolysis could have an immune-mediated mechanism, caused by a 'sensitization' of red blood cells by repetitive exposure to malaria + suboptimal quinine, with formation of 'auto-antigens' and thus induction and accumulation over time of 'auto-antibodies' [6,21,29,30]. It was also postulated that BWF could be precipitated by malaria or quinine in subjects with a 'pro-haemolytic' acidemic state, in turn caused by malaria itself or other very heterogeneous environmental factors (e.g. cold weather, heavy work, bad nutrition, and generally 'unhealthy' living habits) [1,2,4,13,29]. Oxidative stress was suggested more recently to contribute to haemolysis [31–35].

Treatment of BWF has been debated and controversial since the observation of the syndrome [14,36]. However, it was early recognized that supportive therapy targeting urine output and anaemia was pivotal [8,13,36,37].

Although seemingly infrequently, physicians still confront with BWF. However, despite its severity, BWF is a neglected condition and management guidelines or simply evidence-based clinical recommendations for its treatment are unavailable [38]. Stimulated by the recent observation of BWF in a child in Italy [39], the aim of this scoping review was to appraise available data on clinical picture and management of BWF and on its physiopathology, which could guide rationally the clinical management of BWF cases.

Materials and methods

Search strategy

The research questions addressed by this scoping review were (a) what are the characteristics (patient type, trigger cause, complications, treatment, outcome) of BWF cases reported in the literature? (b) What is known about the physiopathological mechanisms of BWF?

Protocol registration was not required (www.crd.york.ac.uk/prospero). References were identified through searching the MEDLINE (PubMed), EMBASE, LILACS, Web of Science, and Scopus databases. The first search was conducted on 12 June 2022; the second search on 9 April 2023 (Supplementary File 1). Potentially eligible articles were also identified through the reference list of reviews and relevant publications. No restriction was applied regarding language, publication type, and publication date. Search results were combined and duplicates removed before screening for relevance. The work is presented according to the PRISMA checklist for scoping reviews (Supplementary File 2 and [40]).

Inclusion and exclusion criteria, study selection, data extraction, and data synthesis

BWF was defined as intravascular haemolysis and haemoglobinuria occurring in patients with malaria, resulting in the output of dark urine. BWF cases were considered 'confirmed' if observation of *Plasmodium spp.* parasites was reported and haemoglobinuria occurred within days from the onset of malaria symptoms; 'probable' if *Plasmodium spp.* parasites were not detected but haemoglobinuria occurred within hours/few days from the intake of quinine or another antimalarial drugs.

Papers reporting original data on BWF cases or investigating the physiopathology of BWF were eligible for inclusion. Papers were excluded if (a) full text was not available and/or data could not be extracted from full text or abstract; (b) BWF was not the subject of the paper; (c) duplication; (d) narrative reviews, commentary, or other publication types not reporting original data. No language restriction was applied.

Two authors (PR and FT) reviewed the titles and abstracts, selected the papers potentially eligible, and extracted the data from the full text or abstract of those available. Doubts about eligibility and inclusion of a paper were resolved through discussion. Screening was carried out using the Rayyan online systematic review managing system (www.rayyan.ai). Data were extracted by the two authors using a pre-set Excel file.

For papers reporting cases of BWF, data extracted were (a) study design; (b) definition of case(s) (confirmed/probable); (c) patients' characteristics including age (children/adults) and geographical origin in respect to place of malaria infection (autochthonous or visitor/expatriate); (d) most likely place of malaria infection and place of clinical management of BWF; (e) number of malaria cases, of BWF cases, and species of *Plasmodium* involved; (f) BWF trigger event; (g) G6PDH deficiency or Coombs test positivity; (h) severity of malaria [38] before the onset of BWF; (i) BWF-related complications such as acute renal failure (as reported by the authors) and severe anaemia (<6 g/dL Hb or requiring transfusion); (j) clinical management; and (k) outcome (death/survival). For papers investigating the physiopathology of BWF, study design, and principal findings were extracted.

