Transfusion Replacement Strategies in Jehovah's Witnesses and Others Who Decline Blood Products

Thomas G. DeLoughery, MD, MACP, FAWM

Departments of Medicine, Pathology, and Pediatrics, Knight Cancer Institute, Oregon Health & Science University, Portland, Oregon

Correspondence:
Thomas G. DeLoughery, MD, MACP, FAWM
Oregon Health & Science University
3181 SW Sam Jackson Park Rd
Mail Code: OC14HO
Portland, OR 97239-3098
Phone: (503) 494-4335
Fax: (503) 494-3257
Email: delought@ohsu.edu
Twitter: @bloodman

Abstract: The use of blood transfusions is a mainstay of modern medical practice. Jehovah's Witnesses decline the use of blood transfusions as a matter of faith, however, and other patients do so for personal reasons. In all cases, it is important to document what blood products can or cannot be used. It is also essential to test all patients for iron deficiency, and to address any correctable factors in those who are anemic. This article reviews a variety of options that are available to aid in caring for patients who refuse blood transfusions, ranging from tranexamic acid to erythropoiesis-stimulating agents. With the use of these treatments, patients who decline blood transfusion can be safely managed in situations ranging from elective surgery to stem cell transplant to pregnancy.

Keywords
Blood transfusion, erythropoiesis-stimulating agents, Jehovah's Witnesses, tranexamic acid

Introduction

A challenging situation is the patient with severe anemia/bleeding who has clearly expressed a wish to decline blood transfusions. This article reviews why certain patients decline blood transfusions, the various options for the treatment of severe anemia, how to prepare for surgery patients who decline blood products, and the emergency treatment of severe bleeding in these patients.

Patients Who Decline Blood Transfusions

Jehovah's Witnesses

Jehovah Witnesses is a Christian denomination that was founded in the 1870s. The group's views on transfusion are based on multiple biblical passages, such as the following:

- Genesis 9:4: "But flesh [meat] with … blood … shall ye not eat."
- Leviticus 17:12-14: "… No soul of you shall eat blood … whosoever eateth it shall be cut off."
- Acts 15:29: "That you abstain … from blood …"
- Acts 21:25: "… Gentiles … keep themselves from things offered to idols and from blood …"[1,2]

This religious prohibition applies to major blood fractions—that is, red blood cells, granulocytes, platelets, plasma, and whole blood.[1]

It also applies to autologous blood transfusion because blood is removed from the body. The decision regarding the use of minor blood fractions, which are derived blood products such as cryoprecipitate and immunoglobulins, is considered a matter of conscience and is left to the individual. The elders at a patient's church, who can help review options with the patient, may be a useful resource. In addition, some hospitals will have a dedicated Witnesses liaison to help with counseling. It is important to remember that Witnesses fully embrace other aspects of modern medical care.

Other Patients Who Decline Blood Transfusions

Some patients will decline blood transfusion for personal reasons, such as fear of an infection or immune reaction. In these cases, a sympathetic discussion regarding the true risk associated with transfusion may lead to an acceptance of transfusion. Other patients may have deep-seated personal beliefs regarding transfusion that must be respected. The consulting hematologist needs to be understanding, clearly document the patient's reason for declining transfusion, and specify what products/interventions are acceptable to the patient.

The Evidence for the Benefits of Blood Transfusion

Despite the widespread acceptance of blood transfusion in clinical medicine, the evidence base for its benefits is relatively sparse. Starting in 1991 with the TRICC trial,[2] a series of randomized controlled trials raised the threshold for when blood is to be transfused. It is now accepted that a stable patient with hemoglobin readings in the range of 7 to 8 g/dL will not benefit from transfusion, and that transfusion to a hemoglobin level above 7 g/dL can harm a patient with gastrointestinal bleeding.[3,4]

