

Haemato-Biochemical Alterations in Dogs Naturally Infected With *Babesia gibsoni*

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ABSTRACT

Babesia gibsoni is a small intraerythrocytic parasite of dogs, and infected animals are usually described as anaemic, thrombocytopenic and biochemically disturbed. This narrative review asks how consistent those descriptions really are, and how much a clinician or researcher can infer from a blood count and a serum profile alone. It draws on published work on the biology and epidemiology of canine babesiosis, on the pathophysiology of haemolysis, inflammation and organ injury, and on laboratory methodology, including reference intervals and sample handling, and it reports no new patient data. The recurring picture is of red cell destruction with a variable regenerative response, a fall in platelets, shifting white cell counts, raised globulins with lower albumin, and changes in liver and kidney markers that track the severity and duration of disease. Yet none of these findings is specific. Their size depends on parasitaemia, chronicity, immune-mediated components, co-infection, breed, and the reference interval used to call a value abnormal. Studies of the large and small species of *Babesia* are often blended, although they behave differently. The review concludes that haemato-biochemical patterns are useful as a supporting pattern but not as proof of infection, and it outlines the reporting standards that would make future case series comparable.

Keywords: *Babesia gibsoni*; Canine babesiosis; Haematology; Serum biochemistry; Reference intervals; Haemolytic anaemia; Narrative review

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1. Introduction

Few diagnoses in small-animal practice are suggested as often by a laboratory printout as canine babesiosis. A dog presents with lethargy, pale gums and dark urine, the blood count shows anaemia and a low platelet count, and the clinician reaches for a smear or a molecular test to confirm what the numbers already hint at [1, 2]. *Babesia gibsoni*, a small piroplasm that lives inside red cells, is one of the organisms behind this picture, and it has become a recognised cause of illness in

dogs on several continents [3, 4].

The usual textbook account lists the abnormalities: a falling red cell mass, thrombocytopenia, a disturbed white cell count, raised globulins, lowered albumin, and signs of strain on liver and kidney [5, 6]. That account is useful, and it is also incomplete. The same changes occur in other tick-borne infections, in immune-mediated disease and in plain haemorrhage [7, 8], and their size in any one dog depends on how long the parasite has been present, how many red cells it has reached,

and how the dog's own immune system has responded [9]. A laboratory finding is therefore evidence about a process, not a label for an organism.

This review asks how consistent the haemato-biochemical alterations of *B. gibsoni* infection really are, what produces them, and how far they can be trusted when a clinician or a researcher has only a blood count and a serum profile to go on. It sets out the biology that explains the changes, summarises the findings reported in the literature on canine babesiosis, and spends time on the complications that make comparison between studies difficult: the non-specific nature of the changes, the effect of parasitaemia, chronicity and co-infection, and the habit of calling a value abnormal against a reference interval that may not fit the dogs in question. The aim is a fair account of what is known and what is merely repeated.

The article is a narrative review. It draws on published work on the biology and epidemiology of canine babesiosis, on the pathophysiology of haemolysis and inflammation, and on laboratory methodology, and it deliberately reports no new patient data. Where the literature on *B. gibsoni* specifically is thin, we say so and describe what a convincing study would need to contain, instead of quoting figures we have not been able to check against their sources.

2. Literature Review

2.1 The Parasite and Its Hosts

Babesia species are tick-transmitted protozoa that multiply inside the red cells of vertebrate hosts, and the genus has a long history in veterinary science [10]. Much of its success rests on a long adaptation to particular hosts and vectors, which also explains why closely related species can differ so much in the disease they cause [11]. In dogs, the older division into large and small forms is still the most practical: the large forms, such as *B. canis* and *B. rossi*, are the subject of most of the clinical literature, while the small forms include *B. gibsoni* and species described later [5, 12].

