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WJCCM

World Journal of Critical Care Medicine

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AIM AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a bimonthly peer-reviewed, online, open-access, journal supported by an editorial board consisting of 105 experts in critical care medicine from 27 countries.

WJCCM aims is to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of critical care medicine. *WJCCM* covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, cardiopulmonary cerebral resuscitation, fluid resuscitation and tissue perfusion, coagulant dysfunction, hemodynamic monitoring and circulatory support, ICU management and treatment control, application of bronchofiberscopy in critically ill patients, and critical care medicine-related traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of critical care medicine-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

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EDITORIAL

Once more unto the breach, dear friends, once more

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Abstract

The first issue of the *World Journal of Critical Care Medicine* (*WJCCM*), whose preparatory work was initiated on December 16, 2010, will be published on February 4, 2012. The *WJCCM* Editorial Board has now been established and consists of 105 distinguished experts from 27 countries. Our purpose of launching the *WJCCM* is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

Key words: Critical care medicine; Biomedical sciences; Peer-reviewed; Open-access; Journal

Peer reviewer: Paolo Cotogni, MD, Anesthesiology and Intensive Care, Department of Medicine, S. Giovanni Battista Hospital, University of Turin, C.so Bramante 88-90, 10126 Turin, Italy

INTRODUCTION

Greetings! I am Derek S Wheeler, MD, FAAP, FCCP, FCCM, an Associate Professor from the University of Cincinnati College of Medicine, OH, United States (Figure 1), and together with Yaseen Mohamed Arabi, MD, FCCP, FCCM, Associate Professor, King Saud Bin Abdulaziz University, Saudi Arabia, we will be the co-Editor-in-Chief of the *World Journal of Critical Care Medicine* (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492). We are excited to bring you the inaugural issue of the *WJCCM*, a bimonthly, peer-reviewed, online, open access journal supported by an editorial board of over 105 specialists in critical care representing over 27 countries across the globe. Each and every member of the editorial board is an expert and leader in the field of critical care medicine. We pledge to bring you, the readers of our new journal, the very latest in scientific and technological advances pertaining to the care of critically ill or injured children and adults.

The specialty of critical care developed with the recognition that patients with acute, life-threatening illnesses or injuries were best treated in a geographically distinct area of the hospital, the early precursors of the modern day intensive care unit (ICU). Indeed, Florence Nightingale, perhaps the very first ICU nurse, first recognized the distinct advantages of caring for and monitoring wounded British soldiers as close as possible to the nursing station during the Crimean War of the 1850s[1-5]. Today, the ICU brings together physicians, nurses, pharmacists, and allied health providers from a variety of backgrounds, including surgery, anesthesiology, internal medicine, emergency medicine, and pediatrics to care for the critically ill. Indeed, modern ICUs now serve as a focal point or nexus in the complex network of the hospital environment, interacting with virtually every other unit in the hospital. Moreover, there is a growing trend for the development of the "ICU without walls" concept[6], as most critical care teams are involved with outreach programs[7], telemedicine[8] and rapid response systems[9].

There is no question that critical care medicine continues to be an important specialty. The United States currently spends approximately 16% of the gross domestic product (GDP), (nearly $2.3 trillion) on health care, which represents approximately $7400 per person per year. Approximately 1% of the GDP is spent on intensive care services[10-15]. At the same time, the number of ICU beds in the U.S. continues to grow at a rapid pace, with nearly 15% of all hospital beds categorized as ICU beds[14-16]. Several factors are believed to be responsible for this increase. For example, the U.S. population is growing older, and patients are living longer, even in the face of diseases that were previously considered universally fatal. In addition, hospitalized patients are becoming more dependent upon the use of invasive devices and technology. However, this story is far from complete, as a very different picture emerges outside of the United States. For example, in the United Kingdom, ICU beds account for only about 2% of the total hospital beds, as only the most critically ill patients are admitted to the ICU in the United Kingdom and Western Europe[17]. Several studies have shown that there is significant variation between countries on the exact definition of an ICU bed[18,19], which also may partly explain some of the differences in total ICU beds as a function of total hospital beds between different countries.

There are now several different journals dedicated to the care of critically ill and/or injured children and adults. The breadth and depth of the critical care literature mirrors that of the enormous growth of the biomedical literature over the past decade. According to a recent article in the *Wall Street Journal*, the number of research journals increased over 23% from 2001 to 2010. There are now over 30 000 research journals worldwide that publish nearly 2 million research articles on an annual basis[20]. This vast literature leads to a logical question - why do we need yet another journal dedicated to the specialty of critical care? The simple answer is that we can no longer afford to ignore the fact that critical care is a global specialty. As some of the studies referenced above will attest, there is significant variation in the definition, structure, and processes of critical care between different countries. Critical care services in North America may be very different from critical care services in South America, Australia, Asia, Europe, and Africa. The resources available to an ICU practitioner in Africa may be strikingly different compared to the resources available to an ICU practitioner in Western Europe, Canada, Australia, or the United States. Moreover, the diseases of interest to the ICU practitioner in Southeast Asia may be very different from the diseases of interest to the ICU practitioner in Northern Europe. A global specialty like critical care deserves a truly international journal that is available to everyone around the world. The *WJCCM* is an open access journal, which means that readers around the world will be able to immediately download and read, free of charge, high-quality, peer-reviewed articles directly from the journal website. Our goal is to provide an international perspective on the specialty of critical care. As such, we believe our journal will be of interest to readers all over the world.

SCOPE

WJCCM covers topics concerning severe infection, shock and multiple organ dysfunction syndrome, infection and anti-infection treatment, acute respiratory distress syndrome and mechanical ventilation, acute kidney failure, continuous renal replacement therapy, rational nutrition and immunomodulation in critically ill patients, sedation and analgesia, cardiopulmonary cerebral resuscitation, fluid resuscitation and tissue perfusion, coagulant dysfunction, hemodynamic monitoring and circulatory support, ICU management and treatment control, application of bronchofiberscopy in critically ill patients, and critical care medicine-related traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of critical care medicine-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in the journal, *WJCCM* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

COLUMNS

The columns in the issues of *WJCCM* will include: (1) Editorial: To introduce and comment on the substantial

advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in critical care medicine; (8) Brief Articles: To briefly report the novel and innovative findings in critical care medicine; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJCCM*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of critical care medicine; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in critical care medicine.

CONCLUSION

Again, we are very excited to embark on this exciting new endeavor. We hope that you will enjoy the fruits of our labor and take advantage of all that the *WJCCM* will offer. We also hope that you will consider the *WJCCM* worthy of submitting your best works, including original articles, reviews, clinical practice guidelines, commentaries, observations and short reports. Truly, the success of our journal will depend greatly upon the quality of articles submitted for consideration for publication! We look forward to working with you to assure the success of the *WJCCM*. Once again, greetings and welcome!

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EDITORIAL

Post-cardiac arrest syndrome: Mechanisms and evaluation of adrenal insufficiency

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Abstract

Cardiac arrest is one of the leading causes of death and represents maximal stress in humans. After restoration of spontaneous circulation, post-cardiac arrest syndrome is the predominant disorder in survivors. Besides the post-arrest brain injury, the post-resuscitation myocardial stunning, and the systemic ischemia/reperfusion response, this syndrome is characterized by adrenal insufficiency, a disorder that often remains undiagnosed. The pathophysiology of adrenal insufficiency has not been elucidated. We performed a comprehensive search of three medical databases in order to describe the major pathophysiological disturbances which are responsible for the occurrence of the disorder. Based on the available evidence, this article will help physicians to better evaluate and understand the hidden yet deadly post-cardiac arrest adrenal insufficiency.