In addition, several published studies have examined outcomes in patients who decline blood transfusions. A 1996 study by Carson and colleagues found a mortality rate of 33% in surgery patients who declined blood transfusions when their preoperative hemoglobin level was less than 6 g/dL.[5] In anemic patients, the risk for death was increased if cardiovascular disease was also present and/or 2 or more units of blood was lost. A 2002 study found an increased risk for death in patients with low postoperative hemoglobin levels, showing an odds ratio of 2.5 for mortality with each decrease of 1 g/dL in the postoperative hemoglobin level.[6] In an updated study from this group, published in 2014, the odds ratio for mortality had improved to 1.84, suggesting improvement in the management of these complex patients.[7] For patients undergoing elective cardiac surgery, the role of proper surgical planning is made clear. In a meta-analysis of 6 cardiac surgery studies involving 564 patients who declined blood, no differences were observed in a variety of outcomes, as well as a trend toward improved survival. A more recent retrospective propensity-controlled study of patients undergoing cardiac surgery showed improved outcomes in bloodless patients, with fewer cases of renal failure and shorter hospital stays.[8] The conclusion one can draw from these studies is that improving blood counts if possible before any procedure is vital. With aggressive planning, outcomes are not adversely affected in patients who decline transfusions.

Pre-procedure Screening

The cornerstones of care for bloodless patients are documentation and preparation. In the pre-procedure clinic visit, attention should be paid to several aspects of care.[9] The first and most vital goal is to establish what products and procedures are acceptable. As noted earlier, although Jehovah's Witnesses traditionally decline all major blood fractions, such as red blood cells, their acceptance of minor blood fractions varies greatly. It is also important for patients who decline blood products for nonreligious reasons to define their wishes concerning acceptable products and procedures and ensure that they are understood. Many Jehovah's Witnesses will have a card outlining their wishes and advance directives that can be scanned into the medical records. At a minimum, the patient's wishes in the case of any contingency should be clearly documented.[10]

The next step is to assess the patient's hematologic status. All patients should undergo a complete blood cell count. If patients are anemic, a thorough work-up is done, with the focus on correctable items. An iron panel should be obtained for patients with iron deficiency anemia. In those with macrocytic anemia, the methylmalonic acid and homocysteine levels should be measured to rule out a deficiency in B_{12} or folate. Patients with high reticulocyte counts need to be assessed for hemolysis, especially autoimmune hemolytic anemia. If hemolysis is present, immunosuppression can be used to maximize blood counts before procedures.

The consulting hematologist needs to discuss with the care team the hematologic expectations for any procedures. A precise plan for blood management must be discussed and agreed upon by the care team. Before surgery, the operating surgeon needs to have a clear understanding of the following:

- The hemoglobin level required for the surgery to be performed;
- The amount of expected blood loss;
- Whether the use of antifibrinolytics such as tranexamic acid would be appropriate;
- The appropriateness of cell recovery with a cell saver.

Tool Kit

Multiple approaches are available to maximize the hematologic and hemostatic profile of patients undergoing bloodless surgery before, during, and after the procedure, including the use of iron replacement, erythropoiesis-stimulating agents (ESAs), tranexamic acid, recombinant factor VIIa (rFVIIa), prothrombin complex concentrate (PCC), fibrinogen concentrate, thrombopoietin agonists, interventional radiology, and artificial blood or artificial oxygen carriers (Table). This tool kit of agents and techniques forms the backbone of any approach to the variety of situations in which the consulting hematologist may be called upon to guide the management of these patients.

Iron Replacement

As noted earlier, it is important to maximize the iron status in all patients because this will often be the key determinant of the hematologic response to anemia/blood loss. A ferritin level above 100 ng/dL rules out absolute iron deficiency in the absence of any inflammatory process.[11] It is increasingly recognized that many patents also have functional iron deficiency that will respond to iron therapy. These include patients with heart failure, those with renal disease or on dialysis, and those receiving therapy with ESAs. Although different thresholds exist, measurement of the ferritin level and iron saturation can identify these patients.

For patients found to be absolutely iron deficient, it often is best to give intravenous iron owing to time constraints. Modern iron preparations are associated with a low rate of reactions, and options are available to replete iron in 1 to 2 clinic sessions.[12] For patients with functional iron deficiency, intravenous iron is mandatory because oral iron has been shown in clinical trials to be inadequate and/or the response is too slow. The risk for infusion reactions with modern iron preparations is low, at 1% to 3%. For patients who have severe iron deficiency anemia, the blood counts and ferritin level should be rechecked in 2 weeks to see if another dose of iron is needed.