B. gibsoni was first thought of as an Asian parasite, but the organism is now known from other regions, and its molecular detection has made it possible to separate it from other small *Babesia* that look alike under the microscope [3, 12]. The route of infection is not only through ticks. In some settings the infection has been linked to dog bites and to fighting, and a breed association with certain terriers has been reported in surveys [4, 13]. Transmission through

transfused blood has also been documented [14], and blood collected from dogs confiscated from fighting operations has yielded the parasite [15]. These routes matter for laboratory interpretation because they imply that the infected population is not a random sample of dogs: it is enriched for particular breeds, ages and living conditions, all of which have their own baseline blood values.

A comparative point deserves mention. Human babesiosis, caused by other species, shows a similar spread from silent infection to life-threatening haemolysis, and the same dependence on the host's immune competence [16]. The lesson carried across species is that the organism alone does not fix the outcome. In dogs, asymptomatic carriage has been documented in survey work [17], which means that a dog can be infected and yet have a blood profile within the usual limits.

2.2 Clinical Picture and Why It Varies

Reviews of canine babesiosis describe a range of disease from mild and subclinical to severe and complicated [1, 18]. The classical presentation includes fever, lethargy, pallor and discoloured urine, but clinical series show that the proportion of dogs with each sign differs between regions and between species of parasite [19]. A review of the European situation made the point that the name covers more than one disease, with different species behaving differently in the dog [20].

The severe end of the spectrum has been studied most closely in the large forms. The South African experience with *B. rossi*, for example, documented complications involving the kidney, liver, lungs and brain that were not simply a consequence of anaemia [21], and work on *B. canis* has described a systemic inflammatory picture resembling sepsis in some dogs [22]. It would be unwise to carry these findings straight across to a small *Babesia* without evidence. Where reports on *B. gibsoni* describe similar organ involvement, they should be read as a hypothesis that the organism behaves like its larger relatives, not as a settled equivalence.

Chronicity adds another layer. Small *Babesia* infections have a reputation for persisting after the acute illness has settled, and treatment does not always eliminate the parasite [23]. A dog sampled during a relapse or from a long-standing infection may therefore present a quieter, more inflammatory profile than one in the first week of illness, and a case series that mixes both stages averages two different pictures into one. A dog sampled on the first day of illness behaves

differently on paper from one sampled after weeks of untreated infection.

2.3 How Red Cell Changes Arise

The red cell is both the home of the parasite and its victim. Multiplication inside the cell damages it, and cells carrying the parasite or altered by the immune response are removed more quickly than normal [1, 2]. In addition, many dogs with babesiosis develop antibodies directed against their own red cells, which adds destruction beyond what the parasite itself causes [8, 9]. The consequence is an anaemia that can fall faster than the bone marrow can respond, so the early sample may show a low red cell mass with little sign of regeneration, and a later one a vigorous regenerative response [6].

The immune-mediated component is the most contentious part of this story. The consensus statement on the diagnosis of immune-mediated haemolytic anaemia stresses that infectious disease should be excluded before the process is called primary [8], and the older treatment literature on idiopathic disease shows how much management and prognosis depend on that distinction [24]. For a clinician faced with a positive antiglobulin test in a dog from an endemic area, the sensible reading is that infection and immune destruction can coexist, not that one rules out the other. For a reviewer, it means that studies reporting an immune component without saying how infection was excluded or confirmed are hard to interpret.

2.4 Platelets, White Cells and Inflammation

A low platelet count is among the most consistently reported findings in canine babesiosis and is often the first abnormality noticed [1, 25]. The causes are probably several, including consumption, sequestration and immune destruction, and a low count is common to other tick-borne infections, notably ehrlichiosis [7]. Thrombocytopenia is therefore a useful prompt and a poor discriminator.

White cell findings are less consistent. Reports describe low, normal and raised counts, and the direction depends on stage, severity and the presence of other disease [18, 19]. Part of the explanation is that babesiosis is an inflammatory disease as well as a haemolytic one. Excessive pro-inflammatory cytokine concentrations have been reported in dogs with the virulent form of disease caused by a large *Babesia* [26], and the immunopathology of canine vector-borne infections more generally involves activation of both innate and adaptive responses [9].