Key words: Adrenal insufficiency; Cardiac arrest; Post-resuscitation period; Post-cardiac arrest syndrome

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INTRODUCTION

Sudden cardiac death is one of the leading causes of death in Europe as it affects 350 000-700 000 individuals per year[1]. Although restoration of spontaneous circulation (ROSC) may be achieved, prognostication for cardiac arrest victims remains dismal, as only 17% survive to hospital discharge[2]. Patients with ROSC have not only suffered a situation characterized by maximal stress, but are also going to pass through the "Clashing Rocks" of post-cardiac arrest syndrome. This syndrome combines three major pathophysiological processes, the post-arrest brain injury, the post-cardiac arrest myocardial dysfunction, and the systemic ischemia/reperfusion syndrome[3]. Post-cardiac arrest syndrome has been characterized as a sepsis-like syndrome because it is associated with increased immunoinflammatory status, hemodynamic instability and multiple organ dysfunction[4]. Recent studies have shown that adrenal insufficiency frequently occurs after ROSC and compromises the outcome of victims[5,6]. Although this matter is not recent, the pathophysiology of post-arrest adrenal insufficiency has not been elucidated.

The PubMed, CINAHL and Scopus databases were comprehensively searched for relevant studies, using keywords: "cardiac arrest", "post-cardiac arrest syndrome", "adrenal insufficiency". All human case reports, animal studies, reviews and randomized controlled studies were included in our search and cross-referencing was

performed using the bibliographies from the articles obtained. Selection of studies was based on the population, outcomes, research method, and results of the studies. Pediatric studies were not included.

In order to present significant science, lesser quality studies were excluded from our research to reduce the risk of errors and bias. More specifically, from 62 records identified through database searching and 4 additional records identified through other sources, 5 duplicates were removed. The remaining articles were assessed for eligibility and 4 articles were excluded due to systematic errors. Finally, 57 articles were included in this qualitative synthesis. This article reviews the basic pathophysiological disturbances which are responsible for the emergence of post-cardiac arrest adrenal insufficiency.

ANATOMY AND PHYSIOLOGY

The adrenal glands are located at the top of the kidneys in the retroperitoneum. In each gland there are two distinct regions, an inner medulla which is richly innervated by preganglionic sympathetic fibers and is the source of catecholamines, and an outer cortex which secretes several hormones.

The adrenal cortex, the outer portion of the adrenal gland, secretes hormones directly into the bloodstream which have an effect on the body's metabolism, on chemicals in the blood, and on certain body characteristics. These hormones are glucocorticoids, mineralocorticoids, and androgens. Glucocorticoids have potent anti-inflammatory and immunosuppressive properties. The secretion of these hormones is controlled by a close integration between the nervous and endocrine systems[7]. Cortisol and other glucocorticoids are secreted in response to adrenocorticotropic hormone (ACTH). In healthy subjects, 90% of plasma cortisol is bound to globulin and albumin, and only 10% is in the free or biologically active form[8].

ACTH is secreted under the control of the hypothalamic peptide, corticotrophin-releasing hormone, and binds to receptors in the plasma membrane of cells in the zona fasiculata and reticularis of the adrenal gland[7,9]. Hormone-receptor engagement activates adenyl cyclase, leading to elevated intracellular levels of cyclic adenosine monophosphate which leads ultimately to activation of the enzyme systems involved in biosynthesis of cortisol from cholesterol. Any type of physical or mental stress results in elevation of the cortisol concentration in blood. In contrast, cortisol secretion is suppressed by classical negative feedback loops.

The adrenal medulla, the inner part of the adrenal gland, secretes the catecholamines epinephrine and norepinephrine. Catecholamines are produced mainly by the chromaffin cells of the adrenal medulla from further metabolic modification of dopamine. Catecholamines are released in response to stress and are water-soluble (50% bound to plasma proteins) molecules.

ADRENAL GLAND DURING CARDIAC ARREST

The onset of cardiac arrest causes a unique situation which is characterized by maximal stress. The loss of blood flow results in the withdrawal of hypotension-induced baroreflex and an increase in vascular resistance[9]. Shortly after the arrest, the blood flow to the adrenal glands is gradually reduced and minimizes in a few seconds[10,11]. The acute onset of ischemia activates the sympathetic system and norepinephrine is released by the adrenal glands and the sympathetic nerve terminals[12]. Despite the 10- to 100-fold elevation in endogenous plasma catecholamines, the adrenal blood flow not only remains inadequate, but after a while it worsens due to adrenal microvessel contraction[13]. Adrenomedullin, a vasodilator peptide with a half-life of about 20 min, is partly responsible for this phenomenon as it dampens baroreflex-driven responses and buffers sympathetic actions[14]. The resulting anoxia has a major impact on the function of the adrenal gland which may already be compromised by preexisting conditions affecting the hypothalamic-pituitary-adrenal axis[15].

The cellular response to oxygen is coordinated by the hypoxia-inducible factor (HIF) and its regulator, the Von Hippel-Lindau tumor suppressor protein[16]. HIF1 consists of a heterodimer of two proteins, the HIF1-α which accumulates under hypoxic conditions and activates transcription of endothelial nitric oxide synthase (eNOS), and the HIF1-β which is constitutively expressed[17,18]. Hypoxia also induces p53 protein accumulation and initiation of apoptosis, while p53 directly interacts with HIF1-α and limits hypoxia-induced expression of HIF1-α[19]. If the restoration of blood flow is not recovered quickly, the adrenal gland damage will be permanent due to cell death[20,21].

In response to the stress of global ischemia, various inflammatory cytokines are synthesized and released[22], while the complement cascade is activated resulting in chemotaxis and adherence of polymorphonuclear leukocytes (PMNs)[19], increased vascular permeability, activation of blood coagulation, platelet activation, and endothelial and tissue damage[23-26]. At the same time, toxic reactive oxygen species (ROS) and cytokines, two of the factors responsible for post-arrest adrenal insufficiency, are released from the activated PMNs (Table 1). In addition, the activated platelets release vasoactive substances causing vasoconstriction which is further enhanced by expression of cyclooxygenase-2 in response to hypoxia and ischemia, the presence of several cytokines, and by increased oxidative stress[27,28].

Intracellular acidosis which is established shortly after the development of anoxia causes mitochondrial oxidative phosphorylation to stop resulting in adenosine triphosphate (ATP) depletion and acceleration of anaerobic glycolysis. The concentration of pyruvate increases and hydrogen ions and lactate are produced[29]. The prolongation of ischemia further decreases the intracellular pH,

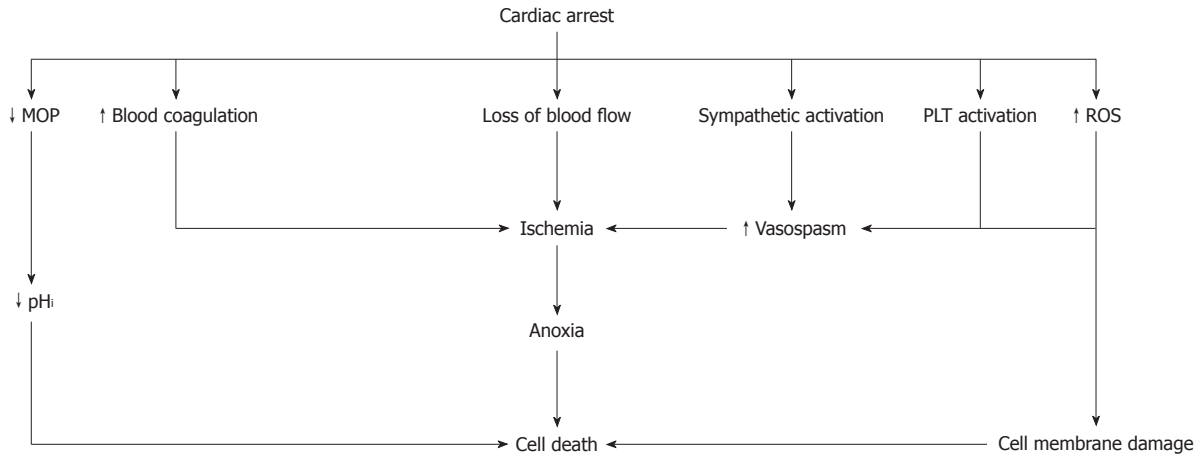

Figure 1 The main pathophysiological disturbances occurring in the adrenal gland during cardiac arrest. MOP: Mitochondrial oxidative phosphorylation; pHi: Intracellular pH; PLT: Platelets; ROS: Reactive oxygen species.

