A review: transfusion reactions

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Generally, transfusion of blood components is a safe and often life-saving procedure. However, there are instances when transfusion can lead to an adverse outcome and even death. These fatalities may result from "transfusion reactions," the transmission of infectious agents that lead to, for example, acquired immunodeficiency syndrome (AIDS), hepatitis, or disease states induced by transfusion in susceptible persons, such as posttransfusion purpura (PTP) or iron overload.

This article limits this discussion to those events commonly referred to as transfusion reactions, specifically, hemolysis, acute and delayed; febrile reactions; anaphylaxis; sepsis; acute lung injury; transfusion-associated graft-versus-host disease; and transfusion-associated circulatory overload. For further discussion of transfusion-transmitted infectious disease, PTP, and iron overload, the reader is referred to the transfusion medicine literature.

Hemolysis

The evaluation of acute transfusion reactions is discussed in detail in many texts and manuals. However, some basic facts that the transfusionist must know are as follows:

- Stop the transfusion as soon as a reaction is suspected. This limits the amount of the blood component the patient receives.
- The IV line should be kept open with 0.9% sodium chloride, and all blood products and patient IDs should be checked.
- The transfusion service should be notified and sent appropriate samples, as listed in Table 1.

<table>
<thead>
<tr>
<th>Items</th>
<th>Send to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood samples</td>
<td>To transfusion service for serologic evaluation</td>
</tr>
<tr>
<td>Red top tube (no serum separators)</td>
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<tr>
<td>Lavender top (EDTA) tube</td>
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<tr>
<td>Urine sample</td>
<td>To chemistry to test for hemoglobin</td>
</tr>
<tr>
<td>All tags and paperwork, the administration set (needle removed), and IV solutions</td>
<td>To transfusion service for clerical check and evaluation of non-immune hemolysis</td>
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Not all hemolysis is caused by immune mechanisms, and the transfusion service can often make such determinations by observing the blood component, tubing, and IV solutions. Hemolysis in the blood bag shows that damage occurred before the blood reached the patient. Improper storage temperature or contamination might be the cause. If hemolysis is observed in the tubing but not in the bag, there may have been a hypotonic solution used in the administration set or a faulty blood warmer.

Acute Hemolytic Transfusion Reactions

In all discussions of transfusion reactions, first and foremost discussed are acute hemolytic transfusion reactions (HTRs). These occur because of antibodies in the recipient against antigens on the red blood cells (RBCs) being transfused. This antigen-antibody reaction activates complement, the coagulation cascade, the kinin system, and cytokines, which in turn may result in disseminated intravascular coagulation (DIC), shock, renal failure, and death. Most life-threatening reactions of this type are caused by serologic incompatibility in the ABO system. These reactions, which can have an onset within minutes, are primarily due to IgM antibodies that bind complement and, as a consequence, produce intravascular hemolysis. However, fatal hemolysis due to IgG antibodies from other blood group systems does occur, even though these reactions are generally less severe than those mediated by IgM antibodies in the ABO system. IgG antibodies, such as those in the Rh system, do not usually bind complement and they cause extravascular hemolysis.

The most common initial signs of an acute HTR are fever and chills, but chest pain, nausea, flushing, dyspnea, generalized bleeding, back pain, and other nonspecific symptoms may occur. As little as 10 mL of incompatible blood can cause a reaction, but clinical severity is proportional to the volume infused. In an anesthetized patient, excessive bleeding is often the first sign of an acute HTR. Emergency treatment must be started as soon as possible to ameliorate the life-threatening sequelae that may ensue. While awaiting confirmation from the blood bank, this diagnosis must often be made based on the clinical picture and available evidence. Patients should be moved to an intensive care unit so that close monitoring can take place. Aggressive
fluid replacement is necessary to treat the hypotension and shock. Diuretics are often part of the treatment. Intravenous furosemide will increase renal blood flow. Mannitol, an osmotic diuretic, increases the blood volume and might indirectly increase urine output. If vasoressors are needed, dopamine is the best choice because of its dilatory effects on the renal vasculature when used in doses of 1–5 μg/kg/min.

