DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

COAGULOPATHY OF ACUTE HEMORRHAGE

SUMMARY

Hemorrhage is the second most common cause of death among injured patients who reach the hospital alive in developed countries (1). Control of hemorrhage and prompt correction of hypothermia, acidosis, and coagulopathy are cornerstones of trauma care (2). Suggested resuscitation endpoints for coagulopathic bleeding include euthermia, pH > 7.2, prothrombin time and partial thromboplastin time less than 1.25 times control levels, a platelet count above 100,000/mm^3, and fibrinogen above 100 mg/dL.

RECOMMENDATIONS

- **Level**
  - None
- **Level II**
  - Platelet (PLT) transfusions are indicated in the following situations:
    - Neurosurgical procedures or CNS trauma with PLT count <100,000.
    - Surgical and obstetric patients with microvascular bleeding and PLT count <50,000.
    - Any patient with PLT count <20,000.
  - Fresh frozen plasma (FFP) (10-15 ml/kg) is indicated in the following situations:
    - Microvascular bleeding with elevated PT or PTT (> 1.5 X normal).
    - Microvascular bleeding following transfusion of more than one blood volume.
    - Microvascular bleeding where PT and PTT cannot be obtained in a timely fashion.
    - Urgent reversal of warfarin therapy.
  - Cryoprecipitate should be administered in the following situations:
    - Microvascular bleeding with fibrinogen concentrations less than 100 mg/dL (or when fibrinogen concentrations cannot be measured in a timely fashion).
    - Bleeding patients with von Willebrand's disease.
- **Level III**
  - Rewarming strategies to correct hypothermia
    - Remove blood or saline-soaked dressings and increase room temperature.
    - Place convective-air or aluminum space blankets over the patient.
    - Use humidified mechanical ventilator circuits warmed to 41°C.
    - Use fluid warmers for the infusion of large volumes of warmed fluids at 42°C.
    - For patients refractory to above measures consider pleural/peritoneal lavage, or continuous arterio-venous rewarming.
  - Correction of Acidosis
    - Consider bicarbonate administration when pH < 7.2
  - Treatment of Transfusion-related Hypocalcemia
    - Consider calcium replacement when transfusing blood faster than 1 unit / 5 minutes.
  - Refractory Coagulopathy
    - Consider use of recombinant Factor VIIa (Novoseven™) for refractory hemorrhage.

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Coagulopathy, defined as a prothrombin time (PT) or partial thromboplastin time (PTT) 1.5 times normal, is present in approximately 25% of patients presenting with severe trauma. Resuscitation with cold blood and fluids creates a vicious cycle of worsening hemodilution, acidosis, hypothermia, and coagulopathy. Trauma patients with the combination of an Injury Severity Score (ISS) > 25, pH < 7.10, temperature < 34°C, and systolic blood pressure < 70 mmHg have a 98% likelihood of developing a life threatening coagulopathy (PT and PTT > 2 times normal) (3). Prompt recognition and treatment of coagulopathic bleeding is, therefore, essential to improving patient survival from severe trauma or critical illness.

LITERATURE REVIEW

Early Measures

Arrest hemorrhage by applying pressure, ligation of bleeding vessels, early definitive operative management, or the application of damage control techniques. Resuscitation should be performed judiciously, avoiding displacement of established clots, hemodilution, and increasing acidosis while ensuring adequate organ perfusion. Obtain a disseminated intravascular coagulation (DIC) panel (PT, PTT, fibrinogen level, and platelet count) early in the course of resuscitation due to inherent delays in obtaining results to these tests and rapid changes in coagulation function in bleeding patients.

Hemodilution

Current packed red blood cells (pRBCs) contain no functional platelets and only 35 ml of plasma from which the labile coagulation factors V and VIII are largely absent. By the time 10 units of pRBCs have been administered, at least 70% of the patient's original plasma has been lost and only about 10% has been replaced. At that time, a mild prolongation of PT and PTT will be measurable (4). Treatment with 6 units of plasma will correct the coagulation time abnormalities, but still leave the clotting factor concentrations at approximately 60% of normal.