Data are presented as numbers and percentages, and summary of findings, grouped by paper focus (clinical description or physiopathology). As per scoping review requirements, no meta-analysis and quality assessment of included papers were carried out.

Results

The literature search and papers selection are schematized in Fig. 1. Of the 101 papers finally included, 96 reported clinical cases of BWF and 7 investigated its physiopathology (2 papers were

included in both groups). Full data extracted are available in Supplementary File 3. The year of publication ranged from 1903 to 2023.

Demographic and clinical profile of BWF cases

The 96 papers reporting data on clinical cases of BWF (54 case reports, 34 case cohorts, 5 case-control studies, 2 clinical trials, and 1 review with original data) described 26 112 malaria cases and 1162 BWF cases. Of BWF cases, 576 (49.6%) were confirmed (i.e. occurred in patients with confirmed malaria diagnosis; 2.2% of malaria cases): 542 with *P. falciparum*, 8 *P. vivax*, 6 *P. falciparum* + *P. malariae* mixed infection, 2 *P. falciparum* + *P. vivax* mixed infection, 1 *P. knowlesi*, and 17 undetermined species.

Patients' demographic characteristics are summarized in Fig. 2. The reported origin of infection of the majority ($n = 932$; 80.2%) of BWF cases was sub-Saharan Africa. Of the 981 cases for whom demographic data were available, the majority were children ($n = 733$; 74.7%). Regarding type of case, when considering the 961 (82.7%) cases for which these data were extractable, the majority of BWF cases were observed in autochthonous children ($n = 727$; 75.7%), followed by autochthonous adults ($n = 147$; 15.3%).

Clear information regarding the severity of malaria before the occurrence of BWF was available only for 342 (29.4%) BWF cases. Of these, malaria was indicated as being severe initially in about two-third of cases ($n = 259$; 75.7%), but it must be noticed that in 178 of these cases, severe malaria was a study inclusion criterion.

Presence of acute renal failure was explicitly indicated in at least 561 BWF cases (48.3%) and of severe anaemia in 610 (52.5%); other reported complications described as associated with BWF were respiratory failure in two cases, disseminated intravascular coagulation and acute respiratory distress syndrome in one case, and diffuse petechial haemorrhages in one case.

Clinical management and outcome of BWF cases

Clinical management of the BWF attack was described for at least 794 cases. Until the mid-1950s, support therapy with a variety of means was described, spanning from simple rehydration to single or combined use of alcoholic (e.g. champagne) and non-alcoholic products (including but not limited to coconut water, calomel, *Vitex peduncularis* extract, strychnine, and various 'anti-sera' in the hypothesis that these would replace a 'deficit of anti-haemolytic factors' [41]). Strong importance was given to alkaline purging and alkaline rehydration, with the rationale of 'preventing low pH-induced precipitation of haemoglobin in renal tubules, as well as to fasting and avoiding patient's movement or transport.

Blood transfusion was first recorded in 1928 [42] and dialysis in 1968 [43]. Until 1945, quinine (as well as quinacrine) was kept being used to treat malaria in BWF cases; later, however, change of

