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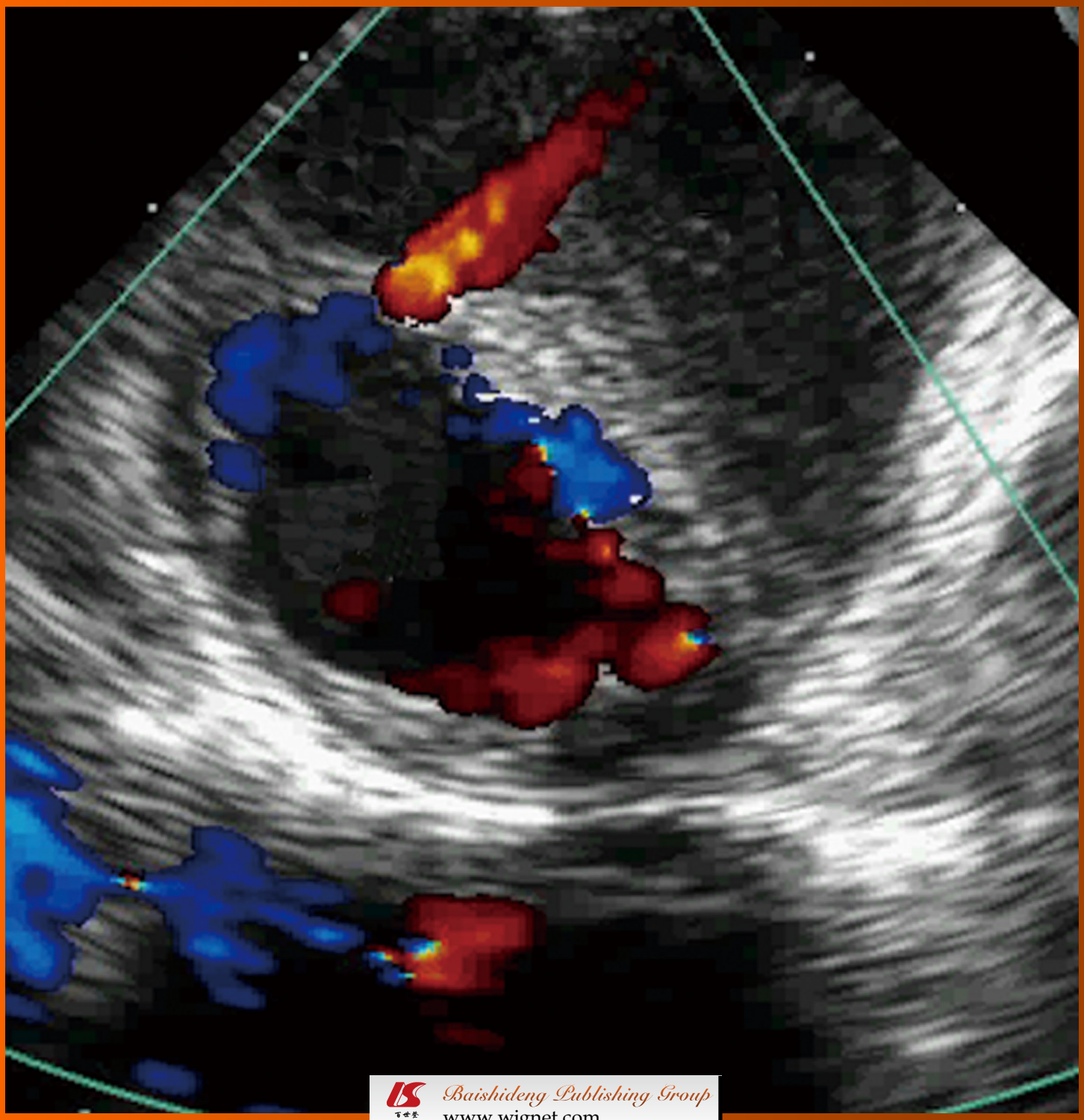

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EDITORIAL

Infection control in severely burned patients

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Abstract

In the last two decades, much progress has been made in the control of burn wound infection and nasocomial infections (NI) in severely burned patients. The continually changing epidemiology is partially related to greater understanding of and improved techniques for burn patient management as well as effective hospital infection control measures. With the advent of antimicrobial chemotherapeutic agents, infection of the wound site is now not as common as, for example, urinary and blood stream infections. Universal application of early excision of burned tissues has made a substantial improvement in the control of wound-related infections in burns. Additionally, the development of new technologies in wound care have helped to decrease morbidity and mortality in severe burn victims. Many examples can be given of the successful control of wound infection, such as the application of an appropriate antibiotic solution to invasive wound infection sites with simultaneous vacuum-assisted closure, optimal preservation of viable tissues with waterjet debridement systems, edema and exudate controlling dressings impregnated with Ag (Silvercel, Aquacell-Ag). The burned patient is at high risk for NI. Invasive interventions including intravenous and urinary chateterization, and entubation pose a further risk of NIs. The use of newly designed antimicrobial impregnated chateters or silicone devices may help the control of infection in these immunocomprimised patients. Strict infection control practices (physical isolation in a private room, use of gloves and gowns during patient contact) and appropriate empirical antimicrobial therapy guided by laboratory surveillance culture as well as routine microbial burn wound culture are essential to help reduce the incidance of infections due to antibiotic resistant microorganisms.

Key words: Severe burn injury; Infection control; Wound care; Infection control programs; Surveliance

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INTRODUCTION

Infection and sepsis are among the most prominent causative factors in burn related mortality and morbidity[1,2]. The prevention and control of infectious diseases among burned patients present a specialized problem, as the environment in burn units can become contaminated with resistant organisms. Lack of proper wound care, edema formation and lack of resusciation may actually increase the size and/or depth of the wound[3] (Figure 1). Early burn wound excision is now performed within the first few days after burn injury and has resulted in improved survival and infection control in severely burned patients[4-6]. In modern burn care and management, there are many additional tools for controlling wound-related sepsis.

EPIDEMIOLOGY OF BURN WOUND INFECTIONS

Burn wound infections are one of the most important and potentially serious complications that occur in the acute period following injury[7,8]. Approximately 73 % of all deaths within the first 5 d post-burn have been shown to be directly or indirectly caused by septic processes[9].

Until the development of effective topical antimicrobial chemotherapeutic agents in the mid-1960s the wound was the most common site of infection, causing devastating morbidity and, when invasive, virtually universal mortality in burn patients[10]. Since then infection in sites other than the burn wound, principally the lungs, has remained the most common cause of death in burn patients[11]. The continually changing epidemiology of infection in critically ill, severely burned patients is a result of greater understanding and improved techniques for burn patient management and burn wound care. Currently, blood-borne and urinary tract infections are more commonly seen than invasive wound infections in severely burned patients[8].

CLASSIFICATION OF BURN WOUND INFECTIONS

The main signs of wound infection are dark brown, black, or violaceous discoloration of wound which can be focal, multifocal, or generalized, as well as conversion of partial-thickness injury to full-thickness necrosis and hemorrhagic discoloration of subeschar tissue. Edema and/or violaceous discoloration of unburned skin at wound margins (most commonly seen with *Pseudomonas* infections) and unexpectedly rapid slough of eschar, most commonly due to fungal infection, are other well-known signs. There are three accepted forms of burn wound infections: (1) Cellulitis; (2) Invasive wound infections within unexcised eschar (necrotising infection-fasciitis); and (3) Burn wound impetigo.

Burn wound cellulitis results from an extension of infection into the healthy, uninjured skin and soft tissues surrounding the burn wound or donor site. It is characterised by erythema of surrounding unburnt skin (1-2 cm beyond the wound), pain and oedema, extending the usual rim of inflammation commonly seen in burns. In the past, Group A β-hemolytic streptococci are the most common offenders in case of cellulitis[12]. However, recent studies have shown that this is not currently the case[13]. Staphylococcus aureus has now become the principal etiological agent of burn wound cellulitis and, along with pseudomonas aurginosa, remains a common cause of early burn wound infection in many centers[14].

Patients with areas of unexcised deep partial-thickness or full-thickness burn wound have an increased risk of developing an *invasive infection*. The histological examination of a burn wound biopsy is the most reliable and expeditious means of confirming a diagnosis of invasive burn wound infection. It is well known that conversion of a partial burn into a full-thickness burn is possible, if infection occurs. In the case of viral burn wound infections, the diagnosis may also be confirmed by histological examination of scrapings from the cutaneous lesions. Histological stages of microbial status of burn wound biopsy are described as a parameter of invasive wound infection: Stage Ⅰ, Microorganisms present on wound surface or penetrating to variable depth of burn eshcar; Stage Ⅱ, Microorganisms present in viable tissue immediately adjacent to subeschar tissue.

In a group of 19 patients with histologically documented invasive burn wound sepsis, only the 5 patients in whom no positive blood cultures were obtained survived, with their infected tissue excised before dissemination to remote tissues and organs had occurred[15]. Although *Pseudomonas aeruginosa* is the gram-negative organism that most often causes invasive burn wound infection, virtually any bacterium can be present in severely burned patients (Figure 2). Anaerobic organisms such as *Clostridium* sp. and facultative anaerobes such as *Aeromonas* sp. can

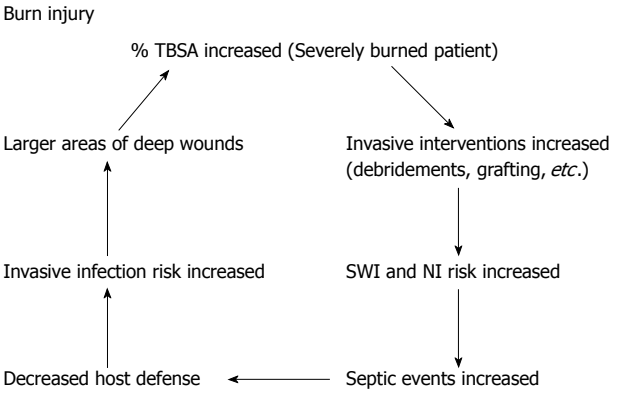

Figure 1 Vicious circle for increased infection risk in severely burned patient. SWI: Surgical wound infections; NI: Nasocomial infections; TBSA: Total burned surface area.

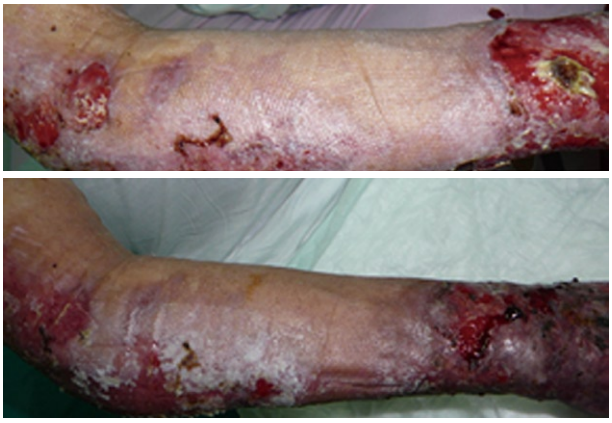

Figure 2 An example for burn wound infection. Top: Nine days following admission a severe edema and inflammation at the periphery of the wound is seen with a positive wound culture for pseudomanas auerginosa; Bottom: Following treatment with topical octenidine dihydrochlorure (octenidex, senamed medical, Turkey) and sterile petroleum gauze (jelonet, Smith and nephew, United Kingdom), and peroral ofloxacine 500 mg × 2 for day, rapid epitheliazation and decreased edema was achieved at the 10th day of the treatment.

cause invasive burn wound sepsis. Clostridial infections have characteristically occurred in patients in whom associated mechanical trauma or vascular occlusion have resulted in ischemic damage of muscle and subcutaneous tissue[16]. Effective treatment of deep tissue delayed infections requires surgical excision of all affected tissues and use of broad spectrum antibiotics against aerobic and anaerobic microorganisms. Application of an effective topical antimicrobial agent substantially reduces the microbial load on the wound surface[17,18]. Silver sulfodiazine is mostly used for both ambulatory and hospitalized patients. Silver nitrate is not routinely used now as it discolors the wound bed. Mafenide acetate cream is used after debridement of burn eschar[19].