Table 1 Causes of post-cardiac arrest adrenal insufficiency

Adrenal gland ischemia and anoxia
Increased inflammatory response
Oxidative stress
Ischemia/reperfusion injury
Activation of apoptosis and programmed cell death
Malfunction of hypothalamic-pituitary-adrenal axis
Down-regulation of adrenal cell membrane receptors
Adrenomedullin secretion
Abnormalities in nitric oxide production
Drugs administered during cardiopulmonary resuscitation
Low levels of cortisol binding protein
Hypoalbuminemia

while damage to the cell membrane by ROS leads to a progressive increase in membrane permeability and severe derangements of intracellular electrolytes (Figure 1).

PATHOPHYSIOLOGICAL DISORDERS DURING CARDIOPULMONARY RESUSCITATION

During optimal cardiopulmonary resuscitation (CPR), the cardiac output is between 25% and 40% of pre-arrest values[30]. Although the peak systolic arterial pressure ranges between 60 and 80 mmHg[31,32], the adrenal gland blood flow is minimal as most of the blood pumped out of the heart supplies the brain and coronary arteries. The exact amount of blood supplying the adrenal glands during CPR is unknown. However, based on the available evidence, it should not differ significantly from the amount of blood which flows before the initiation of resuscitation[30]. Regarding this issue, two possibilities exist; either the adrenal glands remain anoxic and/or a small amount of blood is flowing into the glands. In the first case, the resuscitability of the glands is further compromised as cell death continues due to the prolongation of ischemia. In the second case, the small amount of blood flowing into the glands promotes the onset of the ischemia/reperfusion response (I/R) which is characterized by ROS generation and neutrophil activation. Despite the deleterious effects of I/R, the low concentrations of oxygen which are transferred to the adrenal glands enhance the production of small amounts of ATP which contribute to tissue survival.

Due to the systemic I/R response, blood coagulation is activated which, together with the effect of catecholamines and the accumulation of activated PMNs and platelets result in microvascular obstruction[33]. These effects are responsible for the low concentration of serum cortisol which is often observed at the end of cardiac arrest[34].

POST-RESUSCITATION PERIOD

After ROSC, hemodynamic instability and left ventricular dysfunction are the main characteristics of survivors (Figure 2). Although arterial hypotension serves as a stimulus for continued endogenous catecholamine synthesis and release, such a relationship has not been demonstrated[13]. Prengel *et al*[35] found that the concentrations of plasma catecholamines after ROSC are initially high but gradually decrease during the immediate and early post-resuscitation period[3]. One possible explanation for this phenomenon is that when ROSC is recovered, the high concentrations of endogenous and exogenous catecholamines begin to metabolize. The "stunned" adrenal glands fail to synthesize and release these substances or release small amounts due to several reasons. First, the function of the glands is dependent not only on the number of the cells which survived the period of extreme anoxia, but, also, on the effect of preexisting conditions affecting the hypothalamic-pituitary-adrenal axis[15]. Second, the I/R syndrome inactivates several metabolic enzymes and injures the cells which survived[36]. Third, synthesis and release may decrease after down regulation of the cell's receptors due to the increased concentrations of plasma catecholamines. Another reason is the increased concentration of adrenomedullin which is secreted in

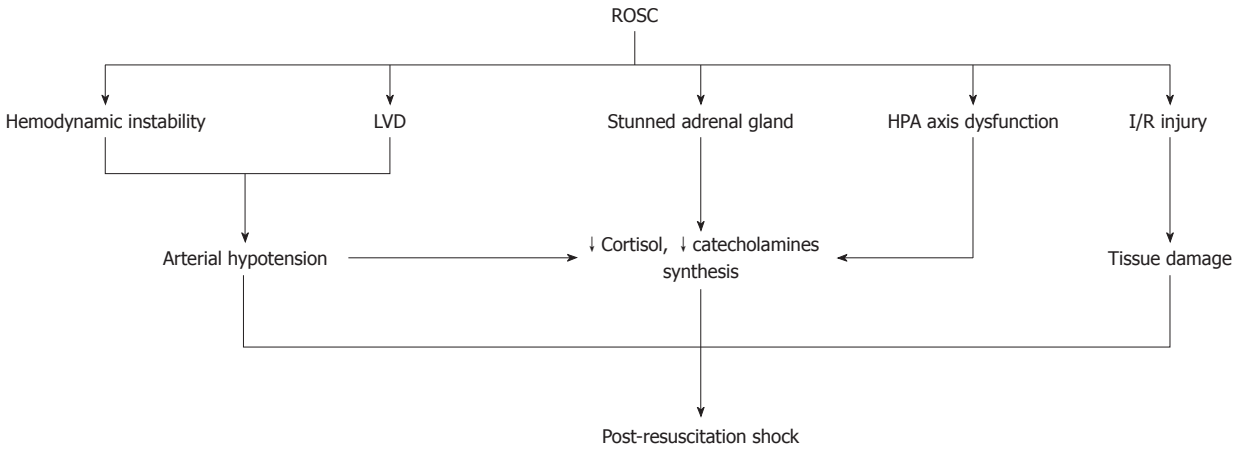

Figure 2 The main pathophysiological disturbances occurring in the adrenal gland after restoration of spontaneous circulation. ROSC: Restoration of spontaneous circulation; LVD: Left ventricle dysfunction; HPA: Hypothalamic-pituitary-adrenal axis; I/R: Ischemia/reperfusion.

response to increased epinephrine[14]. Finally, post-cardiac arrest brain injury is responsible for the degeneration of selectively vulnerable neuron subpopulations over a period of hours to days[3]. Degeneration of hypothalamus and/or pituitary gland will result in failure of the hypothalamic-pituitary-adrenal axis[37].

There is a negative correlation between the interval from collapse to the start of CPR and the plasma cortisol level after ROSC[5,38]. Adrenal insufficiency, a consequence of anoxia and high concentrations of epinephrine during cardiac arrest and CPR intervals[5], is correlated with poor outcome[6]. The chemical changes that occur during cardiac arrest predispose to a massive burst of ROS and cytokine production during the first minutes of ROSC which directly inhibit adrenal cortisol synthesis[18,39,40]. Moreover, some drugs administered during CPR inhibit the activity of enzymes involved in cortisol synthesis[41]. The resulting low concentration of cortisol not only adversely affects the post-resuscitation hemodynamic status, but decreases the production of nitric oxide (NO) which possesses anti-inflammatory and anti-ischemic properties[42]. Endothelial NO is a second messenger which is produced by eNOS. NO production is stimulated by a variety of mechanical forces, such as shear stress and cyclic strain, and humoral factors including acetylcholine, vascular endothelial growth factor, and angiotensin- Ⅱ[43]. Exposure of adrenal endothelial cells to hemodynamic disturbances during cardiac arrest and CPR results in the activation of several signal transduction pathways leading to eNOS activation. eNOS plays a crucial role in the state of blood vessel vasodilatation, modulates platelet aggregation as well as platelet and PMN adhesion to the endothelium, and can interact with various proteins resulting in inhibition of apoptosis[44]. During cardiac arrest and after ROSC, the abnormalities in NO production contribute to the occurrence of adrenal insufficiency and low cortisol creating a harmful vicious cycle[44-49].

EVALUATION OF ADRENAL FUNCTION

The incidence of adrenal insufficiency in the critically ill is 30%-60%, while its most prominent manifestation is hypotension which is refractory to vasopressors[50-52]. Other clinical manifestations of adrenal insufficiency (such as electrolyte abnormalities and hyperpigmentation) are not specific enough to suggest the diagnosis. In mild or chronic cases, the hemodynamic changes are often a reflection of hypovolemia, while in acute adrenal failure the hemodynamic changes are similar to those of hyperdynamic shock.