In recent years the study of biologic mediators, called cytokines, has been a triumph in our understanding of inflammation, immune response, hematopoiesis, hemostasis, and shock. This group of soluble glycoproteins regulates intercellular communication, and can be pyrogens in addition to their many other effects. They act over short distances and interact with other cells via high-affinity cell surface receptors, sending a signal across the cell membrane, thus activating intracellular biochemical pathways. This is how cytokines work in hematopoiesis when they bind to receptors on bone marrow stem cells, and how they maintain our immunity in working order by binding to receptors on lymphocytes, natural killer cells, and mononuclear phagocytes.1 Unfortunately, the pro-inflammatory subset of cytokines may also be the culprits in much of the symptomatology seen in a variety of transfusion reactions.

A series of studies has created experimental models of HTRs, illustrating the role that cytokines play. (See Table 2 for an overview of the cytokines and some of their actions.) Early in the course of ABO incompatibility, tumor necrosis factor (TNF) is produced, causing fever and hypotension. Interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1) follow. IL-8 causes neutrophil chemotaxis and neutrophil activation, while MCP-1 acts in a similar manner on monocytes. Mononuclear phagocytes seem to be of prime importance in elaborating cytokines, and also cause expression of procoagulant activity through the factor VII–tissue factor pathway (see below). A heat-sensitive factor in plasma, consistent with complement, is necessary in all of the above reactions except the generation of MCP-1.2–5

While all of the former reactions were observed in vitro, a chance to authenticate these observations in vivo occurred serendipitously in a 47-year-old man participating in a study of activation of the inflammatory response by bypass surgery.6 He was group O, D+, and 100 mL of group A, D+ blood was given by accident immediately after surgery. Postoperative TNF was 27.8 pg/mL, but following transfusion the TNF rose to 387.8 pg/mL, and 48 hours later was still 133.3 pg/mL. The other patients in the study did not have a postoperative increase in TNF.

TNF is a multifunctional cytokine that also affects the endothelial cells. The result is to decrease thrombomodulin, a protein that enhances anticoagulation (through protein C). TNF also causes the endothelial cells to increase tissue factor production. Tissue factor is a lipoprotein that activates factors that lead to coagulation. Thus, TNF most likely triggers DIC in hemolytic reactions, both by driving coagulation and inhibiting anticoagulation.7

In vitro models of the extravascular hemolysis seen with IgG antibodies have also been constructed by incubating IgG-coated RBCs with monocyte suspensions. Interleukin-1ß (IL-1ß), interleukin-6 (IL-6), and interleukin-8 (IL-8) were increased in one study,8 while TNF was more significantly elevated in another.9 IL-1ß has many biologic effects, including fever, malaise, T and B cell activation, and, in high enough concentrations, hypotension and shock (see Table 2). Both studies showed the presence of erythrophagocytosis, and with immunocytochemical stains it was shown that monocytes that had ingested RBCs were the cells producing cytokines.8 In extravascular hemolysis, the coated cells are removed this way in the spleen and in the liver. In addition, an IL-1 receptor antagonist (IL-1ra) exists, which inhibits the activity of IL-1 by competing for receptor sites. Its production is also stimulated by IgG-coated RBCs.10

In 1977, Goldfinger11 pointed out that acute HTRs are an iatrogenic disease, thus we should recognize them early and act to block the complications. We must understand that this transfusion complication is not only the most likely to result in death but usually could have...
been avoided. During the first 10 years of mandatory reporting of transfusion-associated deaths to the Food and Drug Administration (FDA), the deaths due to acute hemolytic reactions caused by “blood given to the wrong person” accounted for 49 percent of the total number of deaths. Errors existed at all stages of identification, from the time of phlebotomy to the time of transfusion.12

**Febrile Non-Hemolytic Transfusion Reactions**

Febrile non-hemolytic transfusion reactions (FNHTRs) are the most frequent complication of RBC and platelet therapy, and consist of an increase in temperature of at least 1°C in association with transfusion, without any other cause. These reactions are more common in multiply transfused patients or multiparous women, because these patients are more likely to have antibodies to transfused white blood cells (WBCs), which are often the cause of these reactions. These leukocytes are in the product incidentally, and are of no therapeutic benefit. Antipyretics are an effective treatment and the reaction is not serious. However, since fever is the initial sign of the more ominous hemolytic reactions already discussed, it is necessary to stop the transfusion and proceed with a blood bank evaluation. Other more serious causes of temperature elevation, such as hemolysis or bacterial contamination, will then be ruled out. FNHTRs are actually diagnosed by the exclusion of other causes of fever.