In a molecular study, a total of 228 different *Candida* species were obtained from various body locations of burn patients. Species identification revealed that *C. albicans* was the most common followed by *Candida tropicalis*. The risk factors for fungal infection in burns are age of patient, total burn size, full-thickness burns, inhalational injury, prolonged hospital stay, late surgical excision, open dressing, artificial dermis, central venous catheters, antibiotics (imipenem, vancomycin, aminoglycosides), steroid treatment, long-term artificial ventilation, fungal wound colonisation, hyperglycaemic episodes and other immunosuppressive disorders[20,21].

Impetigo involves the loss of epithelium from a previously reepithelialized surface, such as grafted burns, partial-thickness burns allowed to close by secondary intention, or healed donor sites. Treatment consists of unroofing all abscesses, meticulous cleansing of the infected areas twice daily with a surgical detergent disinfectant, and twice-daily application of a topical antibacterial ointment, such as mupirocin which has potent inhibitory activity against gr (+) skin flora such as coagulase (-) staphyloccoci and staphylococcus aureus including methicilline-resistant staphyloccus aureus[22].

NASOCOMIAL AND SURGICAL WOUND INFECTIONS IN BURNED PATIENTS

The mode of infection transmission may be by contact, droplet or airborne spread. Modern burn centers have a contained perimeter that is designed to minimize the unneccessary traffic of health care workers and visitors. Modern infection control practice requires strict compliance with a number of environment control measures that include hand washing and the use of personal protective euipment. All personel must be gowned (either disposable or reuseable gowns) during the contact with the patient. All equipment in the isolation room must be regularly cleaned.

With universal employement of early excision and grafting, a burn wound transforms to an open burn-related surgical wound. This means that open burn- related surgical wound infection (SWIs) get more clinical attention than bacterial colonisation of an unexcised wound. New refinements of the standardized definitions for infection and sepsis in burn patients have been proposed by many authors. They assert that suspicious systemic infection (sepsis) should be considered as a clinical syndrome defined by the presence of signs and symptoms of systemic infection even with negative blood microbial cultures. It was recommended that systemic infection should be identified according to positive blood microbial culture or clinical response to antimicrobials[23].

It has been believed that the surgeons are likely to have overestimated the infection rate because they did not use standardized, written definitions[24]. To prevent unnecessary use of antimicrobial agents, burn surgeons were advised to apply standardized, written criteria, like those developed by the Centers for Disease Control (CDC).

The burned patient is at a high risk for nasocomial infection (NI) as a result of the nature of the burn injury itself, the immunocompromising effects of burns, prolonged hospital stays and intensive diagnostic and therapeutic procedures[25]. There are conflicting results from different burn centers regarding the most commonly seen infections in acute burn care. Some reports suggest that burn wound infection is the most common type of ifnfection, whereas other reports show predominance of pneumonia and primary blood stream infection[26,27]. The same authors concluded that these differences might be related to the variation in the rates of usage of invasive devices such as ventilators, catheters *etc*.

The percentage of total burned surface area (TBSA) is a significant risk factor for burn wound infections, although it is not a risk factor for the device-associated infections. Duration of use of urinary catheters and ventilation are identified as risk factors for the corresponding hospital-acquired infection. As an effective infection control policy, decreased usage of invasive devices, better infection control procedures and improved aseptic technique while inserting devices could decrease the rates of NI on burn units[28].

SWI is the third most commonly reported nosocomial infection and accounts for 14%-16% of all NI among hospital inpatients[29]. The most widely used definition of SWI is that employed by the CDC's National NI Surveliance System[30]. Surveillance for SWIs is a very important part of any nosocomial infection surveillance strategy. Posluszny *et al*[31] evaluated the SWI impact on rates of regrafting and the relationship between SWIs and NIs. They found that 24 of 62 burned patients with TBSA of 20% or more had a SWI and that development a SWI with the need for regrafting increased overall length of stay and was closely associated with number of NIs. As a result of the increased need for operative events, presence of a SWI may be a risk factor for the development of NIs.

In 2007, experts in burn care and research met in Tucson Arizona to develop a standardized definition for sepsis and infection-related diagnoses in the burn population[32]. In order not to overestimate or underestimate the infection rate among burned patients surgeons

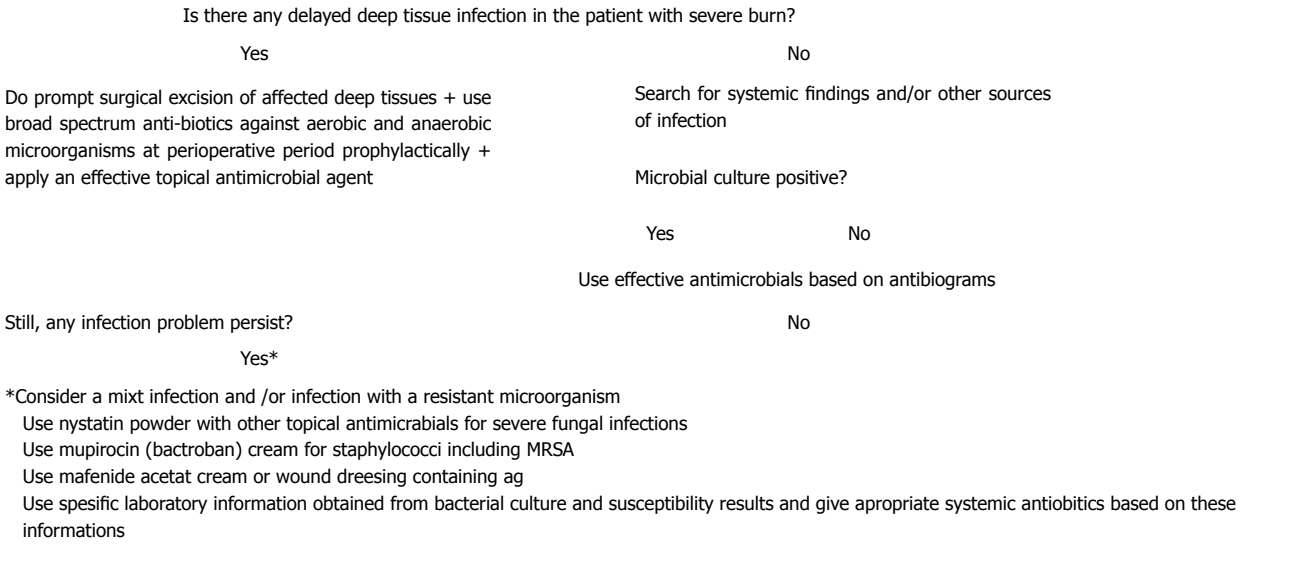

Figure 3 Diagram showing the management of infection problems in severe burns.

should use these updated definitions so that the results of fortcoming reports sould more accurately reflect reality. Communication of timely, accurate, risk-stratified data on SWI rates is essential if surveillance is to become an indispensable tool for surgeons[33]. Figure 3 show an algorythm for management of burn wound infection problems.

SYSTEMIC ANTIBIOTIC USE IN BURNS

Most antimicrobial therapy prescribed for burn patients is administered topically. Antibiotic resistant microorganisms have been associated with infections of burn wounds[34]. Risk factors for acquisition of an antibiotic resistant organisms include receipt of antibiotics prior to development of infection and extended duration of hospitalization. Burn centers should routinely determine and track the specific pattern of burn microbial flora and trends in the nasocomial spread of these pathogens[35]. In order to overcome infection by resistant microorganisms, the following two precautions must always be taken: (1) Antibiotic utilization should be based on monitoring of antibiotic resistance trends within individual burn centers. Empirical treatment algoritms spesific to each burn unit should be developed secondary to the outcome analysis of laboratory surveliance systems involving periodic sampling of burn wounds; and (2) Systemic antibiotic administration in burn patients must be carried out for a short period of time, for example immediately before, during and after surgical interventions, especially in patients with severe burns (TBSA = 40%, or more). Prophylactic antibiotics promote the development of secondary infections (otitis, diarrhea *etc.*) and should not be used routinely in the management of all burn victims.

ADVANCES IN BURN WOUND CARE

Patients with large burn wounds are routinely debrided at the first medical facility able to provide this service. This process may include debriding residual blisters, especially if the blisters are large or cover large surface areas. The choice of which topical burn dressing to apply to the wound is based on several factors: material at hand, provider preference, adjacent wounds, anticipated time and distance between successive medical facilities. Advances in wound care may be classified under the following subheadings: (1) Advances in wound exudate and edema control; (2) Optimising the wound environment with ideal skin disinfectants; (3) Advances in wound debridement systems; and (4) Enhancements to systemic care and management through new technologies.

There is now a wide range of wound dressings available. Various types of wound dressing offer effective control of different aspects of wound healing. Table 1 shows these among the therapeutic tools which have been in routine use for wound treament over the last two decades.

Burn wounds often involve contiguous areas of open soft tissues wounds that are the result of direct tissue loss, degloving injuries, or surgical debridement. Wounds of this nature are left open for serial debridement and until definitive coverage or closure can be performed. In many cases, negative pressure wound dressings such as the vacuum-assisted closure (VAC, KCI, San Antonio, TX) dressings that use open-pore foam are ideal. The VAC Instill was introduced in 2003 and differs from traditional VAC therapy because it allows the clinician to add solutions to the wound, as well as apply negative pressure. A wound culture may be obtained prior to starting the VAC Instill to select an optimal solution for a specific patient[36]. Other major tools to control burn wound exudate are non-adherent hydro-alginates and polyurethans. These dressings are sterile, non-woven pads composed of a high G (glucuronic acid) alginate, carboxymethyl cellulose and silver (Ag) coated fibers, laminated to a perforated non-adherent etyhlenemethyl acrylate wound

Table 1 Therapeutic tools used for controlling different aspects in the wound treatment

Epithelialization	Infection control	Macerattion	Tissue necrois
Collagen	Detergents	Alginates	Osmotic autolysis
Hyalurinic acid	Disinfectants	Hydrocolloid fibers	Larval autolysis
Growth factors	Advanced medications: Ag	Polyurethans	Enzymatic autolysis
VAC	Systemic antibiotherapy	VAC	Ultrasonic debridement
Artificial derma	VAC instill		Waterjet (Versajet) debridement
Skin grafting			Surgical debridement

VAC: Vacuum-assisted closure.

contact layer. Their composition allow management of exudates in moderate to heavily exuding wounds, creating a moist wound healing environment favourable to effective wound management and allowing intact removal. Ag kills a broad spectrum of microorganisms associated with the bacterial colonisation and infection of wounds. Ag impregnated hydrofiber dressings (Aquacell Ag Convatec, USA) provide a continious antimicrobial activity for Pseudomonas aurginosa, methicilline resistant sphylococus aureus and vancomycine resistant enterococus. A newly developed nanocrystalline silver dressing (Acticoat, Smith and Nephew) overcomes some shortcomings of older dressings, such as the need of daily change of dressings and increased patient comfort by providing sustained release of Ag up to 7 d[37].

Techniques used in wound cleansing include high-pressure irrgation, swabbing, low-pressure irrigation, showering, bathing and washing the affected area under a running liquid or total immersion in a whirlpool bath. A variety cleansing liquid are used including water, saline and antiseptic solutions. Most of these antiseptic solutions are toxic to fibroblasts and keratinocytes are some patients may be sensitive to some wound cleansers[38]. Irritation of intact healthy tissues seriously impacts the rate of tissue repair. For indications such as wound antisepsis and treatment of mucosal infections, where a prolonged antiseptic treatment is required, octenidine along with polyhexanine have been found to be the most effective microbistatic and microbicidal treatment[39]. The role of antiseptics on wounds is now being reconsidered in order to formulate rigid guidelines or to propose an algorithm.

VersaJet have several advantages for burn wound debridement. These include reduced blood loss, optimal preservation of viable tissues and effective elimination of bacterial colonization. The over 50% reduction in the death rate among patients with TBSA, compared to earlier published results, may be a result of use of these technologies[40].