Adrenal insufficiency should be suspected in any resuscitated patient who develops an unstable or reduced blood pressure of unclear etiology, or has hypotension that is refractory to fluid resuscitation and vasopressors. However, the disorder may not be evident clinically and has to be uncovered by biochemical evidence of abnormal adrenal responsiveness[50]. Unfortunately, there is not enough evidence to support the use of the ACTH test in cardiac arrest patients. This test not only uniquely explores the adrenal reserve, rather than the entire hypothalamic-pituitary-adrenal axis, but, also, it is poorly reproducible. Moreover, the results may not be immediately available and may vary depending on the assay used for analysis. In addition, cortisol transport proteins in blood are diminished in acutely ill patients, while cytokines released during the post-resuscitation period can blunt end-organ responsiveness to cortisol[39]. Consequently, blood cortisol levels may underestimate the severity of abnormal adrenal responsiveness in patients with ROSC.

CONCLUSION

Post-cardiac arrest adrenal insufficiency contributes to poor survival. The etiology of this disorder is multifactorial and its severity varies. Unless diagnosed early, most patients will suffer refractory shock. This article encompasses all the available evidence and presents the pathophysiology and the diagnostic limitations of post-cardiac arrest adrenal insufficiency.

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OBSERVATION

Physician staffing pattern in intensive care units: Have we cracked the code?

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Abstract

Intensive care is slowly being recognized as a separate medical specialization. Physicians, called intensivists, are being specially trained to manage intensive care units (ICUs) and provide focused, high quality care to critically ill patients. However, these ICUs were traditionally managed by primary physicians who used to admit patients in ICUs under their own care. The presence of specially trained intensivists in these ICUs has started a "turf" war. In spite of the availability of overwhelming evidence that intensivists-based ICUs can provide better patient care leading to improved outcome, there is hesitancy among hospital administrators and other policy makers towards adopting such a model. Major critical care societies and workgroups have recommended intensivists-based ICU models to care for critically ill patients, but even in developed countries, on-site intensivist coverage is lacking in a great majority of hospitals. Lack of funds and unavailability of skilled intensivists are commonly cited as the main reasons for not implementing intensivist-led ICU care in most of the ICUs. To provide optimal, comprehensive and skilled care to this severely ill patient population, it is imperative that a multi-disciplinary team approach must be adopted with intensivists as in-charge. Even though ICU organization and staffing may be determined by hospital policies and other local factors, all efforts must be made to attain the goal of having round-the-clock onsite intensivist coverage to ensure continuity of specialized care for all critically ill patients.

Key words: Intensive care units outcome; Intensive care; Physician staffing

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INTRODUCTION

"Who should 'man' the intensive care unit (ICU)?" has been an issue of contention for many years now. Doctors belonging to different specialties have made their claims to manage ICUs and treat critically ill patients. However, recent years have seen "critical care" emerging as a distinct specialty and doctors have started specialized training in this field. Those specialized in this field of medicine are known as "intensivists". However, specialized training in this field is not widely available in many countries and the number of these specialist intensivists is not adequate to meet the ever-increasing need[1,2]. Moreover, the distribution of these specialists is uneven even in advanced countries[3]. Problems such as lack of proper training in the field of intensive care, lack of proper curriculum, lack of awareness among doctors of different specialties and lack recognition of intensive

care as a specialized branch of medicine have hampered the growth of this specialty[4]. In addition, conflicting data regarding outcome benefits among patients admitted to ICUs led by intensivists, have also added to the controversy[5]. Through this article, we intend to review the world literature regarding the staffing patterns in ICU and their impact on patient outcomes.

"OPEN" *VS* "CLOSED" ICUs

The realization that more severely ill patients require extra care, in a specialized place by dedicated, trained staff led to the development of ICUs as specialized designated areas in hospitals specially designed to manage critically ill patients. Conventionally, patients were admitted by their treating physicians to these designated units where they continued to remain primarily responsible for the care of their patients. In this "open ICU", different physicians could admit their patients and remain responsible for all decisions regarding patient management. The major drawback of this concept was that these physicians might not have received specialized training for managing critically ill patients and in addition they might not be able to devote their full time and attention to care of ICU patients because of their out-patient responsibilities and the need to care for other hospitalized patients admitted out of ICUs.

As the concept of ICUs being specialized units evolved, the concept of specialized doctors managing ICUs also became important. Hence, the idea of creating "closed ICUs" was born in which patients were admitted by the treating physicians directly under the care of doctors specialized in the field of critical care medicine. These doctors or "intensivists" would be directly responsible for managing the patients admitted to their ICUs, decide who is to be admitted and discharged, and which other specialists to consult. These intensivists typically have no outpatient responsibilities and devote their full time to managing ICU patients. However, a major shortcoming of this concept is that the treating physician, who initially saw the patient and who admitted the patient to ICU, loses all authority and control over patient management.

A third type of ICU, which is in between these two extremes has been developed and adopted effectively in some centers, the so-called "semi-closed" ICUs[6]. In this model, even though the intensivists are in-charge of the ICU, the patient's primary physician frequently takes rounds along with the ICU team and contributes to patient management. Therefore, the primary physician does not feel alienated and actively participates in the care of the patient.

There is abundant data which suggests that patient care may be more efficient in "closed ICUs" which may lead to better patient outcomes in terms of shorter ICU and hospital length of stay, reduced duration of mechanical ventilation and reduced mortality[7-9]. Improved patient outcomes have been shown to persist even when the closed ICU concept was applied across various specialty ICUs including medical[7,8], surgical[10], oncology[11], trauma[12] and neurology[13] ICUs.

According to estimates, 162 000 lives could be saved annually if intensivists staff all urban adult ICUs in the United States[14,15]. Other parameters such as bed utilization[11], more confidence in clinical judgment by the supporting staff[7] and hospital costs and post-operative complications are improved[7,8,10,11-13,16]. Improvement in patient outcomes have also been shown to exist across different patient sub-groups, including patients undergoing major surgeries like esophageal resection[17], or abdominal aortic surgery[18] or those with serious medical disorders like acute lung injury[16].

A large meta-analysis, including nine studies, demonstrated that the relative reductions in mortality rates in intensivist-led ICUs range from 15% to 60%. This meta-analysis also demonstrated that with full implementation of intensivist-model ICUs, at least 53 850 lives could be saved annually in the United States alone[19].

Even though several studies have exhibited improved patient outcomes in intensivists-based ICUs, the exact rationale behind such improved outcomes is not clear. Various explanations have been proposed although several factors working in conjunction may lead to better patient care and hence, improved outcomes. Intensivists are principally trained to manage critically ill patients. They also tend to spend most of their working time in ICUs, and hence might be more capable to avert, identify early, and manage life-threatening complications in critically ill patients. Intensivists-based ICUs also tend to be more organized and provide continuity of care which may lead to improved family and patient satisfaction[20]. Intensivists can also synchronize communication and collaboration with the patient, attendants and even specialists belonging to other fields to provide comprehensive patient care. Moreover, they may be better equipped to apply latest cutting edge technology, have up-to-date knowledge of pertinent guidelines and protocols and may be more likely to apply evidence-based medicine to ensure optimal patient care.

A large multi-center study[21] showed that patients admitted to an intensivists-based ICU were more likely to receive evidence-based therapy such as stress ulcer or deep vein thrombosis prophylaxis, a spontaneous breathing trial for weaning from mechanical ventilation, sedation intervals for patients on mechanical ventilation and intensive insulin treatment. Timely discharge of patients from ICUs, which is more likely in intensivists-based ICUs, can reduce ICU length of stay, hence reducing the morbidity and mortality related to prolonged ICU stay[9].

