# Massive transfusion: a question of timing, detail, a golden ratio

## Kevin B. O'Reilly

December 2014—Here it was, the kind of massive postpartum hemorrhage case for which the team at Duke University Medical Center had spent months preparing. The multidisciplinary group had agreed on which laboratory tests would be done in such a case, determined which blood products would be delivered, and decided which members of the OB team would be sent racing to retrieve the potentially life-saving package.

For the two labor-and-delivery nurses designated as runners, the quickest way to get down to the blood bank was the elevator. The elevator was working, but the nurses' badges did not allow them access to it.

"They had to run all the way down the hall, then all the way down the stairs. It took much longer," says Evelyn Lockhart, MD, a pathologist who specializes in transfusion medicine and led the Duke team in implementing a massive transfusion protocol for postpartum hemorrhage.

"It was a surprise to us all," Dr. Lockhart says. Fortunately, the only harm associated with the inaccessible elevator was a couple of winded nurses. That is because the elevator flap came as part of a simulation, and no woman's life was in danger. It turned out that access to the elevator was restricted to emergency department personnel. That changed soon enough, before any real-life obstetric massive transfusion protocols, or MTPs, were initiated.

**Dr. Lockhart**

The story illustrates an essential truth in the world of massive transfusion, experts tell CAP TODAY. While a randomized clinical trial likely to be published could help answer persistent questions about which blood component ratio can best reduce the mortality rate in massive transfusion cases, experts say that fine-tuning the timely communication, processing, and delivery elements of the MTP are just as essential as determining what "golden ratio" of blood products to prepare.

"[Timing] is clearly important. There's plenty of data over the years to show it, and it's a common phrase that every minute counts. In some patients, it doesn't, but in these patients it really does," says John B. Holcomb, MD, director of the Center for Translational Injury Research and chief of the Division of Acute Care Surgery at the University of Texas Health Science Center at Houston.

**Dr. Holcomb**

Dr. Holcomb also is principal investigator of the Pragmatic, Randomized Optimal Platelets and Plasma Ratios trial, dubbed PROPPR for short. The 12-center study aims to compare the efficacy of a 1:1:1 ratio of plasma, platelets, and red blood cells with a 1:1:2 ratio of those same components. Half of the 680 patients enrolled were

randomized to receive transfusions using the 1:1:1 ratio, while the other half got the 1:1:2 package. The question the trial seeks to answer: Will more plasma save more lives? The primary outcomes are 24-hour and 30-day mortality.

"The rationale for the 1:1:1 ratio is that the closer a transfusion regimen approximates whole blood, the faster hemostasis will be achieved with minimum risk of coagulopathy," reads the description available at ClinicalTrials.gov (http://j.mp/propprtrial). It says: "The current [Department of Defense] guideline specifies the use of 1:1:1, and this practice is followed on almost all combat casualties. In other observational studies, leading centers have reported good outcomes across a range of different blood product ratios. For example, a 1:2 plasma:RBC ratio is used with little guidance regarding platelets. The proposed randomized trial is intended to resolve debate and uncertainty regarding optimum blood product ratios."

Because the study's results were, as of early December, under review for potential publication at a peer-reviewed medical journal, Dr. Holcomb declined to reveal what his research team has discovered. But the study may not settle all the outstanding questions, according to Pampee P. Young, MD, PhD, medical director of transfusion medicine at Vanderbilt University Medical Center. Along with Dr. Lockhart, she spoke at the CAP '14 session, "Massive Transfusion Protocols in Trauma and Obstetrics," which drew a standing-room-only crowd.

"I think most trauma surgeons and most transfusion medicine doctors will agree that something greater than 1:2 [fresh frozen plasma] to red cells is important, but whether that's 2:3 or it's 1:1 has not been definitively determined, and probably won't be for a while," Dr. Young tells CAP TODAY. "[PROPPR] is looking at 1:1 versus 1:2, but I don't think most people would argue that you need something higher than 1:2. This raises the question of whether 1:2 is sufficient, but it doesn't answer the question: Could you have a lower ratio?

"Our institution compared, while adjusting by severity of injury, 2:3 versus 1:1 and found no difference," says Dr. Young, who co-wrote a paper documenting the results involving 211 patients (Cotton BA, et al. *J Trauma.* 2008;64:1177–1183). "Looking at a historical control, we showed a 74 percent increase in survival. That's not trivial."

A key shortcoming with the previous MTP literature—largely retrospective series—that the PROPPR trial aims to address is that of survivorship bias. Richard M. Kaufman, MD, medical director of the blood bank at Brigham and Women's Hospital, explains the issue.

