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Letter to the Editor

The Centers for Disease Control and Prevention and State Health Departments should include Blood-Type Variables in their Babesiosis Case Reports

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Babesiosis is a growing threat in the United States (US) – likely due to climate change [1]. Babesiosis is an infectious disease caused by *Babesia* parasites, which invade red blood cells (RBCs). [2] Parasitized RBCs can (1) hemolyze or (2) block microvascular blood flow by adhering to vascular endothelium [3]. Because babesiosis is a serious "emerging disease" in the US, the Centers for Disease Control and Prevention (CDC) designated babesiosis "a nationally notifiable disease" in 2011 [2]. This means US state and territorial health departments are encouraged to report babesiosis cases to the CDC. For the 5-year period from 2011 to 2015, CDC received 6277 "confirmed" and 1335 "probable" babesiosis case reports [2]. Of concern, the most recent year analyzed (2015) had the highest total number of cases (confirmed + probable) [2].

State health departments individually decide how to investigate and report cases of babesiosis. Because *Babesia microti* is endemic [4] in Rhode Island, clinicians are required (by state regulations) to report suspected, confirmed, or probable babesiosis cases to the Rhode Island Department of Health within 4 days [5]. Rhode Island requires local healthcare workers to complete as much of the state's babesiosis Case Report Form (CRF) as possible before sending it to the Rhode Island Department of Health. Rhode Island's babesiosis CRF includes data elements that describe the patient's risk factors, treatment, clinical complications, final outcome (hospital discharge date or death), and other information. [6] To complete the CRF, state health department officials may request medical records from the healthcare facility (personal communication with the Rhode Island Department of Health).

Rhode Island's babesiosis CRF is impressive: It includes data elements relevant for disease risk and prognosis, including age, immunosuppressive conditions, history of tick bite, travel, prior transfusion, organ transplantation, and splenectomy. [6] Unfortunately, we have never seen blood-type variables (ABO blood group, RhD status, etc.) of the patient – and of the donor when simple or exchange transfusion has been used – among the data elements specifically requested on any babesiosis CRF (neither state CRFs nor CDC's CRF) [6,7]. Yet blood-type is likely an important, yet unknown, risk / prognostic factor for babesiosis.

Notably, blood-type is strongly linked to the morbidity and mortality [8,9] of *Plasmodium falciparum* (*Pf*) malaria (a parasitic disease similar to babesiosis). Regarding ABO blood type, "ABO is an independent risk factor for survival among children with malaria" [8]. *Pf*-malaria patients who have the following RBCs have significantly better clinical outcomes: type O [8], HbAS [9], HbAE [10], HbAC [11], α- [12] and β- [13] thalassemia minor, heterozygous southeast Asian ovalocytosis [14], and other "malaria-resistant RBCs" [15]. In sharp contrast to *Pf* malaria, the impact of RBC variables on babesiosis-disease progression is unknown. We were unable to find any study which correlated blood-type with babesiosis outcomes. This is unfortunate because RBC variables may have therapeutic implications for the treatment of babesiosis patients. Public health officials should be aware that researchers have recommended that malaria-resistant RBCs be used when *Pf*-malaria patients need simple or exchange transfusion. [16–22] Since the pathogenesis of babesiosis is also likely to be affected by RBC-related variables, it seems prudent to report the RBC variables of babesiosis patients – and of the donors when transfusion is used to

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treat babesiosis.

Perhaps this disparity in RBC-related research is because the number of babesisosis cases is small compared to the estimated 228 million [23] cases of malaria in year 2018. A retrospective study of babesiosis in the Midwestern US examined just 38 babesiosis cases at 3 different locations over 13 years (2005–2017) [24]. Historically, studies have analyzed small sample sizes that can make it difficult to identify new associations between, for example, RBC variables and babesiosis-disease progression.

Fortunately, guided by recent malaria-research findings, CDC and state health officials now have the opportunity to help clinicians assess how key RBC variables of both patients and transfusion donors impact babesiosis outcomes. Currently, state babesiosis CRFs ask about (1) risk factors such as age, travel history, recent transfusions, splenectomy, immunosuppressive medications, etc. and (2) complications and outcomes such as acute respiratory distress, altered mental status, disseminated intravascular coagulation, hepatic compromise, etc. [6] Using this (limited) data, CDC was able to explain that hospitalizations for babesiosis were more common among asplenic and elderly patients. [2] CDC noted that "72.6% among those aged ≥80 years (552 of 760)" and "106 of 126 [84.1%]" of babesiosis patients who were apslenic had to be hospitalized [2]. If blood type and other RBC variables were to be added to CRFs, more patient-outcome associations could be quantified – some of which might have important therapeutic implications. Unlike individual hospitals, with enhanced data collection health departments could collect enough data so RBC variables of both patients and transfusion donors might be correlated with babesiosis outcomes.

It seems prudent to assume ABO and RhD blood types (such as O+, O-, A+, etc.) impact babesiosis outcomes given that RBC variables are strongly linked to *Pf*-malaria morbidity and mortality. Hospitalized babesiosis patients have their blood typed if transfusion is anticipated to correct anemia or exchange transfusion is warranted because disease is severe. Of note, the MNS blood-group system might be especially relevant because *in vitro* studies found that *Babesia divergens* (the parasite that most often causes babesiosis in Europe) uses M and S antigens to invade human RBCs. [25,26] Interestingly, the *Pf* parasite also uses antigens in the MNS blood group to invade RBCs. [27] Although not all babesiosis patients need blood transfusions, conceivably, all hospitalized babesiosis patients could be typed for ABO and MNS blood-group antigens if babesiosis trends worsen and collecting this data becomes a priority in the US. Regardless, given the potential therapeutic implications, it seems prudent to assume ABO and MNS blood types may impact babesiosis outcomes given that RBC variables markedly impact *Pf*-malaria outcomes.

In conclusion, based on prior *Babesia*- and *Pf*-parasite research data, it is biologically plausible that ABO and MNS blood types (and other RBC variables) are relevant for the prognosis and treatment of babesiosis patients. So, to advance patient care, we urge CDC and state health officials to modify the CRFs for babesiosis. Of note, CDC's example CRFs [7] serve as guides for state CRFs to "promote standard data collection" [2]. In fact, some states (ex. Florida, Maryland, Oregon) use CDC's Babesiosis CRF as the official state version. We recommend reporting patient blood type – or, if simple or exchange transfusions were used, donor as well as patient blood type – by adding these 2 data elements: "ABO/RhD blood type (O+, O-, A+, etc.)" and "MNS-antigen blood type." Furthermore, it would be ideal if babesiosis CRFs encouraged clinicians to report "all other known RBC variables" (such as RBC phenotype / genotype, sickle-trait status, G6PD deficiency, etc.) because such data might also help improve patient care. In general, RBC- and transfusion-related data may help clinicians and researchers (1) better understand why some patients become severely ill and (2) determine if exchange transfusions of special babesiosis-resistant RBCs can reduce morbidity and mortality. Although this extra reporting might be considered an unwarranted burden, Mary Lasker warned, "If you think research is expensive, try disease!" [28] Also, the COVID-19 pandemic is reminding us that preparing for the "worst-case" babesiosis scenario may be prudent as babesiosis cases in the US continue to increase. Ideally, with the support of state health departments, CDC can collect patient and donor RBC-related data that can help frontline clinicians optimize simple and exchange transfusions for babesiosis patients before this tick-borne disease becomes more problematic.

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