Artificial Blood Development

Implications for Military Medicine

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ABSTRACT

Massive hemorrhaging remains the most common cause of preventable battlefield deaths. Blood used for trauma care requires a robust donation network, capacity for long-term storage, and extensive and accurate testing. Bioengineering technologies could offer a remedy to these constraints in the form of blood substitutes—fluids that could be transfused into patients to provide oxygen, carry away waste, and aid in coagulation—that would be used in prolonged casualty care and in far-forward settings, overcoming the obstacles of distance and time. The different molecular properties of red blood cells (RBCs), blood substitutes, and platelet replacements contribute to their respective utilities, and each type is currently represented in ongoing clinical trials. Hemoglobin oxygen carriers (HBOCs) are the most advanced RBC replacements, many of which are currently being evaluated in clinical trials in the United States and other countries. Despite recent advancements, challenges remaining in the development of blood alternatives include stability, oxygen capacity, and compatibility. The continued research and investment in new technologies has the potential to significantly benefit the treatment of life-threatening emergency injuries, both on the battlefield and in the civilian sector. In this review, we discuss military blood-management practices and military-specific uses of individual blood components, as well as describe and analyze several artificial blood products that could be options for future battlefield use.

KEYWORDS: *artificial blood; blood substitutes; red blood cell substitutes; platelet replacements; biomanufacturing*

Introduction

Massive hemorrhaging has been the foremost cause of preventable deaths for Warfighters for centuries, and the recent combination of improvised explosive devices, increased caliber weaponry, and armor-piercing munitions has led to a higher incidence of hemorrhagic wounds since the 1990s.[1] The current battlefield standard of care is to preferentially provide cold-stored low-titer O whole blood that is predominantly collected at military and federal installations.[2] However, this strategy depends on blood donations and a reliable cold-chain transport process. In this review, we examine military blood-management practices and the military-specific uses of individual blood components. We also provide an overview of several artificial blood products that could eventually be used for hemorrhagic management at the point of care.

Human Blood Composition

A brief description of the components of blood is necessary to review its wide array of functions, as well as to better appreciate blood's complexity with respect to its artificial manufacture. Blood is a complex fluid composed of cellular and acellular components that are essential for human life. In addition to oxygen delivery, blood is responsible for waste removal, nutrient delivery, and the maintenance of fluid balance in tissues, with important roles in the lymphatic, immune, and digestive systems (Table 1). Blood's myriad functions result from its complex components: erythrocytes (RBCs), leukocytes (white blood cells [WBCs]), and platelets. RBCs are integral to oxygen transport and are essentially transport vessels for hemoglobin, the protein that delivers oxygen to tissues from the lungs. WBCs are components of the immune system, comprising various cell types that fight infection. WBCs include immune response–mediating T and B lymphocytes, bactericidal neutrophils, natural killer cells that limit the spread of damaged cells and cells infected by pathogens, parasite-fighting eosinophils, and allergen-response–initiating basophils. Platelets are cellular fragments vital to blood coagulation in response to blood vessel injury.[3] Acellular components of blood are essential for maintaining homeostasis. Electrolytes such as sodium, potassium, chlorine, and bicarbonate regulate osmotic pressure and are vital in nerve excitation, muscle contractions, and cell metabolism. Various proteins such as albumin, insulin, and antibodies regulate fluid balance, act as signaling hormones, or defend the body from infection, respectively. Inactive molecules—for instance, fibrinogen and prothrombin—respond to specific signals and aid in the coagulation cascade when the body suffers trauma.[4]

Blood Management in the Military

The military healthcare system is self-contained, encompassing all aspects of the distribution, storage, and transfusion of collected blood. The Armed Services Blood Program collects whole blood and produces apheresis products (e.g., RBCs, plasma, platelets) at many military and federal installations

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TABLE 1 *Various Cellular and Acellular Blood Components and Their Functions*[4]

