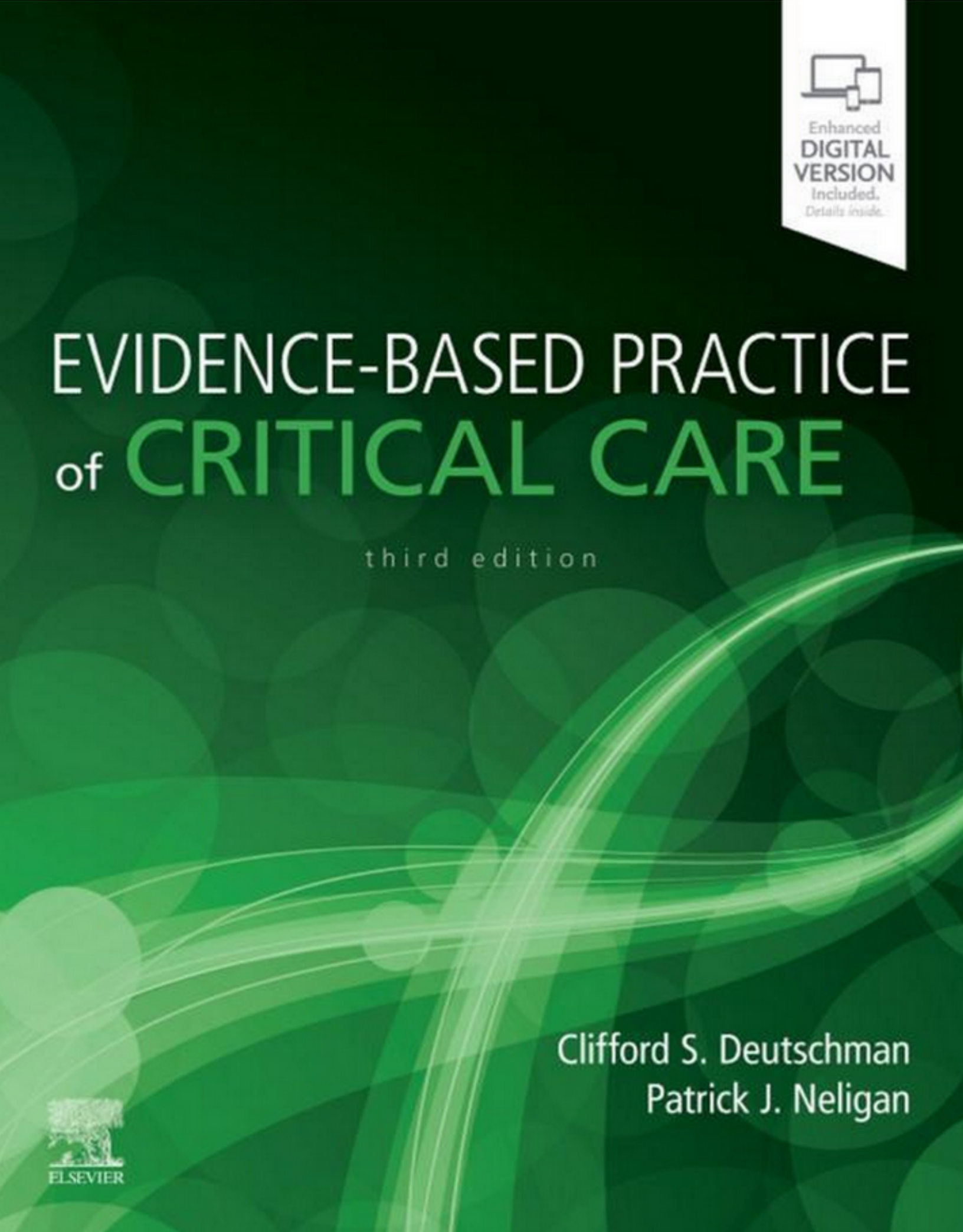
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third edition
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To my family:

Cate, Beth, and Nicki, who make us so proud, and Chris,
for truly being my better half for three and a half decades.

Clifford S. Deutschman, MS, MD

To Diane, David, Conor, and Kate and to
my parents, Maurice and Dympna Neligan,
for their continued support and wisdom.

Patrick J. Neligan, MA, MB, FCAI, FJFICIMI

In memory of Brian Kavanagh

friend and colleague, clinician and scientist
contributor to the first edition, mentor to many of the authors of this one
and, too sadly, not here to be embarrassed by this dedication.

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PREFACE

We are delighted to present this third edition of *Evidence-Based Practice of Critical Care*. Critical care is a fast moving field with an abundance of new publications that result in subtle but frequent changes in our thinking. To produce a state of the art book that covers the full spectrum of our specialty has required the participation of a large number of experts and their mentees. We are truly grateful for their participation. We would like to thank the many critical care practitioners who have purchased the prior editions of the book and complimented us on its value and content. This edition is not an updated facsimile of the second. We have significantly revised the content:

- Some of the basic principles we highlighted previously have stood the test of time—at least of the last few years. These successes reinforce our belief that care of the critically ill patient will continue to improve.
- Evidence continues to support the value of consistently applying proven interventions (Chapters 1, 2, 8, 38). However, while we may now have a better sense of which individual approaches carry the most profound benefit (Chapters 9, 16, 18, 24, 34), we are profoundly aware that many may not (Chapters 25, 48) and that, in most cases, the evidence remains equivocal (Chapters 7, 8, 18, 20, 26, 57, 73, 84).
- We have a better understanding of some aspects of the pathobiology of critical illness (Chapters 14, 17, 25, 29, 38, 40, 41, 62, 63, 69), but a great deal remains elusive (Chapters 5, 32, 33, 38, 69).
- The use of large datasets to identify disorders has increased (Chapters 1, 2, 3, 5, 13, 21, 31, 34, 37, 38), mostly to the benefit of critically ill patients. Data-based approaches have aided in the early identification of disorders of profound importance, for example, sepsis (Chapter 31). The impact of comorbidities as well as preexisting and predisposing conditions is now clearer (Chapters 5, 11, 15, 21,79), but controversy remains (Chapter 27).
- Critical illness does not end with discharge from the ICU; in fact, some unfortunate patients never fully recover (Chapters 3, 22, 40). A pathobiologic understanding is only just emerging (Chapters 3, 4, 12, 40, 41) and identification/validation of therapeutic approaches is limited (Chapter 4, 22).
- Definitions for sepsis, acute respiratory distress syndrome (ARDS), and ventilator-associated pneumonia have been revised (Chapters 13, 30, 47). It is now appreciated that a definition ("what a thing *is*") differs from the clinical criteria used to identify a disorder (Chapters 13, 30, 31, 47) because there are few gold standards that can be used to unequivocally identify most diagnoses that underlie critical illness. Critical criteria to identify patients with sepsis and ARDS have been derived and validated using large datasets (Chapters 13, 31). There remains a pressing need to develop and validate evidence-driven consensus criteria for other disorders (e.g., brain death, Chapter 87).
- Many aspects of critical care practice remain poorly understood, controversial, or unproven (Chapters 25, 26, 32, 33, 39, 57, 68, 73). And while some of the things we do may be bad (Chapters 6, 10, 24, 60, 61), we continue to do them.
- Early identification of several disorders, especially those involving infection, trauma, or the vasculature, is of paramount importance (Chapters 34, 38, 46, 52, 53, 54, 64, 65, 66, 67, 74, 75, 77, 80).
- Determining if outcomes from critical illness have improved, or if interventions have been effective, remains problematic (Chapters 2, 5, 17, 18, 19, 20, 21, 22, 37, 38, 39, 47, 68, 73). And we continue to search for the elusive "better way" (Chapter 84).
- Critical care practice has long been recognized as a "team sport." We recognize that the critical care team is composed of diversely educated coequals; while each member may have a specific area of expertise, we also support and learn from each other (Chapters 85, 86).
- The results of many studies continue to be negative or equivocal. But we have increasingly come to recognize that this result is virtually unavoidable when we globally apply a specific therapy to all patients with a given disorder. A major challenge for future critical care practitioners will be to identify those specific patients in whom a therapeutic approach is most likely to work. Genetics or other aspects of the host response will be major determinants (Chapters 5, 32, 33, 40, 41, 46, 63), but so will the characteristics of the disorder, for example, the importance of the specific infecting agent that precipitates sepsis remains virtually unexplored (Chapter 43).
- Finally, critical care practice has become more patient-centric (Chapters 2, 3, 4, 5, 84, 86, 88), and this trend must continue.

Reading, writing, and editing the chapters in this book has been hugely enjoyable and thought provoking. In particular, we would like to commend the individuals who are contributing for the first time, having not participated in the first two editions. It is gratifying to recognize that their enthusiasm for critical care equals our own, and that their understanding of our field exceeds our own. These individuals represent the future of critical care—and the field is in good hands.

Clifford S. Deutschman
Patrick J. Neligan
March 2019

Is Hypothermia Useful to Prevent Brain Injury after Cardiac Arrest? In Other Settings?

Laura Dragoi and Damon C. Scales

Sudden cardiac arrest remains a common and deadly problem, with an incidence of around 100 per 100,000 individuals and an associated mortality rate at hospital discharge of 20–30%.[1,2] Overall, survival has improved, with increased rates of bystander cardiopulmonary resuscitation (CPR) and advances in prehospital resuscitation, but in-hospital strategies to improve outcomes after cardiac arrest remain limited. Therapeutic hypothermia (TH)—or cooling the body—is one of the few treatments that has been well studied and should be considered for all appropriate patients who have return of spontaneous circulation (ROSC) after cardiac arrest.

The first modern case reports reporting better patient outcomes and a decrease in mortality after TH were published in the late 1950s.[3,4] However, the widespread adoption of hypothermia as a treatment strategy did not occur until after the publication of randomized controlled trials (RCTs) in the early 2000s.

MECHANISMS OF ACTION

The mechanisms through which TH is thought to protect the brain after ischemia–reperfusion injury are complex. In the acute phase, during the first 24–48 hours after cardiac arrest, TH is thought to reduce cerebral blood flow and cerebral oxygen consumption, preserve energy stores, and reduce the release of excitatory amino acids.[5] TH may also prevent mitochondrial dysfunction, suppress ischemia-induced inflammatory reactions, decrease oxidative damage, improve brain glucose metabolism, and alter both immediate early gene expression and cellular stress response.[6,7] In the subacute phase, which ranges from 1 to 7 days, hypothermia may also prevent apoptosis, reduce inflammation and associated cerebral edema, and attenuate disruption of the blood–brain barrier.[7]

RANDOMIZED CONTROLLED TRIALS OF MILD THERAPEUTIC HYPOTHERMIA

Two landmark trials highlighted the benefits of hypothermia after out-of-hospital cardiac arrest (OOHCA) in the early 2000s. A quasi-RCT compared moderate induced hypothermia (targeting a body temperature of 32–34°C) to normothermia (targeting 37°C).[8] The study included 77 patients who presented with ventricular fibrillation (VF) and remained in persistent coma after ROSC. In the hypothermia group, a temperature of 33°C was maintained for 12 hours after arrival at hospital and then patients were actively rewarmed. More patients in the hypothermia group (49% vs. 26%, $P = .046$) survived to hospital discharge with good enough neurologic function to be discharged to home or a rehabilitation facility. A larger RCT (Hypothermia After Cardiac Arrest, HACA study) conducted in Europe also compared mild hypothermia (targeting 32–34°C) for 24 hours followed by passive rewarming vs. standard normothermia in 276 patients with VF and pulseless ventricular tachycardia (VT).[9] More patients treated with hypothermia achieved the primary outcome of favorable neurologic outcome measured at 6 months after cardiac arrest (55% vs. 39%, $P = .009$). Both RCTs showed marked improvement in rates of survival, with good neurologic outcome with hypothermia.

Although the use of hypothermia to improve neurologic outcome was supported by subsequent meta-analyses, some experts noted that their results were primarily influenced by these two relatively small RCTs with a high risk of bias, both of which compared hypothermia to no temperature management in the control groups.[10,11]

The Targeted Temperature Management Trial was conducted to address these concerns.[12] This RCT included 950 patients with ROSC after cardiac arrest from any underlying arrhythmia, and compared TH or TTM to a target temperature of 33°C vs. a target temperature of 36°C. Both arms in this trial involved active temperature management using sedatives, neuromuscular blocking agents, and surface cooling or invasive cooling techniques. There was no difference between groups in rates of the primary outcome of all-cause mortality at 180 days or in rates of the secondary composite outcome of poor neurologic function or death. The investigators concluded that both strategies could be considered in survivors of cardiac arrest.