Erythropoiesis-Stimulating Agents

The role of ESAs has been controversial.[13] It is clear that the use of ESAs can raise the hemoglobin concentration to a desired level before a surgical procedure. Data also exist to support the idea that "priming" the patient with an ESA can help speed the postoperative recovery of hemoglobin. For preoperative use, several protocols are available. The US Food and Drug Administration (FDA) has approved the following:

- If the preoperative period is at least 3 weeks: 600 U/kg subcutaneously every week, total of 4 doses (last dose is at the day of surgery);
- If the preoperative period is less than 3 weeks: 300 U/kg once daily, total of 15 doses.

Table. Agents for Maximizing Hemostasis

Iron replacement • Low-molecular-weight iron dextran, 1000 mg × 1 • Ferric carboxymaltose, 750 mg × 2 • Ferumoxytol, 1020 mg × 1 or 510 mg × 2
Erythropoiesis-stimulating agents • Darbepoetin alfa • Epoietin alfa-epbx
Tranexamic acid • 1000 mg intravenously or 1300 mg by mouth before surgery • Topical for hip/knee arthroplasty: 1000 mg
Recombinant factor VIIa • 90 μg/kg × 1

Prothrombin complex concentrate
• Coagulopathy: 50 U/kg
• Reversal of Xa inhibitors: 50 U/kg
• Warfarin reversal
  • If INR 2-4: 25 U/kg (not to exceed 2500 U)
  • If INR 4-6: 35 U/kg (not to exceed 3500 U)
  • If INR >6: 50 U/kg (not to exceed 5000 U)

Fibrinogen concentrate • 70 mg/kg will raise fibrinogen level by 120 mg/dL • (Desired rise in fibrinogen level)/1.7 × body weight
Thrombopoietin agonists • Avatrombopag, 20 mg daily • Eltrombopag, 50 mg daily • Lusutrombopag, 3 mg daily
Artificial blood • Glutaraldehyde-polymerized bovine hemoglobin, 2-bag loading dose

INR, International Normalized Ratio.

An "ultra–short-term" protocol has also been published. Administration begins the day before cardiac surgery and consists of 40,000 U of erythropoietin along with intravenous iron, vitamin B_{12}, and folic acid. This protocol has been shown to reduce transfusion requirements significantly.[14]

One consideration with ESAs is that some of them contain human albumin as a preservative. The agents darbepoetin alfa (Aranesp, Amgen) and epoetin alfa-epbx (Retacrit, Pfizer) do not contain albumin as a preservative and should be used preferentially in these patients.

Optimal ESA dosing is unclear for patients who present with severe anemia after trauma or before surgery. Furthermore, patients with severe inflammation may not respond to ESAs owing to marrow suppression. A dose of up to 40,000 U daily is often used.

The risks of ESAs need to be factored into care plans.

The use of ESAs has been associated with a worsening of cancer outcomes, and an FDA black box warning states that their use increases the risk for arterial/venous thrombosis and promotes tumor progression. However, in severely anemic patients, these risks are outweighed by the benefits of improved oxygen-carrying capacity. To put ESAs in perspective, concerns exist that blood transfusions also may increase the risk for tumor progression.[15] With patients who are candidates for preoperative ESAs, especially if they are undergoing curative cancer surgery, an informed discussion about these risks needs to take place. Furthermore, severe anemia or bloodless surgery does not contraindicate aggressive venous thromboembolism prophylaxis, given that pulmonary embolism in a profoundly anemic patient may well be a terminal event.

Tranexamic Acid

In the past decade, a resurgence of interest in antifibrinolytic agents has taken place. Both tranexamic acid and epsilon-aminocaproic acid block fibrinolysis by mimicking fibrin lysine residue and binding to plasminogen, preventing it from binding to fibrin.[16]

Tranexamic acid is the preferred antifibrinolytic agent because it is 10 times more powerful than epsilon-aminocaproic acid and has more favorable pharmacokinetics that allow oral dosing 3 times daily. In addition, extensive data support its use in various clinical situations.