Catheter tips are susceptible to colonization through hematogenous seeding of organisms from the colonized burn wound. Biofilms may grow within the medical devices, so preventive measures should be taken against the obvious problem. All types of intravascular devices (IVDs) are associated with a substantial risk of bloodstream infection (BSI). National surveliance studies for 2001 showed that catheter-associated urinary tract infections were 6.7 per 1000 urinary catheter days, catheter-

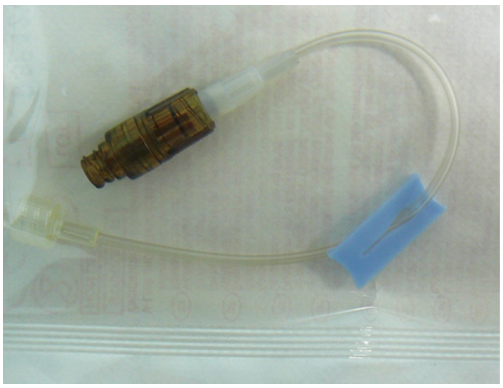

Figure 4 V-link luer activated device with Vitalshield protective coating, non-DEHP catheter extension set (Baxter ref vmc 8374).

associated BSIs were 7.0 per 1000 central venous catheter days, and ventilator-associated pneumonia were 12.0 per 1000 ventilator days[41]. Novel securement devices and antibiotic lock solutions have been shown to reduce the risk of IVD-related BSI in prospective randomized trials[42]. Introducing an antimicrobial solution into the catheter lumen limits biofilm formation. In the United States catheter-associated urinary tract infections make up 40% of all hospital-acquired infections with approximately 3% of these assessed as connected or contributing to mortality[43]. A variety of specialized urethral catheters have been designed to reduce the risk of infection. These include antiseptic impregnated catheters and antibiotic impregnated catheters. Antiseptic catheters are impregnated with either silver oxide or silver alloy (Figure 4). Nanosilver particles stably embedded in the polycarbonate matrix release minute quantities of bacterisidal ionic silver from the surface into the fluid pathway. Silver oxide catheters are not associated with a statistically significant reduction in bacteriuria in short-term catheterized hospitalized adults but silver alloy catheters have been found to significantly reduce the incidence of asymptomatic bacteriuria in hospitalized adults catheterized for < 1 wk[44]. A novel nanosilver impregnated polycarbonate-valved needleless connector has been approved by The Food and Drug Administration and is now in use in many hospitals in USA. Anti-infective impregnated central venous catheters are recommended if institutional rates of infection are above 3.3 BSIs per 1000 IVD-days despite full adherence to maximal barrier precautions, especially for patients at high risk for IVDR (IVDs related) BSI. Patients receiv-

ing total parenteral nutrition and those who are neutrogenic or who have a CVC that is likely to remain in place for more than 4 d are good examples for these patient groups.

HOSPITAL INFECTION CONTROL POLICIES, CULTURING AND SURVELLIANCE STUDIES

Empirical antimicrobial therapy to treat fever should be strongly discouraged because burn patients often have fever secondary to the systemic inflammatory response to burn injury. Prophylactic antimicrobial therapy is recommended only for coverage of the immediate perioperative period around excision or grafting of the burn wound. Infection control programs need to document and report burn wound infections according to recent classification systems. The incidence of infections reported among burn patients has been found closely related to the person who is assessing the patient for infection. On the basis of the infection control assessment, using the CDC's definitions, individual researcher's rates can be compared with the pooled means from prevoius prospective studies, especially those using multivariable analysis to assess independent risk factors for infections. Preparation of burn unit-specific antibiograms will reveal effective topical antimicrobial agents. Surveillance for surgical site infections and reporting of these rates to surgeons has been shown to reduce the rates of infection[45].

The infection control literature indicates that precise, written definitions are essential to accurately identify hospital-acquired infections. It has been suggested that because of discrepancies between the surgeon's assesment and infection control assesment, burn patients are over-treated with antimicrobial agents and antimicrobial use could possibly be decreased if more precise definitions of infection were used in clinical practice[46]. Burned surface area, the number of comorbidities, and invasive device use were significantly associated with nosocomial infection in the logistic regression model of risk factors for infection, as identified by either set of criteria. Decreased use of invasive devices, and improved aseptic technique when inserting devices could decrease the rates of nosocomial infections in burn units. CDC has developed evidence-based guidelines for preventing central venous catheter-associated BSIs[47]. Thus, wherever possible, use of indwelling devices should be minimized and these devices should be removed when no longer needed.

ISOLATION GUIDELINES AND ENVIRONMENTAL MEASURES

The followings are the key general measures for preventing the spread infection within burned patients; the implementation of contact precautions (single use masks, gowns, and gloves are worn while in contact with the patient and the hands are washed after finishing contact with the patient), cohort nursing (grouping patients of a given colonization status, with designated Health Care Workers, and a targeted minimum ratio of 1:1 of nursing staff to patients), strict adherence to aseptic techniques for changing dressings, hand disinfection and location of hand disinfectant (alcohol 70% isopropanol/ethanol) dispensers near all beds and installation of Laminar airflow techniques in burn units. Timely closure of the burn wound and the use of a dedicated operating theatre for burn surgeries are other positive factors for controlling burn-related infections in burn units.

DEBATABLE ISSUES ON PREVENTIVE MEASURES FOR BURN INFECTION

The first debatable issue is the use of selective oral bowel decontamination therapy. This was never widely adopted as routine therapy become unneccessary with the advent of early excision wound therapy[48]. The other main point of discussion is hydrotherapy usage in burns. Despite the recognised risk of immersion hydrotherapy treament in burn units, this was a standard practice in many burn centers until 1990s[49]. In addition to possible microbial contamination of the tank water, aerators and agitators in hydrotherapy tubs were difficult to clean leading to risks of cross-contamination between the patients. This problem was partially solved with adding disinfectants to the hydrotherapy tank water, thereby decreasing the microbial load on the burn wound surface and on health care workers[50]. Instead of immersion, showering with a hand-held sprayer has gradually replaced hydrotherapy for cleansing and debridement of the burn wound. Outbreaks of pseudomonas and MRSA related to shower hydrotherapy have been reported[51].

CONCLUSION

Although eradication of infection in burn patients is impossible, a well conducted surveliance infection control program, using novel antimicrobial devices in long-stay patients and analytical antimicrobial therapy may help to reduce infection and mortality rates in burn centers. To limit use of antimicrobial agents and, thereby, reduce the incidence of antimicrobial resistance, burn surgeons should minimize use of prophylactic antimicrobial agents and apply standardized written criteria, such as those developed by the CDC and by Garner *et al*[26]. Infection control programs must now strive to apply essential control measures and preventive technologies with all types of IVDs in order to reduce the risk of IVDR BSIs in the management of severely burned patients.

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OBSERVATION

Michael Blaivas, MD, *Series Editor*

Update on point of care ultrasound in the care of the critically ill patient

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Abstract

One of the most exciting developments to come to the aid of the critically ill patient in recent years is not new at all, but rather has been repackaged and evolved to a level where point-of-care use by critical care physicians has been made possible. Critical care or point-of-care ultrasound dates back more than twenty years, but has come to prominence in the last 5 years and is spreading quickly. Multiple critical care societies have taken up ultrasound policy and training and one organization has been formed that concentrates only on point-of-care ultrasound in critical settings and interventions. The amount of literature generated on the topic is increasing rapidly and hardly a major clinical journal exists that has not published ultrasound related topics.

Key words: Critical care; Ultrasound; Point-of-care ultrasound; Resuscitation; Cardiac; Echocardiography

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INTRODUCTION

Ultrasound has been spreading persistently in clinical medicine for more than two decades. However, it was not until the last 5 to 7 years that we have seen a true explosion in point-of-care ultrasound use in the care of critically ill patients. The term point-of-care ultrasound accurately describes the great utility of the powerful imaging modality when it falls into the hands of the clinician providing the actual medial care to the patient rather than going through an intermediary, the imaging consultant. There is good reason for this great spread and a booming popularity among clinicians of a variety of specialties. Once seen as having utility in cardiac anatomy evaluation and the occasional gallbladder infection that crept up in the intensive care unit (ICU), point-of-care ultrasound now touches virtually every disease process seen in the critically ill patient. Vascular access under ultrasound guidance is the standard of care in many settings and complications encountered obtaining vascular access without ultrasound use are hard to justify[1-3]. Other procedures are more frequently performed under ultrasound guidance as new applications continue to be developed[4]. There are several critical ultrasound topics that stand out among others in their utility, popularity and potential impact on patient care.

LUNG ULTRASOUND

Perhaps second to no other single issue, pulmonary pathology in the critically ill patient can both affect multiple other organ systems as well as be effected by other organ systems. Similarly, unlike any other single point-of-care ultrasound application in the critical care setting, lung

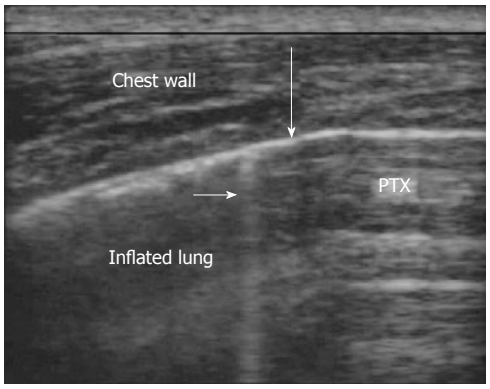

Figure 1 An ultrasound depiction of a pneumothorax is shown. This is the lung point. To the right of the image air blocks visualization of typical lung artifacts. On the left, the visceral and parietal pleura are sliding past each other. The large arrow shows where they meet. The small arrow shows a B line, seen only in inflated portions of the lung.

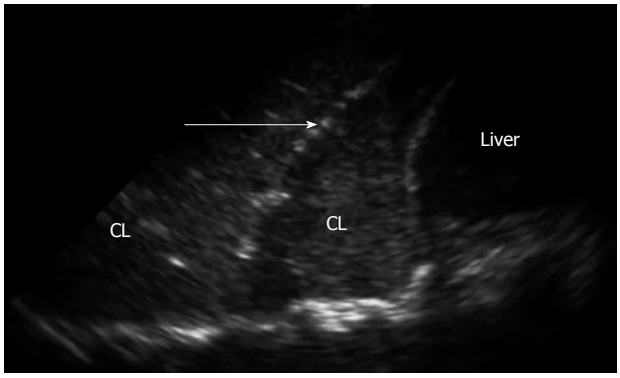

Figure 2 Pneumonia is seen just above the liver and diaphragm. An air bronchogram is also seen (arrow). Air can actually be seen moving through the bronchus within the consolidated, infected lung in real time. CL: Consolidated lung.

ultrasound has gained rapid popularity after finally being accepted in a variety of clinical situations. Its use was initially popularized in the detection and ruling out of a pneumothorax in the traumatized patient (Figure 1)[5-7]. However, there was much more to lung ultrasound than the simple, yet effective, addition to the standard Focused Assessment with Sonography in Trauma examination. While ruling out a pneumothorax, a common and potentially deadly complication in the critically ill patient, researchers recognized many additional features of the lung under ultrasound interrogation[8]. It was noted by some groups that ultrasound was also useful for the detection of pulmonary edema, pneumonia and even pulmonary embolism (Figure 2)[9-11]. This expanded list of pathology that can be evaluated by ultrasound has been well studied in multiple clinical settings. Interestingly, as a single modality it can be used as an initial, and often definitive, approach to the dyspneic or hypoxic patient. Such patients are a common and significant challenge in many critical care settings. In fact, many practitioners who are facile with the technology noted that chest X-ray use dropped dramatically and ultrasound even competed with computed tomography in cases of abscess and fluid collections.

Not just in the research stages, lung ultrasound has been described as part of protocols with great utility in the intensive care arena, regardless of where that is[12,13]. In fact, a consensus conference was recently completed on ultrasound applications using a rigorous evidence based medicine model and will be published in 2012[14]. The panel of over 30 internationally recognized experts from a variety of clinical specialties and nearly a dozen countries produced a comprehensive evidence based assessment of lung ultrasound and created direction for future researcher and education. The mere fact that a lung ultrasound consensus conference was held and supported by so many societies and international experts underlines the importance of this unique application. An application created entirely by clinicians and not borrowed from traditional imaging providers such as the consultant based service of radiology.