Platelets are lost more slowly than plasma proteins because a third of platelets are sequestered in the spleen and an additional fraction are adherent to the endothelium. As a result, platelet counts rarely fall below 100,000/mm^3 before 12-20 units of pRBCs have been administered in situations of otherwise uncomplicated hemorrhage (5). In a study of 39 massively transfused patients, platelet counts below 50,000/mm^3 were found in 75% of patients who received 20 or more units of pRBCs and in no patients who received less than 20 units (6). Treatment with 6 units of whole blood derived platelets will replace roughly 20% of the normal platelet mass. Giving 1 unit of whole-blood-derived platelets will increase the platelet count of a non-immunized individual by approximately 10,000/mm^3.

Hypothermia

Hypothermia is a frequent pathophysiologic consequence of severe injury and subsequent resuscitation (7). It is estimated that as many as 66% of trauma patients arrive in the emergency department with hypothermia (8). Gregory et al. found that hypothermia developed at some point in 57% of the trauma patients studied, and that temperature loss was most severe in the emergency department setting (9).

Gentilello classified the severity of hypothermia in the trauma patient as mild (36°C to 34°C), moderate (33.9°C to 32°C), and severe (below 28°C) (7). Body temperatures less than 33°C produce a coagulopathy that is functionally equivalent to factor deficiency states seen when coagulation factor concentrations are less than 50% (10). Thrombin generation on platelets is reduced by 25% at 33°C. The average size of aggregates formed by thrombin-activated platelets was decreased by 40% at 33°C and platelet adhesion was reduced by 33% (11). Adverse clinical effects such as cardiac dysrhythmias, reduction in cardiac output, increase in systemic vascular resistance, and a left shift in the oxygen-hemoglobin saturation curve have been described. Mortality rates as high as 100% are seen in patients with severe hypothermia and severe injury. The most significant effect of hypothermia in trauma is coagulopathic bleeding due to prolonged clotting cascade enzyme reactions, dysfunctional platelets, and fibrinolysis (10,11).

Rewarming Strategies

Rewarming strategies initiated in the emergency department and operating room are aggressively continued in the intensive care unit. Strategies include passive and active external rewarming and active core rewarming.

Passive External Rewarming

Passive external rewarming involves removing blood- or saline-soaked dressings or blankets, increasing ambient room temperature, and decreasing air flow over the patient by keeping the room doors shut.

Active External Rewarming

Active external rewarming devices include fluid/air circulating blankets, aluminum space blankets and overhead radiant warmers. Conductive rewarming with fluid-filled heating blankets placed under the patient is relatively inefficient because of minimal body-blanket contact, estimated to be less than 30%. Convective-air and aluminum space blankets placed over the patient provide greater heat exchange by creating a 43°C microenvironment around the patient, which effectively stops heat loss. Superior warming is achieved when standard cotton blankets are placed over these blankets and the edges secured, although this limits patient access. Head covering is of prime importance; because significant vasoconstriction does not occur in scalp vessels, and as much as 50% of radiant heat loss occurs from the neck up (7). Aluminized caps are effective warmers, but their use is limited in head injured patients with intracranial pressure (ICP) monitors. The effectiveness of overhead radiant warmers is unclear. When aimed directly onto vasoconstricted skin, these warmers may cause inadvertent burns; yet when directed over a blanket, they provide no direct heat exchange to the patient. During laparotomy, it is recommended that covering exposed bowel with moist towels be avoided because it can increase evaporative heat loss by nearly 250% (7). Dry towels or plastic bags are superior.

Core Rewarming

The hypothermic trauma patient requires active core rewarming which may include airway rewarming, heated body cavity lavage, heated intravenous fluids, continuous arteriovenous rewarming (CAVR), and extracorporeal circulatory rewarming. Humidified ventilator circuits can be warmed to 41°C. Heated gastric, bladder, or colonic lavage is relatively ineffective because of the small surface area for heat transfer (7). Peritoneal lavage is generally not feasible in most trauma patients undergoing laparotomy. Rarely, pleural lavage has been used with the placement of two ipsilateral chest tubes enabling continuous flow of heated water.

