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Use of Uncrossmatched Erythrocytes in Emergency Bleeding Situations

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UNCROSSMATCHED erythrocytes are a lifesaving bridge between a hemorrhaging patient of unknown ABO blood group not receiving erythrocyte transfusions and the provision of crossmatched units. Unless the recipient's ABO group is known, group O uncrossmatched erythrocytes will be issued, which are compatible with the preformed anti-A and/or anti-B (hemagglutinins) that are present in all recipients who are not blood group AB (table 1). Issuing group O erythrocyte units prevents acute, intravascular hemolytic reactions from occurring when uncrossmatched erythrocytes are transfused to a recipient of unknown ABO group. An acute (occurring within 24 h of the transfusion) intravascular reaction occurs when complement-fixing antibodies, such as the naturally occurring IgM isotype anti-A and/or anti-B found in all recipients who are not blood group AB, bind to their target antigen and fix complement, thereby causing the destruction of the erythrocytes inside the vascular system.[1] These reactions can be life threatening because of the nature of the substances released from the lysed erythrocytes. In contrast, an extravascular hemolytic reaction is caused by IgG antibodies and tends to be less life threatening because the erythrocytes are destroyed in a contained manner in the liver and spleen, thereby not releasing intra-erythrocyte substances directly into the bloodstream. Thus, uncrossmatched erythrocytes can be administered to any patient with severe anemia or acute hemorrhage whose life would be compromised by waiting for crossmatched erythrocytes to become available. This Clinical Focus Review will briefly discuss how the blood bank performs pretransfusion testing, review the safety of using uncrossmatched erythrocytes in patients requiring urgent transfusions, and examine some newly emerging trends in the kinds of blood products that are used in the resuscitation of trauma patients.

What Does the Blood Bank Do with the Patient's Specimen?

When the blood bank receives a specimen for pretransfusion testing, the technologists follow procedures that comply with U.S. Food and Drug Administration and AABB (formerly the American Association of Blood Banks) regulations to ensure transfusion safety. The technologists check that the patient identifiers are printed on the requisition and on the tube of the patient's blood, and that these identifiers match each other. If a discrepancy is found, the sample is destroyed and not tested, as there is a high rate of wrong blood-in-tube errors, where the blood in the tube does not come from the person whose name is on the label.[2,3]

The sample then undergoes two different tests: one test determines the recipient's ABO group (sometimes called a "type"), and the other test determines if the recipient has additional antibodies against erythrocytes other than the expected anti-A or anti-B (sometimes called a "screen," hence, these two tests are often collectively referred to as a "type and screen"). Under normal circumstances, a type can be performed and interpreted in 15 min, while the antibody screen can take up to 45 min to perform and interpret. In a patient without unexpected erythrocyte antibodies (*i.e.*, a negative antibody screen) on the current sample, and in any historical samples that had been previously performed, many hospitals can use a computer to select and crossmatch an ABO compatible erythrocyte unit

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Table 1. Serologic Findings of the Various ABO Groups, and Erythrocytes and Plasma Compatibilities

		Antigens on Erythrocytes	Antibodies in Plasma	Erythrocytes That Can Be Safely Transfused	Plasma That Can Be Safely Transfused
Recipient ABO Group	A	A	B	A, O	A, AB
	B	B	A	B, O	B, AB
	O	None	A, B	O	A, B, O, AB
	AB	A, B	None	A, B, AB, O	AB

The emerging evidence of the safety of transfusing group O whole blood and group A plasma in the resuscitation of trauma patients of unknown ABO group is challenging the dogma of compatible plasma groups in this type of recipient. The safety of using group O whole blood and group A plasma for recipients of unknown ABO group in nontrauma situations has not yet been demonstrated.