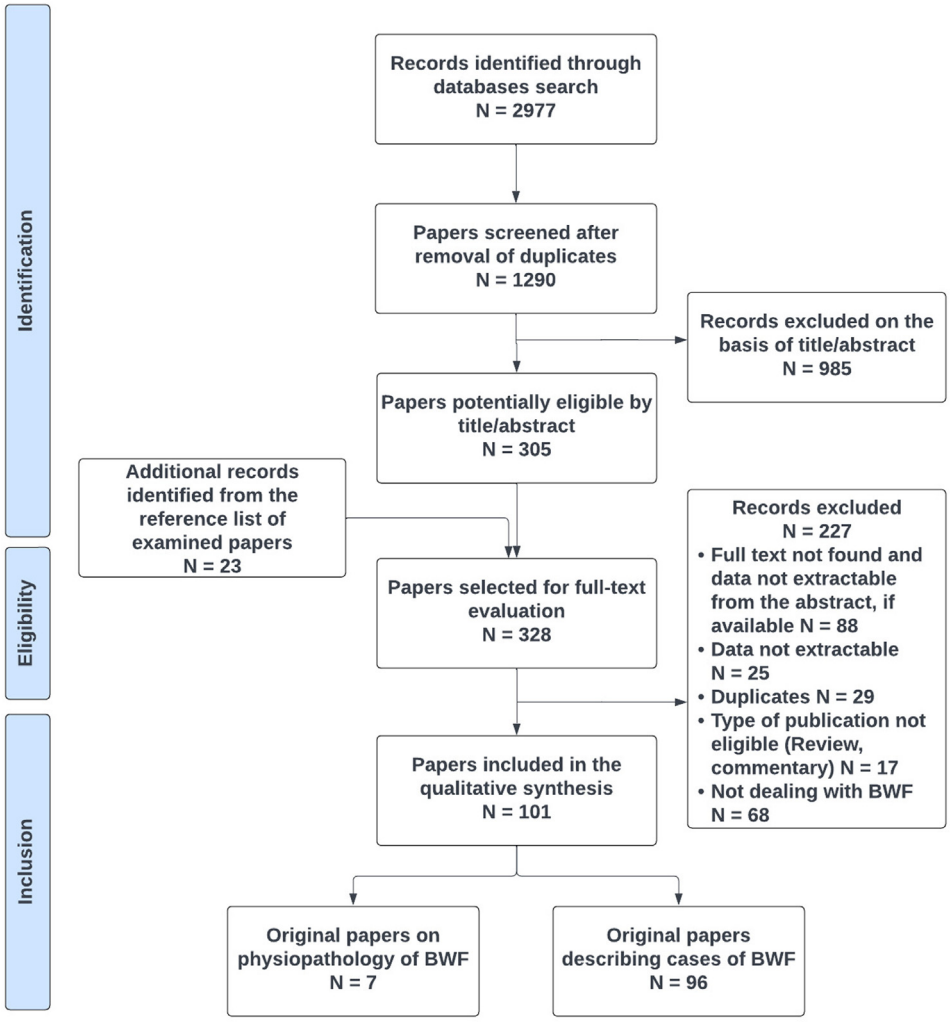


Fig. 1. Paper selection flowchart.

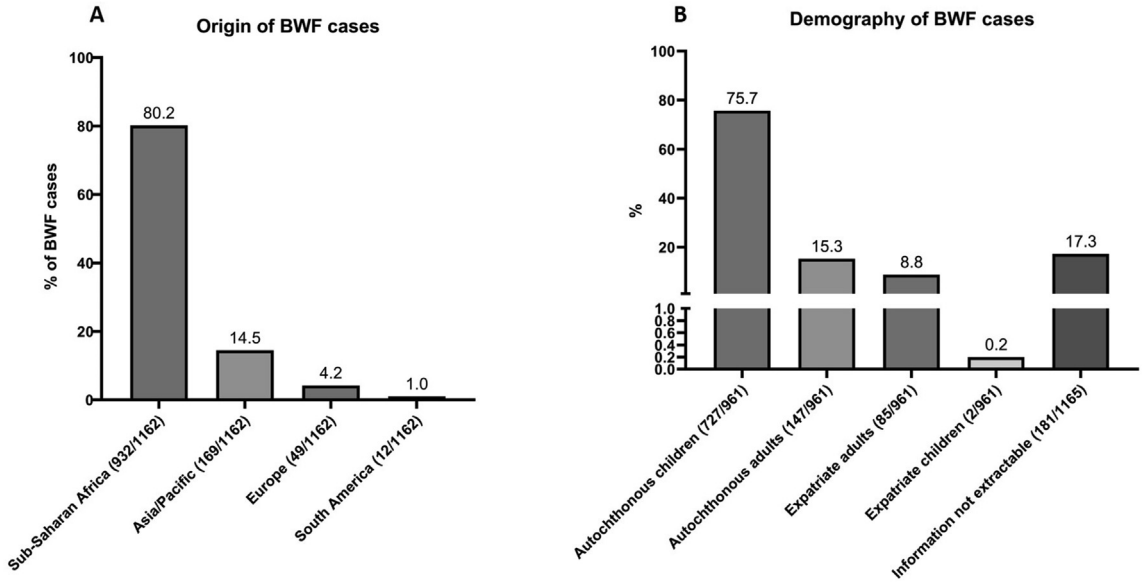


Fig. 2. Origin (a) and demographic characteristics (b) of BWF cases. BWF, blackwater fever.