Inflammation changes the leukogram in ways that a stress response, a co-infection or a corticosteroid course can also change, which is why the white cell count is the weakest part of the laboratory pattern (Table 1).

Table 1. Haematological findings commonly described in canine *Babesia gibsoni* infection.

Parameter	Commonly described change	Main caution
Red cell mass	Fall, often marked [1, 2]	Early samples may look normal
Regeneration	Variable; may lag behind loss [6]	Timing of the sample matters
Platelets	Reduced [1, 25]	Shared with other tick-borne disease [7]
Total white cells	Low, normal or raised [18]	Co-infection and stress shift the count
Parasite on smear	Small rings, easily missed [3]	Low parasitaemia needs molecular testing
Antiglobulin test	Sometimes positive [8]	Positive result does not exclude infection

Note: Qualitative summary of directions described in the cited literature. No values are given because magnitudes depend on stage, parasitaemia and laboratory.

2.5 Serum Biochemistry

Serum chemistry in canine babesiosis reflects four processes at once: haemolysis, inflammation, reduced oxygen delivery and, in some dogs, direct organ injury. Haemolysis raises bilirubin and, if hepatic uptake is limited, alters the balance between its forms [1, 2]. Chronic antigenic stimulation tends to raise globulins [9], while albumin often falls as a negative acute-phase protein and through losses and altered distribution [27, 28]. A proteomic study of dogs naturally infected with *B. canis* found changes in a range of serum proteins, which supports the idea that the acute-phase response is a prominent feature of the disease [29].

Liver enzymes are commonly raised to a mild or moderate degree in reports, and the usual explanation is hypoxia and inflammation rather than primary hepatic disease [5, 6]. Urea and creatinine are more variable. In severe cases, particularly in large *Babesia* infections, reduced renal perfusion and pigment injury can produce azotaemia [21], yet many dogs show no such change. Table 2 summarises the directions commonly described and the explanations offered. It should be read as a guide to what is often seen, not as a list of what must be seen. One raised value can have several causes at once, so serial samples say more than a single one.

Table 2. Serum biochemical findings and their usual explanations.

Analyte	Commonly described change	Likely contributor
Total protein and globulins	Globulins raised [9]	Chronic antigenic stimulation
Albumin	Lowered [27, 28]	Negative acute-phase response, losses
Bilirubin	Raised [1]	Haemolysis, hepatic involvement
Liver enzymes	Mild to moderate rise [5]	Hypoxia, inflammation
Urea and creatinine	Raised in severe cases [21]	Reduced perfusion, pigment injury
Acute-phase proteins	Raised [29]	Systemic inflammation

Note: Directions are those discussed in the cited reviews and case series; they are not attributed to any single study.

2.6 Reference Intervals and Sample Handling

A value is abnormal only against something. Reference intervals are statistical constructs, derived from a defined group of healthy animals with a defined method on a defined analyser, and guidance on how they should be established stresses that they transfer poorly between laboratories and populations [30, 31]. For haematology the issue is acute. Sighthounds, for instance, differ from other dogs in several red cell and platelet values, and a count that would be called abnormal in one breed can be ordinary in another [32]. A study that compares infected dogs of mixed breed with an interval taken from the analyser manufacturer may therefore label some dogs wrongly, in either direction.

Sample handling matters as well. Haemolysis in the tube, whether caused by the disease or by collection, interferes with a number of routine chemistry measurements [33], and this is awkward in a disease that is itself haemolytic. The practical consequence is that the serum of a dog with babesiosis may be partly spoiled by the same process under study, and a careful report states how the sample was collected, stored and checked for haemolysis. Few do. A pattern that disappears when the reference interval is changed is not a pattern a laboratory would defend.