Component of Blood	Function
Erythrocytes (RBCs)	Deliver oxygen to tissues via hemoglobin
Leukocytes (WBCs)	Defense against pathogens: bacteria, viruses, parasites
T-Lymphocytes	Kill infected cells and coordinate immune responses
B-Lymphocytes	Produce antibodies and serve as immune system's memory
Natural killer cells	Members of the innate immune system that kill cells infected by pathogens
Neutrophils	First-line defense, especially against bacteria
Eosinophils	Fight parasites and aid in allergic reactions
Basophils	Serve in allergic reactions
Platelets	Cell fragments that form blood clots in response to vessel injury
Electrolytes (Na^+, Cl^-, K^+, HCO_3^-, Ca^{2+})	Maintain blood osmolarity and regulate nerve function, muscle contractions, and cellular metabolism
Proteins	Regulate fluid balance, act as hormones, protect from infection, aid in clotting
Albumin	Maintain blood osmolarity and carry water-insoluble molecules
Antibodies	Circulate in the blood and bind to non–self-molecules (such as allergens and pathogens)
Clotting proteins	Fibrinogen, prothrombin, von Willebrand factor (vWF), coagulation factors

RBCs = red blood cells; WBCs = white blood cells

and military-leased facilities, as well as aboard ships.[5] Technicians divide whole blood into components: RBCs, fresh-frozen plasma (i.e., plasma frozen within 24 hours), cryoprecipitate, and platelets. Logisticians then distribute these products worldwide to military medical treatment facilities for transfusions, to armed forces blood-processing laboratories for support of military or contingency operations, and to civilian hospitals and local governments under specific circumstances or when excess products are available.[5]

Although prompt transfusion is often a key intervention, not all echelons of care have the same blood-product resources available (Table 2). Additionally, some models have predicted a shortage of blood units in the millions, both nationally and internationally,[6,7] which does not account for how a conflict with a near-peer threat would further exacerbate a strained supply line. Blood substitutes offer the potential to supplement the use of blood units in military medical treatment facilities, civilian emergency rooms, and ambulances. Furthermore, blood substitutes would provide an advantage during prolonged casualty care situations and at low-level care facilities before more robust care could be administered at higher-level trauma centers. Overall, using blood substitutes could ease the logistical burdens of maintaining whole human blood and somewhat alleviate the need for difficult triage decisions of who should receive scarce units of donated blood based on likelihood of survival, especially in a high-casualty scenario.

Even though the military supplies many of the approximately 13 million units of blood that are collected annually within the United States, it inevitably encounters blood shortages, both domestically and in deployed areas. During the SARS-CoV-2 pandemic, the American Red Cross and the Armed Services Blood Program reported decreased donations because of blood drive cancellations and persons who were unable or unwilling to travel to donation sites.[8–10] Blood donation faces other challenges, including blood transportation issues, the limited shelf lives of all blood products, and the relatively large quantities of blood required for typical military trauma patients, which tax already limited supplies. Human blood has a shelf-life of up to 6 weeks, at which point the blood is deemed "expired" and no longer usable. However, several recent studies have shown that blood can expire as soon as 3 weeks.[11]

TABLE 2 *Blood Product Availability at Military Roles of Care*

Role of Care	Provider Examples	Blood Products and Hemorrhage Interventions
Role 1: First responders	• Self-aid • Buddy aid • Combat life saver • Combat medic	• Low-titer type O whole blood • Tourniquet • Hemostatic agents • Ranger type O low-titer (ROLO) program (*unit dependent) Tranexamic acid (TXA)—reduce bleeding
Role 2: Forward resuscitative care	• Forward surgical teams • Landing helicopter dock vessels	• Low-titer type O whole blood • Fresh-frozen plasma • Cryoprecipitate • Platelet products (*limited due to short shelf life) • Walking blood banks • Recombinant Factor VIIa (clotting)
Role 3: Theater hospitals	• Combat support hospitals • USNS Mercy/Comfort	• Blood type matching • Fresh-frozen plasma • Cryoprecipitate • Packed red blood cells • Apheresis platelets • Role 2 resources
Role 4: Definitive care	Landstuhl Regional Medical Center (Germany) Brian D. Allgood Army Community Hospital (Republic of Korea) Walter Reed National Military Medical Center Brooke Army Medical Center	Role 3 resources with definitive medical and surgical care in medical centers outside the combat zone (OCONUS or CONUS)

CONUS: the continental United States; OCONUS: outside the contiguous United States
*Should be considered in operative planning purposes for forward deployed providers and unit medical officers due to disproportionate resources available between different units.