**Dr. Kaufman**

"The question is always: Did the FFP transfusions promote survival, or is the FFP transfusion something that happens to patients who survive? The studies have been inherently confounded. That doesn't mean the idea of transfusing plasma preemptively is wrong. It just means that you have to be cautious in how you interpret the studies," says Dr. Kaufman, assistant professor of pathology at Harvard Medical School.

For now, Dr. Kaufman and his colleagues at BWH have opted for a 1:1 ratio of plasma to red cells.

"What we have settled on is that we do feel that, in looking over cases in the past, patients really did get behind. They would get a lot of red cells and their clotting factors would get diluted. And by the time the PT and PTT came back, they would have been really hemodiluted, and then it's hard to catch up."

"There hasn't been, really, a large randomized trial comparing lab-directed therapies versus one of these fixed-ratio approaches, and there may never be such a study," Dr. Kaufman adds. "Anyway, we're just doing the best we

can. . . . It's really tricky."

**Dr. Young**

About two-thirds of hospitals with MTPs use a plasma-to-RBC ratio of 1:1 in trauma cases, Dr. Young said during her CAP '14 talk, summarizing the results of a 14-hospital survey (Young PP, et al. *Transfus Med Rev.* 2011;25[4]: 293–303). The rest use ratios involving less plasma in differing degrees, just one example of what she characterized as "wide variation" in massive transfusion practice. About half of hospitals use a ratio of red blood cells to platelets that is 6:1 or greater.

**Dr. Sanddal**

More than 60 percent do not routinely use cryoprecipitate, while 15 percent usually give recombinant factor rVIIa. Nearly 70 percent keep thawed AB plasma on hand in the event of MTP initiation, and all hospitals switch to type-specific plasma once that information is obtained, Dr. Young said.

Since 2006, the American College of Surgeons' Committee on Trauma has required that hospitals seeking trauma center verification have an MTP in place. The 2014 edition of the committee's Resources for Optimal Care of the Injured Patient states: "Trauma centers of all levels must have a massive transfusion protocol developed collaboratively between the trauma service and the blood bank."

But the ACS has avoided getting into the nitty-gritty, such as specifying the best blood component ratio for trauma centers to use in MTPs, says Nels Sanddal, PhD. He manages the college's Trauma System and Verification, Review, and Consultation Program.

"We want them to have one, we want them to monitor it, to see that it's being initiated appropriately, and we want them to follow up and see if it seems to make a difference," Dr. Sanddal says. "We're not being prescriptive about what the particular ratio of blood products is. What we want for them to do is to have one, and use it, and evaluate it."

When inspecting a trauma center, Dr. Sanddal and his team will ask both the trauma and blood bank teams for their understanding of how the MTP should work.

"We'll ask the trauma program staff: What do you think you're going to get when you initiate the massive transfusion protocol? Then we go to the blood bank and say: When you get a call for the MTP, what do you do? What do you scramble, and how do you put it together? How much time does it take? What goes down in the first cooler? What about the second cooler? We try to verify it from both ends."

Dr. Sanddal says he usually sees a "high degree of concordance," which appears to speak well of MTP communication at trauma centers across the country.

"The great news is most centers that we visit have one," he adds. "Whether or not they are initiating that protocol,

I can’t guarantee, but they have a protocol in place.”

The life-saving, complication-reducing promise of the MTP does not reside entirely in the blood component ratios transfused, Dr. Young said in her CAP ’14 talk. “The protocolization of the process matters. It’s important to have quality improvement efforts around this,” she said, urging a defined process for how MTPs are started and ended, how unused products get returned, and how cases are reviewed for problems.

Dr. Young noted research done at Stanford University Hospital that compared their experience in the two years before and after instituting an MTP. The hospital did not change its 1:1.8 ratio of plasma to red blood cells before and after, thus allowing for a natural experiment to see what kind of impact the protocol itself seemed to have. Examining patients who needed 10 or more units of red blood cells during their first 24 hours after admission, researchers found a mortality rate of 45 percent among 40 patients in the two years before implementing the MTP. Post-MTP, the death rate fell to 19 percent among 37 patients.

“Our data underscore the importance of expeditious product availability and emphasize that massive transfusion is a complex process in which product ratio and time to transfusion represent only the beginning of understanding,” the study’s authors concluded (Riskin DJ, et al. *J Am Coll Surg.* 2009;209[2]:198–205).

**Dr. Shaz**

Beth H. Shaz, MD, chief medical officer of the New York Blood Center, a member of the AABB’s board of directors, and former medical director of the transfusion service for Atlanta’s Grady Memorial Hospital, makes the point well.

“The massive transfusion protocol is about more than just the blood,” she says. “The logistics of it are not simple. . . . You really need to spell out each person’s role, and what’s expected for each step.”