3. Materials and Methods

3.1 Scope and Question

The review asks a single question in two parts: what haematological and serum biochemical alterations are reported in dogs infected with *Babesia gibsoni*, and how far can those alterations be taken as characteristic of the infection? The

question was divided into the sub-questions that a laboratory study would have to answer: how infection was confirmed, how the dogs were chosen, which reference intervals were used, how co-infection and immune-mediated disease were handled, and how the sample was collected and analysed. None of these steps is difficult, but each one is easy to skip.

3.2 Literature Assembly

The review draws on peer-reviewed work in four areas: the biology and epidemiology of canine *Babesia*; the clinical pathology of canine babesiosis and related tick-borne infections; the immunopathology of haemolysis and the acute-phase response; and the methodology of reference intervals, sample handling and evidence synthesis. Sources were chosen for relevance, citation in the field and the clarity of their methods. Studies of large *Babesia* species are used for what they teach about mechanism and complications, not as evidence of effects in infection with *B. gibsoni*.

We did not run a formal systematic search and we do not claim one. This is a narrative synthesis, and the choice of sources reflects the authors' judgement. Narrative reviews have a legitimate place in a field where the question is one of interpretation as much as of counting [34], but they are open to selection bias, and quality tools exist to help readers judge them [35]. The practical consequence is that the review is a better guide to what a good study should contain than to the exact size of any reported change, and it avoids quoting figures from individual studies that could not be checked against the primary papers for this article.

3.3 Appraisal Framework

To judge how far a report can be trusted, we used a short framework with four questions. Was infection confirmed by a method able to separate *B. gibsoni* from other small *Babesia* [3, 12]? Was co-infection looked for, given how often tick-borne pathogens occur together [36]? Were abnormal values defined against a suitable reference interval [30, 32]? And were the numbers large enough, and the uncertainty reported clearly enough, to support the claim being made [37, 38]? Table 3 lists the sources of variation we looked for. Where a report was silent on an item, we counted it as unreported instead of assuming it had been handled well.

Table 3. Sources of variation to record when reporting haemato-biochemical findings.

Source of variation	Effect on interpretation	What to report
Reference interval	Same value may be normal or abnormal [30, 31]	Source, population, method
Breed	Sighthound values differ [32]	Breed and age
Co-infection	Overlapping changes [36]	Tests used to exclude it
Immune-mediated component	Adds haemolysis [8, 24]	Antiglobulin result
Sample handling	Haemolysis alters chemistry [33]	Collection and storage
Small series	Unstable estimates [37, 38]	Numbers, intervals

Note: Items summarise the methodological literature cited in the text and do not describe any single study.

4. Results

4.1 From Parasite to Laboratory Finding

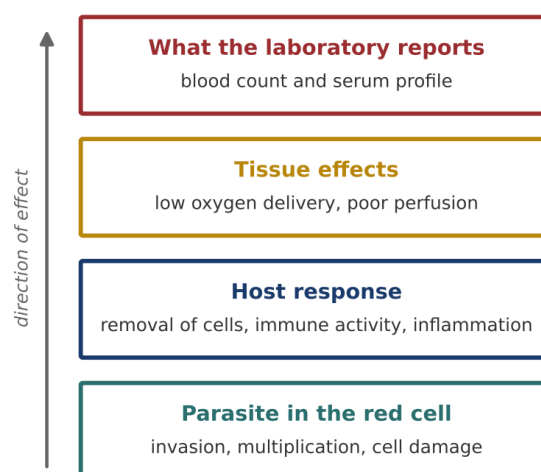
Read together, the mechanistic literature describes a chain of events that begins with the parasite in the red cell and ends with the numbers on the report (Figure 1). Parasite multiplication and immune removal reduce the red cell mass; the resulting anaemia lowers oxygen delivery; inflammation reshapes the protein profile; and strain on perfusion and pigment load touches the liver and kidney in the more severe cases [1, 6, 21]. Each link has its own modifiers, and the laboratory sees only the end of the chain.