Numerous clinical trials show that tranexamic acid lessens blood loss in patients undergoing lower-limb or spinal orthopedic surgery. It also decreases mortality in cases of severe trauma and postpartum hemorrhage[17,18] and is often used in the supportive care of any patient with severe bleeding. Tranexamic acid has few associated risks. Most trials—most importantly those of orthopedic surgery in a lower limb—have shown no increased risk for thrombosis.[16] Tranexamic acid in very high doses is associated with an increased risk for seizure in open-chamber cardiac surgery, but this has not been seen with lower doses.[19] It should be part of any surgery of a lower limb or the spine, and it should be strongly considered for any patient undergoing surgery with expected blood loss of more than 500 mL. The dosing of tranexamic varies considerably. For orthopedic procedures, the most common dosage is 1000 mg given intravenously before surgery or 1000 mg delivered topically into the wound. The dosage for trauma is a 1000-mg bolus followed by 1000 mg over 8 hours, and the dosage for postpartum hemorrhage is 1000 mg intravenously followed by a second dose in 30 minutes if bleeding persists.

Recombinant Factor VIIa

Recombinant factor VIIa was initially approved for use in patients who have hemophilia with inhibitors. Soon after approval, an explosion in off-label use took place in patients with any type of severe bleeding. Both observational data and clinical trials show that in most of these situations, the use of rFVIIa offers no advantage.[20,21] Its use is still recommended in cases of postpartum hemorrhage when more conservative measures fail, and some practitioners still give it as a rescue agent for uncontrolled bleeding.[22,23] For maximal benefit, the patient's pH level should be above 7.2, and the patient should not be hypothermic.[24] The most consistent dosing recommendation is 90 μg/kg × 1.

Prothrombin Complex Concentrate

PCC is a plasma-derived product. As a minor fraction, it may be acceptable to some patients declining blood transfusion. PCC consists of all the vitamin K–dependent proteins. Some products contain minimal amounts of factor VII and are known as "3-factor" PCCs, whereas other have the same amount of factor VII as of other factors and are called "4-factor" PCCs. PCC is clearly indicated for patients on warfarin who are bleeding when a quick reversal of the coagulopathy is desired.[25] PCC may also play a role in the reversal of directly-acting oral anticoagulants.[26] The role of PCC in other bleeding is inadequately studied. Some practitioners will use these products in lieu of fresh frozen plasma if coagulopathy develops during massive bleeding in patients who decline blood transfusions.[27] A related product, called activated PCC, has been reported to be useful in cases of severe bleeding during cardiac surgery.[28]

Fibrinogen Concentrate

An infusion of cryoprecipitate is usually used for fibrinogen replacement, but some have advocated the use of fibrinogen concentrates for massive bleeding.[29] Because these are blood derivatives, patients must be consulted before their use. The target fibrinogen level should be greater than 200 mg/dL in postpartum hemorrhage and greater than 150 mg/dL in other patients.[30]

Thrombopoietin Agonists

In patients with liver disease, the platelet count can be low owing to both hypersplenism and a lack of hepatic thrombopoietin production. For patients who require a procedure and have a platelet count below 50,000/μL (100,000/μL if they are undergoing neurosurgery), the use of thrombopoietin agonists can raise the platelet count to safe levels before and after the procedure.[31] Dosing is 20 mg daily for avatrombopag (Doptelet, Dova), 3 mg daily for lusutrombopag (Mulpleta, Shionogi), and 50 mg daily for eltrombopag (Promacta, Novartis). These agents should be started at least 2 weeks before surgery to allow a rise in the platelet counts to desired levels, then continued for 2 weeks following the procedure to ensure hemostasis.[32]

Interventional Radiology

The use of interventional radiology to embolize a bleeding vessel selectively can be considered for patients with massive bleeding. Uterine artery embolization can be used

in patients with postpartum hemorrhage to avoid urgent hysterectomy. In patients with trauma, targeted embolization to a bleeding vessel can allow time for the patient to be stabilized and permit more aggressive surgery to be performed later.

Artificial Blood or Artificial Oxygen Carriers

The ideal agent for patients who decline transfusions would be a true blood substitute that could replace red cell transfusion. However, despite decades of research and clinical studies, this goal remains as elusive as ever. Currently, glutaraldehyde-polymerized bovine hemoglobin (Hemopure, HbO2 Therapeutics) is available only as part of a clinical trial or on a compassionate-use basis. The crosslinking of the hemoglobin in this product allows an extended half-life of 19 hours. The hemoglobin P50 is also much higher than that in red blood cells (40 vs 27 mm Hg) to facilitate oxygen delivery.[33] Glutaraldehyde-polymerized bovine hemoglobin can raise the oxygen-carrying capacity and can be given in multiple units over days to weeks.[34] A major issue is that it causes plasma to turn red, as in severe hemolysis, which interferes with many chemistry tests.[35] The interference can vary by laboratory assay and analyzer manufacturer, so close cooperation is needed with the clinical laboratory if this product is used. Also, glutaraldehyde-polymerized bovine hemoglobin can bind nitric oxide, increasing blood pressure and the risk for tissue ischemia. Given regulatory issues, it can take an average of 24 hours to obtain the product, which may be a challenge when patients with trauma and massive hemorrhage are being treated.