Substitute Blood Products Summary

Artificial blood and blood components have several distinct advantages over donated blood. First, after they are manufactured, blood substitutes are sterilized to destroy any viral or bacterial agents, thereby eliminating the risk of transmitting infectious diseases; although human blood products are screened for pathogenicity, there is still a risk of infection from pathogens such as human immunodeficiency virus and syphilis, as well as hepatitis B and C.[12] Second, artificial blood products may have longer shelf lives and less stringent storage requirements than donated blood, making them easier to manipulate and use. Third, blood substitutes can be engineered to be blood-type specific, thus avoiding immunologic reactions. Lastly, patients whose religious beliefs prevent them from accepting donor blood may be willing to accept blood substitutes.[13]

Given the predicted future strain on supply, as well as growing concerns of a major conflict abroad, RBC substitutes offer a solution for the medical field that can have a lifesaving effect on patients suffering from battlefield injuries, blood diseases such as hemophilia, and deficiencies in blood coagulation factors. The compatibility, effectiveness, and viability of RBC substitutes are stringently established before administration. The manufacturers of these products must consider rate of delivery, packed-cell volume, quantity, and types of blood components because transfusions can cause a number of adverse reactions that would be a further insult to an already injured patient.[14,15] Conventional RBC substitutes belong in one of two main categories: HBOCs or perfluorocarbons; however, recent advances in biomanufacturing capabilities continue to produce additional options. RBC substitute product names and characteristics, and the status of current clinical trials, are summarized in Table 3. Reported adverse-event profiles of select products are summarized in Table 4.

Hemoglobin-Based Oxygen Carriers

HBOCs, which covalently bind oxygen-like native hemoglobin, can be genetically engineered or derived from hemoglobin in expired human blood or bovine blood.[16] Three types of HBOCs are currently in development: surface-modified HBOCs, cross-linked HBOCs, and liposome-encapsulated HBOCs.

In surface-modified HBOCs, large molecules such as polyethylene glycol chains are added to lysine groups on the surface membrane.[16] Surface-modified HBOCs are smaller than erythrocytes, which better facilitates their entry into small vessels that are otherwise not easily reached by conventional RBCs. This property is clinically relevant to treating ischemic strokes, where occluded vessels prevent adequate perfusion by RBCs.

Cross-linked HBOCs feature more enhanced oxygen-carrying capacities through intermolecularly cross-linked alpha and beta subunits.[16] This cross-linking reduces hemoglobin's affinity for oxygen, thus enabling more efficient delivery, and reduces renal filtration, thereby augmenting retention within the host. One inherent disadvantage of the cross-linked variant is its inability to convert Fe^{3+} (ferric state) to Fe^{2+} (ferrous state), the only absorbable form of iron. To account for this, researchers have developed a cross-linked HBOC using methemoglobin with attached reducing agents to convert iron in the heme group from the Fe^{3+} state to the Fe^{2+} state in normal hemoglobin. However, this variant features a lower O_2-carrying capacity,[17] leaving room for future improvements. Examples of surface-modified and/or cross-linked HBOCs in various stages of development and approval include Hemotech (HemoBiotech),[18] Hemospan (MP4OX; Sangart),[19] Hemopure (HBOC-201; Hemoglobin Oxygen Therapeutics),[20–23] Oxyglobin (HBOC-301; Hemoglobin Oxygen Therapeutics),[24] PolyHeme® (polymerized human hemoglobin, pyridoxylated; Northfield Laboratories),[25,26] Diaspirin (DCLHb; Baxter Healthcare),[27,28] and ErythroMer (KaloCyte).[29,30]

Liposome-encapsulated HBOCs (LEHs) feature hemoglobin that has been packaged inside a stable lipid membrane with embedded cholesterol for additional integrity.[16] As a result, LEHs are both smaller than natural RBCs and have a much longer shelf-life. The main drawback involves the shortened half-life while in circulation.[31] Researchers have addressed this by placing an actin matrix in the liposome's aqueous core, which extended the half-life and augmented the overall stability and solubility of one LEH. Of note, OxyBridge™ (VIR-HBOC; VirTech Bio), derived from human hemoglobin, is one LEH in development with some demonstrated potential in multiple animal studies.[32,33]