The chain explains why the same infection can produce different reports. A dog in the early haemolytic phase will have a low red cell count and little else wrong; one in a prolonged infection may have raised globulins and low albumin with a less dramatic red cell picture [9, 27]; and one with a large immune-mediated component will show the features of that process in addition [8, 24]. Averaging these into one set of group means conceals the very variation a clinician needs to understand. This is why the same infection can look dramatic in one clinic and mild in the next.

4.2 Which Alterations Recur

Across the clinical and review literature on canine babesiosis, some directions of change recur often enough to be treated as the usual pattern (Figure 2). Red cell mass and platelets are usually lower, globulins and bilirubin usually higher, albumin usually lower, and liver enzymes mildly raised [1, 2, 5]. White cell counts and renal markers are the most variable. The figure is a qualitative matrix of the directions described, not a plot of data, and it

deliberately carries no magnitudes.



Modifiers at every level: parasite load, duration, co-infection, breed

Figure 1. Chain from parasite invasion to laboratory findings (schematic, not data).

What matters for interpretation is how little of this pattern is specific. Thrombocytopenia and anaemia are shared with ehrlichiosis and other infections [7, 36]; hypoalbuminaemia and a raised globulin fraction are shared with many chronic inflammatory conditions [27, 28]; and mild liver enzyme rises accompany almost any systemic illness. A pattern of several abnormalities occurring together, in a dog from an endemic area, with a compatible history, raises suspicion. It does not prove anything. Read this way, a normal value early in the illness is not evidence that the parasite is absent.

	Usually lower	Variable	Usually higher
Red cell mass	●	•	•
Platelets	●	•	•
White cell count	•	●	•
Globulins	•	•	●
Albumin	●	•	•
Bilirubin	•	•	●
Liver enzymes	•	•	●
Urea / creatinine	•	●	•

Qualitative directions only; schematic, not data

Figure 2. Qualitative matrix of changes described in the literature (schematic, not data).

4.3 Parasitaemia, Chronicity and Co-infection

Three factors, more than any other, determine how a given dog will look on paper. The first is parasitaemia. Small *Babesia* can be scarce on a smear even in a sick dog, which is one reason

molecular methods were developed for their detection [3], and low numbers of organisms are compatible with substantial anaemia when the immune-mediated component is large [8]. A study that classifies dogs as infected by smear alone will therefore miss some, and one that relates blood values to parasitaemia needs a method capable of measuring it. Timing interacts with all of this. Parasite numbers in the circulation may fluctuate, so a dog sampled at a low point can look more reassuring than its disease warrants, and a transfusion or antiprotozoal treatment given before sampling can change both the smear and the count [14, 23]. Reports seldom say when in the illness the blood was drawn, or what had been given beforehand.

The second is chronicity. Experience with treatment shows that clearing the parasite is difficult in some dogs and relapse is recognised [23, 39], so dogs in a series may be at very different points in the disease. Follow-up of blood values after treatment is a common outcome measure, yet the recovery of the count depends on whether the underlying cause was the parasite, the antibody, or both. The third is co-infection. Dogs exposed to ticks are often exposed to several pathogens, and kennel studies have documented infection with more than one agent in the same animals [36]. A thrombocytopenia attributed to *Babesia* may owe something to *Ehrlichia* [7], and without testing for both the attribution is a guess.

Put plainly, the haematology of *B. gibsoni* is the haematology of a particular dog on a particular day. Averages from a group of mixed stage and mixed co-infection status describe nobody in the group. That is a modest claim, and it is the one the evidence will currently bear.

4.4 Quality of the Evidence

Reports on haemato-biochemical changes in babesiosis commonly share a set of limitations (Table 3). Case series are often small, and small studies in any field produce unstable estimates and tend to overstate effects when they reach significance [37, 40]. Dogs from the same kennel or household are not independent observations, and treating them as if they were gives a false sense of precision [38]. These problems are shared with much of clinical veterinary research, and babesiosis is not special in having them; they matter here because the argument for a characteristic profile rests largely on this kind of report.