antimalarial drug in case of BWF onset was implemented, with the first mention of use of artemisinin derivatives to treat malaria in patients with BWF occurring upon quinine intake reported in 2005 [44]. Use of corticosteroids was reported only in 23 cases [39,44–51], the first time in 1953 [45].

Outcome was reported for 535 patients: 438 (81.9%) survived the BWF episode and 97 (18.1%) died.

Triggering causes and physiopathology of BWF

In papers describing clinical cases of BWF, the triggering cause was reported for 552 (47.5%) cases.

In the majority (n = 389; 70.4%), this was identified as the administration of quinine, followed by artemisinins (n = 82; 14.9%), and halofantrine (n = 16; 2.9%). It must be noticed, however, that two large randomized controlled AQUAMAT and SEAQUAMAT trials carried out in African children and all-age Asian patients [52,53], comparing intravenous artesunate and quinine for the treatment of severe falciparum malaria, did not find statistically significant difference in the occurrence of BWF after administration of the two drugs. Other drugs reported as causing single or a few BWF cases were mefloquine, mepacrine, proguanil, chloroquine, lumefantrine, primaquine, sulfadoxine-pyrimethamine, and amodiaquine, cumulatively reported to having being the triggering cause in 46 (8.3%) cases. BWF cases reported as having occurred without any apparent triggering stimulus were a minority (n = 19; 3.4%). Results are summarized in Fig. 3.

Only seven studies addressing the physiopathology of BWF, published between 1909 and 2018, were available for data extraction and review [32,54–59]. Three studies carried out in the 1900s investigated the ability of quinine itself to cause haemolysis and sensitize red blood cells to the haemolytic effect of other causes [54–56]. Overall, they concluded that quinine alone was able to induce haemolysis only at concentrations not reached *in vivo* in clinical practice. Although Grewal [55] found that quinine could increase the susceptibility of red blood cells to other haemolytic substances (e.g. saponin), Bennett and Desforges [56] did not find increased susceptibility to haemolysis because of G6PDH deficiency.

Furthermore, the two case-control studies investigating differences in G6PDH deficit between patients with BWF and controls (patients with malaria without BWF) found no significant difference in this trait between groups [57,59]. Bodi et al. [58] in a case-control study carried out in Congo in children with falciparum malaria and presenting (n = 43) or not (n = 86) BWF, found that BWF was associated with quinine intake (OR 47.31). Furthermore, anti-malaria IgG1 were significantly higher in BWF cases than controls, suggesting a possible role of these antibodies in haemolysis. Marcsisin et al. [32] found that products of cytochrome P450 (CYP)-mediated quinine metabolism generated dose-dependent oxidative stress in