Specific Situations

The products and methods previously outlined can be integrated into a variety of clinical situations to manage patients who wish to avoid blood products.

Surgery

For patients undergoing elective surgery with any expectation of blood loss, a preoperative visit must take place at least 1 month ahead of the planned date. This visit will allow time for assessments to determine whether iron replacement, an ESA, or other treatments are needed to maximize the patient's blood counts before surgery, and to undertake any needed interventions. For the surgery itself, the use of tranexamic acid should be strongly considered. When appropriate, the use of topical hemostatic agents such as topical thrombin (made with recombinant thrombin) can reduce blood loss.[9] The use of blood salvage techniques in surgery is generally acceptable to Jehovah's Witnesses as long as the blood remains in continuity with the body in an uninterrupted circuit.[36] Blood draws should be kept to a minimum throughout the hospital stay to conserve blood, and pediatric tubes should be used to limit blood loss. If severe symptomatic anemia occurs postoperatively, an ESA should be started at 40,000 IU/d (along with intravenous iron) until the hemoglobin level is approximately 7 or 8 g/dL. Boosting the hemoglobin level higher increases the risk for thrombotic complications.

Medical Illness

When a patient who declines blood transfusion is hospitalized for a nonsurgical reason, blood conservation remains a key part of therapy. As with surgical patients, blood draws for tests should be kept to a minimum. The patient's iron status should be assessed, and iron supplementation should be given if a deficiency is noted, especially if concurrent heart failure or renal disease is present. Patients admitted with gastrointestinal bleeding should have an aggressive endoscopic work-up to identify and treat any sources of bleeding.

Autoimmune Hemolytic Anemia. Of the acquired severe anemias, autoimmune hemolytic anemia can be especially challenging to manage because the threat of low blood counts persists for weeks. Frontline therapy for warm antibody disease consists of prompt immunosuppression with corticosteroids. Rituximab also should be administered in light of randomized trial data supporting its benefit in warm antibody disease. This therapy should be started immediately because response may be delayed.[37] ESAs can be a useful adjunct because many patients may not be able to mount a sufficient bone marrow response. Immediate therapy for cold antibody disease is more difficult because corticosteroids are not effective. Simple measures like keeping the patient's room warm can slow the rate of hemolysis. Rituximab should be started for long-term control, and bendamustine (Treanda/Bendeka; Teva) can be added for patients with lymphoproliferative disorders.[38] The C1s blocker sutimlimab, which is currently under FDA review, has been shown to reduce the rate of hemolysis rapidly and will be first-line therapy for patients with cold agglutinin disease who decline transfusion.[39] For severely anemic patients, the compassionate use of glutaraldehyde-polymerized bovine hemoglobin may be warranted.

Cancer. Blood transfusion plays a role in 2 aspects of cancer care. The first is to support patients during aggressive cancer resection surgery, and the second is to support patients receiving antineoplastic therapy. For patients who decline transfusion, issues related to ESA use during preparation for cancer surgery are (1) the FDA black box warning and (2) guidelines discouraging ESA use in patients with cancers that can be cured.[40,41] Given that the disease of patients who cannot undergo cancer surgery most likely will not be cured, the risk of ESA use is an acceptable one for most patients. As noted before, the risk

of ESA use is balanced by the data suggesting that blood transfusion may increase the risk for cancer recurrence.[42] ESAs also have been shown to increase the risk for thrombosis, especially in patients with cancer, so adherence to the guidelines regarding thrombosis prophylaxis is essential. During surgical procedures, the principles already outlined should be followed, with attention given to blood conservation and the use of ESAs/iron supplementation in an effort to maximize blood counts. Although concern has been expressed in the past about using blood recovery techniques in cancer surgery for fear of spreading tumors, studies have not validated this fear.[43] Thus, blood salvage—with techniques such as leukoreduction—can be used in major surgeries.