Perfluorocarbons

Perfluorocarbon-based artificial oxygen carriers (PFOCs) are another RBC substitute. As their name suggests, PFOCs are derived from perfluorocarbons and are structurally like hydrocarbons, with fluorine atoms instead of hydrogen atoms. Synthetically engineered to carry both O_2 and CO_2 through mechanisms other than covalent bonding, PFOCs have been used to oxygenate premature babies with respiratory distress syndromes.[34] Examples of PFOCs in various stages of development and approval include Perftoran® (Vidaphor; Perftoran USA),[35] Oxycyte (Synthetic Blood International),[36–38] Oxygent (Alliance Pharmaceutical),[39] PHER-O2 (Sanguine),[40] and Fliosol-DA (perfluorocarbon emulsion; Green Cross).[41]

Biomanufactured Red Blood Cells

Within the past 20 years, many research groups have focused on using human umbilical cord blood (UCB) cells to generate enucleated RBCs from $CD34^+$-positive UCB cells in culture.[42–44] However, scaling up production levels remains a key issue to produce sufficient numbers of RBCs necessary for transfusions and other medical treatments. The future of scalability of these UCB cells and other RBC substitutes could rely on bioprinting technologies. nScrypt, a company that designs and manufactures 3D printing devices, has developed a ruggedized bioprinter for use in military environments.[45] The research division of nScrypt, known as Sciperio, has been collaborating jointly to provide on-demand human blood to the military at the point of injury through the development of RBCs. This project will use several nScrypt print heads to supply necessary growth enhancers to a bioreactor, which will enable cellular amplification and differentiation to generate a scalable effect.[46]

Another group of researchers has synthesized cells using donated human RBCs coated with a layer of silica.[47] The silica coating is layered with negatively and positively charged polymers, after which the silica is dissolved, leaving a flexible scaffolding over which natural RBC membranes are layered to create artificial RBCs. These synthetic cells, which are similar in charge, shape, and size to RBCs, move through model capillaries with relative ease and last up to 48 hours in mice.[47]

TABLE 3 *Developmental Stages of Red Blood Cell and Platelet Replacement Products*

Product Name	Type	Source	Action	Clinical Trials	Approval
Hemotech[18]	Cross-linked and surface-modified–HBOC	Bovine hemoglobin conjugated with ATP, adenosine, and reduced glutathione	Oxygen carrier	Preclinical and initial clinical trials undertaken outside U.S.	None
Hemospan (MP4OX)[19]	Surface-modified–HBOC	Oxygenated polyethylene glycol-modified human hemoglobin	Oxygen carrier	Phase III clinical trials in U.S. complete	None
Hemopure (HBOC-201)[20–23]	Cross-linked and polymerized HBOC	Bovine hemoglobin	Oxygen carrier	Expanded access (compassionate use) and investigation new drug trials underway to treat anemia	Approved in South Africa and Russia
Oxyglobin (HBOC-301)[24,31]	Cross-linked and polymerized HBOC	Bovine hemoglobin	Oxygen carrier	Canine anemia trials were completed in late 1990s	Approved for veterinary use
PolyHeme®[25,26]	Cross-linked and polymerized HBOC	Glutaraldehyde, human hemoglobin	Oxygen carrier	Phase III clinical trials in U.S. ongoing	None
Diaspirin (DCLHb)[27,28]	Cross-linked HBOC	Human hemoglobin	Oxygen carrier	Phase III clinical trial in U.S. complete	None
ErythroMer[29,30]	Cross-linked, polymeric nanoparticle HBOC	Amphiphilic polymerization of hemoglobin using polyethylene imine	Oxygen carrier	Animal testing only	None
OxyBridge™ (VIR-HBOC)[32,33]	HBOC: Surface-modified–, cross-linked LEH	Hyperpolymerized human hemoglobin	Oxygen carrier	Animal testing only	None
Perftoran® (Vidaphor)[35]	PFOC	Perfluorocarbon emulsion in a surfactant and electrolyte solution	Oxygen carrier	Outside U.S. only	Approved in Russia and Mexico for hemorrhagic shock
Oxycyte[36–38]	PFOC	Perfluorocarbon-based oxygen carrier	Oxygen carrier	Phase II clinical trials for treating traumatic brain injury completed in U.S., Israel, and Switzerland	None
Oxygent[39]	PFOC	Emulsion of perfluorooctyl bromide	Oxygen and CO_2 carrier	Phase II trials to determine oxygen-carrying capacity in non-traumatic respiratory-compromised patients	None
PHER-O2[40]	PFOC	Perfluorocarbon-based oxygen carrier	Oxygen carrier	Preclinical trials ongoing	None
Fluosol-DA[41]	PFOC	Perfluorocarbon emulsion	Oxygen and CO_2 carrier	Phase III clinical trials in U.S. complete	FDA approved in 1989 and removed from market in 1994
SynthoPlate[50]	Platelet	Liposome with integral vWF and collagen-binding peptides	Hemostatic agent	Animal testing only	None
PlateletBio[51–53]	Platelet	Platelet-like cells	Platelet replacement and hemostatic agent	Novel research	None