Use of warmed intravenous fluids is one of the simplest and most effective means of providing heat to the core in patients requiring massive fluid resuscitation. Current fluid warmer technology allows large volumes of warmed fluids to be infused quickly at 42°C, the current standard recommended by the American Association of Blood Bank (12). Blood-warming methods include surface-contact warmers, counter-current warmers, and heated-saline admixture (13). In-line microwave blood-warming technology (in development) has been shown to heat blood safely to 49°C and shows great promise for the future (14).

Cardiopulmonary bypass has limited applicability in trauma patients due to the need for systemic anticoagulation. An alternative is continuous arteriovenous rewarming (CAVR) (15). In CAVR, percutaneously placed 8.5 French femoral arterial and venous catheters, and the patient's blood pressure, create an extracorporeal arteriovenous circuit that uses the heating mechanism of a counter-current fluid warmer. Early studies have shown the greater effectiveness of CAVR in comparison with traditional warming techniques in rapidly rewarming trauma patients with severe hypothermia (16). However, widespread use of this device has been limited due to: 1) the learning curve for involved personnel; 2) the infrequency of use at many trauma centers; 3) its negligible effect on long-term survival; and 4) its associated increase in respiratory distress syndrome, length of hospital stay, and cost. Veno-venous bypass, although more complex than arteriovenous systems, can also be performed by using a conventional roller pump to drive blood through a heat exchanger, however, this requires the constant attention of qualified personnel (17).

Acidosis
The association between high lactate levels and increasing risk of death was first described over 40 years ago by Broader and Weil (18). Since then, several investigators have demonstrated increasing risk of death with metabolic acidosis as demonstrated by arterial pH, lactate, and base deficit clearance (19). The deleterious effects of acidosis on the cardiovascular system include decreased cardiac contractility and cardiac output, vasodilation and hypotension, decreased hepatic and renal blood flow, bradycardia, and increased susceptibility to ventricular dysrhythmias (20). Acidosis directly reduces the activity of the extrinsic and intrinsic coagulation pathways as measured by PT and PTT and also diminishes platelet function as measured by platelet aggregation and platelet factor III release (7). These adverse effects are generally not seen until pH decreases below 7.2 (20).