In contrast to popular evidence, a single, retrospective multi-center study found that high-intensity ICU physician staffing was associated with a higher severity-adjusted mortality[5]. Even though the authors could not provide any reasonable justification for these unanticipated results, they attributed this to the discontinuity of care which may occur when patients are transferred to and from a closed

ICU which may affect the outcome, unfavorably. However, the association between high-intensity staffing and poor outcome, in this study, was only present in patients with low severity of illness, which may suggest that less ill patients may have been exposed to unnecessary risks in the ICU which may have led to more complications and hence worse outcome[5]. Furthermore, it may be more reasonable to believe that trained intensivists may be more likely to perform invasive procedures with their inherent risk of complications which may have affected patient outcomes[22].

To improve the quality, safety, and economic value of healthcare, the Leapfrog Group was established in 2000 which comprised representatives from a group of prominent employers. To achieve their goals, they have made certain recommendations based on evidence-based medicine which includes an ICU-physician staffing (IPS) standard. According to this IPS standard, they have recommended that intensivists must manage or co-manage ICU patients, and should exclusively provide clinical care in the ICU during daytime hours, but during off-hours a fundamental critical care support-certified non-physician should be physically present to provide cover in the ICU and the intensivists should remain on-call and return pages within 5 min 95% of the time[23]. Other international societies like the European Society of Intensive Care Medicine[24] and American College of Critical Care Medicine (ACCM)[25,26] have also recommended that intensivist-led care must be provided to all critically ill patients admitted to ICUs.

TWENTY FOUR HOURS INTENSIVIST COVERAGE

Several studies have suggested that even daily rounds by a trained intensivist can improve patient outcomes leading to shorter ICU stays, reduced post-operative complications, and hence, lower hospital costs. Hospital mortality has been shown to be reduced by up to three times when intensivists take daily rounds in the ICU[17,18]. However, to really have a significant impact on patient outcome, it has been suggested that ICUs should have a trained intensivist physically present at all times 24 h per day and 7 d per week[27-29].

The need to provide immediate aggressive care to critically ill patients cannot be overstressed. It is imperative that subtle changes suggestive of any deterioration in a patient's condition must be immediately identified and corrective measures taken as early as possible to improve outcome. Trained intensivists are obviously more likely to recognize such slight changes in patient parameters and hence their 24-h presence in the ICU may allow early detection of potential problems and complications and the institution of appropriate interventions. Twenty-four-hour intensivist coverage may ensure increased compliance with evidence-based medicine leading to family satisfaction[30]. Moreover, round-the-clock intensivists coverage will facilitate consistency of care and allow patients to receive appropriate treatment by a skilled intensivist at all times.

Data from several studies suggest that 24/X7 in-house intensivist coverage may improve the outcome of critically ill patients[28-33]. Based on such data, an ESCIM task force issued recommendations on minimal requirements for ICUs. They emphasized that ICU should be led by a trained intensivist and that there should be a qualified intensivist present on-site 24-h per day in moderate-and high-intensity care units[24]. Similarly, other critical care societies like ACCM and the Society of Critical Care Medicine have also recommended that round-the-clock intensivist coverage is the ideal model for managing critically ill patients in the ICUs[26].

Time of admission and discharge from ICU may also affect patient outcomes, with patients being admitted or discharged during "off-hours" having a worse outcome[34,35]. During these "off-hours", ICU staffing may be reduced both in terms of numbers and expertise which may compromise patient care[3]. Several studies have shown that a significant majority of patients are admitted to ICUs during off-hours[28,36,37]. The presence of 24 h on-site intensivists ensure that high quality standardized care is always available to the patients, especially during the first few hours immediately after ICU admission, which is the most crucial time period affecting outcome[28,37,38].

BARRIERS TO IMPLEMENTING INTENSIVIST COVERAGE

Even though there is abundant evidence showing improved patient outcomes in intensivists-based closed ICU models, and various critical care organizations have recommended this model to be implemented in all ICUs[24-26], implementation of such high-intensity staffing is still inadequate even in developed countries[3,39]. Even in the United States, more than half of ICUs do not have any intensivists coverage, and high-intensity coverage is present in a mere 26% of ICUs. The staffing pattern is even worse in medical ICUs and more so in smaller non-teaching hospitals. In addition, Leapfrog standards of intensivists staffing are maintained in only 4% of adult ICUs[3]. A survey of Canadian ICUs also showed that dedicated overnight on-site physician coverage was available in only 60% of ICUs, and only 15% of ICUs had a trained ICU staff physician[39]. Furthermore, they found that almost half of these physicians, who were present during the night hours, had less than 3 mo ICU experience[39].

Several reasons for non-adherence to recommendations suggesting intensivists staffing have been proposed including acute shortage of trained ICU physicians, and anticipated high costs associated with 24 h on-site intensivist coverage[4]. It is projected that the shortage of skilled ICU staff is to get worse in the coming years[2] and hence, alternative measures to alleviate this shortage must be considered. Protocolized ICUs and telemedicine have been proposed to allow more efficient use of

the scarce skilled manpower and promote standardized care, especially in remote areas ensuring better clinical outcomes and better utilization of the hospital's financial resources[40-42]. The issue pertaining to increased financial burden involved in employing intensivists to manage ICU patients may not be valid. Data suggest that implementation of the intensivists-based ICU model according to the Leapfrog group's standards can significantly reduce healthcare cost[43], as adoption of this model may lead to more rational resource utilization by avoiding unnecessary ICU admissions, preventing and timely managing complications, reducing ICU length of stay, and promoting early discharge from ICUs[18].

CONCLUSION

Critically ill patients not only require trained physician care but also require comprehensive ICU care involving a multi-disciplinary team. This team may involve the services of trained ICU nurses, respiratory therapists, physiotherapists, or pharmacists. The need to involve other specialists in the care of critically ill patients who have multi-system disorders cannot be overstressed. Hence, ICU teams may be designed using a multi-disciplinary approach with intensivists as in-charge of patient care and actively involving the primary physician and other specialists to ensure optimal patient care and better outcomes. ICU organization and staffing may depend on local factors and hospital policies, however all effort must be made to attain the goal of having round-the-clock on-site intensivists coverage to ensure continuity of care.

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GUIDELINES FOR CLINICAL PRACTICE

Contemporary view on neuromonitoring following severe traumatic brain injury

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Abstract

Evolving brain damage following traumatic brain injury (TBI) is strongly influenced by complex pathophysiologic cascades including local as well as systemic influences. To successfully prevent secondary progression of the primary damage we must actively search and identify secondary insults e.g. hypoxia, hypotension, uncontrolled hyperventilation, anemia, and hypoglycemia, which are known to aggravate existing brain damage. For this, we must rely on specific cerebral monitoring. Only then can we unmask changes which otherwise would remain hidden, and prevent adequate intensive care treatment. Apart from intracranial pressure (ICP) and calculated cerebral perfusion pressure (CPP), extended neuromonitoring ($SjvO_2$, $ptiO_2$, microdialysis, transcranial Doppler sonography, electrocorticography) also allows us to define individual pathologic ICP and CPP levels. This, in turn, will support our therapeutic decision-making and also allow a more individualized and flexible treatment concept for each patient. For this, however, we need to learn to integrate several dimensions with their own possible treatment options into a complete picture. The present review summarizes the current understanding of extended neuromonitoring to guide therapeutic interventions with the aim of improving intensive care treatment following severe TBI, which is the basis for ameliorated outcome.

INTRODUCTION

Severe traumatic brain injury (TBI) is associated with a high risk of mortality and persistent deficits, which may preclude successful reintegration, thereby having dramatic consequences not only for the individual patient but also for society due to the tremendous socio-economic burden involved.