Not all patients who have this type of reaction will have it again after subsequent transfusions, and the reaction may be prevented entirely by the use of antipyretics as pretreatment. However, after a second reaction it is common practice to issue leukocyte-reduced products. This strategy reduces the occurrence of FNHTRs, but does not eliminate all of them, and is more likely to be of benefit with the transfusion of red cells (RBCs) than with the transfusion of platelets.14 The reason for the persistence of these reactions, even after leukocyte reduction, may be the production of cytokines. However, the cytokines are produced by donor leukocytes in the product, rather than by the recipient at the time of transfusion, as was described in hemolytic reactions above.

Heddle et al.15 first demonstrated that the age of platelet products, as well as the leukocyte count, correlated with the likelihood of a febrile reaction. A subsequent study showed that the supernatant portion of the platelet concentrate (PC) was more likely to cause a reaction than the cellular portion, and when a reaction occurred, there was a positive correlation with high concentrations of IL-1ß and IL-6.16 Other studies also
proved that increased levels of TNF, IL-1, IL-6, and IL-8 in platelets with longer storage time presented a greater risk for FNHTRs. Prestorage filtration was shown to prevent the production of cytokines in the products during storage. Cytokines increase in the supernatant portion of RBCs during storage, although they do not reach the levels observed in platelet concentrates. However, RBCs also are less likely to produce FNHTRs if WBC levels are reduced before storage rather than after storage.

Conclusions based on the data in these papers are that monocytes remain metabolically active during storage, and produce cytokines that will be released into the product. Monocytes make up a large percentage of the WBCs, as opposed to RBCs in PCs, and are more active in this product, because of the higher storage temperature. Bedside filtration to remove leukocytes will not remove the offending agents, which are soluble in the supernatant portion. The only realistic way to protect platelet recipients from this type of febrile reaction is prestorage leukocyte reduction.

Anaphylactic and Cutaneous Hypersensitivity Reactions

Life-threatening anaphylactic reactions may occur within minutes after the infusion of only a few mL of blood. The patient may exhibit coughing, bronchospasm, and respiratory distress, followed by vascular collapse and shock. Fever is absent, but flushing of the skin and gastrointestinal symptoms such as nausea, vomiting, or diarrhea may occur. The absence of IgA, which occurs in approximately 1 in 700 persons, can be responsible; however, the recipient must also have anti-IgA present, so the actual occurrence is substantially lower than 1 in 700. Previous pregnancy or transfusion might account for the presence of anti-IgA, but in some people who have anti-IgA and in whom IgA is absent, the immunizing event is never discovered. The antibodies may be class-specific, directed against the alpha heavy chain, or type-specific, directed against the heavy chain subclass. People with normal or deficient levels of IgA may make antibodies to the heavy chain subclass that they do not possess (two antigenically distinct subclasses exist). The anti-IgA that causes these reactions is almost always a potent IgG or IgM antibody, not IgE antibody. Occasionally, other antibodies can be the cause, such as those directed at soluble plasma proteins or drugs such as penicillin.

The severity and rapid onset of this reaction illustrates the importance of the transfusionist staying with the patient during the first 15 minutes of the transfusion. The blood component must be stopped immediately and the hypotension vigorously treated. Epinephrine subcutaneously administered early in the course of treatment is vital. Known IgA-deficient patients with anti-IgA should receive blood without IgA. Deglycerolized or extensively washed RBCs will suffice. If components with plasma are needed, there is no other alternative; IgA-negative products from an IgA-deficient donor must be provided.

Cutaneous hypersensitivity or allergic reactions commonly cause urticaria and local erythema in the absence of fever. The allergies may be to plasma proteins. These reactions are mild and occur commonly. It is sensible to salvage the blood component, rather than increasing donor exposure by discarding it and transfusing another product. The transfusion may be paused while an antihistamine is administered, then restarted when the symptoms subside. Judgment must be practiced; if the reaction involves systemic signs, it might progress to an anaphylactic reaction and should be stopped. If a patient has a history of these reactions, pretreatment with antihistamines is helpful. In patients with a history of severe reactions, RBCs may be washed prior to transfusion to remove plasma proteins.