in nonurgent situations. Known as an electronic crossmatch, this process ensures that an ABO compatible erythrocyte unit is issued for the recipient and it takes ~5 min to perform. Thus, in a patient without unexpected antibodies, crossmatched erythrocytes can be available in about an hour after the blood bank receives a properly labeled sample and a second confirmatory specimen for patients new to that blood bank. In a patient who has a positive antibody screen, the specificity of the antibody(ies) must be determined, erythrocyte units lacking that specific antigen(s) must be found, and a lengthier crossmatch process known as a serologic crossmatch must be performed, wherein the recipient's plasma is mixed with a sample from the donor erythrocyte unit. Regardless of the required crossmatching process, when all of the pretransfusion testing is complete and the erythrocyte units are shown to be compatible with the recipient's plasma, the units are called crossmatched erythrocytes. These processes are summarized in figure 1. If the patient requires urgent erythrocyte transfusion before the type and screen is finished, uncrossmatched erythrocytes will be issued.

What's the Difference between Crossmatched and Uncrossmatched Erythrocytes?

Crossmatched erythrocytes have been shown to be compatible with the recipient's plasma. However, there is nothing different about the actual erythrocyte unit itself, whether it is issued in a crossmatched or uncrossmatched manner. There are no differences in the quantity of erythrocytes in a crossmatched *versus* uncrossmatched unit, the additive solution used, the nature of the donor, or the unit's maximum

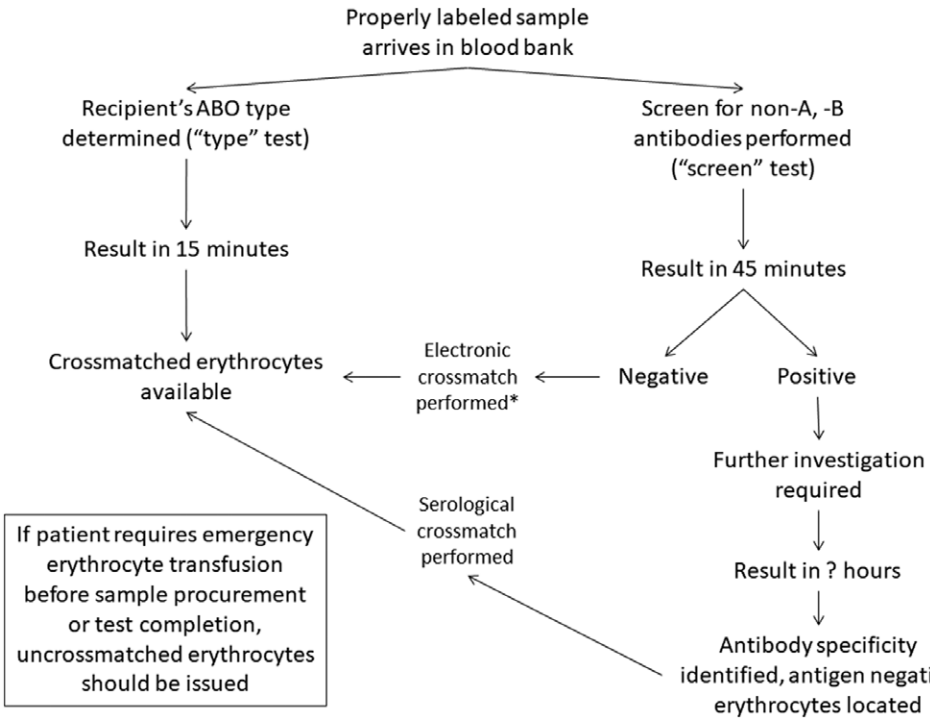

Fig. 1. Description of the blood bank's workflow in establishing the recipient's ABO type and detection of unexpected erythrocyte antibodies other than anti-A and/or anti-B. The times listed represent the ideal turnaround times. The amount of time required to investigate a positive antibody screen and find antigen negative units depends on the nature and number of the antibody(ies) detected. *The electronic crossmatch can be performed if the patient's current antibody screen is negative along with any historical antibody screens.

potential storage length. Note that not all uncrossmatched erythrocyte units are group O; if the patient's blood group is known but the antibody screen is not yet completed, ABO group-specific uncrossmatched erythrocyte units can be issued (*e.g.*, a group A erythrocyte unit could be issued to a group A recipient).