CARDIAC ULTRASOUND

Cardiac ultrasound in the critically patient has come a long way from simply looking for possible pericardial effusion in the arresting patient or penetrating chest trauma. Point-of-care ultrasound protocols now specifically focus on cardiac ultrasound to evaluate ejection fractions, cardiac output and patient volume status[15-17]. The dynamic nature of the techniques and ability to repeat an examination rapidly, as needed without additional radiation or waiting on an imaging specialist to perform the examination and interpret it, allows the individual intensivist to monitor patient progress and effects of therapeutic interventions[18]. Even something as simple as pulse detection in a pulseless patient has been redefined as cardiac ultrasound will frequently show cardiac activity and not cardiac standstill in patients that appeared to be in full arrest[19]. Transesophageal echocardiography, once seen exclusively in cardiology labs has been used extensively by anesthesiology in cardiac surgery and has also shown promise in critical ill patients outside of the operating room[20-22]. Since many critically ill patients are intubated, airway management is not an issue, and Transesophageal Echocardiography (TEE) has a number of distinct advantages over Transthoracic Echocardiography (TTE). The images obtained are highly superior to transthoracic echocardiography and acute measurements can be made in patients that are covered by bandages, edematous, suffer from burns or have severe lung disease that interferes with TTE examinations. TEE imaging does not interfere with resuscitation efforts and a patient can even be shocked for ventricular fibrillation with the probe left in place[22]. Pulse check or rather echo checks with TEE are nearly instantaneous and do not interfere with cardiopulmonary resuscitation efforts in any way (Figure 3).

If mechanical contractility without palpable pulse is identified, especially if the ejection fraction is assessed to be life sustaining, the management can then focus on hypotension rather than asystolic type resuscitation pathways. In fact, when point-of-care ultrasound has one of

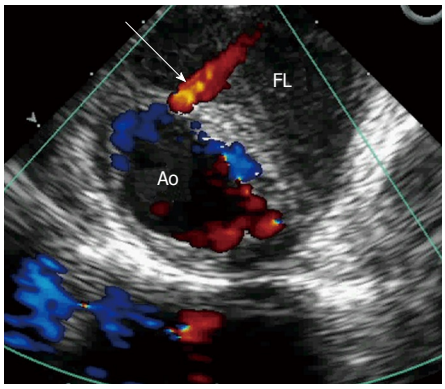

Figure 3 A jet of blood (arrow) is seen dissecting from the true lumen into the false lumen in this patient with a thoracic aortic dissection. Ao: Aorta; FL: False lumen.

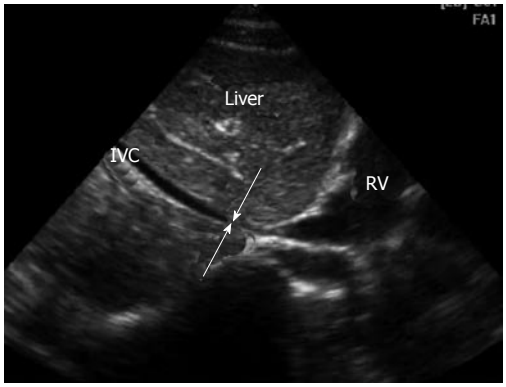

Figure 4 Inferior vena cava flat in this hypotensive and volume depleted patient. Arrows show the barely open inferior vena cava suggesting need to considerable fluid resuscitation to correct hypotension. RV: Right ventricle of the heart; IVC: Inferior vena cava.

its greatest advantages is when different applications are combined into a survey to answer specific questions such as cause of undifferentiated hypotension in a particular patient (Figure 4)[23-25]. The causes behind hypotension can range from blood loss, to pneumothorax or cardiogenic shock. Several hypotension protocols have been described and evaluated. Such protocols allow physicians to narrow their differential diagnosis more and do so more rapidly than without point-of-care ultrasound use.

As invasive monitoring is called more and more into question, pulmonary wedge pressures are being replaced by ultrasound evaluations that can rapidly tell the clinician the patients volume status and their response to diuresis, volume resuscitation or addition of various pressors. Simple assessment of the inferior vena cava and cardiac chambers can give the intensivist tremendous information on how to proceed with patient resuscitation and what interventions may work while others may actually hinder progress. It is likely that in the future these ultrasound assessments will become more automated such as creation of automatic ejection fraction and cardiac output calculations that allow clinicians of lower ultrasound skill levels to still obtain critical non-invasive data.

PROCEDURAL GUIDANCE

More and more procedures on critically ill patients are being performed under ultrasound guidance. Ultrasound guidance for vascular access has now been accepted as the standard of care and several consensus conferences on the topic are in the process of being published[26]. However, ultrasound guidance for critical care procedures goes far beyond ultrasound guidance for vascular access. Traditional blind procedures such as paracentesis and thoracentesis are performed by intensivists under ultrasound guidance at the patients bedside[27,28]. In addition new applications that were typically not done under ultrasound until critical care physicians explored these new applications along with other colleagues. Ultrasound guided crycothyrotomy and tracheostomy can keep the patient in the ICU and decrease complications[29]. When pain is an issue such as for extremity injury or even post surgical abdominal wall pain, regional nerve blocks under ultrasound guidance are more likely to be effected and have proven to be easy for non-traditional users to learn.

TRAINING AND PRIVILEGING

The standards for training of critical care physicians in point-of-care ultrasound is still a work in progress. Society recommendations should be followed when ever possible. Training is complicated by the presence of two potential pathways. Fellowship training as well as post graduate training of critical care physicians already in practice. Both pathways are in the process of ramping up and fellowships are incorporating ultrasound training at the same time that multiple courses are poping up around the world to train physicians in practice how to perform critical care ultrasound. Privileging or credentialing varies from region to region. North American models often involve hospital based privileging, where a physician is credentialed to perform ultrasound based on specialty society standards. In other parts of the world a certificate is necessary from a national or international body. These may be obtained after course completion but should also involve proctoring or mentoring and verification of ultrasound skills as well as the clinicians ability to incorporate ultrasound into their clinical decision making.

CONCLUSION

Few disease processes have not been touched by critical care or point-of-care ultrasound. In fact, a time may be coming when much of the evaluation of a critically ill patient is performed not which a stethoscope and physical examination but rather point-of-care ultrasound following a set of symptom based scanning protocols. These will improve assessment accuracy, decrease costs and most likely save lives.

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GUIDELINES FOR CLINICAL PRACTICE

Use of hypothermia in the intensive care unit

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Abstract

Used for over 3600 years, hypothermia, or targeted temperature management (TTM), remains an ill defined medical therapy. Currently, the strongest evidence for TTM in adults are for out-of-hospital ventricular tachycardia/ventricular fibrillation cardiac arrest, intracerebral pressure control, and normothermia in the neurocritical care population. Even in these disease processes, a number of questions exist. Data on disease specific therapeutic markers, therapeutic depth and duration, and prognostication are limited. Despite ample experimental data, clinical evidence for stroke, refractory status epilepticus, hepatic encephalopathy, and intensive care unit is only at the safety and proof-of-concept stage. This review explores the deleterious nature of fever, the theoretical role of TTM in the critically ill, and summarizes the clinical evidence for TTM in adults.

Key words: Targeted temperature management; Therapeutic hypothermia; Cardiac arrest; Normothermia; Intracerebral pressure; Critical care

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INTRODUCTION

Since the time of the Edwin Smith Papyrus's, and undoubtedly before, physicians have employed hypothermia (HT). HT has been used for treatment of cancer pain, induction of electrocerebral silence in surgery, tetanus, traumatic brain injury (TBI), and even status epilepticus (SE)[1-6]. It is unquestionably the greatest tool for neuroprotection in surgical cases requiring circulatory arrest and the standard of care for ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest (CA)[7-9].

Temple Fay, Claude Beck, and Charles Bailey ushered in the modern era of HT in the 1930s and 1940s with their work on TBI and circulatory arrest for cardiac surgery[6]. Fays work demonstrated the absence of irreversible neurologic change in humans refrigerated to as low as 26 ℃[10]. In this era and into the 1960s, patients were often cooled over 24 h, and to temperatures below 28 ℃. With increased awareness of the numerous cardiac, pulmonary, and infectious side effects, interest waned[11-17]. These side-effects were a function of the duration and depth of HT, and the state of intensive care unit (ICU) care at the time. Interest in HT again developed in the 1990s, when data from TBI, stroke, and CA animal models demonstrated mild to moderate HT (30-35 ℃) for 2-24 h produced sizeable improvements in outcome[18-21].

Modern ICU protocols for HT follow a "one temperature fits all" mentality. Rather than augmenting HT based on brain metabolism or surrogate markers, most centers cool to 32-34 ℃. While the appropriateness of this strategy is a matter of debate, evidence now supports the use of HT in the ICU setting. The most impressive current data comes from the CA literature where the number needed to treat for a good outcome from an out-of-hospital ventricular tachycardia/fibrillation is 5-6[8,9].

A growing body of evidence is building favoring maintenance of "normothermia" in the critically ill[22,23].

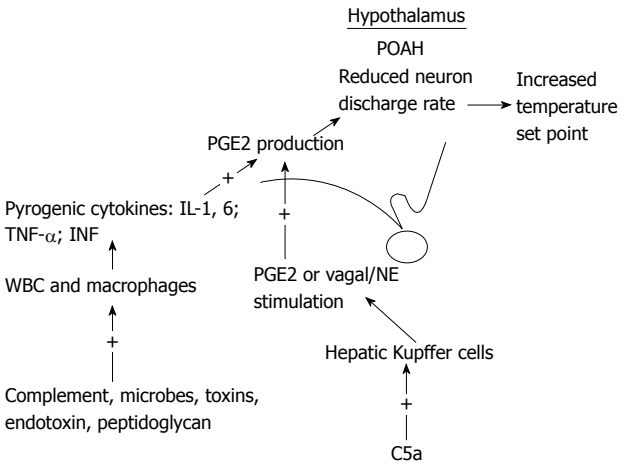

Figure 1 Schematic of fever production. POAH: Pre-optic area of the anterior hypothalamus; IL: Interleukin; TNF: Tumor necrosis factor; INF: Interferon; WBC: White blood cell; PGE2: Prostaglandin E2; NE: Norepinephrine.

This use of cooling techniques to maintain temperatures in the HT to normothermia ranges has prompted a new nomenclature, targeted temperature management (TTM)[24]. This review with briefly summarize the proposed mechanisms by which TTM is thought to work, identifys the disease processes with the strongest evidence for use in adults to-date, and addresses the logistics of TTM delivery.

PHYSIOLOGY OF TTM

Role of fever in critical illness

Is fever bad? This ubiquitous response to infections, lesional, or toxic exposure alerts clinicians that "something is wrong." Potentially blunting this response could be deleterious. Patients with community-acquired pneumonia, *Escherichia coli* bacteremia, and *Pseudomonas aeruginosa* sepsis have improved survival if they develop fever[25-27]. Yet, the development of fever in the medical ICU (MICU) portends poor outcome[28]. In the neurocritical care unit (NCCU), fever occurs in 60%-91% of this population, and 20%-33% of fevers in the NCCU are unexplained[29,30]. In this population, the presence of fever, regardless of etiology [stroke, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), TBI, SE], is associated with increased morbidity and mortality[30-33]. In CA, HT may be a desired target[8,9].

As data accumulates, fever increasingly appears to play a deleterious role in the ICU population. Fever results from neurons in the preoptic anterior hypothalamus (POAH) decreasing their rate of discharge (Figure 1). This may result from pyogenic cytokines [i.e., interleukin 1 (IL-1), 6; tumor necrosis factor α (TNF-α)] producing prostaglandin E2 (PGE2), which then acts upon the POAH. Stimulation hepatic Kupffer Cells by complement also increase PGE2 production. Temperature elevations increase proinflammatory cytokines and lead to the accumulation of neutrophils in damaged tissue, increasing inflammation[34-40]. The development of fever increase neuronal excitotoxicity and glutamate release, accelerating free radical production[41,42]. Fever also causes a variety of physiologic derangements including weakening of the blood-brain barrier (BBB), hemodynamic instability, and cardiovascular dysfunction[43]. The unanswered question remains, how should fever be treated? Should clinicians control the expression of fever, or control the humors responsible for its development?