She also voiced a note of hope that treatment of life-threatening bleeds will see a superior fix that bests early delivery of plasma.

“We’re getting a better understanding of early trauma induced coagulopathy, or acute trauma coagulopathy. We’re finally learning about what that is. Right now, we just have plasma to address it. As we learn more, maybe there’s something better, right?” Dr. Shaz says. “[The MTP] is the next rung on the ladder, but we’re not done.”

One potential improvement in the treatment of life-threatening bleeding is greater use of antifibrinolytics such as tranexamic acid. The CRASH-2 trial found that early use of the medication helped cut the mortality rate among trauma patients by nine percent, and the risk of bleeding death by 15 percent compared with placebo (CRASH-2 trial collaborators. *Lancet.* 2010;376[9734]:23–32). The World Maternal Antifibrinolytic Trial, WOMAN for short, has so far randomized nearly 15,000 patients as part of its study of whether tranexamic acid could help reduce deaths in severe postpartum hemorrhage. The World Health Organization already recommends the medication in treating such bleeds.

Trying to refine the MTP process at participating centers was one of the key charges for Dr. Holcomb and the team conducting the PROPPR trial. An important goal of the study was to eliminate substantial differences in blood product delivery as a factor that could skew the intended comparison between component ratios. After much work, the participating medical centers were able to reduce the median delivery time of that first round of products to eight minutes (Baraniuk S, et al. *Injury.* 2014;45[9]:1287–1295).

How can other hospitals achieve that kind of turnaround time when the MTP is initiated?

“What they should do is what we did for this study,” Dr. Holcomb says. “There’s no reason why not to do it for routine clinical practice. You get your ER doctors, blood bankers, and nurses all in the room and figure out how to make the delivery of blood products faster. You put the products in the ED. You put those blood products in prehospital, so you don’t have to rely on crystalloid. You hone every step of the practice. These patients need a different process than patients who get one unit on the floor who are hemodynamically stable.”

“We had 12 centers and 680 patients,” Dr. Holcomb says of the PROPPR trial. “We had literally hundreds and hundreds of providers who were able to do this. I think that speaks of the ability of any center to do this if they want to.”

To get the sites participating in PROPPR up to speed, Dr. Holcomb’s team organized clinical site visits that involved unannounced MTP simulations.

“We’d call or email or use whatever the system was in the hospital to say we have a massive transfusion case, that a guy’s rapidly bleeding, and we need six [units of plasma], six [units of RBC], and one [unit of platelets, typically a pool of six units]. And then we timed how long it took to get the blood products from that call to the bedside. We had an observer on the way who observed, independent of the actions being taken. If this guy had to stop and fill out 27 forms, well that’s a problem. That might be OK if the patient needs one unit of blood product and is hemodynamically stable, has a hemoglobin of six and you just want to go to seven.”

Improvement came from emphasizing the urgency to blood bank technologists and technicians, and “creating not a separate, but a streamlined process,” Dr. Holcomb says. “I would emphasize that each place is very, very different. So I’m not sure there was a common denominator, but each site could get better by many minutes.”

Dr. Holcomb’s previous research, the Prospective, Observational, Multicenter, Major Trauma Transfusion Study (called PROMMT for short), found room for improvement in transfusion among the 10 level-one trauma centers studied. Among the massively bleeding adult trauma patients studied, 10 percent of those who survived for three hours—“the peak time of hemorrhagic death”—had not received any plasma by that point, while 28 percent had not yet received platelets. “Once bleeding patients have been identified, constant ratios are not infused and heterogeneous transfusion practice persists,” the study concluded (Holcomb JB, et al. *JAMA Surg.* 2013;148[2]:127–136).

Dr. Lockhart, now associate medical director of the transfusion service at the University of New Mexico Hospital, a level-one trauma center, says that simulations are a crucial part of the iterative process of making MTPs go more smoothly. This can especially be the case at smaller hospitals where massive transfusions—defined as patients needing or predicted to need 10 units or more of packed red blood cells during the course of 24 hours—are even rarer events.

“It’s part of developing and validating the protocol, before you go live, to put it through its paces from stem to stern,” she says. “Does the team recognize when there’s excessive hemorrhage? Does the team activate the protocol appropriately? Everyone should be notified . . . there should be a communications tree in place. Are the blood samples collected that need to be collected? Are they going where they need to go? Does the runner know where they need to go—is there a clear path from point A to point B?”

In another Duke MTP simulation done in the middle of the night, a runner found an unexpectedly locked door, Dr. Lockhart says.

“The runner had to do a big loop around to reach the blood bank. You’ve got to know that sort of thing beforehand. And do [the simulation] at all times, when you’re at the most skeletal of skeletal.”