ATP = adenosine triphosphate; HBOC = hemoglobin oxygen carrier; LEH = liposome-encapsulated HBOC; PFOC = perfluorocarbon-based artificial oxygen carrier; vWF = von Willebrand factor

Platelet Replacements

Platelets are essential elements of blood that are responsible for coagulation. However, their broader roles include immunologic responses, angiogenesis, tissue regeneration, and wound healing. Physical, spatial, and temporal factors influence different populations of platelets. Therefore, the in vitro production of platelets could allow these different functions to be tailored for specific uses. In response to injury and trauma, platelets that produce stromal cell-derived factor 1 (SDF-1), a CXC chemokine that binds to the CXCR4 receptor, have been shown to promote the recruitment of endothelial progenitor cells to arterial thrombi in vivo.[48] Researchers have recently generated platelets in vitro in a novel microfluidic system, demonstrating the formation of a significant number of functional platelets from their precursor, megakaryocytes.[49]

Two platelet substitutes in development are SynthoPlate (Haima Therapeutics) and PlateletBio (PlateletBio). SynthoPlate is a hemostatic agent that is generated as a liposome with integral von Willebrand factor and collagen-binding peptides. In murine and porcine studies, it has reduced life-threatening hemorrhage and prevented exsanguination.[50] In a much earlier stage of development, PlateletBio consists of artificial platelet-like cells specifically designed to replace platelets and act as a hemostatic agent.[51–53]

Blood Product Comparison

RBC replacements are leading the artificial blood race, and one HBOC (Hemopure) is FDA-approved for compassionate use. However, unencapsulated HBOCs might not be the ideal

TABLE 4 *Reported Adverse Event Profile of Different Blood Substitutes*

Blood Substitute	Reported Adverse Events
PolyHeme® (polymerized human hemoglobin)[61]	• Arrhythmia • Nausea • Increased pancreatic enzymes • Pneumonia • Multiple organ failure • Hypercoagulable state
Hemospan (MP4OX)[15,19]	• Hypertension • Nausea • Increased pancreatic enzymes • Increased transaminases • Jaundice • Stroke (age-related)
Hemopure (HBOC-201)[62,63]	• Reversible cardiac lesions (animal models) • Hypertension • Jaundice
Perftoran[35]	• Flushing • Rash • Pruritis • Dyspnea • Transient headache, chest/back pain
Oxycyte[64,65]	• Dose-dependent increase in blood viscosity • Flu-like symptoms • Thrombocytopenia
Oxygent[65]	• Transient headache, back pain • Flu-like symptoms • Thrombocytopenia

RBC replacement because of their complete reliance on hemoglobin. When outside erythrocytes, hemoglobin can rapidly break down from its connected tetramer configuration into subunit dimer or monomer configurations, which can cause kidney damage.[27] To address this unfavorable stability feature, researchers have encapsulated hemoglobin configurations in a lipid bilayer and have demonstrated increased storage stability and viscosity to prevent aggregation during transfusion. Because of the smaller size of these carriers relative to RBCs, encapsulated hemoglobin can penetrate blockages and access hypoxic tissues, such as those affected by stroke or clotted vessels.[54] Encapsulated hemoglobin blood substitutes can also take advantage of modulating surface level charges, including PEGylation, of their lipid membranes to increase circulation half-life.[54–56] With each successful extension of hemoglobin half-life, it becomes increasingly likely that encapsulated HBOCs will soon be available blood substitutes.