Physiology of thermoregulation

Humans rigorously regulate core body temperature. Heat loss occurs as the result of convection, conduction, radiation, and evaporation. Sensation of temperature change is largely controlled by the transient receptor potential (TRP) family of ion channels[44,45]. TRPs are expressed by sensory neurons and activated at various temperatures. Information from these channels in the skin and core organs eventually arrives at the hypothalamus. Behavioral and autonomic responses then effect change to alter temperature. Behavioral defenses play less of a role in the ICU. The autonomic response controls the amount of heat the core organs will expose to outer world through precapillary sphincters, vasodilation, vasoconstriction, shivering, and sweating control[46,47].

Contracting near 37 ℃, arteriovenous shunting occurs largely in the hands and feet *via* special connections between arterioles and veins[48]. These shunts have a profound effect on core temperature, and are the first line of thermoregulation. Another means limiting heat loss is through vasoconstriction[49]. Should these mechanisms be insufficient, shivering is typically initiated a degree below the shunting threshold[50]. Signals originating in the POAH descend, eventually reaching the α-motor neurons of the spinal cord. Motor neuron groups are recruited, beginning with the γ motor neurons and ascending to the α motor neurons. Shivering increase metabolism, but loses efficacy with age and prolonged duration[51].

These differences are paramount in understanding TTM. As it does little to address shunting of blood flow to core organs, paralysis is only minimally effective in reducing the febrile response, and thus is of limited benefit in TTM[52-55]. When shivering occurs, effective treatments include sedation and focal hand and face warming, with or without surface warming[56-59]. Reducing the shivering threshold may abate much of this problem from occurring. However, the largest obstacle in controlling the fever response is the arteriovenous shunts and systemic vasodilation/vasoconstriction[49,60-62]. Interventions that relax sphincters or produce vasodilatation (i.e., magnesium, propofol) result in superior heat transfer[62]. Arguably, the fastest method of heat exchange would be to directly cool the core organs.

Protective physiology

Injury to the brain and spinal cord occurs in two phases. In the peri-insult period, neuronal membranes become disrupted *via* insufficient energy, metabolic disturbance, and/or excitotoxicity, heralding necrosis. In the h to d

Table 1 Potential therapeutic effects of hypothermia

Effect	Mechanism	Onset and duration of effect
Improved energy balance	Reduced cerebral metabolism for O_2 and glucose. O_2 consumption reduced 5%-6%/1 ℃ between 22-37 ℃ and ATP hydrolysis decreased by a similar rate	Hours to d. Metabolism may begin to increase after 24 h
	Reduced ATP demand and promotes glycolytic production of ATP. Net increase ATP	
	Decreased mitochondrial dysfunction	
	Improved recovery of high-energy phosphate compounds upon improvement of perfusion demand and following rewarming	
Anti-epileptic effect	Attenuation of $[K^+]_{ex}$ increases with resulting decrease in Ca^{2+} influx. Temps between 31%-33% have demonstrated decreased duration, amplitude, and frequency of ictal discharges	Hours to days. This anti-epileptic effect may continue for a period of time following rewarming
	Increased duration between depolarizations with slowing return of membrane potential	
	Decreased synthesis, reuptake, and release of excitatory neurotransmitters including glutamate	
Neuro-protective	Reduced CNS edema-Improves BBB and energy reserve for membrane pumps via better energy balance	Hours to days
	Prevent/reduce apoptosis-Hypoxia/ischemia can induce apoptosis and calpain-mediated proteolysis. HT mitigates the initiation of these processes.	Hours to weeks
	Intracellular alkalinization	Hours to days
	Less Excitotoxicity-Ca^{++} accumulation precedes neuronal damage in sensitive brain regions. Excessive pre-synaptic release of glutamate activates NMDA and non-NMDA post-synaptic receptors with resulting Ca^{++} entry and release of intracellular Ca^{++} stores. This $[Ca^{++}]_{in}$ increases activates Ca^{++} dependent enzymes producing cell injury. Decreased release of glutamate may reduce mitochondrial dysfunction, DNA damage, and decreased activation of kinases and excitotoxic cascades	Minutes to 72 h
	Anti-oxidant effects-30%-40% decrease in Krebs cycle metabolites with shunting to Pentose Phosphate Pathway occurs. This shunting of metabolites may result in increased NADPH/NADH, improved glutathione reduction, peroxide detoxification, and reduced membrane peroxidation	Hours to days
	Suppression of inflammatory reaction and impaired leukocyte function	First hour to first week
	Improved microcirculation, improving CBF and reducing cerebral edema	Hours to days

Adapted from references 69, 73, 74, 92, 146, 207. Number in right column refer to numbered entry in "mechanisms" column. ATP: Adenosine triphosphate; BBB: Blood-brain barrier; HT: Hypothermia; NADPH: Nicotinamide adenine dinucleotide phosphate; CBF: Cerebral blood flow.

following injury, programmed cell death occurs. Thus, the role for TTM can be grossly divided into two therapeutic time windows: Early/ischemia and late/reperfusion. Early mechanisms revolve around improving energy balance, reducing metabolic demand, and reducing membrane and mitochondria injury[63-65]. Later mechanism involve the consequences of reperfusion injury including suppression of spreading depression and epileptic discharges, reducing inflammation, reducing cerebral edema, bolstering the BBB, and reducing apoptosis (Table 1).

Although TTM offer an array of potential therapeutic actions, yet the, specific targets to focus this therapy remains largely unknown. For example, the metabolism suppressive roles of TTM are intuitively important for a disease process like stroke, but may be less important for a disease such as ICH (Figure 2)[66-68]. In ICH, the reduction of cerebral edema and suppression of inflammation may play a larger role[68,69]. Thus, the role of TTM may vary depending on the disease.

Early phase protective physiology

Membrane and mitochondrial effect: Within seconds of interrupted blood supply, the high energy phosphate compounds adenosine triphosphate and phosphocreatine (ATP and PC) plummet[70]. These reductions cause the tissue to transition from aerobic to anaerobic metabolism; increasing intracellular levels of inorganic phosphate, lactate, and H^+. This leads to an intracellular increase in calcium (Ca^{2+}). With failure of ATP dependent Na^+ and K^+ pumps, the excess Ca^{2+} causes mitochondrial failure, activation of intracellular kinases and proteases, and neuronal depolarization[71,72]. These depolarizations lead to accumulation of glutamate and excitatory neurotransmitters, leading to more Ca^{2+} influx *via* glutamate receptor stimulation, producing a maelstrom of cellular destruction. This disruption of ionic balance leads to cell swelling and rupture, exposing the interstitial tissue to excitatory neurotransmitters.

Evidence from animal models of global hypoxic-ischemia (HI) and TBI demonstrate inhibition of glutamate release, and suppression of reactive oxygen species (ROS) formation between the temperatures of 30 ℃-33 ℃[73]. The decreased synthesis, reuptake, and release of excitatory neurotransmitters, including glutamate, are thought responsible[74-76]. Temperature influences the membrane permeability of K^+, Na^+, and Ca^{2+} with secondary effects on cerebral energy state[73,77]. Animal models of focal and global ischemia demonstrate mild-to-moderate HT is as-

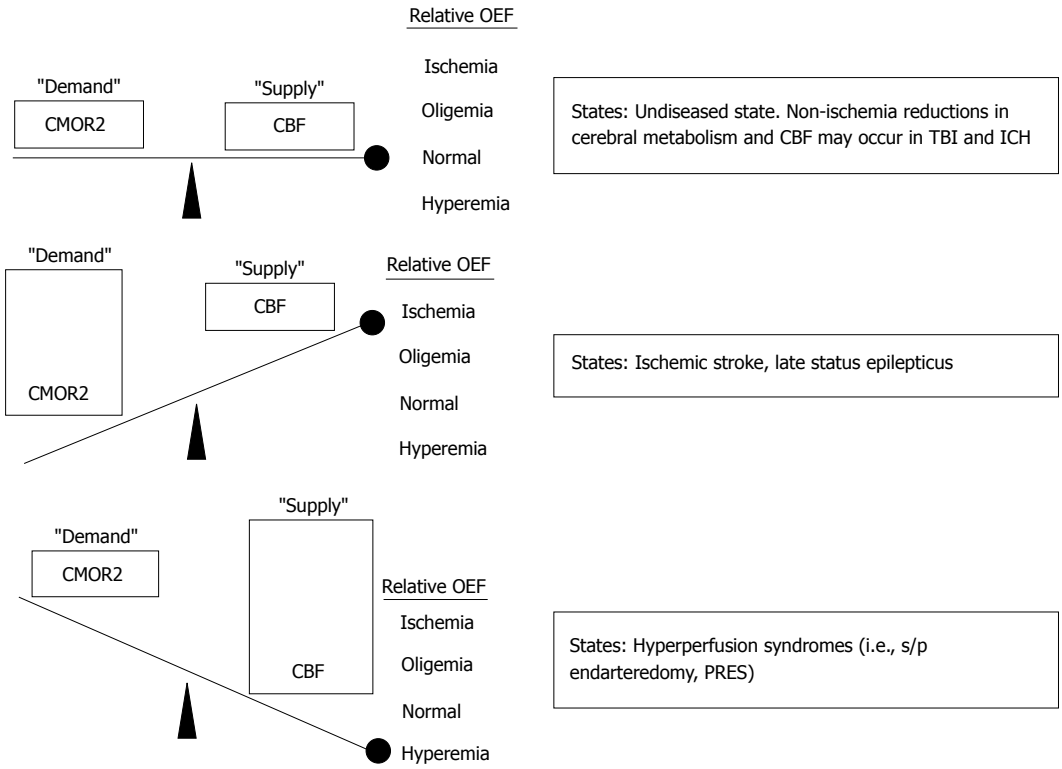

Figure 2 Metabolic pattern of common neurocritical care unit disease. CBF: Cerebral blood flow; TBI: Traumatic brain injury; ICH: Intracerebral hemorrhage.

sociated with attenuation of the initial rise of extracellular K^+ (K_e) and delayed terminal depolarization[78,79]. Less neuronal loss after reperfusion in animals treated with HT suggests the temperature dependent influx of Ca^{++} could be linked to changes in K^+ efflux, raising the link between HT and suppression of intracellular Ca^{2+} accumulation[77].

Post reperfusion, the mitochondrial electron transport chain generates free radicals[80-88]. This is referred to as ischemic-reperfusion (IR) injury. Compounds including peroxynitrite (NO_2^-), hydrogen peroxide (H_2O_2), superoxide (O_2^-), and hydroxyl radicals (OH^-) may damage cells *via* membrane and nucleic acid peroxidation, triggering apoptosis[76,89-91]. HT limits the production of free radicals, with lower temperatures appearing to be more effective[89,92].

Energy balance: Central to TTM is the supply-side economics tenant of supply and demand. Specifically, HT reduces metabolic demand for oxygen and glucose, improving the supply of ATP[93]. HT decreases brain consumption of oxygen approximately 5%-6%/1 ℃ between 22-37 ℃, with commensurate reductions in ATP hydrolysis and CO_2 production[67,70,93,94]. In a study of 10 patients with severe TBI (defined at GCS < 7), HT between 32-33 ℃ decreased $CMRO_2$ by 45% without changes in cerebral blood flow (CBF)[95]. This suggests that HT may produce a state of relative hyperemia. HT attenuates, but does not stop, ATP and PC depletion, and pH reduction, in HI models[42,73,96]. The development of acidosis, known to increase cell loss, is controlled in part by slowing the rate of high energy phosphate consumption[73].

In the post ischemic period, hypothermic animals and humans demonstrated faster recovery of pH[97]. Studies with magnetic resonance spectroscopy (MRS) have suggested HT attenuates the development of acidosis in long-term ischemia and decreases the decline of high energy phosphates approximate 5% per 1 ℃[98,99]. Although lactate levels still increase, HI animal models treated with HT demonstrate faster clearance of lactate, improved glucose utilization, resolution of pH, and quicker recovery of high-energy phosphates compared with normothermic (NT) controls[73].