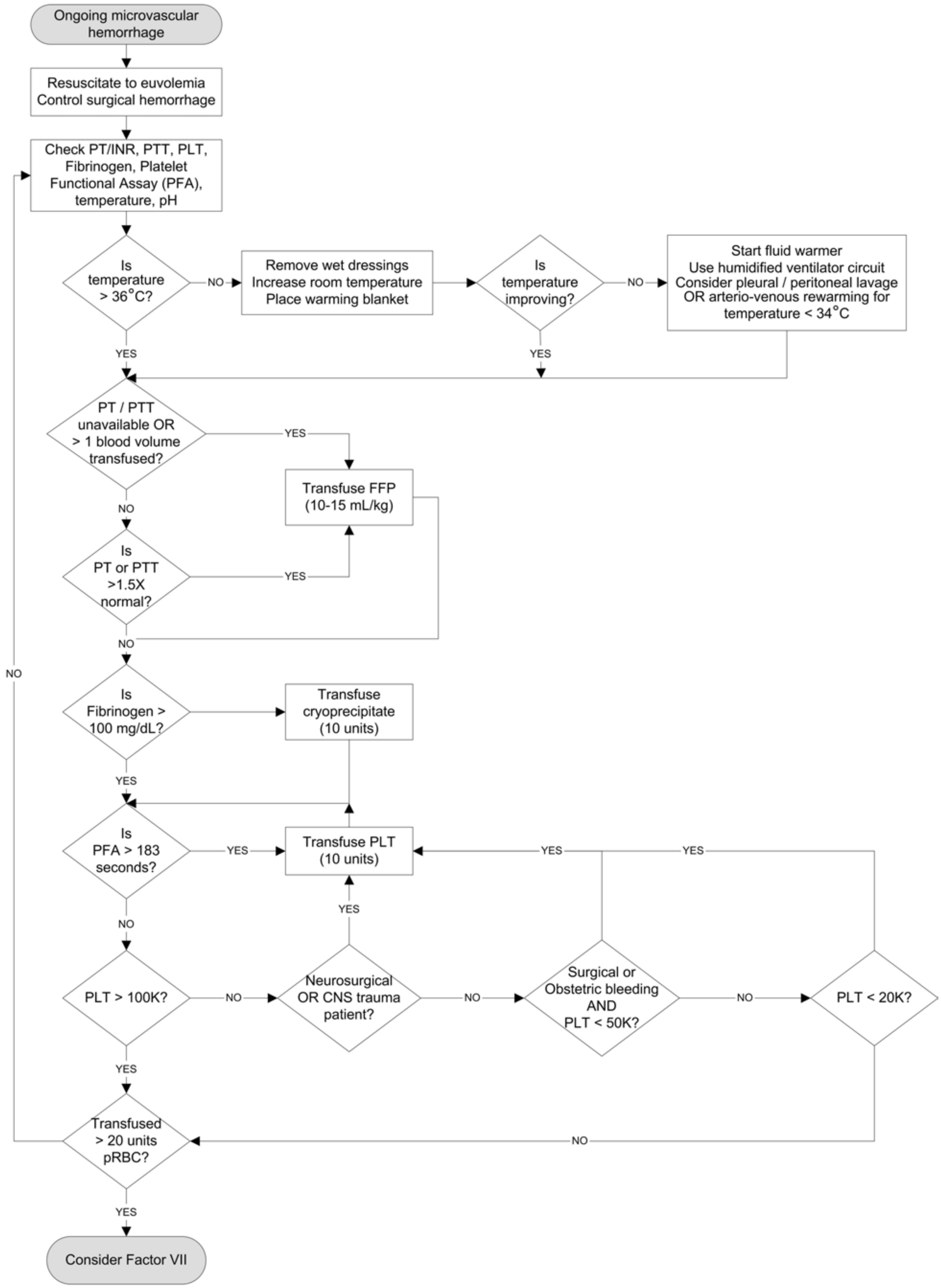
Therapy for metabolic acidosis remains directed toward correcting the underlying hypoperfusion. Resuscitation endpoints include normalization of arterial pH, base deficit, and lactate. In clinical trials, researchers have failed to demonstrate any clear advantage of bicarbonate administration, whereas the potential adverse effects are well documented (21). Bicarbonate administration should be deferred until the pH persists below 7.2, despite optimal fluid loading and inotropic support (22).

Storage Complications
After 2 weeks of storage, pRBCs have a pH below 7.0, and each unit has an acid load of approximately 6 mEq (12). One of these mEq of acid comes from the fact that pRBCs are made from venous blood with a starting pH of 7.35, a second mEq is acquired in buffering the citric acid in the anticoagulant, and 4 mEqs are generated by glycolysis during pRBC storage. Seven units of pRBCs are expected to increase the whole body base deficit of a 70 kg man by 1 mEq/L. Five units of cold pRBCs would be expected to reduce the body temperature of a 70 kg man by about 1°C.

Hypocalcemia
Each unit of blood contains approximately 3 gm of citrate, which binds ionized calcium. The healthy adult liver will metabolize 3 gm of citrate every 5 minutes. Transfusion at rates higher than one unit every five minutes or impaired liver function may thus lead to citrate toxicity and hypocalcaemia. Hypocalcaemia does not have a clinically apparent effect on coagulation, but patients may exhibit transient tetany and hypotension. Calcium should be given if there is biochemical, clinical or electrocardiographic evidence of hypocalcaemia.