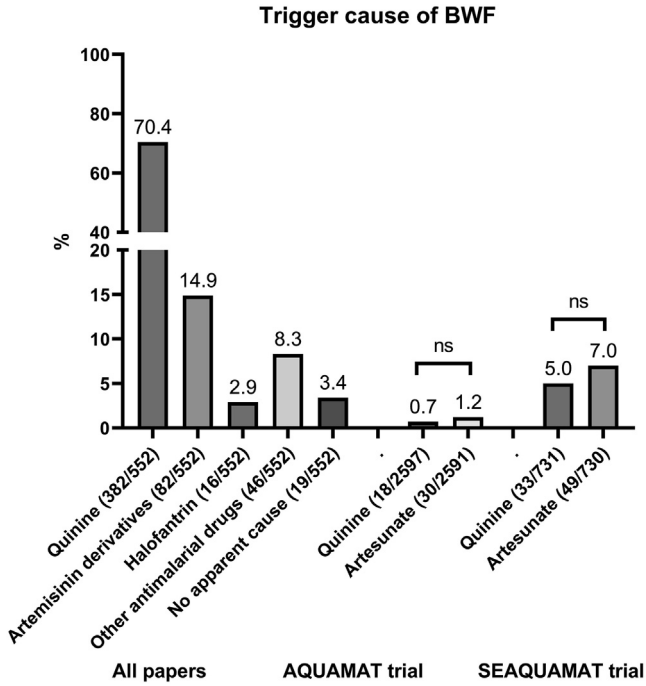


Fig. 3. Reported trigger of BWF cases. AQUAMAT trial [53]; SEAQUAMAT trial [52]. For these two trials, BWF cases are reported having occurred after the study enrolment and start of study treatment; BWF cases observed at enrolment were not included in the analysis because it was not clear if and in what proportion a triggering cause was present. BWF, blackwater fever; ns, not significant difference.

human erythrocytes *in vitro*, suggesting that this could become important in individuals with high oxidative stress background, such as those infected with malaria or with G6PDH deficiency. Among case-reports and case-cohorts, deficit of G6PDH was evaluated in 72 patients and present in only 5 (6.9%) cases; the Coombs test was reported only for 21 cases and was positive in 13 (61.9%).

Discussion

This scoping review aimed to appraise available data on clinical picture, management, and physiopathology of BWF, which could guide rationally its clinical management.

In 1936, Krishnan [11] wrote 'the aetiology of blackwater fever is one of the unsolved puzzles in tropical medicine'. Again, in 1951 an anonymous author wrote 'the putting forward of theories about the causation of blackwater fever is a function inversely proportional to knowledge of the established facts, and the ordinary doctor may well become lost in a fog of surmise' [8]. These statements are still valid today.

With all caution needed because of the high percentage (113/214; 52.8%) of potentially eligible papers that were not accessible for data extraction, and to the difficulty in extracting data from very old papers, a first comment can be done regarding BWF patients' characteristics. Indeed, whereas the historical perception was that the patients with typical BWF were semi-immune expatriates; the majority of BWF cases reported in the available published studies were autochthonous children (75.7%), followed by autochthonous adults (15.3%). These results could still be compatible with the hypothesis that lack of complete by-standing immunity could be involved in the pathogenesis of BWF, because children in endemic areas may fulfil this characteristic. Furthermore, the 18 cases of BWF observed in autochthonous adults and published before 1980 were largely from Asia or Europe (e.g. Greece), where malaria was present but not holoendemic (i.e. not leading to by-standing immunity). On the contrary, those from sub-Saharan Africa were reported after this date, when it could be speculated that malaria control and prevention interventions could have influenced the level of immunity even of autochthonous adults.

The interpretation of these results in terms of most affected patients' groups and possible physiopathologic mechanism is, however, difficult. On the one hand, because of the often cumulative description of cases, it was not possible to univocally attribute each case to year of occurrence. In addition, a reporting bias could not be excluded, deriving from the more frequent and careful observation and description of BWF cases when occurring in expatriates (e.g. military personnel) because of their better access to medical attention compared with autochthonous people. Furthermore, more than half of BWF cases that could be retrieved in this review were 'probable'; therefore, other causes of passing of 'dark urine' than haemoglobinuria could have been possible [60,61], and, even when haemoglobinuria was actually assessed, other causes of intravascular haemolysis could have been present.

The autoimmune mechanism of haemolysis in BWF still lacks confirmation. The possible involvement of an autoantigen-autoantibody pathogenic mechanism [6,21,29,30] was investigated in the mid-1990s by Foy and his group. In narratively described experiments of blood transfer between BWF, malaria-positive or malaria-negative individuals, Foy supported the 'circulating haemolysin' theory by observing that transfused healthy red blood cells were haemolysed during BWF attacks [16,20,62], whereas plasma transfused from a patient having BWF attack did not induce BWF, possibly because of the too small quantity of plasma transferred [16,18,19]. Bodi et al. [58] found that anti-malaria IgG1 were significantly higher in BWF cases than controls, suggesting a possible pathogenic role of these antibodies in haemolysis; and among case reports, Coombs test was reported as positive in 61.9% of the few cases where the test was performed. However, no other study specifically investigated this aspect.