An approximate 30% decrease in Krebs cycle and glycolytic intermediates, except glucose-6-phosphate, occurs with a marked decrease of Krebs cycle activity during HT[93]. Experimental work with MRS in moderate HT (31 ℃) has demonstrated a 30%-40% decrease in cortical and hippocampal metabolism, with shunting of intermediates to the pentose phosphate pathway (PPP). This corresponds to increases in nicotinamide adenine dinucleotide phosphate (NADPH)[73,93]. One could hypothesize that increase shunting to the PPP could reduce oxidized-glutathione, increase peroxide detoxification, and limit oxidative stress. HT causes intracellular alkalinization, promoting glycolysis[93]. Glycolysis may help to increase ATP levels during HT in conjunction with ebbing demand[93]. In piglet model studies with phosphorus MRS, after and during circulatory arrest at NT (37 ℃) and HT (15 ℃), HT animals displayed slower decay rate of high energy phosphate compounds, improved recovery

of ATP and PC, and improved recovery of intracellular pH[100]. This suggests HT ameliorates injury independent of phosphate compound stores. High energy phosphate compounds are depleted with ischemia in both HT and NT; however, tissue recovers ATP and other high energy phosphate compounds faster if occurring during HT[101]. Gerbils treated with HT (34 ℃) during bilateral carotid artery occlusion experienced a 10%-20% improved metabolic recovery during reperfusion compared to NT controls, displaying less histopathologic evidence of neuronal damage in the cerebral cortex and hippocampus. Animals treated with HT during ischemia demonstrated less cytotoxic edema, as noted by diffusion-weighted imaging and apparent diffusion coefficient on magnetic resonance imaging, than NT controls[20,102].

Cerebral blood flow: While metabolic reductions are clearly demonstrated, evidence for changes in CBF is variable. During cooling, $CMR_{glucose}$ and CBF are directly proportional to intrinsic flow and metabolic rate with reductions normally in the most metabolically active areas[103]. In the uninjured brain, animal data routinely demonstrates CBF and $CMRO_2$ are closely coupled from 33 ℃-35 ℃, with reduction in CBF nearly parallels that of $CMRO_2$ with an 8% decrease per ℃[104]. This relationship is inconsistently coupled from 28 ℃-33 ℃, and below 28 ℃ studies report the development of both ischemic and hyperemic states[77]. The cerebral vasculature retains its responsiveness to CO_2 even at reduced temperatures. Given relatively small differences between α-stat and pH-stat for temperatures ≥ 32 ℃, the low end of the typical target range in the ICU setting, it is unlikely that either acid-base measure would effect brain physiology[104].

However, in the diseased state, this coupling may not hold. Review of experiment literature demonstrates increases, no change, or decreases in CBF[21,77,105,106]. Clinically, TBI studies have demonstrated similar findings[95,107]. The clinical data for other disease states is even less clear. Studies in high grade SAH patients (World Federation of Neurosurgical Societies Grade Ⅳ or Ⅴ) cooling to 35 ℃, then 33 ℃ over two d, have demonstrated $CMRO_2$ and CBF reductions to a greater degree on the side ipsilateral to the ruptured aneurysm[108]. Using a similar protocol, another report demonstrated relative hyperemia ipsilateral to the site of aneurysm rupture, suggesting less autoregulation coupling in the most traumatized tissue[109]. Work in stroke patients has demonstrated early in HT, the decrease in CBF is greater than the commensurate decrease in $CMRO_2$, resulting in relative ischemia[110]. Again, the loss of autoregulation appears to play a role.

Late phase protective physiology

Inflammation: In the h to first week following injury or ischemia the inflammatory response develops. Mediated initially by astrocytes, microglia, and endothelium, the release of TNF-α and IL-1 stimulates leukocyte activation and allow for crossing of the BBB[70,111]. Concurrently, adhesion molecules on leukocytes and endothelium emerge. Activation of complement pathways further aid the accumulation of neutrophils, and later monocytes-macrophages, in damaged tissues. This leukocyte infiltration and cytokine production exacerbate injury[111-113]. HT suppresses this inflammatory reaction through attenuating adhesion molecule upregulation and inflammatory cytokine release[36,114-118]. Further, the function of neutrophils and macrophages are impaired, particularly at temperatures < 33 ℃. Experimental stroke models have demonstrated genes for inflammation are suppressed with TTM[119]. However, similar findings are not seen with TBI and CA, once again suggesting the role of TTM will vary with the disease[120-122].

Blood-brain barrier and edema: Following ischemia-reperfusion or trauma, the BBB often becomes disrupted, potentiating cerebral edema[123-125]. Cerebral edema has been implicated in delayed neurological deterioration, and worse outcome, through the elevation of intracerebral pressure (ICP)[126]. Elevations in ICP reduce the ability of blood to reach the brain, exacerbating the injury and producing ischemia. In ICH the formation of perihematomal edema contributes to approximately 75% of total volume change[127]. Animal models of ICH demonstrate a large perihematomal area that undergoes neuronal death characterized by increased water content and inflammation[128]. TTM may be an effective means to limit cerebral edema[68,129].

TTM reduces the disruptions in the BBB caused by IR injury and trauma[123-125]. TTM decrease the extravasation of hemoglobin following TBI[34]. Following IR injury or trauma, regional production of endothelin (ET-1), thromboxane A2 (TxA2) and prostaglandin I2 (PGI2), become altered, affecting endothelium[130,131]. ET and TxA2 act as vasoconstrictors, and PGI2 as a vasodilator. These injurious conditions typically favor vasoconstriction, and platelet aggregation *via* TxA2, promoting regional hypoperfusion. Animal data in TBI suggest the imbalance between TxA2 and PGI2, and excessive ET-1 production, are mitigated by TTM[132,133]. Further, reductions in inflammation and improved membrane integrity further contribute to reductions in cerebral edema[63]. Finally, reduced temperatures limit the activity of matrix metalloproteinases limiting BBB breakdown[134,135].

Cortical spreading depression and epileptic discharges: Clinical evidence has demonstrated TTM to be effective in treating refractory SE[2,136,137]. Another neuro-electrical phenomenon, cortical spreading depression (CSD), has been correlated to the development of ischemia in TBI and stroke[63]. TTM has demonstrated suppression of CSD[33,102,138]. HT diminishes and slows axonal depolarizations, limiting the release of glutamate and attenuating the development of spreading depression[33,102,138,139]. Further, HT (31-33 ℃) HT decreases the duration, amplitude, and frequency of ictal discharges; lengthens the duration between depolarizations; slows the return of membrane

potential; and is associated with decreased $CMR_{glucose}$[140-145]. Thus with decreasing temperature an inverse relationship to cerebral electrical activity develops[2,142,146,147].

Electroencephalogram (EEG) provides a consistent and reproducible means of qualifying cerebral metabolic rate[148-150]. EEG activity correlates directly with cerebral metabolism and indirectly with neuroprotection[148]. Both animal and human studies demonstrate an abrupt change in EEG activity between 30-33 ℃[150-152]. Low amplitude Δ activity is noted as the predominant pattern at around 30 ℃[149,152]. When concerned about neuroprotection, cooling to a specific temperature may not be advisable as systemic temperatures are not indicative of brain temperature or metabolism[148,149].

Apoptosis: Beginning in the 48-72 h after an ischemic or traumatic injury, HT interrupts the activation and propagation of apoptosis[153-158]. HT attenuates release of cytochrome c, up-regulation of *Fas* and *Bax*, and caspase activation[159-161]. Further, HT increases *p53* expression, promoting tissue repair[162]. The anti-apoptotic signaling pathways for *Erk1/2* and *Akt* are activated too[163-166].

INDICATIONS FOR TTM

Despite nearly 3600 years of use, and a plethora of experimental data, remarkably few clinical indications exist for TTM[65]. To date, the strongest evidence for use in adults is in out-of-hospital pulseless ventricular tachycardia/ventricular fibrillation (VF/VT) CA, ICP control, and fever control in the NCCU population[24,65].

Cardiac arrest

TTM at 32-34 ℃ for 12-24 h in patients comatose after out-of-hospital cardiac arrest (OHCA) with initial rhythms of VF or pulseless VT has become the standard-of-care[8,9,24]. In this population, the number needed to treat for an outcome of good or minimal disability is 5 to 6. Both of these landmark studies demonstrated improved outcomes, and the larger trial demonstrated a reduction in mortality, with TTM[8,9]. Evidence suggests TTM in this population is well tolerated, with no neurocognitive deficits associated with therapy[167]. With respect to patients with cardiogenic shock or requiring primary coronary angiography, TTM can be delivered safely, improving outcomes and not significantly increasing "door-to-balloon" times[9,168,169].

Despite the evidence favoring TTM for OHCA in VT/VF, consensus is not unanimous. A recent meta-analysis of 5 randomized controlled trials of TTM in CA totaling 478 total patients concluded there was a lack of firm evidence for benefit[170]. The authors cite a number of criticisms. The HT after Cardiac Arrest (HACA) study, recruited only 8% of screened patients, and was stopped for slow recruitment[8,170]. This study lacked a predefined power calculation too. Decisions regarding withdrawal of therapy cannot be standardized, and may have influenced the outcomes. The smaller Bernard trial and colleagues evaluated outcome at discharge, finding good outcomes (discharge to home or rehab) in 49% of HT patients and 26% of controls[9,170]. There was no difference in mortality. This differed from the HACA trial that measured outcomes at six mo, using the Pittsburgh- Glasgow Cerebral Performance Category.

In spite of these differences, the strength of these findings has made TTM for OHCA from VT/VF the standard-of-care. However, fewer than 20% of patients with CA fulfill the inclusion criteria for these studies[171]. Regarding the use of TTM with in-hospital CA and pulseless electrical activity (PEA)/asystole (AS), a recent consensus report of five different critical care professional societies concluded the evidence was insufficient to make any recommendations regarding PEA/AS[24]. Similarly, this group could not make a recommendation for or against the use of TTM for in-hospital VT/VF arrest. Therefore, TTM plays more a supportive role in the story of CA.

What about PEA/AS and in-hospital VT/VF arrest make it different than out-of-hospital VT/VF arrest? PEA/AS tend to have a longer time to ROSC[172,173]. In-hospital VF/VT CA is generally a very different entity caused by acute respiratory distress, distributive shock, electrolyte anomalies, or pulmonary embolism[174]. With the advent of "rapid-response" and "pre-code" teams, in-hospital arrest is becoming less common[175]. Regarding PEA/AS, a large, retrospective review demonstrated despite similar percentages of treatment with TTM, patients with out-of-hospital PEA/AS treated with TTM demonstrated only a 15% good outcome compared to 44% with VT/VF[172]. Those treated with TTM in the PEA/AS cohort had a longer delay to receiving basic life support, and a longer time to return of spontaneous circulation (ROSC), than those not receiving TTM. Perhaps, it is time to ROSC, not initial rhythm, clinicians should concern themselves with?

Once TTM has been initiated, what are the best prognostic tools? How does TTM change these? The 2006 American Academy of Neurology (AAN) guidelines on prognosis following CA are largely developed from studies prior to the TTM era. In sum, the absence of motor reaction to noxious stimuli, loss of brain stem reflexes, presence of myoclonic SE, bilateral absence of cortical somatosensory evoked potentials (SSEP) N20 responses, and serum neuron specific enolase (NSE) > 33 mg/L in the first 3 d following CA predict poor outcome[176]. Since these guidelines have been published TTM has been increasingly used for CA. Reports of patients with NSE levels > 33 mg/L, absent N20 SSEP response, and myoclonic SE recovering have been made suggesting our current prognostic tools need re-fitting[177-179].

First, does treatment with HT delay waking, potentially resulting in premature withdrawal of artificial organ preservation therapies? A recent retrospective review of 227 patients attempted to answer this question[180]. One hundred and twenty-eight patients treated with, and 99 patients not treated, with TTM were analyzed comparing

time to awakening. It is important to note that patients not treated with TTM had rhythms other than VF or were in-hospital CA. Further, this center employs a strict sedation protocol to minimize the confounding effect of these drugs on neurologic examination. Patients who survived regained consciousness at a median of 2 d (range 2-8 d) in the TTM group, and at 2 d (range 1-7 d) in the non-TTM group[180]. Thus, TTM appears to not delay awakening following CA.