Based on the cumulative evidence, the International Liaison Committee on Resuscitation (ILCOR) issued an advisory statement on TTM in 2016. They recommended that TTM (as opposed to no TTM) should be provided to all patients with OHCA who present with a shockable rhythm yet who remain unresponsive after ROSC (strong recommendation, low-quality evidence); that TTM is suggested for adults with

OHCA who present with a non-shockable rhythm yet who remain comatose after ROSC (weak recommendation, very low-quality of evidence); and that TTM is suggested for adults with in-hospital cardiac arrest with any initial rhythm (weak recommendation, very low-quality evidence).[13] Similarly, the American Heart Association (AHA) recommended that TTM be provided to all cardiac arrest patients with shockable rhythms and non-shockable rhythms, including those with in-hospital cardiac arrest.[14] However, based on the results of the TTM trial, the AHA guidelines recommended that the target temperature range be broadened to 32–36°C.

Controversy has persisted about the interpretation of the TTM trial results.[12] Specific concerns have included that the temperature separation between the two groups may have been insufficient to lead to clinically important outcome differences; that the trial was designed and analyzed as a superiority trial rather than a noninferiority or equivalence trial to justify changing practice from cooling to a target of 33°C; and that outside of a carefully conducted trial, targeting a higher temperature may increase the risk of potential hyperthermia when selecting a higher target temperature if protocols are not carefully monitored and implemented. Reflecting these concerns, some guidelines have continued to recommend that patients be cooled to a target temperature of between 32 and 34°C.[15,16]

The results of ongoing trials should offer additional insights. The TTM-2 trial (ClinicalTrials.gov Identifier: NCT02908308)[17] is currently enrolling patients and will compare clinical outcomes among 1900 patients allocated to receive TTM to a target temperature of 33°C vs. early fever avoidance. Similarly, the HYPERION trial (ClinicalTrials.gov Identifier: NCT01994772)[18] is comparing neurological outcomes among 584 patients with non-shockable rhythms who are either cooled to between 32.5 and 33.5°C or treated with normothermia at a target temperature of between 36.5 and 37.5°C.

TIMING AND DURATION OF COOLING

Animal studies suggest that earlier initiation of TH after return of spontaneous circulation leads to better neurologic outcomes compared with delayed cooling.[19,20] However, RCTs in humans examining earlier initiation of cooling (e.g., in the prehospital setting) have not shown improved neurologic outcomes compared with when TH is initiated after hospital arrival.[21,22]

The optimal duration of hypothermia is also unclear. A large RCT in 335 cardiac arrest patients compared TH at 33°C for 24 hours vs. 48 hours after ROSC but observed no differences in rates of good neurologic outcomes at 6 months.[23] Guidelines currently recommend at least 24 hours of TTM based on the protocols that were used in the HACA and TTM RCTs.[9,12–14,24]

HOW TO DELIVER THERAPEUTIC HYPOTHERMIA

The delivery of TH can be divided into three phases: induction phase, maintenance phase, and rewarming phase.[6] During the induction phase, the body's normal counter-regulatory mechanisms to decrease heat loss must be overcome. The most effective of these counter-regulatory mechanisms are vasoconstriction and shivering. To prevent shivering, most patients will require treatment with sedative medications and often neuromuscular blocking agents. Different methods have been used for the induction of hypothermia, including surface cooling with ice packs applied to the groin and axilla, wet towels, pre-refrigerated cooling pads, external air or cold water circulating blankets. Specialized intravascular cooling catheters that may provide faster induction of hypothermia and more reliable temperature control are available but are more invasive, requiring insertion into a central vein and having associated risks of infection and thrombosis. Other induction methods that have been less frequently studied include evaporative transnasal cooling and immersion baths. The comparative efficacy of different induction methods has been explored in several small studies, but none have demonstrated improved clinical outcomes.[25–27] All cooling devices used for induction of hypothermia should be left in place during the maintenance phase to ensure that the temperature remains at the desired target, and during the rewarming phase to control the rate of rewarming and prevent rebound hyperthermia. Sedation should also be continued through the maintenance phase to prevent shivering. Most hypothermia RCTs have used gradual passive rewarming, achieved by stopping sedative agents and allowing the temperature to slowly increase until a normal body temperature is reached.

SIDE EFFECTS OF HYPOTHERMIA

The most common adverse events associated with hypothermia are arrhythmias and electrolyte disorders.[12] Mild hypothermia targeting a temperature of 32–36°C may be associated with bradycardia, cold diuresis, and increased urine output, and these may necessitate treatment with positive chronotropic agents or fluid replacement, respectively. Electrolyte disturbances can occur during TH. In particular, induction of cooling can lead to hypokalemia, and hyperkalemia may develop during the rewarming phase. Changes in magnesium and phosphate concentrations can also occur, and so electrolytes should be monitored frequently, especially during the induction and rewarming phases.[28]

Some studies have shown that hypothermia is associated with reduced immune function and, in particular, with higher rates of pneumonia.[29] Although there are theoretical concerns that hypothermia may interfere with hemostasis,[30] mild TH to between 32 and 36°C has not been associated with major bleeding complications in any of the large cooling trials.[8,9,12]

HYPOTHERMIA FOR TRAUMATIC BRAIN INJURY

The administration of hypothermia in traumatic brain injury (TBI) has been studied as a general treatment for severe TBI to prevent increases in intracranial pressure (ICP) and as a

rescue treatment when other methods to decrease a high ICP have failed.

Studies of hypothermia as a general treatment for TBI have yielded conflicting results, probably due to heterogeneity of design, including differences in the temperature targeted during cooling, duration of treatment, and rate of rewarming.[31–34] The Brain Trauma Foundation Guidelines[35] currently do not recommend hypothermia to improve outcomes in patients with diffuse injury. The recently published POLAR trial[36] compared early prophylactic hypothermia with normothermia among 511 patients with severe TBI and observed no differences in neurologic outcomes between the two groups.

Hypothermia has also been used as a rescue strategy for patients who develop severe elevations in ICP that remain unresponsive to other treatments. The Eurotherm3235 RCT[37] enrolled 387 patients with ICP elevations >20 mm Hg and lasting more than 5 minutes, and compared standard ICP treatment strategies with hypothermia, targeting a temperature between 32 and 35°C. In this RCT, fewer patients had a favourable outcome at 6 months in the hypothermia group—and this led to early termination of the trial.

In summary, strong evidence is lacking to support the use of hypothermia as a general treatment strategy in patients with TBI or as a rescue therapy for patients who develop raised ICP.