REFERENCES

1. Sauaia A., Moore F.A., Moore E.E., et al. Epidemiology of trauma deaths: A reassessment. *J Trauma*. 1995;38:185-193.
2. Stewart R.M., Myers J.G., Dent D.L., et al. Seven hundred and fifty-three consecutive deaths in a level 1 trauma center: the argument for injury prevention. *J Trauma*. 2003;54:66-71.
3. Cosgriff N., Moore E.E., Sauaia A., et al. Predicting life threatening in the massively transfused trauma patient: Hypothermia and acidosis revisited. *J Trauma*. 1997;42:857-861.
4. Reiss R. F. Hemostatic defects in massive transfusion: Rapid diagnosis and management. Am J. Crit Care. 2000;9: 158-165.
5. Slichter S. J. Identification and management of defects in platelet hemostasis in massively transfused patients, in Collins J.A. Murawski K., Shafer A.W. (eds): Massive Transfusions in Surgery and Trauma. New York, NT, Liss, 1982, pp 225-258.
6. Leslie S.D., Toy P.T. Laboratory hemostatic abnormalities in massively transfused patients given red blood cells and crystalloid. *Am J Clin Pathol*. 1991; 96:770-3.
7. Gentilello L.M., Jurkovich G.J. Hypothermia. In: Ivatury RR, Cayten CG, eds. The Textbook of Penetrating Trauma. Baltimore: Williams & Wilkens; 1996;995-1005.
8. Luna G.K., Maier R.V., Pavlin E.G., et al. Incidence and effect of hypothermia in seriously injured patients. *J Trauma* 1987;27:1014-1018.
9. Gregory J.S., Flancbaum L., Townsend M.C., et al. Incidence and timing of hypothermia in trauma patients undergoing operations. *J Trauma* 1991;31:795-800.
10. Frank S., Beattie C., Christopherson R., et al. Unintentional hypothermia is associated with post operative myocardial ischemia. *Anesthesiology* 1993;78:468-472.
11. Britt L., Dascombe W., Rodriguez A. New horizons in management of hypothermia and frostbite injury. *Surg Clin North Am* 1991;71:345-370.
12. American Association of Blood Banks. Technical Manual. Standards for Blood Banks and Transfusion Services. 18th Ed. Bethesda, MD: American Association of Blood Banks; 1998.
13. Iserson K., Huestis D. Blood warming: Current applications and techniques. *Transfusion* 1991;31:558-571.
14. Pappas C, Paddock H, Goyette P, Grabowy R, Connolly R, Schwaitzberg S. In-line microwave blood warming of indate human packed red blood cells. *Crit Care Med* 1995;23:1243-1250.
15. Gentilello L.M., Cortes V., Moujaes S., et al. Continuous arteriovenous rewarming: Experimental results and thermodynamic model simulation of treatment for hypothermia. *J Trauma* 1990;30:1436-1449.
16. Gentilello L.M., Rifley W.J. Continuous arteriovenous rewarming report of a new technique for treating hypothermia. *J Trauma* 1991;31:1151-1154.
17. Gregory J.S., Bergstein J.M., Aprahamain C., et al. Comparison of three methods of rewarming from hypothermia: Advantages of extracorporeal blood warming. *J Trauma* 1991;31:1247-1252
18. Broder G., Weil M.H. Excess lactate: An index of reversibility of shock in human patients. *Science* 1964;143:1457-1459.
19. Abramson D., Scalea T., Hitchcock R., et al. Lactate clearance and survival following injury. *J Trauma* 1993;35:584-589.
20. Wildenthal K., Mierzwaiak D.S., Myers R.W., et al. Effects of acute lactic acidosis on left ventricular performance. *Am J Physiol* 1968;214:1352-1359.
21. Mixock B.A., Falk J.L. Lactic acidosis in critical illness. *Crit Care Med* 1992;20:80-92.
22. Wilson R.F. Shock. In: Critical Care Manual: Applied Physiology and Principles of Therapy. Philadelphia: FA Davis; 1992:267.
23. Moore E.E. Staged laparotomy for the hypothermia, acidosis, and coagulopathy syndrome. *Am J Surg* 1996;172:405-410.



Approved 10/17/06