Next, in the TTM era, what clinical or paraclinical findings predict outcome? Regarding the neurologic assessment, reports are variable. A recent prospective study of 111 CA survivors treated with TTM demonstrated status myoclonus, absent motor response to pain, and incomplete brain stem reflexes did not predict poor outcome in all patients[181]. In fact, this study found a motor score on the Glasgow Coma Scale (GCS) $\leqslant$ 2, or decerebrate/extensor posturing, has a false-positive prediction of mortality of 24% at 36-72 h. However, the specifics of type, amount, and duration of sedatives were not reported in this study, complicating its interpretation. These motor findings have been previously reported in smaller studies[182,183]. In another study comparing predictors of recovery in CA patients treated with and without TTM at a single center, of 14 patients with a motor score $\leqslant$ 2 at day two, 2 survived with a good or moderate outcome as scored by the Cerebral Performance Categories Score (CPC)[184].

Brainstem reflexes offer no clearer insight. In the aforementioned study, patients treated with TTM did not recover if pupillary response to light and corneal reflexes were absent up to 5 d[184]. Similar findings have been previously reported[182]. Notably, Fugate *et al*[184] reported no patient with a spontaneous downward gaze survived. While the absence of cranial nerve reflexes and purposeful motor responses at day 2-3 are concerning, they are not conclusive of final outcome. A recent study reported absence of one or greater brainstem reflexes had a false positive rate (FPR) of 4% when measured between 36 and 72 h in predicting mortality[181]. However, the effect of sedation in this study is uncertain and complicates many studies in TTM.

Do biomarkers offer a better prognostic option? The 2006 AAN guidelines, NSE was reported to have a 0% FPR for predicting poor outcome between 24 and 72 h following CA if > 33 mcg/L[176]. The increased use of TTM in CA calls into question reliance of the absolute value of this benchmark[184,185]. NSE between 24 and 48 h in patients randomized to TTM or no-TTM found higher values in the TTM group[185]. This suggests TTM may affect the normal clearance of NSE. Of note, a study evaluating serial NSE levels in CA patients treated with TTM suggest a downward trend of NSE values portend good outcome, suggesting TTM affects the normal clearance of NSE[184].

Recently a prospective, observational study looked at the patterns of various prognostic markers in patients still comatose three d following HT for CA[186]. The authors note NSE levels > 33 mg/L demonstrated extensive diffusion weighted MRI changes, in all patients. Of patients who underwent SSEP studies, all died who had NSE values of > 27 mg/L and bilateral loss of N20 peaks. All patients lacking pupillary light reflex or corneal reflex and having an NSE > 33 mg/L died. In fact, no patient with a NSE > 27 mg/L made a recovery.

Table 2 Qualitative description of Electroencephalogram pattern

Malignant EEG Patterns	Benign EEG Patterns
Non-reactive background	Generalized slowing
Burst-suppression associate with generalized epileptic activity	Mixed α-theta frequencies
Diffuse periodic complexes on a non-reactive background	Reactive background
Generalized suppression to < 20 mV	Continuous rhythm
Status epilepticus	

EEG: Electroencephalogram.

What role do electrodiagnostic studies play in prognostication? SSEP use is limited by inter-observer variability and sensitivity of system noise[187]. Despite this, SSEPs in the 2006 AAN guidelines reported a FPR of 0.7% for poor outcome when N20 responses were absent bilaterally[176]. A recent retrospective review of 36 patients treated with TTM for CA, and demonstrating bilaterally absent or minimally present N20 response at day 3, reported recovery of consciousness and cognitive function in 2 patients[178]. This suggests these studies may not be as useful in the setting of TTM.

Electroencephalography may provide a means of prognostication, particularly when complimented by other biomarkers or exam findings. Although a universally accepted classification system is lacking, a few patterns are generally accepted as benign or malignant (Table 2). When correlating to NSE, a continuous EEG pattern demonstrated lower NSE levels compared to a burst-suppression, or flat and non-reactive, background[186]. Recent studies have demonstrated the ability of EEG to identify patients with a poor prognosis based on malignant patterns and good prognosis based on benign patterns[184,188,189]. Patients presenting in a burst-suppression pattern at either initiation of EEG or normothermia, or in SE at normothermia did not regain consciousness.

If a continuous EEG pattern was present at either initiation or normothermia, 29/32 and 54/64 patients regained consciousness respectively. The positive predictive value of this was 91%[188]. Examining this dynamic testing further, a study of post-CA comatose patients receiving continuous EEG, the background activity to repetitive vocal, visual, and nociceptive stimuli correlated to in-hospital mortality and neurologic outcome at 2 mo[189]. Survivors in this cohort never demonstrated a non-reactive background to stimulation, epileptiform discharges, or prolonged periods of flat EEG. Recently, two patients treated with TTM having continuous EEG were reported who demonstrated a continuous α pattern that

attenuated to verbal or noxious stimuli[190]. These changes occurred both during and after cooling. Both patients made an excellent recovery.

Increased intracerebral pressure

HT decreases ICP, but how[24]? In the uninjured brain, CBF and cerebral metabolic rate are closely coupled from 33-35 ℃; with that coupling becoming inconsistent between 28-33 ℃[67,93,103,191-194]. The 2011 consensus review of TTM in critical care contends the uncertainty of the mechanism of action for ICP reduction in TTM precludes an affirmative recommendation. Are the elevations of ICP a marker of disease severity or a target where treatment will improve outcome? During TTM, ICP most likely falls secondary to a pleiotropic mechanism. HT decreases brain consumption of oxygen ($CMRO_2$) approximately 5%-6%/1 ℃ between 22-37 ℃ and slows ATP hydrolysis by nearly the same rate[77]. In a study of 10 patients with sever TBI (defined at GCS < 7), HT between 32-33 ℃ decreased $CMRO_2$ by 45% without changes in CBF[95]. This suggests that HT may produce a state of relative hyperemia. However, this study also reported $CMRO_2$ may start to increase after 24 h of cooling[95]. It is notable that post-cooling normothermia values for $CMRO_2$ remained approximately 15% below baseline values. Similar to $CMRO_2$, reductions in $CMR_{glucose}$ and CBF are found to be directly proportional to intrinsic flow and metabolic rate with the highest reductions in the normally most metabolically active areas[103]. While metabolic reductions may contribute to lower ICP, this is likely not the full explanation.

Although recent meta-analysis of TTM in stroke found current evidence too heterogeneous to recommend TTM in stroke patients, some findings are noteworthy[24,195]. Previous work with TTM to a goal temp of 33 ℃ for 48-72 h found ICP elevation positively correlated to the rate of rewarming and were associated with poor outcome[196]. A larger study found slowing the rate of rewarming lead to a statistically significant reduction in mortality of patients with large MCA strokes treated with surface delivered TTM to 33 ℃[197]. This suggests *something* with cooling is rewarming rate dependent. Although different disease mechanisms, clinical studies in TBI found continued reduction in brain metabolism persisting after rewarming, suggesting the elevations in ICP found upon warming are not likely the result in changes in cerebral metabolism[95,196].

A recent study with endovascular delivered TTM compared eighteen patients[129]. Seven patients were deemed, "effectively cooled" or below 34.5 ℃ within 8 h of therapy initiation. This group maintained a temperature of 33.5 ℃ ± 0.6 ℃ for 12-24 h. Eleven patients were not effectively cooled, maintaining a temperature of 35.7 ℃ ± 0.7 ℃ for 12-24 h. All patients had CT scans at admission, at 36-48 h, and at 30 d post stroke. CSF volume at these three time points served as indirect markers of cerebral edema. Specifically, a larger CSF volume presumed less cerebral edema. The authors found a statistically

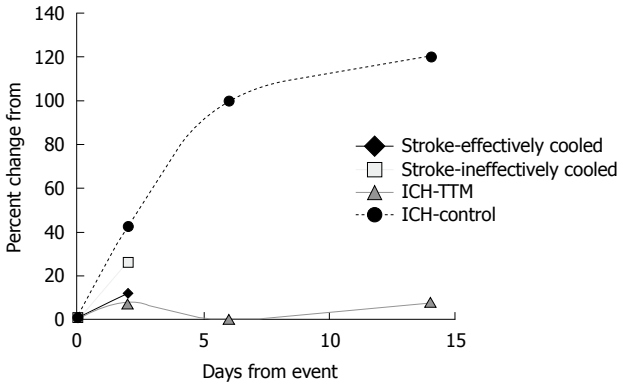

Figure 3 Approximate percent increases in cerebral edema, over time, in stroke and intensive care unit patients treated with and without targeted temperature management. Changes between stroke patients effectively and ineffectively cooled, and changes between intensive care unit patients receiving targeted temperature management (TTM) and controls not receiving TTM, are significant. Stroke patients day two measurements are between 36-48 h. ICH: Intracerebral hemorrhage.

significant difference in the CSF volume of those effectively cooled, compared to the 11 not so, at this second measure suggesting less cerebral edema (Figure 3)[129].

This edema reducing phenomenon may not require cooling to the same degree as for CA. A recent study of 12 patients with > 25 mL of ICH who were cooled to 35 ℃ for 10 d reported reduced cerebral edema (Figure 3)[68]. Perifocal edema was measured on CT. These volumes were compared to cohort of 25, uncooled patients from a local database. In the HT group, edema volume remained stable. The uncooled cohort demonstrated significantly increased cerebral edema. These increases were both in terms of absolute volume and as a ratio of ICH volume[68].

Reductions in cerebral edema, and cerebral metabolism, may not be the only means by which ICP is reduced. The growing evidence for the use of TTM in acute liver failure/hepatic encephalopathy suggests another mechanism. As the development of hyperammonemia overtakes the astrocytes ability to export organic osmolytes to compensate for accumulating glutamine, cerebral edema develops[198]. As serum ammonia levels approach 150 mmol, the risk of elevated ICP increases[199]. To briefly review, glial cells release glutamine, which is metabolized into glutamate in the presynaptic terminals by glutaminase. Glutamate can also be produced by transamination of 2-oxoglutarate, an intermediate in the Citric acid cycle. Experimental evidence has demonstrated TTM to the range of 32-33 ℃ attenuates the uptake of extracellular glutamate[200]. Glutamate levels can be further reduced by a shunting of nearly 1/3 of Krebs Cycle intermediates into the Pentose Phosphate Pathway[201]. This could potentially improve the cell's ability to resist damage from membrane peroxidation.

A series of studies by Jalan and colleagues have noted the beneficial effects of TTM to 32-33 ℃ in patients with HE. One study of 14 comatose patients with elevated ICP reported average ICP reductions from 36.5

to 16.3 mmHg[202]. However, in six patients the results were not sustained requiring intermittent mannitol bolusing. Five patients responded, and one patient succumb to herniation. Yet 13 of these patients went on to successful orthotopic liver transplantation and full neurologic recovery. Another report of five patients with elevated ICP, TTM was maintained through surgery[203]. This strategy improved cerebral perfusion and abated the ICP spikes noted during dissection.

What is the clinician to make of this? The aforementioned consensus review by five international critical care societies ruled the evidence for ICP control by TTM, as it pertains to outcome, is insufficient for an affirmative recommendation at this time[24]. The heterogeneous reporting of ICP, and inconclusive outcome data, between studies lead to this recommendation. As for specific disease process, no recommendation for TTM can be made. As previously noted, evidence for stroke and ICH remains largely at the proof-of-concept and safety stage. Recently, the National Acute Brain Injury Study: HT Ⅱ (NABIS: H Ⅱ) findings were reported[204]. NABIS: H Ⅱ was a randomized, multicenter trial of patients with non-penetrating TBI with ≤ 3 other injured organ systems enrolled within 2.5 h of injury. Patients were cooled to 33 ℃ or 37 ℃ in controls. Primary outcome was 6 mo Glasgow Outcome Scale (GOS) score. This study found no difference at 6 mo GOS score. Citing futility, this study was stopped at the interim analysis of the first 97 patients. Subgroup analysis of patients with evacuated hematomas found those treated with HT had better outcomes compared to the normothermia group. However, this represented only 28 patients. Thus, at least for TBI, HT does not appear to improve outcome.

Normothermia

Nearly 70% of patients in the NCCU experience fever in the first two weeks following injury[205]. The etiology goes unexplained in 1/5 to 1/3 of these patients[29]. The presence of fever increases the risk of poor outcome[23,206,207]. For the NCCU population specifically, after controlling for illness severity and diagnosis (ICH, stroke, or SAH) fever was independently associated with longer ICU stay, higher mortality, and worse outcome[23]. However, is fever causing the miserable outcome or is the miserable outcome heralded by fever?