HYPOTHERMIA IN STROKE

Several small studies[38–41] have demonstrated the feasibility and safety of TH for patients with acute stroke; however, large RCTs testing the impact of hypothermia on important clinical outcomes after stroke are lacking. The Euro-HYP RCT, currently enrolling (ClinicalTrials.gov Identifier NCT01833312), will determine if systemic cooling to a target temperature of 34–35°C started within 6 hours of symptom onset and maintained for 12 hours improves functional outcomes at 3 months compared with TTM between 36.5 and 37.5°C.[42]

AUTHORS' RECOMMENDATIONS

- All patients with cardiac arrest should be considered for targeted temperature management (TTM).
- A core temperature of between 32 and 36°C for 24 hours appears safe and, overall, leads to improved rates of survival with good neurologic outcomes.
- There is currently no clear evidence that induced hypothermia results in better outcomes than maintenance of normothermia.
- There is currently no evidence that TTM for more than 24 hours improves outcomes.
- The use of hypothermia in patients with other etiologies of neurologic injury (e.g., traumatic brain injury and stroke) is not supported by available evidence.

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Abstract: Sudden cardiac arrest remains a common and deadly problem. Therapeutic hypothermia—or targeted temperature management—is one of the few treatments that has been well-studied and, based on the available evidence and guideline recommendations, should be considered for all survivors of cardiac arrest. Maintaining a core temperature of between 32 and 36°C for 24 hours leads to improved rates of survival with good neurologic outcomes. The use of hypothermia in patients with other etiologies of neurologic injury (e.g., traumatic brain injury and stroke) is not supported by available evidence.

Keywords: cardiac arrest, therapeutic hypothermia, targeted temperature management, stroke, traumatic brain injury

1

Has Evidence-Based Medicine Changed the Practice of Critical Care?

Andrew T. Levinson and Mitchell M. Levy

The Evidence-Based Medicine movement, that originated in the mid-1990s, has resulted in monumental changes in critical care medicine. During that period, practice shifted from a reliance on expert opinion to a critical appraisal of the available literature to answer focused clinical questions.[1,2] Systematic examination of what works and what does not, while valuing clinical experience and patient preferences, has led to a surprising and thought-provoking journey that has resulted in dramatic improvements in the care of the critically ill patient. Many of the lessons learned during the evidence-based medicine era would have never been predicted two decades ago.

In this chapter, we describe five important lessons learned in intensive care during the evidence-based medicine era:

1. We need to look beyond single randomized clinical trials (RCTs).
2. It is the small things that make a difference.
3. Accountability is critically important.
4. We often need to do less to patients rather than more.
5. It is the multidisciplinary intensive care unit (ICU) team, not the individual provider, that is the most responsible for good clinical outcomes and high-quality critical care.

LOOKING BEYOND SINGLE RANDOMIZED CONTROLLED TRIALS

By critically appraising the entire body of literature on specific interventions and clinical outcomes, we have learned many lessons about what is most important in the delivery of critical care. However, we have learned that we must wait before we immediately embrace the results of a single RCT with very impressive results and instead base our clinical practices on more comprehensive, cautious, and critical appraisals of all of the available literature.

The decades of critical care research since the 1990s are filled with stories of impressive findings from single-center RCTs that could not be replicated in larger multicenter RCTs. Unfortunately, in many cases, the initial positive single-center results have been embraced by early adopters, only to have the results refuted by subsequent follow-up trials. The story of tight glycemic control in critical illness is illustrative. A single-center study of the management of hyperglycemia in a population consisting primarily of postcardiac surgical patients found that intensive glucose management with insulin infusion with a target blood glucose of 80 to 110 mg/dL dramatically reduced mortality when compared with a more lenient target blood glucose of 160 to 200 mg/dL.[3] The results of this single-center study were embraced by many intensivists and rapidly generalized to a wide variety of critically ill patents. The factors behind this rapid adoption by the field are multiple, including ease of implementation and cost. Unfortunately, a subsequent similar study of medical patients showed no significant benefit of an intensive insulin therapy protocol in the critically ill medical patient.[4] Ultimately, the most comprehensive multicenter trial of medical and surgical critically ill patients found significantly increased mortality in the group randomized to a tight glycemic control protocol, compared with targeting a blood glucose level of less than 180 mg/dL. This excess mortality was likely due to the much higher rates of severe hypoglycemia.[5]

In 2001, the era of early goal-directed therapy (EGDT) was introduced through the publication of a single-center RCT. EGDT was widely adopted, and multiple subsequent published trials, all prospective cohort series, confirmed its benefit.[6] More recently, three large RCTs[7–9] failed to demonstrate a survival benefit when protocolized resuscitation was compared with "usual care." It is possible that these results, at least in part, reflect the effect of the original EGDT trial; the widespread adoption of aggressive, early resuscitation; and the broad-based implementation of the Surviving Sepsis Campaign Guidelines and bundles.[10] If this continues to define usual care, then perhaps it is no longer necessary to mandate specific protocols for resuscitation because it appears that standard sepsis management has evolved to be consistent with published protocols.

The evidence for the use of hydrocortisone in the treatment of septic shock is an example of a sepsis treatment in

which the initial promising study was embraced quite early,[11] only to be questioned by subsequent conflicting evidence.[12] A multicenter placebo controlled trial of hydrocortisone in septic shock which enrolled 3800 patients, published in 2018, has only increased the ambiguity. It found a quicker resolution in shock but no mortality benefit.[13] After more than 15 years and multiple large studies we are still awaiting the final answer about the clinical administration of corticosteroids as an adjunctive therapy in septic shock.

Activated protein C is an example of how little we still currently know about the pathobiology of sepsis and the difficulty in developing targeted therapies. Activated protein C, used as an adjunct therapy for patients with sepsis, was initially thought to be quite promising,[14] but was ultimately abandoned after subsequent RCTs failed to duplicate the original results.[15] Newly adopted medications and interventions based on limited data may suffer the same fate.[16,17]

SMALL THINGS MAKE A BIG DIFFERENCE

The evidence-based era has taught us that small, often neglected or overlooked details of everyday bedside care can play a large role in determining whether our patients survive their ICU stay. Pneumonia that develops after the initiation of mechanic ventilation (ventilator-associated pneumonia [VAP]) is associated with high morbidity and mortality and significantly increased costs for critically ill patients. Several simple targeted interventions to address this problem have significantly reduced VAP rates. Simply keeping our intubated patients' heads elevated at least 30 degrees rather than leaving them supine (as was customary two decades ago) has resulted in major reductions in VAP.[18,19] In addition, a focus on better oral hygiene of mechanically ventilated patients via the administration of oral chlorhexidine has even further reduced the VAP rates.[20–23]

Another simple small intervention in the evidence-based era, the early mobilization of our critically ill patients, has also been found to significantly improve patient outcomes. Critically ill patients were kept immobilized for several weeks in the belief that this was necessary for their recovery. The result was very high rates of ICU-acquired weakness that required prolonged periods of rehabilitation in ICU survivors.[24] More recent studies have shown dramatic improvements in functional status and significantly decreased ICU length of stay (LOS) when critically ill patients are mobilized as soon and as much as possible.[25,26]