Also, the role of oxidative stress, postulated as a possible individual factor making erythrocytes more susceptible to haemolysis, still lacks evidence. The two case-control studies investigating differences in G6PDH deficit between malaria patients with and without BWF found no significant difference in this trait [57,59], and the haemolytic effect of quinine-induced oxidative stress on susceptible individuals, such as those with G6PDH deficiency [32], is still speculative.

Even the predominant association of BWF with quinine intake seems to be questionable in the light of the two clinical trials comparing artesunate and quinine for the treatment of falciparum malaria [52,53], which did not find statistically significant difference in the occurrence of BWF after administration of the two drugs. This discrepancy between results from clinical reports and trials could be because of an under-notification and/or misdiagnosis of BWF after treatment with artemisinin drugs.

A direct consequence of the uncertainty regarding the physiopathology of BWF is the lack of robust rationale to guide its optimal clinical management. In 1928, Low et al. [42] commented 'An experience of 28 years, both abroad and at home, leads me to the conclusion that, apart from careful nursing and attention, there is no specific treatment for this disease'. Since then, very little has changed in the knowledge about how to approach this severe condition.

The large time span of the examined papers, the extreme heterogeneity (and often 'narrative' description) of the clinical pictures and management described, the largely cumulative reporting of data in case series, and the lack of clinical trials addressing specifically the treatment of BWF made a synthesis of therapeutic modalities very difficult and did not allow a sound evaluation of the association between clinical approach and outcome. Furthermore, the lack of rigorous studies addressing the possible physiopathology of BWF does not allow attempting to suggest a rationale (let alone evidence-based) treatment strategy other than the obvious supportive action on severe anaemia and renal insufficiency, when present. The use of corticosteroids is particularly controversial. Its use has been advocated, based on observation of good outcome and apparent prompt 'clearing' of the urine after its administration [39,45,46,63], and on biological rationale in the hypothesis that the mechanism of BWF was immune mediated [39,44]. However, the WHO discourages the use of corticosteroids in malaria [38] and an immune-mediated mechanism of BWF is yet to be proven. In any case, the small number of cases where corticosteroids were included in the clinical management seems indicating that this approach might at least not be harmful (alive outcome in 22/23; 95.7%).

In conclusion, the physiopathology and optimal treatment of BWF remain similarly unknown as they were over a century ago. Only well-conducted prospective studies could attempt answering outstanding questions, but unfortunately, they are extremely difficult to perform because of the low frequency of BWF and its clinical heterogeneity. Currently the best clinical, although empirical, approach seems supporting treatment of severe anaemia and renal insufficiency, if present, whereas change of antimalarial drug and use of corticosteroids remain the object of debate (Table 1).

Table 1
Schematic outline of current treatment approach to blackwater fever

Clinical management of BWF	
Knowns: syndromic approach	Unknowns: BWF-specific approach (possible biological plausibility)
Transfusion if clinically indicated	Stop and change apparent trigger drug if alternatives are available
Maintain diuresis and correct acidosis if present	Corticosteroid treatment
Acute renal replacement therapy if acute renal failure	

BWF, blackwater fever.

Author contributions

FG conceived the study; PR, FT, VAF, and DB designed the study; VAF performed the literature search; PR and FT extracted and analysed the data; PR, FT, DB, and FG interpreted the data; PR and FT drafted the manuscript; all authors edited and approved the final version of the manuscript.

Transparency declaration

The authors declare that they have no conflicts of interest.

This work was supported by the Italian Ministry of Health 'Fondi Ricerca Corrente' to IRCCS Sacro Cuore Don Calabria Hospital – Linea 2.

Data availability

Raw extracted data are available in Supplementary File 3.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.09.009.

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