RED Code

If you get hit by a truck, fixing your body should take second place to fixing your blood.

David Cohen reports

SKIMMING over the London rooftops, the air ambulance takes only minutes to arrive. Its objective: a cyclist who has been hit by a truck. Her pelvis has been crushed and she is haemorrhaging internally from her liver and kidneys. As her blood pressure plummets, the patient goes into medical shock. She is dying.

But the paramedics do not give fluids to boost blood pressure and reverse the shock as they normally would. Instead, they begin a set of new and controversial last-ditch procedures. The patient is anaesthetised and rushed by helicopter to the Royal London Hospital. Over the radio the crew warn the hospital’s waiting trauma team about the patient’s state. “Code red.”

The new approach has arisen because of recent discoveries about what happens in the chaos of major haemorrhage. Doctors have found that some people can bleed to death even after reaching hospital, because their blood simply fails to clot as it should.

“Every stitch you make bleeds, they start bleeding from the punctures at the site of their infusions, everything you do causes bleeding,” says Karim Brohi, a trauma surgeon at the Royal London Hospital. “They bleed from their mouth and nose, and into their lungs, so they start to drown in their own fluids. You’re filled with an impending sense of doom. You just know the patient is going to die.”

It seems that sometimes major injuries trigger a problem with the blood-clotting process, causing blood to leak from the body faster than it can be stemmed. This clotting disorder affects as many as 1 in 4 major trauma victims. So Brohi and others have developed a way of treating people that prioritises fixing their blood over fixing their body. It’s a radical departure from standard procedures, and one that is by no means widely accepted, but if they’re right it could save thousands of lives.

Key to the switch is a new understanding of coagulation: the mysterious, almost magical, process whereby blood changes from a fluid into a solid to form a clot. Coagulation is regulated by a complex network of blood-borne proteins, which ensure that the process is triggered as soon as it is needed and yet only when it is needed; unwanted clots can be lethal in their own right.

Normally, the blood’s viscosity is finely poised. If you cut yourself, blood proteins known as clotting factors trigger coagulation. The end result is a plug made of a stringy protein called fibrin, and tiny cell fragments called platelets. Meanwhile, further from the damage, anticoagulants are made that stop the clotting process from spreading too far.

Some people are born with a blood-clotting disorder, or coagulopathy. Blood may fail to clot when it should, such as in people with haemophilia, or it can be too prone to clotting and trigger a stroke. But any one of us who is injured badly enough can experience acute traumatic coagulopathy (ATC), as Brohi discovered 11 years ago.

Clotting switch

Brohi admits he stumbled on ATC almost by accident in 2000 when he decided to study severe trauma patients who had been admitted to hospital. “We were doing an exhaustive search to understand what the data said about patients’ clotting ability early after trauma, but we weren’t expecting to find anything,” he says.

People who bled heavily were already known to develop some kind of clotting disorder, but it was thought this only became a problem after they had been in hospital for some time, possibly hours after arrival. The problem was thought to result from their deteriorating condition, perhaps exacerbated by the fluids given to raise their blood pressure, which have the unwanted effect of diluting levels of clotting factors.

Brohi analysed the records of more than 1000 patients and, to his surprise, found they often had the clotting disorder on arrival at hospital. It seemed to arise within minutes of injury, as a direct consequence of massive tissue damage. What’s more, 46 per cent of those who had the disorder on admission died, compared with 11 per cent of those who did not (Journal of Trauma Injury, Infection and Critical Care, vol 54, p 1127).

The results flew in the face of conventional wisdom. “We had a lot of difficulty publishing the paper at first,” says Brohi. But a few months later, a study of 20,000 patients in a hospital in Miami showed the same thing, and many studies since have confirmed the finding.

They bleed from their mouth and into their lungs so they start to drown in their own fluids. You just know they are going to die”
Blood bath
Major physical injuries can trigger a breakdown of the natural clotting process, causing blood to leak from the body faster than it can be reabsorbed.

Since then Brohi has focused on unpicking the causes of ATC. By teaming up with Mitchell Cohen, a surgeon and trauma researcher at the University of California, San Francisco, they soon found a likely reason. Normally an enzyme called thrombomodulin is key to helping the body to stop the bleeding. But with ATC, it is not functioning properly. "Thrombomodulin not only helps form a clot, but it also helps turn clotting factors off," Cohen says. After such an extreme injury, our body's natural response to the trauma isn't enough. "Getting hit by a bus is not something we've evolved to deal with small, survivable injuries like cuts and grazes. Whatever we do is not that surprising. Clotting has evolved to deal with major injuries combined with the body's natural response to trauma," says Brohi. In someone experiencing ATC, however, cells in the body have evolved to make a protein called thrombomodulin - not just at the site of injury, but throughout the body. Thrombomodulin switches thrombin from its primary role of forming clots to its other role of activating protein C, leading to a wave of anticoagulant proteins washing through the body. This "thrombin switch" is in people with ATC blood so profusely.