ACCOUNTABILITY IS IMPORTANT

Another important lesson learned during the evidence-based era is the importance of tracking clinical behavior through performance measures. Published reports have demonstrated a significant gap between intensivists' perceptions of their ability to adhere to current evidence-based medicine and actual practice.[27] This dichotomy has been noted in adherence to low tidal volume strategies in acute respiratory distress syndrome and other common "best ICU practices." These findings have led to the development of checklists and performance metrics to foster clinician accountability that have provided tangible improvements in clinical care. Multifaceted interventions using checklists have dramatically reduced catheter-related blood stream infections[28] as well as complications from surgical procedures.[29]

In acute situations, checklists have also been shown to improve delivery of care.[30] Continuous measurement of individual performance in the evidence-based medicine era has allowed ongoing, real-time feedback to individual clinicians and groups of providers. Application of this approach to sepsis care has resulted in significant improvements in adherence to evidence-based guidelines and in patient outcomes.[31]

DO LESS, NOT MORE

The evidence-based era has also taught us that we often should do less, not more, to and for our critically ill patients. We have learned that interrupting sedation and awakening mechanically ventilated patients each day, and thus reducing the amount of medication administered, can reduce ICU LOS.[32,33] When coupled with a daily weaning trial, daily awaking of ICU patients reduced mortality.[34] There remains, however, some clinical equipoise regarding the additive effect of daily sedation interruption in addition to protocolized sedation.[35] It has also been learned that decreasing the need for mechanic ventilation by first using noninvasive strategies in specific groups of patients with acute respiratory distress may improve outcome.[36] In addition, use of smaller tidal volumes in mechanically ventilated patients has been shown to be lifesaving.[37] We have also learned that reducing the amount of blood given to patients who are critically ill, even in some situations where the patient is actively bleeding, can significantly improve outcomes.[38,39]

IT IS NOT JUST THE INTENSIVIST

Finally, it has been learned that it is not the physician, but rather the entire health-care team, that is responsible for the delivery of high-quality care in the ICU. In a large observational cohort study based on the Acute Physiology and Chronic Health Evaluation IV (APACHE IV) model for predicting ICU LOS, investigators found that the key factors for predicting ICU LOS were structural and administrative. Specific APACHE IV variables of importance include reduced nurse-to-patient ratios, specific discharge policies, and the utilization of protocols. Structural and administrative factors were significantly different in high-performing ICUs with decreased LOS when adjusting for patient variables.[40,41]

The use of weaning protocols managed by respiratory therapists has resulted in reductions in the duration of mechanic ventilation relative to the subjective individualized assessment of an ICU clinician.[42,43] In addition, a 2013 study revealed that staffing academic ICUs with intensivists overnight did not change clinical outcomes.[44] Finally, a landmark 2006 study found that empowering critical care nurses to

intervene when they witnessed breaches in sterility was a key component in reducing catheter-related blood stream infections.[28] Taken together, these and other data strongly suggest that it is not solely the intensivist, but the entire critical care team, that is key to high-quality care.

SUMMARY

In summary, it seems that lessons offered by evidence-based medicine suggest that patience, keeping it simple, paying attention to detail, and working as a team are the key elements of good clinical care.

Key Points

1. Look beyond single randomized controlled trials.
2. Small things make a big difference.
3. Accountability is important.
4. Do less, not more.
5. It is not just the intensivist.

AUTHORS' RECOMMENDATIONS

- Single randomized controlled trials may be misleading, and the totality of evidence should be evaluated.
- Simple interventions such as head of bed elevation and early mobilization make a significant difference to outcomes.
- Measuring performance levels with checklists and audit improves outcomes. Accountability is important.
- Taking a conservative approach to interventions and therapies appears to confer patient benefit: "do less, not more."
- High-quality organized multidisciplinary intensive care improves outcomes: it is not just the intensivist.

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Abstract: Evidence-based medicine, in existence for over two decades, has resulted in monumental changes in critical care medicine. In the last 20 plus years, practice has shifted from a reliance on expert opinion to a critical appraisal of the available literature to answer focused clinic questions. Systematic examination of what works and what does not, while valuing clinic experience and patient preferences, has been a surprising and thought-provoking journey that has resulted in dramatic improvements in the care of the critically ill patient. Many of the lessons learned during the evidence-based medicine era would have never been predicted two decades ago. In this chapter, we describe five important lessons learned in intensive care during the evidence-based medicine era: (1) We need to look beyond single randomized clinical trials (RCTs). (2) It is the small things that make a difference. (3) Accountability is critically important. (4) We often need to do less to patients rather than more. (5) It is the multidisciplinary intensive care unit (ICU) team, not the individual provider, that is the most responsible for good clinic outcomes and high-quality critical care.

Keywords: evidence-based medicine, mechanical ventilation, randomized clinical trials, sedation, sepsis treatments, steroids in septic shock

2

Do Protocols/Guidelines Actually Improve Outcomes?

Jon Sevransky, William S. Bender, and Bram Rochwerg

Critical illness and injury that results in intensive care unit (ICU) admission requires complex, coordinated, and often invasive treatment. The sheer number of clinicians, consultants, and caregivers coordinating the rapid delivery of life-saving therapy to patients with evolving physiology in a busy environment can make it challenging to ensure that all patients receive appropriate and evidence-based care. One way to increase the chance of receiving optimal care and to decrease the possibility of unnecessary variation in practice is to create protocols that explicitly delineate desired care pathways. Protocolization allows for consideration of specific preset treatment algorithms for patients who have life-threatening illness or injury. For example, it seems rational that a patient with sepsis admitted to the ICU on Tuesday morning would get similar and appropriate care as a patient with the same complaint admitted late Saturday evening. Thus, standardizing care through the use of protocols would ensure that patients receive similar and appropriate care at various times of the day and week with differing bedside clinicians.

Protocols may be based on local practice, derived from clinician's experiences and modified to suit specific patient phenotypes, or adapted from national or international clinical practice guidelines (CPGs) that provide direction for patients' treatment options. Whether the basis for a specific protocol is local or national, it is imperative that the standardization of clinical practice be modified based on the individual setting in order to fit the available resources and serve the local patient population in the best possible manner.