Attempting to answer this question, one must first inquire what a safe and effective means to do so is. Acetaminophen effectively lowers temperature, but only by approximately 0.2 ℃[195]. Use of endovascular and newer surface cooling systems effectively lowers the fever burden safely, at no increased risk to some patient populations[22,208,209].

The NCCU data represents a mixed population. Certain disease processes may benefit more from TTM targeted at normothermia than others. The development of delayed cerebral ischemia (DCI) after SAH has been associated with a higher fever burden, portending higher morbidity and mortality[210-213]. A recent single center study of 40 consecutive febrile SAH patients maintained at 37 ℃ with a surface cooling hydrogel device (Arctic Sun) during their first 14 d after SAH were matched to 80 SAH patients who underwent conventional fever control (CFC) between 1996 and 2004[214]. The authors found patients undergoing normothermia had a longer ICU stay (19 ± 7 d *vs* 14 ± 8 d, $P = 0.001$) but a similar overall hospital length of stay as compared with CFC patients (28 ± 13 d *vs* 28 ± 21 d, $P = 0.9$). Although a higher proportion of cooled patients underwent tracheostomy and had a higher rate of pneumonia, the proportion of poor outcome at 14 d among cooled patients was no different than among control patients (83% *vs* 85%, $P = 0.7$). However, TTM patients had a statistically significant lower rate of poor outcome at 12 mo (21% TTM *vs* 46% CFC, $P = 0.03$). When entered into a multivariable linear regression model adjusting for age, cooling was associated with improved outcome at 12 mo after SAH, suggesting elimination of fever with TTM may be associated with improved outcome after SAH.

Regarding stroke, the association of fever to poor outcome is strong, but the association of intervention to improved outcome is not so herculean. The 2009 Cochrane review of cooling therapy in acute stroke found no statistically significant effect of pharmacologic or physical temperature-lowering therapy in reducing the risk of death or dependency[195]. However, the pooled data represented a heterogeneous amalgamation of small, phase I trials and acetaminophen studies lacking protocol similarity.

Even murkier is the evidence for fever reduction in the non-NCCU populations. A recent meta-analysis pooled studies representing NCCU, surgical ICU, general ICU, liver-transplant ICU, post-operative ICU, and trauma ICU populations[215]. This found current intravascular and hydrogel cooling systems significantly better at reducing fever burden than traditional cooling blankets and cooling baths. However, these studies were markedly heterogeneous. Concerning was the trend ($P = 0.06$) that hospital mortality for these newer cooling technologies, compared to traditional cooling, was higher at 25.4% *vs* 18% in the pooled analysis.

When comparing the effectiveness of pharmacologic, antipyretic treatments (i.e., NSAIDs, acetaminophen), the authors analysis demonstrated core body temperature reductions favored continuous, dosing rather than blousing, of these medications[215]. Earlier use of these medications at 38.5 ℃, with cooling blankets above 39.5 ℃, demonstrated a significant 1.09 ℃ reduction in mean daily temperatures when compared to more permissive interventions (no intervention until 40 ℃)[216]. As noted with the newer generation of intravascular and hydrogel cooling technology, this earlier use of acetaminophen and surface cooling demonstrated a trend toward increased mortality with $P = 0.09$. Given the motley findings of studies looking at TTM for normothermia, it is not surprising that the American Thoracic Society, European Respiratory Society, European Society of Intensive Care Medicine,

Society of Critical Care Medicine, and Societe de Reanimation de Langue Francaise offer this observation: Regarding fever, it is a generic response to so many pathologic processes that no recommendation can currently be made for or against TTM. If a RCT is considered, focus should probably include severe fever unrelated to infection[24].

LOGISTICS OF DELIVERY

What features of TTM can be manipulated, if any, to improve efficacy and outcome? Is the efficacy of TTM determined by the duration, depth, and cooling-rate of therapy? Currently, TTM for CA is a "one size for all" approach. The target is typically a temperature of 32-34 ℃ for 12-24 h. Would titrating to a biomarker improve efficacy? Given the paucity of evidence, a biomarker targeted approach can not as of yet be advocated. Given the numerous pathways TTM affects, and the variable pathophysiology of diseases present in the ICU, determining which pathway at which time to focus monitoring is difficult. For example, data from TBI suggests cerebral metabolic rate starts to actually increase, approaching pre-hypothermic values, after 24 h of TTM[95]. Evidence from stroke patients treated with TTM demonstrates early in cooling, a state of relative ischemia develops, later replaced by a state of relative hyperemia[110].

Experimental evidence suggests increased duration of HT could improve efficacy. A recent cardiac arrest animal study varied the time from ROSC to the onset of HT, and the duration of HT[217]. Normothermic animals were controls. Good outcomes, as assessed by a standardized behavioral scale, occurred significantly more frequently in animals cooled within 4 h of ROSC. Survival was also significantly improved. When looking at a histological marker, the surviving neuron counts in animals cooled longer (48 h) was significantly greater than in animals cooled for a shorter period (24 h), or not at all[217].

Do these findings clinically translate? Could variation therapy duration improve the clinical outcome? Clinical evidence is lacking. Any effort to extend duration of therapy must weigh the increased risk of infection inherent to prolonged HT duration. Evidence from stroke and TBI patients treated with TTM report increased incidence of pneumonia with TTM times exceeding 48-72 h[197,218]. Recent retrospective review of 421 patients from a single center demonstrated 67% of patients developed 373 infectious complications[219]. These were most commonly pneumonia (85%), bloodstream infections (9%), and catheter-related infections (3%). Gram-negative bacteria were the most frequent isolated agents, occurring nearly 2/3 of isolates. Infected patients were most commonly treated with TTM, and of a longer duration. However, infection did not impact mortality or favorable neurologic outcome.

If prolonged duration of therapy is precarious, could changing the rate of cooling improve efficacy? The question of cooling rate and its effect on patients is understudied. The Bernard and HACA trials achieved a goal temperature typically within 2 h, at a median of 8 h after ROSC[8,9]. An observational study of OHCA, including PEA and AS, have not shown time to initiation of TTM, or time to reach goal temperature, as having an effect on outcome[220]. However, the protocols for HT were not standardized in this review. A recent study in 49 consecutive patients with OHCA (VT/VF, PEA, AS) with ROSC within 60 min of arrest and GCS $\leqslant$ 8 after CPR were prospectively followed. Predictors of good outcome included youth, early CPR, and a faster rate of cooling[221]. Not surprising, larger body surface area slowed the rate of cooling.

Anesthesia literature in patients receiving intra-operative HT for neuroprotection during circulatory arrest for thoracic aorta procedures provides some insight. Electroencephalography was used as a qualitative marker of cerebral metabolic activity[149]. The development of periodic complexes, burst suppression, and electro-cerebral silence patterns were chosen as qualitative markers of decreasing cerebral activity. Previous work has demonstrated reductions in EEG activity during HT to correlate to cerebral metabolism[148,150]. The authors found an association between rate of cooling and EEG endpoints. Specifically, prolonged time to cool to any EEG marker portended prolonged time to cool to reach the next marker[149]. Further, lower temperatures required for a marker were associated with lower temperatures required for subsequent markers. Said another way, a slower rate of cooling required a lower absolute temperature to obtain the necessary cerebral metabolic endpoint. Larger body surface area and increased hemoglobin concentration were found to directly correlate with times needed to reach burst suppression and electrocerebral silence respectively.

As uncertainty remains regarding the duration, depth, and targeting of TTM, could the type of device used effect outcome? Although firm answers are missing, some provocative findings are reported. In a head-to-head, single center, observational comparison of 167 patient receiving either the CoolGard (Zoll Circulation, Chelmsford, Massachusetts) or Arctic Sun (Medivance, Louisville, Colorado) systems, no significant differences were found in the rate of cooling, ICU stay, duration of mechanical ventilation, survival to discharge, survival at 6-12 mo, of neurologic outcomes[222]. Of note, more hypomagnesemia was observed in the endovascular group. The surface-cooled patients had more episodes of hyperglycemia. Of note, a recent prospective, observational, registry-based study of 22 U.S. and European hospitals demonstrated sustained hyperglycemia was associated with increased mortality[220,223].

While the device itself may not change outcome, many practical issue can affect the success of TTM protocols. A Google search demonstrates a number of devices that are commercially available for induction and maintenance of TTM and range from surface and endovascular cooling catheters, cooling helmets, immersion devices, and intranasal device. A recent prospective study of fifty ICU

patients requiring TTM evaluated the rate of cooling, and the variation above/below target temperature during the maintenance phase of TTM[224]. Five commercially available devices were evaluated which included a water circulating external cooling device (Blanketrol Ⅱ, Cincinnati Sub Zero, The Surgical Company), an air circulating external cooling device (Caircooler CC1000, Medeco), a gel-coated adhesive system (Arctic Sun, Medivance), an endovascular cooling system (Icy-catheter, Alsius CoolGard 3000), or conventional cooling with cold saline bolus and surface cooling with ice. This was a mixed group consisting of OHCA, TBI with elevated ICP, or patients with SAH requiring normothermia. The cohorts of 10 per device were well matched for APACHE Ⅱ, age, and BMI. In sum, the water-circulating blankets, endovascular cooling, and gel-adhesive devices provided the fastest rate of cooling. As for maintenance, the endovascular system provided the most reliable temperature control, drifting out of target range < 5 ± 5% of the time. The next closest device was the gel adhesive device, with a variance of approximately 40% ± 20%. Further, the endovascular and gel adhesive systems rated well with ICU nurses regarding maintenance work-load and hygiene, with endovascular cooling also scoring well in reported ease of patient monitoring[225].

CONCLUSION

Despite nearly 3600 years of medical use, the role of TTM remains ill defined. Currently, the strongest evidence for the use of TTM, in adults, is for HT in OHCA for VT/VF, ICP control, and for normothermia in the neurocritical care population. However, even in these disease processes, a number of questions exist. Data on disease specific therapeutic markers, clinical pathophysiology, and therapeutic depth and duration are limited. Further, for disease processes like HE, stroke, refractory SE, and ICH much of the clinical evidence reported is only at the safety and proof-of-concept stage. In sum, though intuitively appealing, TTM remains enigmatic in the ICU. More work is needed to define targets and goal directed therapies before a final "yeah or nea" can be given to this therapy.

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Events Calendar 2012

February 4-8, 2012
41st Critical Care Congress
Society of Critical Care Medicine
Mount Prospect, IL, United States

February 17-21, 2012
12th Annual International Symposium on Congenital Heart Disease
St. Petersburg, FL, United States

February 26-29, 2012
11th International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy
International Convention Center,
Jerusalem, Israel

March 2-3, 2012
Twelfth Annual John M Templeton Jr Pediatric Trauma Symposium
Philadelphia, PA, United States

March 25-30, 2012
5th World Congress of Anaesthesiologists
Buenos Aires, Argentina

April 11-13, 2012
Society of Trauma Nurses 2012 Annual Conference
Savannah, GA, United States

May 3-5, 2012
18th Annual Spring Meeting of the Anesthesia History Association
Kansas City, MI, United States

May 10-11, 2012
National Trauma Institute 2012 Annual Conference
San Antonio, TX, United States

May 18-23, 2012
American Thoracic Society 2012 International Conference
San Francisco, CA, United States

May 24-25, 2012
European Society of Intensive Care Medicine Summer Conference: Trauma Update 2012
The Royal Society,
London, United Kingdom

May 26-29, 2012
10th World Congress for Nurse Anesthetists
Ljubljana, Slovenia

June 4-6, 2012
5th International Conference on Patient- and Family-Centered Care: Partnerships for Quality and Safety
Omni Shoreham Hotel,
Washington, DC, United States

June 28-29, 2012
European Society of Intensive Care Medicine Summer Conference - Acute Kidney Injury
Ecole Normale Supérieure, Amphi Charles Mérieux,
Lyon, France

August 27-28, 2012
Annual Global Healthcare Conference 2012
Singapore

October 13-17, 2012
25th European Society of Intensive Care Medicine Annual Congress
Lisbon, Portugal

November 11-15, 2012
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Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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