To prevent additional damage to the already injured and highly vulnerable brain, especially during the early posttraumatic phase, specific knowledge is essential. An in-depth understanding of interwoven pathophysiologic cascades must be complemented by specific neuromonitoring. Only then can we unmask the presence and extent of typical secondary insults caused by e.g. hypoxia, hypotension, uncontrolled hyperventilation, hypoglycemia as well as hypoventilation, hypertension, and hyperglycemia. Since secondary insults strongly determine quality of survival, it is of utmost importance to prevent these secondary insults. There is increasing evidence which clearly shows that we cannot rely on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) alone to assess additional tissue damage. Therefore, extended neuromonitoring has become indispensable in modern intensive care to unmask otherwise occult signs of cerebral impairment, and during phases of normal ICP. Apart from

diagnosing signs of secondary deterioration, extended neuromonitoring may be helpful in adapting the quality and extent of our therapeutic interventions. In addition to basic neuromonitoring consisting of ICP and CPP, extended bedside neuromonitoring refers to transcranial Doppler/Duplex sonography (TCD), jugular venous oxygen saturation ($SjvO_2$), partial tissue oxygen pressure ($ptiO_2$), and cerebral microdialysis to unmask changes in brain metabolism (glucose, lactate, pyruvate, glutamate, glycerol), and electrocorticography to determine cortical spreading depression (CSD) (Figure 1).

Overall, it is important to refrain from only interpreting one parameter as the different parameters are interwoven and functionally interdependent. Thus, it is important to consider several dimensions simultaneously, integrating e.g. $ptiO_2$, cerebral glucose, CPP, $paCO_2$, and hematocrit. Correct interpretation of these results within the context of the individual situation requires lots of experience in overall clinical management and neuromonitoring. Progressive insight into previously hidden changes which can only be unmasked with extended neuromonitoring is the basis for improved treatment, hopefully resulting in improved outcome following severe TBI.

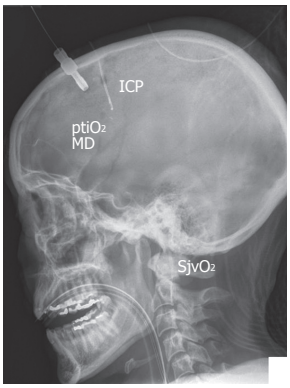

Figure 1 Illustrative lateral X-ray view showing positioning of invasive neuromonitoring to assess intracranial pressure, brain tissue oxygen pressure, brain metabolism using microdialysis, and jugular venous oxygen saturation. ICP: Intracranial pressure; $ptiO_2$: Tissue oxygen pressure; $SjvO_2$: Jugular venous oxygen saturation.

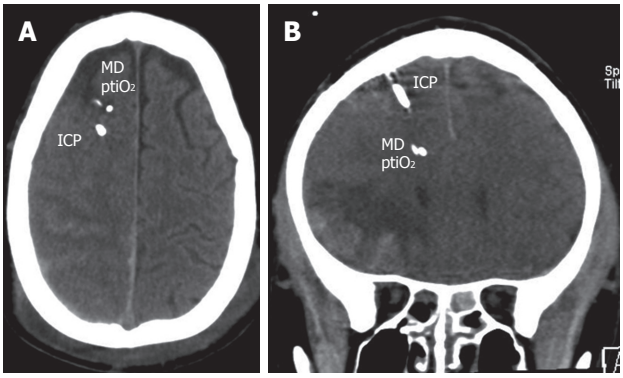

Figure 2 Illustrative examples showing positioning of intracranial pressure, microdialysis catheter, and brain tissue oxygen pressure sensor in the more severely injured hemisphere (A) and within close proximity of a contusion (B). ICP: Intracranial pressure; $ptiO_2$: Tissue oxygen pressure.

BASIC NEUROMONITORING

ICP and CPP

Increased intracranial volume reflected by elevated ICP is the primary parameter used to judge cerebral deterioration during pharmacologic coma. A persistent increase in ICP can induce and maintain a vicious circle[1]. It is important to acknowledge that a normal ICP does not guarantee absence of pathologic processes, especially in conditions in which the ICP cannot be assessed adequately e.g. following craniectomy, CSF leakage, subdural air entrapment, or even sensor malfunctioning. New data clearly show that metabolic and functional alterations unmasked by extended neuromonitoring precede increases in ICP[2].

A very simple measure to indirectly estimate global cerebral perfusion is to calculate CPP = mean arterial blood pressure (MABP) - ICP. A "normal" CPP, however, does not guarantee sufficient cerebral perfusion and oxygenation. To define an optimal CPP leading to optimal cerebral perfusion, other parameters e.g. $ptiO_2$, $SjvO_2$, brain metabolism (e.g. glucose, lactate, lactate to pyruvate ratio) and flow velocity must be integrated. Using extraventricular drainage combined with pressure recording allows us to combine diagnostic and therapeutic options by measuring ICP and draining cerebrospinal fluid to reduce elevated ICP, respectively. Extraventricular drainage, however, is associated with an albeit small risk of additional injury to periventricular structures, hemorrhages, and local infections[3].

Jugular venous oxygen saturation and arterio-jugular venous differences

To assess global cerebral perfusion, oxygen consumption, and metabolic state analysis of $SjvO_2$, various metabolic indices (e.g. oxygen-glucose index, lactate-oxygen index, lactate-glucose index), oxygen extraction ratio, and arterio-jugular venous lactate difference have proven helpful at the bedside[4,5]. $SjvO_2$ correlates directly with perfusion and correlates inversely with cerebral oxygen consumption. Thus, $SjvO_2$ can be used to guide therapeutic interventions, including modulation of MABP and CPP, controlling hyperventilation, guiding oxygen administration, and influencing the extent of pharmacologic coma and hypothermia.

Tissue oxygenation- $ptiO_2$

Measuring $ptiO_2$ not only reflects local changes, but also unmasks cerebral consequences of systemic influences e.g. blood pressure, oxygenation, and anemia. This, in turn, allows us to guide the type and extent of therapeutic interventions[6,7]. Similar to changes in $SjvO_2$, $ptiO_2$ values indirectly reflect cerebral perfusion and oxygenation[8], while low $SjvO_2$ and $ptiO_2$ values unmask reduced cerebral perfusion with cerebral ischemia at $SjvO_2 < 50\%$ and $ptiO_2 < 10$ mmHg. High $SjvO_2$ (> 80%) and $ptiO_2$ values (> 30 mmHg) unmask impaired oxygen consumption en-

countered under conditions of hyperemia/ luxury perfusion.

It is important to correct ptiO2 values < 10 mmHg (Licox®) within 30 min to prevent hypoxia-induced increase in glutamate[9,10], neuropsychologic deficits[11], and poorer outcome with increased mortality[12].

Cerebral microdialysis

Changes in cerebral metabolism assessed by measuring glucose, lactate, pyruvate, glycerol, glutamate, and by calculating the lactate to pyruvate ratio, a marker of hypoxic/ischemic metabolic impairment[13,14], both follow as well as precede increases in ICP[2,10]. Pathologic alterations reflected by low glucose and elevated lactate to pyruvate ratio were recently identified to significantly predict mortality following severe TBI[15]. In addition, increased lactate to pyruvate ratio was associated with subsequent chronic frontal lobe atrophy[16], possibly giving rise to subsequent dementia. Overall, metabolic monitoring can also be used to guide therapeutic interventions to correct e.g. hypotension, hyperemia, vasospasm, hyperventilation, fever, epileptic discharges, hypoglycemia, and anemia. The integration of cerebral microdialysis was an integral part of the "Lund concept" allowing a reduction in CPP levels as low as 50 mmHg[17], thereby substantially influencing treatment options. For best results in potentially optimizing our current therapy, metabolic monitoring using cerebral microdialysis must be combined with other parameters e.g. ptiO2, SjvO2, and CPP.

TCD

TCD can unmask conditions of low flow[18], vasospasm, and hyperemia. Each of these conditions, in turn, will require differential therapeutic interventions: vasospasm requires controlled hypertension and normo- to hypoventilation; hyperemia requires controlled hypotension and hyperventilation; low flow requires increased cardiac output especially in conjunction with bradycardia. The cerebral blood flow velocity determined within the large basal cerebral arteries can be used to reflect regional cerebral perfusion, cerebral autoregulation, and CO2-reactivity[19]. In addition, calculating e.g. the pulsatility index and resistance index allow the non-invasive estimation of ICP and CPP[20,21]. This proves helpful when an ICP probe cannot be inserted due to coagulation disorder or if an ICP probe is damaged. This allows us to bridge the time until a new ICP probe can be inserted. However, an ICP probe needs to be replaced as soon as possible since only continuous ICP readings can be used to reliably adapt therapeutic interventions.