How Can Uncrossmatched Erythrocytes Be Obtained?

Many hospitals stock uncrossmatched erythrocytes in refrigerators that are located in areas of the hospital where patients with massive bleeding may be located, such as the emergency department, intensive care units, and in the operating room area. Uncrossmatched erythrocytes can also be ordered from the blood bank itself, and are often ordered by telephone in emergency situations when it would be impractical to order erythrocytes using a computer or paper-based order entry system due to time constrains. Depending on blood bank policy, uncrossmatched erythrocytes can often also be ordered along with fixed quantities of platelets and plasma for a patient who is predicted to have a massive transfusion by ordering a "massive transfusion protocol (MTP)." The exact quantities of products issued in an MTP, and even the exact name of the protocol, can vary by hospital, so anesthesiologists are advised to consult with their blood bank so that they understand how to order these products and what will be supplied when an MTP is ordered.

What Is the Major Concern in Using Uncrossmatched Erythrocyte Units?

As uncrossmatched erythrocyte units tend to be group O (or ABO identical with the recipient), there is no risk of an immediate, intravascular hemolytic reaction that might occur if, for example, a group A unit is transfused to a group O recipient. However, there is the potential risk of a less severe type of hemolytic reaction occurring if the recipient has unexpected antibodies that target other erythrocyte antigens like D, E, Kell, and Duffy, among others, and the uncrossmatched erythrocyte unit happens to have the corresponding antigen on the surface of the erythrocytes. As these antibodies tend to be of the IgG isotype, they do not normally fix complement and do not usually cause intravascular hemolysis. Instead, erythrocytes coated with IgG antibodies are removed in the liver and spleen without significant liberation of the intracellular contents into the bloodstream. This type of hemolysis is known as extravascular hemolysis and rarely life threatening; however, these reactions can shorten the circulating life span of the transfused erythrocytes, thereby reducing the effectiveness of the transfusion.

Fortunately, encountering a patient with an unexpected antibody is uncommon. A study at an Australian hospital demonstrated that only 1.9% of all patients on whom a type and screen was performed demonstrated a clinically significant (*i.e.*, capable of causing hemolysis) non-ABO antibody.[4] In this study, about 2% of patients admitted to the emergency department or trauma unit had clinically significant antibodies, and the frequency increased with the patient's age. A study of transfused American veterans revealed a similar frequency of 2.4%, although not all of the antibodies reported in this study were clinically significant.[5] Higher alloimmunization rates of approximately 10% have also been reported.[6] The risk of a patient having an unexpected erythrocyte antibody increases proportionate to the likelihood that that patient had been exposed to foreign erythrocyte antigens through pregnancies and/or previous transfusions.

Numerous studies have demonstrated the serologic safety, that is, the lack of acute or delayed (*i.e.*, occurring more than 24 h following the transfusion) hemolysis, among recipients of uncrossmatched erythrocytes. Boisen *et al.* reviewed 11 published studies that reported on the incidence of hemolysis among recipients of uncrossmatched erythrocyte units.[7] In total, 10,916 uncrossmatched erythrocyte units were issued to 2,906 recipients, and the rate of patients with detectable hemolysis determined by laboratory testing and clinical observation was 4 of 2,906 (0.1%). Thus, the overall rate of a patient having a hemolytic reaction to an uncrossmatched erythrocyte is very low.