PFOC products feature some marked advantages over HBOCs, including oxygen dissolution that is unaffected by temperature and pH level, no inherent reactivity with oxygen and other bodily gases, increased solubility of oxygen in plasma, and varying carrying capacities dependent on the fraction of inspired oxygen.[16] PFOCs can also withstand temperatures up to 300°C and are soluble in aqueous states.[17] PFOCs, whose general chemical formula is C_nF_{2n+2}, have an attendant linear morphology that is more conducive than a bent morphology to carrying oxygen. PFOCs require relatively high O_2 pressure for effective carrying capacities because of a linear relationship between the pressure of O_2 and the amount of O_2 dissolved in solution.[17] However, PFOCs have been shown to transiently reduce platelet counts and to accumulate in organs, where they cannot be utilized, which requires their active removal over an 18- to 24-month period.[16] Therefore, researching other RBC replacement technologies is equally important.

Developers of biomanufactured RBCs aim to precisely replicate the naturally occurring physiological and mechanical properties of RBCs for tailored use at the point of care for trauma injuries. Concurrently, researchers are designing relatively portable bioreactors to fabricate RBCs exactly where they are needed. This type of RBC product would essentially eliminate the need for donor blood screening concerns, as well as the logistics of transport and long-term storage. Future research in biomanufactured RBCs should continue to address the twin difficulties of consistently producing sufficient RBCs, as well as the testing and evaluation of biomanufacturing technology in austere environments for point-of-care use.

Because platelets provide critical hemostasis to prevent exsanguination, their role in preventing battlefield deaths cannot be overstated. Human platelets have a shelf-life of days, given their need to be stored at room temperature; however, promising developments in synthetic platelet research—already underway in animal models—could pave the way for more readily available products available to the warfighter. Additionally, as research also increasingly emphasizes their role in improved wound healing, these products have the potential not only to improve survival at time of injury, but also to help long-term healing.

Researchers are also honing methods for preserving specific cells within the blood. Whole blood cannot be frozen because, upon defrosting, many of the cells will lyse and contaminate the plasma with different proteins and debris. RBCs, plasma, and cryoprecipitate, however, are all available as frozen products. For example, a droplet-based (inkjet) bioprinter has been developed that uses anti-Leidenfrost vitrification to successfully cryopreserve RBCs.[57] This technique, in combination with ruggedized bioprinters, could bring this capability to point-of-care use for military personnel. A laboratory in the United Kingdom has recently initiated clinical trials to evaluate the transfusion of laboratory-grown RBCs derived from donor stem cells, which would directly benefit patients who require regular transfusions and potentially demonstrate extended shelf-life.[58] Elsewhere, researchers have also designed both mouse- and human-derived stem cells to produce megakaryocytes as precursors for platelet production. This research could unearth novel determinants of platelet production in humans, thereby providing not only information on the causes of thrombocytopenia, but also a way to generate platelets in vitro for blood transfusion purposes.[59]

Although it is ostensibly much more difficult to utilize and develop, whole blood research could nonetheless yield promising artificial blood products useful in austere environments. In addition to the biomanufacturing of RBCs, various research programs and companies are exploring new methodologies to manufacture whole blood components, including WBCs such as neutrophils and natural killer cells. Ideally, separate blood components could be individually manufactured and incorporated later to have whole blood available at the point of trauma care.

Ultimately, the FDA must approve any artificial blood product prior to use, benefiting not only military and civilian medicine but also opening new paths for research. Using preapproved products reduces the strenuous review processes of research ethical committees in both animal and clinical research trials. It is also possible that blood substitutes could serve as a model for human blood in circulatory system models and 3D-printed

or bioengineered tissues, which would reduce the number of animals needed for such studies. Furthermore, with a greater ability to rapidly prototype, blood substitutes could offer an obtainable and comparatively inexpensive blood model to serve as a proof of concept. Circulatory system models that verify artificial blood rheology could even facilitate moving blood products to human trials, potentially reducing the pharmaceutical industry's financial and intellectual losses.[60]

Conclusion

Engineered blood products represent a unique research and development opportunity to save lives throughout the entire spectrum of care. In a future battlefield with high casualties and limited resources, artificial blood products offer an opportunity for rapid transfusions essential for resuscitation and survival during massive hemorrhage.

Author Contributions

VRM wrote the majority of the manuscript. JRH provided a comprehensive final review and submitted the manuscript. MKD created Tables 1, 2, and 4, helped to create Table 3, and edited the manuscript in response to the first set of suggested of revisions as well as final revisions of accepted manuscript. HC helped create Table 3 and wrote verbiage about it. DP provided references and draft organization. SLB provided a comprehensive review in response to suggested revisions. JB conceived of the review idea and revised drafts for content. All authors reviewed and approved the final draft manuscript.

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