CSD

CSD involving neuronal and glial energy-consuming depolarizations[22] as well as a spreading wave of ischemia and vasoconstriction with subsequent vasodilation[23], contributes to the secondary growth of a pre-existing lesion[24,25] and is associated with decreased cerebral glucose, increased lactate to pyruvate ratio, and elevated lactate[26,27]. CSD can be induced by elevated extracellular potassium, decreased cerebral NO levels and reduced blood and brain glucose concentrations[28,29]. CSD requires the introduction of a special sensor which is positioned under the dura directly on the cortical surface. At present, it is unclear which patients with which lesions will profit from the application of these sensors.

LIMITATIONS

Any neuromonitoring technique is limited by certain restraints making compromises indispensable. Similar to ICP, regional metabolic heterogeneity exists even within the same hemisphere depending on the extension of the lesion and the positioning of the probes relative to the lesion[30,31]. Despite the introduction of multiple probes within the supratentorial compartment the infratentorial areas are not assessed. To prevent additional damage, deep structures such as the basal ganglia are not penetrated under clinical conditions. Furthermore, we must also face local changes at different depths along the probes. To avoid inadequate decision-making the catheters and probes should not be positioned within the core of a contusion as this necrotic tissue will always reveal pathologic values. The consensus recommendation is to place the catheters and probes within the pericontusional tissue to successfully unmask progressive lesion growth, metabolic worsening, and impaired perfusion which may be reversible and amenable to treatment options (Figure 2). In the case of diffuse brain injury, the probes should be positioned within the more severely injured hemisphere. Nonetheless, signs of impaired cerebral metabolism are found even in regions without obvious signs of structural damage. This functional impairment can result from increased ICP due to local changes and can be induced by systemic influences due to e.g. hypotension, hyperemia, vasospasm, hyperventilation, fever, epileptic discharges, hypoglycemia, and anemia.

It is important to acknowledge that local and global monitoring does not exclude each other but successfully extends our insight into otherwise occult changes. In this context, ptiO2 and SjvO2 closely reflect each other[6] and arterio-jugular venous glucose differences have been shown to correspond to local changes in cerebral glucose determined by cerebral microdialysis[32]. Despite these limitations, local as well as global parameters should be monitored in patients with severe TBI who are subjected to pharmacologic coma. Categorically omitting neuromonitoring is a mistake as we deprive ourselves of important information, which is decisive in adapting and modulating our therapeutic interventions. At present, it is difficult to define to what extent basic or extended neuromonitoring significantly determines quality of outcome. In theory, we may expect that the substantial increase in our knowledge using neuromonitoring will translate to improved treatment. By strictly integrating SjvO2, ptiO2, microdialysis, and TCD we are able to individualize the extent, aggressiveness, and duration of therapeutic inter-

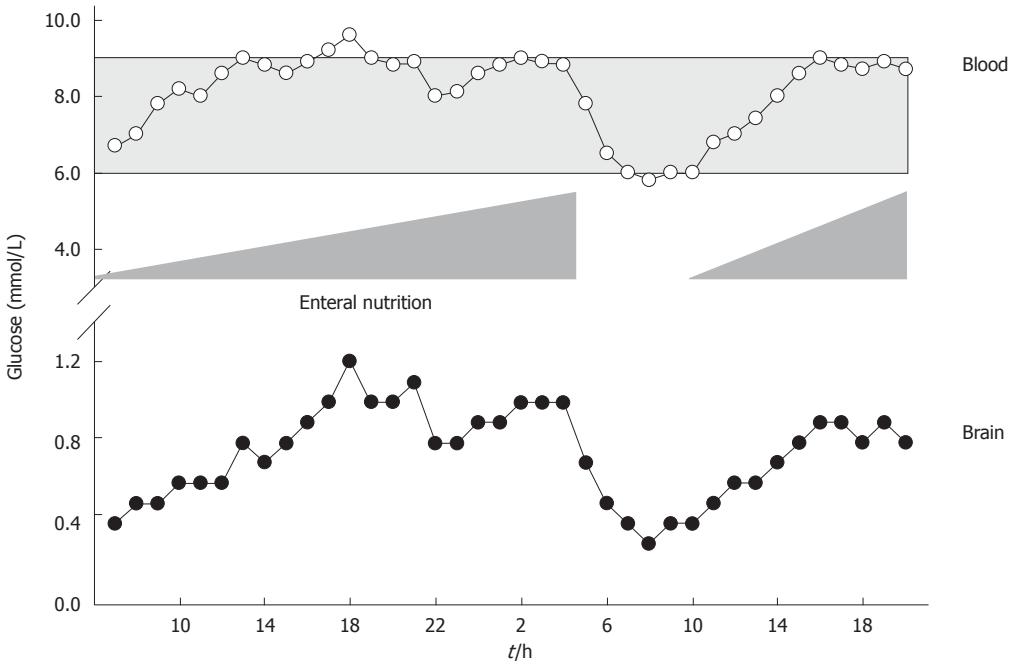

Figure 3 Illustrative case showing the influence of enteral nutrition on arterial blood and brain glucose levels. Based on low brain glucose, enteral nutrition was gradually increased resulting in elevated blood and brain glucose. Due to surgery, enteral nutrition was stopped. This resulted in a decrease in blood and brain glucose. Restarting of enteral nutrition increased blood and brain glucose again.

ventions, thereby reducing the frequency of barbiturate coma, secondary craniectomies, pulmonary dysfunction, and significantly reducing the rate of red blood cell transfusions and associated costs in patients subjected to prolonged pharmacologic coma.

WHAT IS THE IMPACT OF EXTENDED NEUROMONITORING IN ROUTINE INTENSIVE CARE?

While basic neuromonitoring includes neurologic examination, computerized tomography, and ICP, extended neuromonitoring comprises $SjvO_2$, $ptiO_2$, microdialysis, TCD, and electrophysiologic recordings including CSD.

Extended neuromonitoring in daily clinical practice helps to improve our treatment options by characterizing functional influences, defining threshold values, and adapting therapeutic interventions in type, extent and duration. In addition, extended neuromonitoring helps us to prevent induction of additional brain damage due to excessive therapeutic corrections. In this context, aggressive volume administration aimed at improving cerebral perfusion was associated with a sustained risk of acute respiratory distress syndrome[33] and abdominal compartment syndrome[34]. Furthermore, excessive ventilatory support to increase paO_2 can induce additional pulmonary damage[35], aggressive lowering of arterial blood glucose to prevent hyperglycemia-induced cell damage increases the frequency and extent of hypoglycemic episodes[36], and a categorical transfusion regimen to improve cerebral oxygenation may be associated with transfusion-related complications[37].

When only relying on changes in ICP and CPP, we may not only miss important signs of deterioration, but also fail to adequately reduce therapeutic interventions. Based on current evidence, extended neuromonitoring is important to determine optimal CPP, guide oxygenation and ventilation, influence transfusion practice, define optimal blood and brain glucose, and even guide decompressive craniectomy.

GUIDANCE FOR CPP

Calculating CPP does not guarantee adequate cerebral perfusion. Assessing $ptiO_2$ is indispensable in determining optimal cerebral perfusion as CPP significantly influences $ptiO_2$[38]. $ptiO_2$ can be used to determine the lower still acceptable CPP value[39]. Several studies have convincingly shown that the generally recommended CPP threshold of 60 mmHg is insufficient and that even "normal" CPP values cannot protect from cerebral hypoxia and impaired metabolism[14]. Furthermore, regional heterogeneity is characterized by different requirements reflected by different levels of CPP-dependent $ptiO_2$ values. In this context, normal CPP of approximately 70 mmHg is insufficient for the perifocal tissue compared to normal appearing tissue in which $ptiO_2$ was significantly higher[40]. Advancing from observational to interventional studies, integrating $ptiO_2$ in clinical routine by using a $ptiO_2$-supplemented ICP- and CPP-based treatment protocol significantly kept ICP < 20 mmHg, improved outcome judged by the Glasgow Outcome Scale, and reduced mortality rate compared to the standard ICP/CPP-directed therapy[41,42].