Even in the worst case scenario, when patients who have unexpected erythrocyte antibodies are transfused with erythrocyte units that are positive for the corresponding antigen, very few actually hemolyze. In the most informative study of these "worst case scenario" patients,[8] seven patients with clinically significant antibodies that are capable of causing erythrocyte destruction, out of a total of 262 patients who were transfused with uncrossmatched erythrocytes, were transfused with 1 to 4 units of uncrossmatched erythrocytes that were later found to be incompatible with their antibodies; only one patient had biochemical evidence that was suggestive of a hemolytic reaction. That patient had increases in lactate dehydrogenase and total bilirubin, and a decrease in haptoglobin several days after receiving the uncrossmatched unit. No clinical findings (*e.g.*, the appearance of jaundice, hematuria, and fever, among others) suggestive of a hemolytic reaction were mentioned in the report.[8] In fact, since this patient had several other potential etiologies for these biochemical changes, it is not entirely clear that a hemolytic reaction actually occurred.

In another series of 218 uncrossmatched erythrocyte recipients,[9] one patient who had several clinically significant antibodies that are known to cause erythrocyte destruction received four uncrossmatched erythrocyte units due to a gastrointestinal hemorrhage, developed a positive Coomb's test (direct antiglobulin test), as well as changes in total bilirubin and creatinine concentrations suggestive of hemolysis. The other biochemical markers of hemolysis were not measured. Further testing revealed that at least one of the uncrossmatched erythrocyte units must have been positive for some of the antigens against which the patient had antibodies.

Thus, the balance of probabilities in this case suggests that the patient hemolyzed from receipt of the uncrossmatched erythrocyte units. This patient died within a week after the uncrossmatched erythrocyte transfusion, although the role of the hemolysis in his demise is unclear. There were six other patients in this study who also had detectable clinically significant antibodies who did not hemolyze following transfusion of uncrossmatched erythrocytes. Overall in this study, only 1 of 218 (0.5%) patients who received uncrossmatched erythrocytes demonstrated evidence of hemolysis. Thus, these two studies, and the others reviewed in Boisen *et al.*,[7] demonstrate that the rate of hemolysis in hemorrhaging patients who urgently require erythrocyte transfusion is very low, although the exact risk of hemolysis is hard to quantify based on the small number of recipients who had evidence of hemolysis. Uncrossmatched erythrocytes are safe to transfuse in patients whose life would be compromised by the typically short time required to provide crossmatched erythrocytes.

The studies demonstrating the very low rate of hemolysis after transfusion of uncrossmatched erythrocytes have all been in hemorrhaging patients requiring urgent transfusions; the safety of administering uncrossmatched blood to otherwise stable patients without a valid type and screen cannot be inferred from these studies. For example, a stable postoperative patient who requires erythrocyte transfusion to reach a predetermined Hb concentration should not receive uncrossmatched erythrocytes, as it is unclear if the very low rate of hemolysis applies to patients other than those who required emergency transfusions.

It should be noted that detecting hemolysis caused by receipt of uncrossmatched erythrocyte units in trauma patients using laboratory markers is confounded by the nonspecific nature of these tests. Seheult *et al.* demonstrated in a cohort of trauma patients who received ABO identical whole blood (no immune-mediated hemolysis would be expected to occur in these patients) that early in their hospital admission, the lactate dehydrogenase concentration was markedly above the upper limit of normal, while the haptoglobin concentration was at the very low end of normal.[10] The same changes in these parameters would be observed if hemolysis had occurred. Thus, determining if hemolysis actually occurred following the transfusion of uncrossmatched erythrocytes requires clinical and laboratory correlation.

Should Uncrossmatched Erythrocytes Be RhD+ or RhD–?

RhD– females of childbearing age, or those whose RhD status is unknown when they urgently require an erythrocyte transfusion, should receive RhD– uncrossmatched erythrocytes. Some transfusion services have adopted a similar policy for all boys and girls who are younger than 18 yr of age. If an RhD– female of childbearing potential (typically defined as younger than 50 yr old) receives an RhD+ transfusion of erythrocytes during her resuscitation, there is a risk she could become alloimmunized to the RhD antigen, which could lead to hemolytic disease of the fetus and newborn if she subsequently became pregnant and her fetus is RhD+.[11] Three separate retrospective studies of hospitalized RhD– patients who received at least one unit of RhD+ erythrocytes found an RhD alloimmunization rate of approximately 22%.[12–14] Similarly, three studies of RhD– trauma patients who received RhD+ uncrossmatched erythrocytes found rates of RhD alloimmunization between approximately 10 to 25%.[15–17] These rates are considerably lower than the approximately 80% alloimmunization rate seen when healthy RhD– volunteers are intentionally transfused with RhD+ erythrocytes.[18–20]