Over the past few years, guidelines have been established to help direct practitioners in the care of ICU patients with sepsis, acute respiratory failure, and delirium.[1–3] To be considered trustworthy, guidelines are best created using a platform that allows for:

- clear and reproducible documentation of how the guideline was created
- assessment and management of potential conflicts of interest in panel members
- involvement of all relevant stakeholders
- a clear linkage to the summary of the currently available evidence
- clear and actionable recommendations
- an assessment of the level of evidence supporting each recommendation within the guideline

This chapter will review the development and use of protocols and guidelines in critical illness as well as potential limitations and hazards in using such protocols and guidelines.

WHAT IS A PROTOCOL?

Protocols are locally produced care pathways that mandate a course of therapy or care. They are often codified into clinical order sets, serve as a template for the delivery of specific patient care.[4,5] Protocols are most often created with the aim of improving care for specific disorders and ensuring that appropriate, desired, and evidence-based care is delivered to patients who meet specific criteria.[4] Protocols can be produced and used by physicians, nurses, respiratory therapists, and often involve numerous providers allowing for coordinated and optimal clinical management. Protocol initiation may be triggered by admission to an ICU; more commonly, protocol initiation coincides with a specific level of care (e.g., a patient requiring intubation and delivery of invasive mechanical ventilation) or when a patient is diagnosed with a certain disorder (e.g., sepsis). While protocols are often developed from evidence summaries, others may be produced based on experiential practice with certain types of patients.[6]

WHAT IS A GUIDELINE?

Clinical Practice Guidelines (CPGs) are care pathways, constructed from expert opinion based on analysis of evidence, that suggest a course of therapy or care. CPGs are intended to provide contextualized guidance to bedside clinicians and ultimately inform the best care for patients. CPGs have evolved dramatically since the 1990s. This evolution culminated in the publication of the Institute of Medicine's monograph entitled "Clinical Practice Guidelines we can Trust" in 2011.[7] The Institute identified key tenets necessary for the production of trustworthy guidelines. These include:

- transparency
- identification and management of potential conflicts of interest
- comprehensive panel composition including all relevant stakeholders
- ensuring that all recommendations are informed by comprehensive systematic reviews of the relevant evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach is a widely used guideline methodology that systematically includes these crucial components.[8] GRADE is used by many critical care societies in developing their CPGs.[1,3]

We will focus the discussion on GRADE methodology because, in our opinion, it offers distinct advantages over alternatives. These advantages include providing guidance on optimizing panel composition, managing potential conflicts of interest, prioritizing outcomes of interest, assessing the certainty of the evidence based on specific domains, and providing direction on how to move from evidence summary to recommendations.[9] Recommendations are directive and clear; "we recommend" is used for strong recommendations and "we suggest" for conditional or weak recommendations. Although the validity of evidence is crucial in deciding on the strength of recommendations, other concerns are considered when generating recommendations. These factors include cost, individual patient values and preferences, feasibility, and the balance of benefits and harms associated with specific interventions.[10] Most guidelines are reviewed and updated every few years as additional evidence is generated to inform clinical practice.[1,4,5]

HOW DOES A PROTOCOL DIFFER FROM A GUIDELINE?

Guidelines produced using a methodology such as GRADE embrace uncertainty. Strong recommendations, usually appropriate only in the setting of moderate or high certainty evidence, are relatively rare. Recommendations tend to be more nuanced and mandate shared decision-making between clinician, patients, and other stakeholders in order to make the best decision for each individual. Conditional recommendations (also known as weak recommendations) establish the course of action that is likely to be preferred by the majority of patients; however, they recognize that a large minority of patients may in fact choose the alternative. A transparent and comprehensive description of these considerations is provided following each actionable recommendation to better inform clinical decision-making.

Protocols may be derived from guidelines but tend to be created at a local level (hospital or health system). When adapting a guideline into a protocol, it is important to adapt the protocol to address the local patient population, ICU staffing models, available resources, and local practice patterns. While protocols may be equally informed by a summary of the best evidence, they tend to be more prescriptive in their direction. Clinical direction is often provided in an all-or-none sequential manner. This ensures standardization of care and that nothing is missed. An accompanying justification to inform the protocol's specific directions is only rarely provided; rather it is inherently assumed that the protocol was developed with best practices in mind. Given this, one might assume that only interventions with high certainty and clear beneficial effects are the ones that should be incorporated into protocols. We should note that sometimes protocols are developed in order to minimize unnecessary variation in practice even when the evidence supporting the protocol may be less than certain.

As illustrated, guidelines and protocols are not synonymous. Each has inherent strengths, limitations, and distinct settings where they should be used.

EPIDEMIOLOGY OF PROTOCOLS IN THE INTENSIVE CARE UNIT

Given the complex ICU environment, it is not surprising that most institutions have a number of clinical protocols. A survey of 69 United States ICUs demonstrated that the median number of protocols per ICU was 19.[6] Despite some concerns, it has been demonstrated that the presence of a protocol does not adversely affect trainee learning.[11] Importantly, the mere presence of a protocol does not ensure that the protocol will be followed or that patient outcomes will be better in an ICU with more protocols.[6] In fact, protocol uptake and efficacy seems better when implemented for a single illness or process of care than when introduced for all aspects of ICU care.[12–14] A careful attempt to introduce several protocols all at once into multiple Brazilian ICUs did not improve survival. It is possible that the team building necessary for successful implementation of protocols is augmented by focusing on a single process or illness (e.g., sepsis, prevention of catheter-associated bloodstream infections). This approach may be necessary to create changes in care that lead to improved outcomes.[13,14]

CHALLENGES FOR PROTOCOLS IN THE INTENSIVE CARE UNIT

As noted earlier, protocols are often developed to standardize care in a busy environment such as the ICU. The desired goal may be prevention of clinical omissions, especially during times of high acuity or other forms of clinical distraction.[15] The same situational factors that drive the potential benefit of protocols also serve as potential challenges. Patients who are critically ill tend to present with variable phenotypes, including different underlying disorders, different demographics with varying ages and ethnicities, and, at times, different types of acute illness. Developing a single protocol to meet the needs of all patients can be daunting. As discussed earlier, it is crucial that the needs of the patient primarily inform protocol development; however, the available resources of the hospital, including personnel, must be considered. More general protocols can and should be adapted to the environment in which they will be delivered. At times, a protocol may be used on a patient who does not meet the criteria for which the protocol was developed. It is especially important for protocol developers to consider this possibility because of the many syndromes prevalent in the ICU that lack a gold-standard diagnostic test.[1,16]

A more global challenge for protocol use in the critical care setting is to ensure that the clinicians charged with implementing them are willing to do so. One important way of

accomplishing this goal is to assure that protocol development includes all relevant stakeholders (in particular the bedside providers who will be directly involved). This approach provides all parties with a stake in protocol ownership and will help in developing clinical champions for use. Variable compliance with protocols has even been observed even in hospitals where clinicians are invested in implementing standard types of care.[6,17,18] Providing a feedback loop tailored to the ICU and to involved clinicians is also essential so that they better reflect on their own compliance with the protocols.[14,19,20] Lastly, there is an opportunity cost to every protocol developed; time spent developing, championing, and evaluating the use of a protocol cannot be spent on competing tasks.