Mild cutaneous hypersensitivity and anaphylaxis most likely represent two ends of a spectrum. Antigen-antibody interactions stimulate the release of histamine from mast cells and basophils, and lead to the generation of complement-derived anaphylatoxins. Donor basophils may cause the release of histamine into the supernatant portion of stored blood components. However, it is unclear whether these levels of histamine are enough to be clinically significant, and prestorage leukocyte reduction can be helpful. Allergy or anaphylaxis that is generated in vivo will not be influenced by leukocyte reduction.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) results from insult to the lungs and occurs in the few hours following a transfusion. Passive transfer of donor antibody reacting with the recipient’s white cells is the usual cause of TRALI. Therefore, any blood component containing plasma can be implicated. Respiratory distress develops with severe hypoxemia and the chest x-ray will show pulmonary edema, but the patient is not in heart failure or volume overload. Fever, chills, and
hypotension are often present. The mechanism for the injury and the reason it occurs in the lungs is unclear, but it is believed that complement is activated and C5a, a granulocyte chemotaxin, recruits these leukocytes to the lungs. An animal model has suggested a requirement for complement in the presence of an antigen-antibody reaction.\(^{27}\) Damage from neutrophil lysosomal enzymes is sustained in the endothelial wall followed by fluid entering the alveolar space.

In a review of 36 cases, Popovsky and Moore\(^{28}\) find that all reactions began within 4 hours of transfusion. All patients required oxygen support, with most needing mechanical ventilation, but 81 percent made a complete recovery within 4 days. Two patients died and it was believed that the episode of respiratory distress was a contributing factor. In 89 percent of the cases, granulocyte antibody or granulocyte and HLA antibodies were found in the donors.

In another series, Popovsky et al.\(^{29}\) discuss five patients from the Mayo Clinic where leukoagglutinating antibodies were found in the serum of one donor for each patient. Four of the donors had HLA-specific antibodies, and in three cases one antibody corresponded to an HLA antigen in the recipient. Anti-NB2\(^{30}\) and anti-NA2\(^{31}\), which are granulocyte-specific antibodies, as well as anti-5b\(^{32}\), have all been documented in cases of TRALI. In the latter, the corresponding antigen is from a diallelic system (5a/5b) found on granulocytes, lymphocytes, and platelets. The anti-NB2 came from a female donor with three children. She had donated blood 21 times, and TRALI had never occurred with her donated blood even though the frequency of NB2 is 32 percent. Despite the fact that there are many women with multiple prior pregnancies in the donor pool, this type of transfusion reaction is rare. In Popovsky and Moore’s series of 36 patients, the majority of patients had received general anesthesia, as did the patient with the NA2 reaction. The patient who received the anti-NB2 had thrombotic thrombocytopenic purpura (TTP) and was undergoing plasmapheresis.\(^{28}\)

Van Buren et al.\(^{30}\) suggest that in all of the above situations, there may be hypoxic tissue damage that makes patients more susceptible. This theory is important because when patients have other sources of compromise it is more likely that respiratory distress would be attributed to the underlying illness. Yet, with aggressive support, sometimes including steroids, respiratory distress is not only reversible, but normal lung function can return. Thus, this reaction must be recognized. Once a donor has been found to have an antibody that causes this complication, the transfusible product should be restricted to washed or frozen RBCs, and the donor should be deferred from donating products containing plasma.