It is common practice in North America to provide RhD– platelets (PLT) to RhD– children and females of childbearing age. There is a very low (1.4%) rate of RhD alloimmunization following the administration of RhD+ PLTs to RhD– recipients, as PLT units contain very few erythrocytes.[21]

However, sometimes an RhD– female of childbearing age might receive RhD+ erythrocytes or PLTs during her resuscitation because the blood bank's RhD– product inventory had been depleted and could not sustain the patient's ongoing blood product needs (only about 18% of erythrocyte donors in the United States are RhD–), or perhaps because the patient's age or sex had been initially misidentified. In this situation, there are several options to prevent RhD alloimmunization. Rh immunoglobulin (generically known as RhIg; some brand names include RHoGAM and WinRho) can be administered, as it has been shown to be effective in preventing RhD alloimmunization in RhD– pregnant women.[22–24] One standard vial of RhIg, containing 300 micrograms (1500 IU), is effective in neutralizing about 15 ml of erythrocytes. Since an erythrocyte unit contains approximately 200 ml of erythrocytes, ~14 vials of RhIg would be required to neutralize all of the erythrocytes. A standard vial of RhIg is sufficient to neutralize dozens of RhD+ PLT transfusions due to the small quantity of erythrocytes in PLT units.[25] Ideally, RhIG should be administered within 72 h of RhD+ erythrocyte exposure. If the patient becomes (or was already) RhD-alloimmunized, then RhIg should not be administered.

If an RhD– patient receives more than two RhD+ erythrocyte units, one recommendation is to not attempt to neutralize them with RhIg alone, but to perform an erythrocyte exchange transfusion to remove as many of the incompatible RhD+ erythrocytes as possible.[26] Erythrocyte exchange transfusions in adults typically require the use of a machine to remove the patient's autologous erythrocytes and replace them with RhD– erythrocytes; this can require many units of erythrocytes depending on the patient's blood volume. After the exchange, a smaller dose of RhIg can be administered to neutralize the RhD+ that remain in circulation. This procedure was well tolerated in two RhD– trauma patients who received RhD+ erythrocytes during their resuscitation, and in one patient who had an antibody screen performed six months after the RhD+ erythrocyte exposure did not develop anti-D.[27,28]

It should also be noted that other than providing erythrocytes that are matched or identical to the A, B, and RhD antigens, most American blood banks do not generally issue erythrocytes that are matched for any of the several hundred other erythrocyte antigens unless the patient has specific erythrocyte antibodies. The exception is for patients with sickle cell disease because their rate of alloimmunization is much higher than the rate in the general recipient population,[29] and for certain other chronically transfused patients to prevent alloimmunization. Thus, if a recipient of uncrossmatched erythrocytes produces an antibody other than anti-D, this is an adverse event that would not necessarily have been prevented had crossmatched erythrocytes been issued, and should not be considered as an adverse event of transfusing uncrossmatched erythrocytes.

Newly Emerging Trends in the Kinds of Blood Products Used in Trauma Resuscitation