PROTOCOL-DRIVEN CARE VERSUS INDIVIDUALIZED CARE

Increasing evidence suggests that standardizing care is a useful tool for increasing compliance with a desired therapy and, consequently, for improving clinical outcomes. Protocols have been successfully used to:

- limit excessive exposure to sedation
- increase mobilization and early rehabilitation in the ICU
- deliver lung-protective invasive mechanical ventilation
- liberate patients from mechanical ventilation in a timely manner
- facilitate treatment of patients with sepsis[18,21–23]

In fact, protocols aimed at limiting sedation and liberating patients from invasive mechanical ventilation are found in many ICUs and have been used as platforms to extend additional treatments or to add on related protocols; e.g., increasing mobilization or augmenting the involvement of families and caregivers in ICU care.[2] Importantly, protocol use need not limit a clinician's ability to individualize care. For example, the presence of a protocol to assure the use of lung-protective ventilation, a need to correct severe respiratory acidosis, or to treat elevated intracranial pressure, can take precedence over the use of tidal volumes of 6 mL/kg. Similar flexibility can be applied to intravenous fluid resuscitation in sepsis.[24] A protocol in this situation might direct clinicians to administer fluid amounts based on a specific physiologic parameter or on a number of parameters, while ensuring adequate resuscitation.[1,25] It has been argued that protocolization will lead to misalignment of treatment patterns in which the encapsulated care within the protocol could be inappropriate.[26] We believe that one result of allowing individual providers to individualize care for every patient will be unnecessary variation in care. Simply put, for the majority of patients, attempts to individualize care most often reflects the usual practice arm of studies that have demonstrated this approach to be inferior to protocolized care.[21,27]

As future advances in ICU care develop, it may be possible to modify interventions based on individual patients' physiology. For example, assessment of lung compliance using esophageal balloons, currently the subject of a Phase II trial, may allow clinicians to titrate positive end expiratory pressure (PEEP) more precisely.[28] However, physiology-based or individualized care has not always led to improved clinical outcomes. Examples include titration of ventilator support to target higher partial pressures of oxygen, accomplished using higher tidal volumes, inhaled nitric oxide, or higher concentrations of supplemental oxygen,[18,29,30] or adding nonspecific nitric oxide synthase inhibitors to increase blood pressure.[31]

Alternatively, there are a number of instances in which individualized care does make sense—for example, limiting the use of steroids for shock in those at high risk for neuropsychiatric agitation or limiting the use of aggressive life-support modalities based on patients' values and preferences. It is always important to carefully consider the effect on a single patient when using a protocol.

PROTOCOLS AND GUIDELINES: SEPSIS AS A CASE STUDY

Sepsis and septic shock continue to be a frequent and often lethal cause of emergency department and ICU admissions. It is estimated that there are approximately 1.5 million ICU admissions and 300,000 deaths in the United States each year due to sepsis.[32] Because decreased time to appropriate therapy is associated with improved clinical outcomes, sepsis remains a common target for protocol and guideline creation.

The Surviving Sepsis Campaign (SSC), a combined effort of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (as well as other professional societies), was initiated in 2002. The approach used by the SSC was to increase awareness and improve care for patients with severe sepsis and septic shock.[33] Since inception and initial publication, the guidelines have been updated four times. Using formal guideline development methodology, the SSC created evidence-based guidelines for the management of patients with severe sepsis and septic shock with the aim of decreasing mortality and morbidity resulting from sepsis.[33] Using the evidence-based recommendations, the campaign created two bundles, which are in essence protocols, to standardize the treatment of sepsis and to assist with the translation of knowledge to bedside users (clinician and patient). The details[34] are reviewed in Chapter 38. However, two items about the first SSC guidelines should be highlighted. First, both in North America and Europe, implementation efforts across many hospitals led to uptake and improvements in compliance with these bundles, and use of these bundles was associated with decreased mortality after implementation.[35–37] Of note, despite low initial implementation in the United States, improvements over time were associated with an adjusted absolute decrease in sepsis mortality of 0.8% per quarter and an overall drop of 5.4% (95% confidence interval 2.5%–8.4%) over the subsequent 2 years.[34] Similarly, in Spain, an implementation effort (Edusepsis) led to an increase in sepsis bundle compliance which was associated with an improvement in sepsis survival nationwide.[35] Second, some of the items present in these initial bundles, such as early goal-directed therapy, use of tight glucose control, and administration of activated protein C, were later found to have no benefit, and in the case of tight glucose control,

might potentially be harmful. These elements have been removed from the sepsis bundles.[38–40]

The changes in the SSC guidelines highlight the importance of updating both guidelines and protocols to reflect new study findings. With most guidelines, this occurs in cycles every few years.[1,4] There has been a recent push to move towards "living guidelines"; recommendations being constantly updated real-time in response to evolving evidence. However, the cost and human resource implications associated with operationalization is high. Compliance with the updated SSC bundles was noted to be associated with a 25% relative risk reduction in mortality over a period of 7.5 years when studied in nearly 30,000 patients across three continents.[37]

The New York State mandate (Rory's rules) serves as an additional example of how standardizing sepsis treatment can lead to improvements in patient outcomes. Rory Staunton was a young patient who died of septic shock after delayed recognition, and his death led New York State to develop a mandated sepsis treatment protocol. In early 2013 the state of New York began requiring hospitals to initiate evidence-based protocols for the early identification and treatment of severe sepsis and septic shock.[41] While the protocols could be tailored to specific hospitals, they required core measures similar to those included in the SSC bundles—administration of antibiotics within 3 hours of patient identification, drawing blood cultures before administering said antibiotics, and measuring serum lactate levels within 3 hours of hospital presentation. A 6-hour bundle consisted of administration of a 30 mL/kg bolus of intravenous fluid for patients with hypotension or serum lactate measuring ≥4 mmol/L, initiation of vasopressor therapy for refractory hypotension, and repeated measurement of lactate within 6 hours of bundle initiation. The implementation of compliance with this mandate was associated with shorter lengths of stay and lower risk and risk-adjusted mortality.[41] More recent evaluation of the effect of compliance with these bundles suggest that completion of most of the bundle elements was associated with decreased mortality.[42] However, while there is evidence that the implementation of the New York state mandated sepsis initiative has increased compliance with desired care and decreased mortality in patients with sepsis, a smaller study examining compliance and clinical outcomes could not demonstrate benefit with a different set of protocols (SEP-1) in patients with sepsis.[34] While the differences in outcomes between these two studies may be related to the power of the studies or differences between the study sites, this differential finding highlights the need to validate guidelines.