**Bacterial Sepsis**

Of the 355 deaths related to transfusion in the first 10 years of reporting to the FDA, 26 were caused by bacterial sepsis and 13 from platelet products.\(^{12}\) Yet bacterial sepsis may be underestimated as an important cause of transfusion-related morbidity and mortality. Chills, high fever, and hypotension may rapidly progress to endotoxin-mediated shock, with a mortality rate that approaches 50 percent.\(^{33}\) Skin flora, such as *Staphylococcus epidermidis*, diptheroides, *Micrococcus*, and *Sarcina* species, are more likely to grow in platelets that are stored at room temperature. Psychrophilic organisms, those that grow in the cold and can utilize citrate as a substrate for energy, are a significant hazard. Some examples are *Pseudomonas* species, *Yersinia enterocolitica*, *Campylobacter*, and *Serratia* species.\(^{34}\)

Bacteria may contaminate the unit as a result of incomplete cleansing of the phlebotomy site, be present in the donor blood at the time of collection, be introduced during preparation for transfusion, or exist in or on the equipment used for collection. To confirm a septic reaction, cultures of the blood component and the patient’s blood should grow the same organism. A gram stain on the transfused component can be positive, but if not, sepsis is not ruled out. In febrile reactions, it is important to send the remainder of the component to the blood bank so it can be cultured. These reactions may seem like other febrile reactions at first, then become more severe and progress to shock. It might not always be clear which blood component was responsible if the transfusion was more than one unit. Thus, all units would have to be investigated. Treatment includes IV antibiotics and appropriate care for endotoxic shock (fluids, vasopressors, etc.).

*Yersinia enterocolitica* is a psychrophilic organism that can be present in donors who have a gastrointestinal (GI) illness near the time of donation, or who are in an iron overload state. Unfortunately, it also can be present in asymptomatic donors. The Centers for Disease Control (CDC) investigated seven cases of transfusion-associated *Y enterocolitica* between 1987 and 1989.\(^{34}\) All seven patients had received RBCs, and five died. After an investigation identified the implicated donors,
testing for antibody against the specific strain found in each case was performed, and six of the donors had the appropriate serologic findings. Four reported a GI illness in the month prior to donation, and one developed symptoms the day he donated. Two donors denied any illness, but one stated that household members had a GI illness, which makes one suspect an asymptomatic infection in the donor. This organism is a gram-negative endotoxin-producing organism that begins to exhibit logarithmic growth after a lag phase of up to 20 days in RBCs stored at 4°C.35

Three cases of *Serratia marcescens* were found in Denmark in 1991, all resulting from blood transfused after collection into contaminated blood bags.36 In two of the cases the fresh frozen plasma from the same donation was tested and found to be positive. This organism, a gram-negative rod that occurs ubiquitously in soil, in water, and on plant surfaces, was even able to survive freezer temperatures.

Morrow et al.37 described a series of seven septic reactions, one fatal, caused by PCs. The temperature elevations in the patients were higher than those of FNHTRs, but took as long as 4 hours to peak. This finding underscores the need to return components to the blood bank after febrile reactions. If they are thrown away, it is often too late to retrieve the bag after a reaction declares itself as sepsis. Five of these infections were due to skin flora and, interestingly, four of the PCs had been stored for 5 days. Thus, these organisms may need to grow to high enough concentrations before being able to cause infection.

A number of studies have suggested that prestorage WBC filtration is effective in reducing the likelihood of *Yersinia enterocolitica* growth in RBCs; however, there seems to be enough time needed for the WBCs to engulf the organisms.38–41 These studies do not reach a consensus on what amount of time is needed, what filters are best, or at what stage during component preparation filtration should take place. It is not known what effect filtration will have on other organisms. However, in a study by Wenz et al.,42 filtration of random-donor platelet-rich plasma prior to the production of PCs was not seen to cause any increase in the growth of several organisms that commonly grow in this component.

**Transfusion-Associated Graft-Versus-Host Disease**

Transfusion-associated graft-versus-host disease (TA-GVHD) appears to be a more severe version of the graft-versus-host disease that follows allogeneic bone marrow transplant. These diseases share most symptoms, including fever, skin rash, hepatitis, and watery or bloody diarrhea. The mechanism is the foreign T-lymphocytes (graft), which engraft and begin to multiply in the transfusion recipient (host) and attack “foreign” tissue. The host usually is immunocompromised, as is the case in bone marrow transplant recipients. In these transplant patients, however, the bone marrow is the graft, thus this site is spared. In TA-GVHD the bone marrow is affected, and pancytopenia results, accounting for the greater severity. The disease onset is less than 30 days from transfusion. Any product rich in lymphocytes, including RBCs, PCs, and granulocyte concentrates, can be implicated. The mortality rate appears to be 85 percent to 90 percent.43 Cytogenetic or HLA typing of the patient’s lymphocytes after symptoms appear shows the donor type, confirming that engraftment has taken place.