In the United States, only approximately 2 to 3% of donors are group AB, the universal donor of plasma because it does not contain anti-A or anti-B (table 1). Thus, an AB patient or a patient with an unknown blood group who is massively hemorrhaging can quickly deplete a hospital's inventory of AB plasma. To optimize the AB plasma inventory, group A plasma is increasingly used for trauma patients of unknown ABO group, as shown in a recent survey of American trauma centers that found that 69% use group A plasma in this context.[30] The majority of recipients (~85% of Caucasians) will be either group O or A, thus group A plasma will be compatible. However, for the minority of patients who are group B and AB, this plasma will be incompatible with their erythrocytes and could potentially destroy them. In spite of this risk, 62% of these American trauma centers do not have a limit on the number of group A units that can be transfused to trauma patients of unknown ABO group, and 79% do not titer the anti-B in the group A unit.[30] Of the centers that titered the anti-B, the range of acceptable titers ranged from less than 25 to less than 100.[30] If titering is performed, units with higher anti-B titers would not be used for trauma patients of unknown ABO group. Using group A plasma in this setting has been shown to be safe; early and in-hospital mortality, as well as hospital length of stay were evaluated in a retrospective study of 354 group B and AB trauma patients, compared to 809 group A trauma patients who received group A plasma during their resuscitation.[31] The B and AB patients received a mean of four units of group A plasma, and no significant differences in the study endpoints were found. In summary, due to the often limited inventory of group AB plasma, and the emerging evidence suggesting the safety of transfusing group A plasma to massively bleeding patients, anesthesiologists should be aware that an increasing number of hospital transfusion services are issuing group A plasma to massively bleeding patients.

Based on the significant military experience using whole blood (WB),[32,33] several civilian centers have begun using cold stored, group O WB for the resuscitation of trauma patients even before the recipient's ABO group is known. Although the group O erythrocytes in the WB would be compatible with all recipients, recipients who are not group O would be at risk of hemolysis from the plasma in the group O WB as it contains both anti-A and anti-B. However, a recent study of trauma patients who received at least one unit of WB during their resuscitation did not reveal laboratory or clinical evidence of hemolysis among the 27 recipients who were not group O, compared to the 17 group O recipients.[10] Of note, the WB units in this study contained low titer anti-A and anti-B (less than 50). Another major American trauma center that uses WB in trauma resuscitation employs a titer less than 200. The optimal titer threshold that prevents hemolysis, but is not prohibitively hard for the blood center to procure, has not been determined.

Transfusion of uncrossmatched erythrocytes can be lifesaving in the setting of acute hemorrhage when erythrocytes must be transfused before the completion of pretransfusion

Table 2. Key Messages from This Clinical Focus Review

1. Crossmatched erythrocytes can be available for most patients within an hour of the blood bank receiving a correctly labeled sample.
2. Uncrossmatched erythrocytes should not be denied to an acutely hemorrhaging or severely anemic unstable patient if the results of pretransfusion testing are not available when the patient requires an urgent transfusion.
3. The literature indicates an overall risk of hemolysis following the transfusion of uncrossmatched erythrocytes to patients needing an emergency transfusion of 0.1%, however, uncrossmatched erythrocytes should not be used in otherwise stable patients who can wait until crossmatched units become available.
4. RhD – erythrocytes (crossmatched or uncrossmatched) should be preferentially administered to women of childbearing potential whose RhD type is unknown, or to patients where making this determination is difficult; all others, including males, should receive RhD+ erythrocytes.
5. The risk of a RhD– patient forming anti-D after receipt of RhD+ erythrocytes is relatively small, so switching a RhD– patient with significant ongoing erythrocytes transfusion needs to RhD+ (crossmatched or uncrossmatched) erythrocytes will help to preserve the inventory of RhD– erythrocytes for females of childbearing potential (typically defined as ≤ 50 yr old).
6. The risk of forming unexpected antibodies after receipt of uncrossmatched erythrocytes should be identical to that after receipt of crossmatched erythrocytes.
7. Emerging evidence suggests that it is safe to transfuse group A plasma and group O WB to traumatically injured recipients of unknown ABO group. Larger studies will be required to prove these concepts and the safety of using these products for nontraumatically injured patients has not been proven.

testing. In appropriate patients, the risks of administering uncrossmatched erythrocytes is very low and outweigh the risks of waiting for crossmatched erythrocytes to become available. The key messages of this Clinical Focus Review are summarized in table 2.

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Competing Interests

The authors declare no competing interests.