The examples highlighted earlier demonstrate some of the positive effects associated with both guidelines and protocols and how they can be used and adapted to optimize the management of sepsis and septic shock. The implementation of a protocol can create a standardized approach treating sepsis within an institution.[43] In the case of sepsis, synthesizing evidence-based guideline recommendations into a local protocol that fits a specific environment complete with its own particular practice patterns, staffing models, and resources is a challenging but necessary undertaking that requires engagement of a multiprofessional team.

HOW TO DEVELOP A PROTOCOL LOCALLY

It seems obvious but the major local decision to make is what illness or treatment pathway should be addressed with the protocol. As noted, it is best to target a single practice because wholescale adoption of many protocols has not improved outcomes in the critically ill.[12] Once consensus on the value the process has been achieved, a multiprofessional team with adequate representation of all of the involved disciplines should be constructed (Fig. 2.1). Each of the major stakeholders involved in protocol development and implementation should be comfortable communicating with each other as peers and a hierarchical framework should be avoided.

Over 2 years, our own institutions implemented a system-wide sepsis protocol to replace multiple departmental and hospital level protocol. We initiated monthly sepsis meetings that included ward, ICU, and emergency department nursing and physician leadership as well as representatives from our quality management team. These meetings, where everyone is seen as an equal partner in the implementation and continued improvement of our sepsis protocol, have allowed for robust buy-in across our system. Reviews of relative real-time adherence data and identification of opportunities for improvement are more easily accomplished in this collaborative environment as are the execution of projects designed to enhance protocol utilization and adherence. Continued maintenance of this synergistic environment is undoubtedly one of the most important elements for our institution and its delivery of sepsis care as we look to respond to external pressures, such as guideline and regulatory agency changes as well as changing patient demographics.

WHAT OUTCOMES SHOULD BE USED TO VALIDATE A PROTOCOL OR GUIDELINE?

Protocols and guidelines are time intensive to create and implement. For example, generation of the 2016 SSC guidelines involved more than 50 people performing more than 70 literature searches, systematic reviews, data abstractions, and meta-analyses to generate the evidence summary used to inform the guidelines.[1] In addition, creating a local protocol requires time

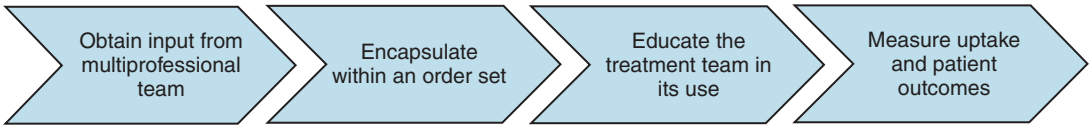

Fig. 2.1 Implementing and validating a local protocol locally.

and commitment from a multiprofessional team. As an example, at one of the author's institutions (JS), it took over a year to create a mobilization protocol, and 2 years to standardize sepsis treatment amongst all practitioners. Because this opportunity cost exists, it is important that we implement protocols that are both feasible to operationalize within an institution and that we meet the initially identified goals, which in general include decreasing practice variability or improved patient outcomes. Some protocols have not improved clinical outcomes, and others proven less beneficial in some hospitals.[44] Table 2.1 provides examples of the level of evidence needed to change clinician behavior. Box 2.1 presents a framework for creating and validating a treatment guideline.

TABLE 2.1 What Level of Evidence Should Change Practice?

Unit of Decision	Evidence Needed to Change Practice
Single Patient	Physicians knowledge and experience: patient preferences
Single Institution	Collective agreement of clinicians based on local implementation; experience with treatment at same institution, ideally backed up by data
Most Physicians	≥1 Randomized controlled trial in a similar patient population; in specific circumstances a strong observational trial may suffice
Treatment Guidelines	≥1 Randomized controlled trial in a similar patient population; review of evidence by multiprofessional including patients, and evaluation or risk benefit and costs of treatment

BOX 2.1 Suggestions for Implementing and Validating a Set of Guidelines Nationally.

1. Assemble a team of experts to review the evidence behind treatment of an illness.
2. Formally assess and manage potential conflicts of interest.
3. Establish questions and outcomes that the team should evaluate using both patient and clinician input. Consider importance from a patient outlook.
4. Perform systematic reviews of the literature for each question of interest and summarize evidence with meta-analysis and pooling of data where appropriate.
5. Use a validated methodology to establish the strength of the evidence.
6. Develop actionable recommendations considering the evidence and certainty (strength) but also the balance between benefits and harms, costs and resources, and patient values and preferences.
7. Disseminate the recommendations, including decision aids if possible.
8. Study the effect of implementing the guidelines on important patient outcomes.
9. Update the guidelines on a regular basis.

SUMMARY

Both protocols and guidelines can improve the care of critically ill and injured patients. Both can increase the likelihood that patients will get appropriate and desired care and can also empower all members of the multiprofessional team. While no one protocol or guideline will be appropriate for all patients, a well-developed protocol is a good starting point to deliver appropriate care for many patients with life-threatening illness and injury.

AUTHORS' RECOMMENDATIONS

- Guidelines are usually intended for wide distribution to hospitals and clinicians over a broad geographic area.
- Protocols tend to be derived from guidelines and are intended for a local hospital or health system.
- It is important that both guidelines and protocols be regularly reviewed and updated.[8]
- Guidelines and protocols should be based on the best available evidence.
- Stakeholders should strive to evaluate the impact of these documents, ensuring their use leads to improvement in patient care.

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Abstract: Critical illness and injury that results in intensive care unit (ICU) admission requires complex, coordinated, and often invasive treatment. The sheer number of clinicians, consultants, and caregivers coordinating the rapid delivery of life-saving therapy to patients with evolving physiology in a busy environment can make it challenging to ensure that all patients receive appropriate and evidence-based care. One way to increase the chance of receiving proper care and to decrease the possibility of unnecessary variation in practice is to create protocols that explicitly delineate desired care pathways. Protocolization allows for consideration of specific preset treatment algorithms for patients who have life-threatening illness or injury. While no single protocol or guideline will be appropriate for all patients, a well-developed protocol is a good starting point to deliver appropriate care for many patients with life-threatening illness and injury.

Keywords: evidence, guidelines, intensive care unit, protocols, sepsis