In her CAP ’14 talk, Dr. Lockhart emphasized the it-could-happen-to-you nature of massive postpartum hemorrhage and advised hospitals of any size with an obstetrics ward to be prepared. She recalled one case at Duke where more than 200 blood products were used.

She noted CDC statistics listing postpartum hemorrhage as the cause of 11 percent of pregnancy-related deaths.

About three percent of deliveries involved postpartum hemorrhage, while the overall PPH rate rose by 28 percent between 1995 and 2004, Dr. Lockhart said. Massive postpartum hemorrhage with coagulopathy is only seen in between 0.15 to 0.5 percent of births, she noted, but a routine delivery can quickly become a matter of maternal life and death.

At Duke, Dr. Lockhart took on the role as the on-call coordinator and consultant for the OB hemorrhage service. She spent "about 15 bucks" at Staples to develop toolkits to put on the labor-and-delivery crash carts as "one-stop shopping for hematologic management." Blood tubes were tied together and came with prefilled lab-routing slips. The forms were color coordinated to the tube tops. Also included are emergency release forms, transfusion algorithms, and scripts for each person's role.

When Dr. Lockhart was at Duke, the massive hemorrhage algorithm called for four units each of red blood cells and plasma and one unit of cryoprecipitate in round one, and six and six of RBC and plasma and one unit of platelets in round two. Rounds three, four, and five—if needed—would see six and six of RBC and plasma, and alternating one unit of cryo or platelets. Dr. Lockhart said delivery and transfusion of blood products should be done in parallel with a definitive clinical intervention such as use of uterotonic agents, tamponade, arterial embolization or ligation, or hysterectomy.

Dr. Lockhart noted that it is difficult to apply the findings from trauma-specific MTP to obstetrics, because trauma data are based on mostly male subjects whose coagulation physiology differs significantly from that of women giving birth. But research has shown that OB hemorrhage protocols can improve how quickly clinicians initiate an MTP, cut blood product use by 62 percent, and slash the rate of disseminated intravascular coagulation by 64 percent (Shields LE, et al. *Am J Obstet Gynecol.* 2011;205[4]:368.e1–e8).

In October 2006, the American College of Obstetricians and Gynecologists issued a practice bulletin on postpartum hemorrhage recommending the posting of management protocols in delivery rooms or operating room suites. In 2010, the California Maternal Quality Care Collaborative issued an obstetric hemorrhage toolkit—available at https://cmqcc.org/ob_hemorrhage—which is now in the process of being updated. Despite the imprimatur of ACOG and quality improvement organizations such as the Joint Commission, adoption of OB-specific MTPs appears far from universal.

A survey of 220 ob-gyns conducted in 2009 found that 58 percent practiced in hospitals that had no MTP to treat severe postpartum hemorrhage. There was a range in practice by birth volume. Nearly 60 percent of hospitals with more than 10,000 deliveries annually had an OB-specific MTP, compared with 32 percent of hospitals with fewer than 2,000 deliveries a year (Triche EW, et al. *Open J Obstet Gynecol.* 2014;4[6]:279–293). Another survey, conducted in 2012 among 60 directors of academic obstetric anesthesia units, found that 67 percent of their units had a PPH protocol (Kacmar RM, et al. *Anesth Analg.* 2014;119[4]:906–910).

ACOG's New York chapter, District II, has undertaken an initiative to address the shortage of OB hemorrhage plans. Of the state's 127 obstetric hospitals, 115 are participating. The statewide effort, known as the Safe Motherhood Initiative, is simultaneously targeting care improvements in severe hypertension and venous thromboembolism, two additional leading causes of maternal death. Checklists, algorithms, risk-assessment tables, and other materials are available at http://j.mp/acognypph. Hospital implementation visits began in September, says Donna Montalto, executive director of ACOG District II. Baseline data have been collected, and the organization is collecting 14 months of data on outcomes post-implementation.

**Montalto**

“All the hospitals are required to create and invoke an MTP, and we provided them with a protocol template on what should be included. That’s a new phenomenon for very small hospitals. There’s usually a hospitalwide massive transfusion protocol, but not specifically for the OB unit,” Montalto says. “Hospitals need to know how to activate the MTP, notify the appropriate staff to release blood and blood products to the OB unit, and perform all the stat labs in a timely fashion. Any provider involved in a severe obstetric hemorrhage can make the decision about escalation and whether to activate an MTP. Again, it’s new for them.”

“It’s a culture change,” she adds. “It’s about embracing that protocol, and systematically looking at a staged checklist. Is everyone on the same page? Oftentimes, they’re not.”

*Kevin B. O’Reilly is CAP TODAY senior editor.*