Transfusion recipients who are immunocompromised are at risk for this complication. Included are lymphopenic patients, patients being treated with chemotherapy and irradiation, those with congenital immune disorders, infants who received intrauterine transfusion and need an exchange transfusion after birth, and patients with Hodgkin’s disease.

An understanding of another risk group has unfolded in recent years. TA-GVHD occurred in 1986 in a Japanese patient who was not believed to be immunocompromised.44 He was transfused with fresh blood following cardiac surgery. Other cases in immunocompetent recipients were also observed. Many occurred following transfused components that were donated by relatives. We now know that if the blood donor is homozygous for one of the recipient’s HLA haplotypes, the donor’s lymphocytes may not be recognized as foreign and destroyed, even in the face of a normal immune system. Thus the transfused lymphocytes are free to attack the host. There is a greater risk of this occurrence if the blood product is from a relative or from one member of a genetically homozygous population to another. Using a mathematical model, Ohto et al.45 showed the frequency of risk of transfusion of blood from HLA homozygotes to HLA heterozygotes with a shared haplotype in different population groups. In American Caucasians, the risk for first-degree relatives is 1 in 475, whereas unrelated persons have a risk of 1 in 7.174. In contrast, the Japanese risk among first-degree relatives is 1 in 102, and unrelated persons have a risk of 1 in 874.45
No treatment influences the outcome in these patients, and the focus is on prevention. Transfusion recipients who are immunocompromised, receiving blood from a relative, or receiving HLA-matched platelets of an A or Bu grade should receive irradiated products. The dose is 25 cGy. At this dose the effectiveness of RBCs and platelets should not be adversely affected.

At this time, the lower threshold for the number of lymphocytes required to cause this reaction is unknown. The only approved prevention is irradiation, and leukocyte reduction is not appropriate for this use. However, one study using an allogeneic mixed-lymphocyte reaction as an in vitro model of TA-GVHD has shown encouraging results with the use of leukocyte reduction.

Perhaps we will learn more about this subject in the future.

Transfusion-Associated Circulatory Overload

Increases in blood volume, which are possible with transfusion of any blood component, may result in circulatory overload. Infants, the elderly, and those with preexisting cardiac disease are more susceptible. Chronic anemia is often compensated with an increased plasma volume; therefore, transfusion in these individuals may result in volume overload. Patients exhibit dyspnea, a rapid increase in systolic blood pressure, and pulmonary edema. The transfusion should be stopped and therapy started with diuretics, oxygen, and mechanical ventilation, if needed.

Strategies exist to prevent this outcome. Transfusions in susceptible patients should proceed at a slow rate, based on the degree of impairment. If the length of an RBC transfusion needs to exceed 4 hours, the unit can be issued from the blood bank in aliquots. Diuretics may be administered prior to transfusion if necessary. Pediatric patients requiring platelets, but unable to tolerate this volume, can have their PCs “super concentrated.”

A series from the Mayo Clinic showed that 1 in 708 patients transfused with RBCs developed circulatory overload. This rate was observed during the years when a transfusion consultation service was available. In the 7 years prior to the service’s availability, the rate of documented cases of TACO was only 1 in 3,168. This difference suggests that physicians need to be aware of the risk of this complication.

Conclusion

Some transfusion reactions are avoidable; others are not. Knowledge of the consequences discussed in this article should prompt those who order blood to evaluate the risks versus the benefits in all cases. The quick recognition of transfusion reactions rests with the entire patient care team. One point that is not new, but will never be outdated, is that careful attention to procedure is necessary—from the phlebotomist, to the blood bank technical staff, to the transfusionist. Not deviating from established procedures minimizes errors that otherwise may lead to unnecessary and devastating consequences.

Potential strategies to treat or prevent some reactions may appear in the future, such as blockage of the actions of cytokines early in the course of acute hemolytic reactions. With further study there may be enough justification for wider application of prestorage leukocyte reduction. In the meantime, positive results can be achieved with awareness and attention to detail.

References

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