ESAs can be beneficial in raising the blood counts of patients receiving aggressive chemotherapy and should be considered even for patients receiving curative therapy. To avoid excess blood loss, the amount of blood drawn should be the minimum required for good patient care.

Acute Leukemia. In the past, a diagnosis of acute leukemia in a patient who declined blood transfusion was a death sentence. This nihilistic view has become outdated, however.[44] Increasingly, targeted therapies are available that can reduce the need for blood products, such as all-trans retinoic acid (ATRA) for patients with acute promyelocytic leukemia and ivosidenib (Tibsovo, Agios) for patients with *IDH1* mutations. In addition, practitioners are more willing to attempt to induce leukemia remission in younger patients because they are more likely to tolerate the severe anemia, and the increased risk for fatal hemorrhage should be weighed against the likelihood of remission. Leuprolide acetate can lessen blood loss in menstruating women, and avoiding medications that can induce gastrointestinal bleeding (nonsteroidal anti-inflammatory drugs) or bone marrow suppression can be helpful in all patients.[44] The use of a less-aggressive induction regimen, such as venetoclax (Venclexta, AbbVie) and azacitidine, may mitigate cytopenias. Despite limited evidence, patients with severe thrombocytopenia are often given a prophylactic antifibrinolytic agent to prevent bleeding. The TREATT trial, which is comparing prophylactic tranexamic acid vs placebo, will soon provide guidance for this situation.[45]

Stem Cell Transplant

Currently, autologous stem cell transplant has excellent outcomes and is often used in patients who decline blood transfusion. Beck and colleagues compared the outcomes of 66 Jehovah's Witnesses undergoing autologous stem cell transplant with those of 1114 non-Jehovah's Witnesses and found no difference in survival.[46] Allogeneic transplants used to be riskier, but the introduction of reduced-intensity transplants and improved supportive care have made this approach feasible in selected patients. Recommendations include using more than 10^7 CD34+ cells per kilogram of body weight to hasten platelet engraftment, avoiding total-body irradiation to lessen mucositis, delaying transplant in a pretreated patients until full platelet recovery, and treating fevers to avoid the detrimental effects on red cell production.[44]

Pregnancy

One of the most common presentations among patients who decline blood products is pregnancy. A part of the evaluation at the initial visit is to assess and replete iron stores given the very high rate of iron deficiency in young women—up to 30% or higher.[11] The vast majority of deliveries will be uncomplicated, but up to 3 in 1000 are complicated by major postpartum hemorrhage.[47] Early and aggressive use of tranexamic acid is necessary for these patients, along with mechanical measures such as balloon tamponade and uterine artery embolization.

Trauma

A patient's wish not to receive a blood transfusion must be honored even in emergency situations. When a patient is unconscious, a card declaring the person's wishes concerning transfusion or a declaration of this wish by the next of kin will suffice. In this situation, the focus should be on all methods available to achieve hemostasis. Tranexamic acid has been shown to improve outcomes in trauma patients.[48] Fibrinogen concentrate can be used to keep plasma fibrinogen levels higher than 150 mg/dL. For patients who consent to receive them, PCCs can be used to manage coagulopathy. Damage control surgery with packing of bleeding areas can stabilize patients. Iron and ESAs should be aggressively used in trauma patients with severe anemia; a suggested regimen is erythropoietin at 40,000 U daily until the hemoglobin level is greater than 7 g/dL.[49]

Major Bleeding

Patients can suddenly present with major bleeding for a variety of reasons, including rupture of an aneurysm or gastrointestinal disease. In these cases, the principles are the same as in trauma—to follow the patient's wishes and immediately attempt to stop the bleeding. The use of agents such as tranexamic acid and fibrinogen concentrates is guided by clinical laboratory results and the specific situation.

Conclusion

The management of profoundly anemic patients who decline blood transfusion can be daunting. Efforts should be made in advance to understand the patient's wishes, to correct depleted iron stores and other causes of anemia if feasible, and to have a clear care plan for surgery or other treatment. Multiple options are available to the providers who treat these patients.

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Disclosures

Dr DeLoughery has no relevant disclosures.

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