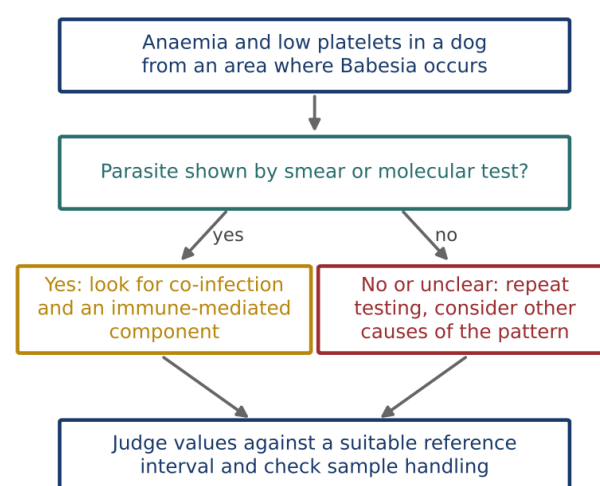
Statistical practice compounds the problem. Results reported only as significant or not

significant discard the size of the difference, which is what a clinician needs, and a p-value is not the probability that an effect is real [41, 42]. A non-significant result in a small series is also not proof of no difference [43]. Where many analytes are compared and only those that reach significance are discussed, the chance of a spurious finding rises.

A more specific weakness is the choice of comparator. Some studies compare infected dogs with a control group that differs in age, breed or living conditions, and others compare with a reference interval supplied by the laboratory. Both can generate differences that have nothing to do with the parasite [31, 32]. Figure 3 sketches a reasoning path for reading an abnormal profile in a suspected case, with the point at which these issues enter.

4.5 Reading a Claim of Characteristic Change

A reader meeting a statement that *B. gibsoni* infection causes a particular laboratory change can ask a short sequence of questions. How was infection confirmed, and could the method tell small *Babesia* apart [3, 12]? What were the dogs, in breed and age, and against what were they compared [30, 32]? Was co-infection excluded [7, 36]? And how was the sample handled [33]? A report that answers all four is rare, and one that answers none should be read as an observation, not as evidence of a characteristic effect.



Schematic reasoning aid, not a validated protocol

Figure 3. Decision sketch for reading an abnormal blood profile in a suspected case (schematic).

Studies on different *Babesia* species are often discussed together, and statements made about the large forms are quoted as if they applied to the

small ones. The European review made the point that the disease differs by species [20], and prognostic marker work in *B. canis* infection shows how much clinical pathology depends on the setting in which it was studied [25]. For *B. gibsoni*, where reports are fewer and often smaller, between-study variation cannot yet be separated from chance, and the honest summary is a range of plausible findings instead of a single profile.

5. Discussion

5.1 Interpretation and Practical Reading

The main finding of this review is a conditional one. Anaemia, thrombocytopenia, raised globulins, lowered albumin and mild liver enzyme rises are the usual accompaniments of *B. gibsoni* infection, and a clinician is right to treat a combination of them in an endemic area as a reason to test [1, 18]. But the same combination is produced by other diseases, its size depends on stage and parasitaemia, and a normal profile does not exclude infection. The question for a clinician is therefore not whether the profile fits but what else could produce it. Nothing in this reading argues against using the blood profile; it argues for reading it in context.

The second conditional concerns the immune system. Since a part of the red cell loss is probably immune-mediated, the laboratory picture combines two processes, and the proportion of each is rarely known [8, 24]. This matters for treatment decisions and for research. A study of laboratory change that does not say whether the immune component was assessed cannot be used to describe the parasite's direct effects.

A third point concerns comparability. Unless studies report the reference interval, the breed, the sample handling and the confirmation method, their findings cannot be pooled, however similar their abstracts sound [30, 31]. This is not a fault of any one author. It reflects the lack of a shared reporting standard, and it is the most fixable weakness in the literature.