So what prompts blood vessels to make thrombin in the first place? "It's a good way to deal with getting hit by a bus," says Brohi. The existence of ATC is now widely accepted, but what to do about it is still contentious. As yet there is no drug that specifically reverses the condition, although several groups are trying to develop one. Cohen's team is looking for drugs that inhibit activated protein C, and they have begun testing compounds in mice and rats. In the meantime, a growing number of doctors are trying to save people by using existing drugs and techniques differently, under a protocol termed damage control surgery, which means doing the minimum work needed to stem the major sources of blood loss, before sending the patient to intensive care where they can be stabilised. Later they can have the time-consuming reconstructive surgery.

The concept has been around for decades but until now has not been used often. What's new is to routinely use this approach on anyone with possible ATC. "If we send blood products up to the helipad if someone is there, we can start working on the patient in theatre," says Brohi. "The blood-chilling technique or a change in the way existing drugs are used. Individual elements of the approach have come under scrutiny, though. For instance, several studies have supported the idea of giving extracellular matrix proteins as a way to help the body use it properly to repair the damage. In people with other clotting disorders, blood-chilling means doing the minimum work needed to correct a problem, whereas in ATC it is just a matter of making sure that the blood doesn't form clots.

"Another crucial element is a switch to what's called damage control surgery, which means doing the minimum work needed to stem the major sources of blood loss, before sending the patient to intensive care where they can be stabilised. Later they can have the time-consuming reconstructive surgery. That's what happened with the cyclist. She was given extra clotting factors and a drug called tranexamic acid that inhibits clot breakdown. "We send blood products up to the helipad if necessary," says Brohi. Another crucial element is a switch to what's called damage control surgery, which means doing the minimum work needed to stem the major sources of blood loss, before sending the patient to intensive care where they can be stabilised. Later they can have the time-consuming reconstructive surgery.

"The concept has been around for decades but until now has not been used often. What's new is to routinely use this approach on anyone with possible ATC. That's what happened with the cyclist. When she reached the operating theatre, the surgeons limited themselves to repairing damaged organs and major blood vessels. Within 25 minutes she was whisked to intensive care to get more blood and extra clotting factors. Only once she was clotting well was her blood pressure returned to normal. Then she was sent back to theatre for further surgery on her pelvis. At the moment only a handful of hospitals use damage control procedures but the number is growing. Even so, the approach has never been compared with standard practice in a randomised trial - not even in animals. Unlike a new drug or medical device, there is no such requirement for a new surgical technique or a change in the way existing drugs are used. Individual elements of the approach have come under scrutiny, though. For instance, several studies have supported the idea of giving extracellular matrix proteins as a way to help the body use it properly to repair the damage. In people with other clotting disorders, blood-chilling means doing the minimum work needed to correct a problem, whereas in ATC it is just a matter of making sure that the blood doesn't form clots.

"Another crucial element is a switch to what's called damage control surgery, which means doing the minimum work needed to stem the major sources of blood loss, before sending the patient to intensive care where they can be stabilised. Later they can have the time-consuming reconstructive surgery. That's what happened with the cyclist. When she reached the operating theatre, the surgeons limited themselves to repairing damaged organs and major blood vessels. Within 25 minutes she was whisked to intensive care to get more blood and extra clotting factors. Only once she was clotting well was her blood pressure returned to normal. Then she was sent back to theatre for further surgery on her pelvis. At the moment only a handful of hospitals use damage control procedures but the number is growing. Even so, the approach has never been compared with standard practice in a randomised trial - not even in animals. Unlike a new drug or medical device, there is no such requirement for a new surgical technique or a change in the way existing drugs are used. Individual elements of the approach have come under scrutiny, though. For instance, several studies have supported the idea of giving extracellular matrix proteins as a way to help the body use it properly to repair the damage. In people with other clotting disorders, blood-chilling means doing the minimum work needed to correct a problem, whereas in ATC it is just a matter of making sure that the blood doesn't form clots.

The evidence is mixed. Some studies have found 1:1:1 is best, and this ratio is now increasingly favoured. But two more recent studies showed no benefit. "I don't think you'd find anyone around the world who thinks this is proven, because it is not," says Thomas Scalea, physician-in-chief at the University of Maryland Medical Center, in Baltimore, who led one of the studies that gave negative results (Annals of Surgery, vol 248, p 578). All the studies so far have been retrospective. In other words, they looked at historical data on what blood products people use and whether they lived or died. There could have been other factors making the outcomes then it’s just science. If it translates, then it is revolutionary.

And the cyclist? Her ordeal was by no means over. She had several further rounds of reconstructive surgery. Two months after the crash, she had to learn how to walk again, and suffered back pain to this day. But she is alive. The experiments were the biggest cause of death for young people.