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Appendix

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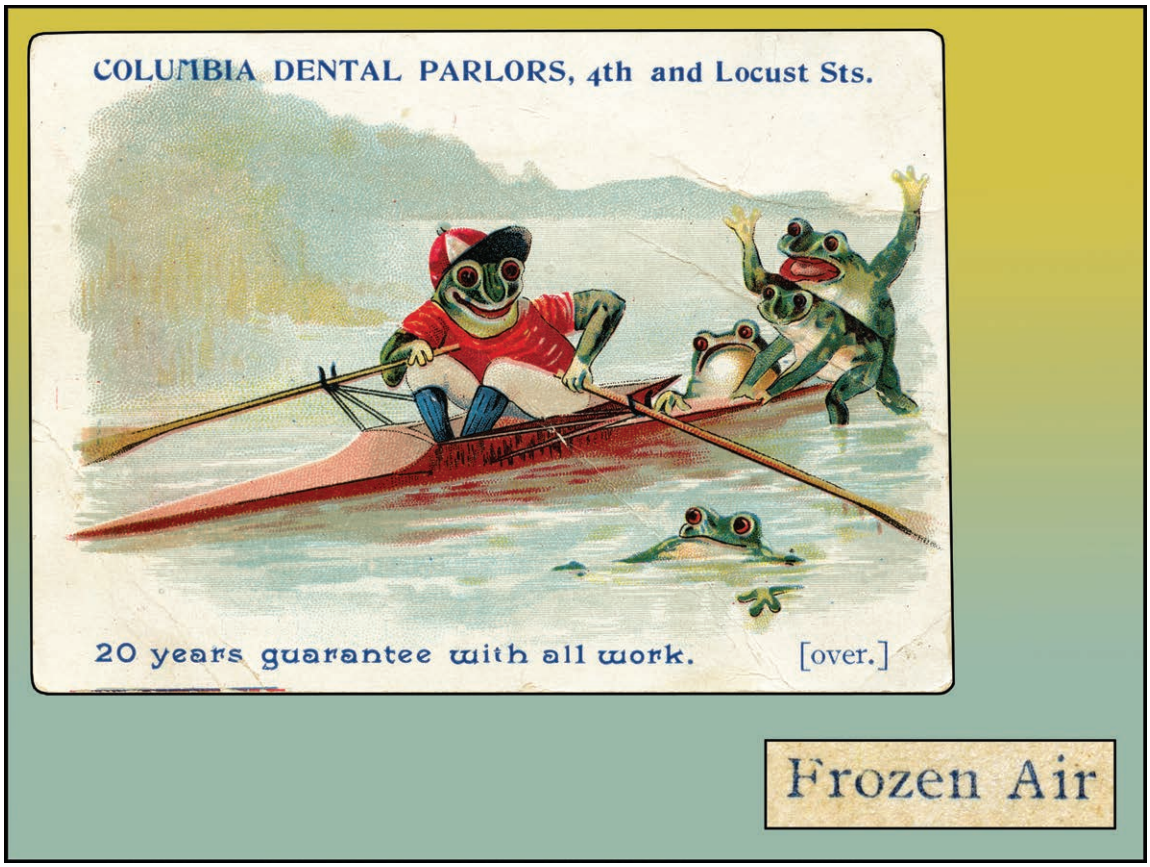
"Frozen Air" Anesthetics in St. Louis by Columbia Dental Parlors



In the wake of the 1893 World Columbian Exposition, a number of "Columbia" Dental Parlors sprung up around the United States. The trade card from one of these parlors depicts four frogs assisting a fifth in rowing a single scull (*top*). The back of the card locates the parlors in the "Trust Building" at "4th and Locust" Streets, which apparently references a former St. Louis Trust Company Building in St. Louis, Missouri. Also on the reverse of this card is a reference to anesthesia with "Frozen Air" (*bottom*). From ether spray to ethyl chloride (and eventually to Somnoform), a variety of vapocoolant sprays were used topically to provide chilling anesthesia for dental and minor surgical cases. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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