Three findings would change this reading. A well-designed study showing a consistent and specific laboratory signature in confirmed *B. gibsoni* infection, against a matched uninfected comparison group, would justify greater diagnostic weight for the profile. Evidence that the immune-mediated share of red cell loss is small in this infection would shift attention towards the parasite itself. And evidence that co-infection is the main driver of some of the biochemical findings would require those findings to be removed from the standard description of the

disease.

5.2 Limitations

This is a narrative review and shares the limitations of that form. The selection of sources reflects judgement, no formal search or quality scoring was done, and the review does not quote numerical results from individual studies, because these could not be checked against the primary reports for this article. A reader who needs a magnitude should consult the original studies directly, applying the appraisal questions above, or wait for a formal systematic review, which methods exist to support [34, 35].

The review also draws heavily on evidence from large *Babesia* species and from other tick-borne infections, which are imperfect proxies for *B. gibsoni*. Mechanistic studies describe how haemolysis and inflammation work in the dog, and we have used them to frame hypotheses, not to assert that every finding transfers. The conclusions should be read in that light. Reviews of this kind are more useful when they say where the evidence stops than when they smooth it over.

5.3 Implications for Study Design

A study that could settle the question would confirm infection by a molecular method capable of identifying the species [3], test for the common co-infecting pathogens [7, 36], record whether an immune component was sought [8], and describe the dogs by breed, age and origin. It would use a reference interval suited to the population and the analyser, or establish one by an accepted method [30, 31], and it would report how samples were collected and checked for haemolysis [33].

On the analytical side, the study would report estimates with their uncertainty instead of a list of significant results [41, 42], would treat dogs from shared households with appropriate care [38], and would follow animals through treatment to show how the profile recovers. These requirements are demanding, but they distinguish a result that another laboratory can use from one that only supports a hunch.

5.4 Directions for Future Work

Three needs stand out. First, a formal systematic review with a transparent search of studies on *B. gibsoni* specifically, ideally separating dogs by stage and co-infection status. Second, well-described case series, or better, prospective cohorts, with the design features above. Third, work on the acute-phase and cytokine response in small *Babesia* infections, where most of the detailed work has concerned the large species [26,

29].

5.5 Practical Reading for Clinicians and Laboratories

For a clinician, the sensible position is neither to dismiss the blood profile nor to overrate it. A suspected case should be confirmed by a method that can detect low parasite numbers [3], and the haematology and chemistry should be repeated as the illness evolves, because a single sample captures a single moment [6, 25]. Where an antiglobulin test is positive, the result should be recorded alongside the infection status instead of replacing it [8].

For a laboratory, the advice is to state the reference interval used and its source, to flag haemolysed samples, and to keep records of breed with results [30, 32, 33]. Such records cost little at the time and make later comparison between centres possible. They are what turn a collection of case reports into a body of evidence.

6. Conclusion

The haemato-biochemical alterations of *B. gibsoni* infection in dogs follow a recognisable pattern, with red cell destruction, low platelets, disturbed white cell counts, raised globulins, lowered albumin and mild changes in liver and kidney markers. The evidence, as we can responsibly summarise it, shows that the pattern is a supporting clue and not a signature: it is shared with other diseases, it varies with parasitaemia, chronicity, immune-mediated destruction and co-infection, and it is judged against reference intervals that do not always fit the dogs in question. Readers should treat claims of a characteristic profile with caution until they meet the reporting standards outlined here.

For the practitioner the message is practical rather than discouraging. Use the blood profile as a prompt, confirm the organism, look for co-infection, and repeat the tests as the illness changes. For the researcher, the opportunity is a set of carefully described studies of confirmed *B. gibsoni* infection that report enough about the dogs, the methods and the reference values to be compared and combined.

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9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

S.S. conceived the review and wrote the sections on parasite biology and clinical presentation. W.B. wrote the sections on haemolysis, immune mechanisms and serum biochemistry. C.T. wrote the sections on reference intervals, methodology and study design. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No animals were used and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

13. References

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