With the help of monitoring brain metabolism using cerebral microdialysis, CPP can be reduced to low values e.g. 50 mmHg without causing additional brain damage[17]. In this context, lactate and the calculated lactate to pyruvate ratio unmask insufficient cerebral perfusion and oxygen delivery leading to energetic and metabolic impairment[17,43]. As shown using the "Lund concept" to treat patients with severe TBI, microdialysis must be included to allow a reduction in CPP providing the therapeutic concept is practiced as published[17]. Improving cerebral perfusion and correcting anemia has been shown to successfully normalize brain lactate to pyruvate ratio, glycerol, and glutamate levels[43]. Whether this is valid for all lesion types is unclear.

GUIDANCE FOR VENTILATORY SUPPORT: OXYGENATION AND VENTILATION

Integrating $ptiO_2$ and $SjvO_2$ in clinical routine can be used to individually define paO_2 and $paCO_2$ targets. These individual targets, in turn, can be used to adjust ventilatory settings, thereby preventing ventilation-induced lung injury and hemodynamic instability.

Oxygenation

Elevating the fraction of inspired oxygen (FiO_2) significantly increased $ptiO_2$[38,44] and reduced cerebral lactate[38]. However, increasing $ptiO_2$ too aggressively by normobaric hyperoxia (FiO_2 1.0) was associated with decreased cerebral blood flow despite improved brain metabolism. This impaired perfusion coincided with poorer outcome 3 mo after TBI. As shown under experimental conditions, increasing oxygen supply alone is insufficient to improve cerebral oxygenation if impaired cerebral perfusion is not corrected adequately[45].

Hyperventilation

Although hyperventilation is an easy and helpful therapeutic intervention to decrease elevated ICP[46], hyperventilation can induce additional secondary ischemic brain damage[47] due to hypocapnia-induced vasoconstriction. This impaired perfusion, in turn, results in metabolic and neurochemical alterations reflected by reduced $ptiO_2$ and $SjvO_2$, and elevated extracellular glutamate and lactate[48]. Interestingly, even small changes in $paCO_2$ within normal limits are detrimental[49]. Consequently, extended neuromonitoring should also be performed in patients during anticipated normoventilation. It is essential to control hyperventilation by using appropriate neuromonitoring techniques to unmask signs of cerebral ischemia due to hyperventilation-induced vasoconstriction, because normal ICP levels achieved by hyperventilation will cause us to miss relevant pathologic processes within the brain. Reduced $SjvO_2$, decreased $ptiO_2$, and signs of metabolic impairment (lactate, glutamate, lactate to pyruvate ratio)[50,51] aid in assessing the lowest possible individual $paCO_2$ level[52-56]. This helps us to avoid active induction of secondary brain damage.

GUIDANCE FOR RED BLOOD CELL TRANSFUSIONS

Cerebral oxygenation is influenced by the number of circulating oxygen carriers, i.e. red blood cells (hematocrit). At present, the optimal hematocrit following severe TBI is controversial. A fast reduction in hematocrit known to significantly reduce cerebral oxygen supply[57] must be avoided. Under controlled critical care conditions with stable CPP and stable oxygenation and ventilation, $ptiO_2$ can be used to define the transfusion threshold[58,59]. Patients with a $ptiO_2$ > 15 mmHg do not profit from red blood cell transfusion[59]. A transfusion of red blood cells in patients with a hematocrit < 30% and a concomitant $ptiO_2$ value below 15 mmHg was able to persistently increase $ptiO_2$ > 15 mmHg[59]. At the same time, CPP must be maintained above 60 mmHg to prevent cerebral hypoxia determined by $ptiO_2$[59]. These data show that $ptiO_2$ can be used to reliably assess the individual transfusion threshold.

GUIDANCE FOR OPTIMAL BLOOD AND BRAIN GLUCOSE

Mitochondrial damage, aggravated oxidative stress, impaired neutrophil function, reduced phagocytosis, and diminished intracellular destruction of ingested bacteria are deleterious consequences of hyperglycemia. Elevated blood glucose > 9.4 mmol/L (> 169 mg/dL) is associated with sustained mortality and morbidity[60,61]. These deleterious consequences can be prevented by normalizing elevated blood glucose levels. Maintaining blood glucose levels within tight limits between 4.4 mmol/L and 6.1 mmol/L (80 to 110 mg/dL)[62], however, is hampered by the risk of hypoglycemia and a strong variation in blood glucose levels[63], which was associated with sustained mortality[62,64,65]. Reducing blood glucose to 4.4-6.1 mmol/L significantly increased extracellular glutamate levels and elevated lactate to pyruvate ratio, reflecting excessive neuronal excitation and metabolic perturbation[66]. Decreased blood glucose and low cerebral extracellular glucose levels were even associated with sustained mortality[67] and induction of CSD at low blood glucose levels < 5 mmol/L[28,68,69]. To define individual blood and brain glucose, void of any deleterious metabolic consequences, extended neuromonitoring is indispensable. In this context, reduced cerebral oxygen consumption, reduced lactate and CO_2 production, increased glucose uptake, elevated cerebral glucose and decreased lactate to pyruvate ratio were observed at arterial blood glucose levels between 6 mmol/L and 9 mmol/L[32]. Based on cerebral microdialysis, insulin should not be given at arterial blood glucose levels < 5 mmol/L as this significantly increased extracellular glutamate and lactate to pyruvate ratio. At arterial

blood glucose levels > 9 mmol/L, insulin administration is encouraged to significantly increase cerebral glucose levels and reduce lactate to pyruvate ratio[32,70]. Based on data obtained by microdialysis, brain glucose should remain above 1 mmol/L since cerebral glucose < 1 mmol/L was associated with increased lactate to pyruvate ratio[32,66,71]. Persistently low brain glucose levels were also associated with electrographic seizures, nonischemic reductions in CPP, decreased $SjvO_2$, increased glutamate levels, and poor outcome[71]. Expanding the assessment of brain glucose from mere monitoring to integration into clinical decision-making allows us to guide adaptation of nutritional support, which is a simple measure to increase both blood as well as brain glucose concentrations (Figure 3). Overall, nutritional support has been shown to improve hormonal status and clinical outcome in patients with TBI[72,73].

GUIDANCE FOR DECOMPRESSIVE CRANIECTOMY

For patients with uncontrollable intracranial hypertension, decompressive craniectomy with dura enlargement has been shown to improve cerebral perfusion, oxygenation, and metabolism[74-78], reflected by increased $ptiO_2$, decreased lactate to pyruvate ratio, reduced glycerol and glutamate levels[79].

Several reports have shown that pathologic neuromonitoring precedes clinical deterioration[75,78,79]. This, in turn, underscores the importance of integrating extended neuromonitoring in clinical routine to support decision-making on when to perform a decompressive craniectomy[78,79].

CONCLUSION

In the contemporary intensive care of patients with severe TBI subject to pharmacologic coma, basic monitoring using only ICP and CPP should be expanded by extended neuromonitoring including e.g. $SjvO_2$, $ptiO_2$, microdialysis, TCD, and electrocorticography. Growing evidence clearly supports the integration of extended neuromonitoring to unmask otherwise occult alterations and to differentially adapt the type, extent, and duration of our therapeutic interventions. By expanding our knowledge and experience, the integration of extended neuromonitoring in daily clinical routine will provide us with the means to improve outcome, which has not been possible by relying on ICP and CPP values alone as practiced in the past.

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REVIEW

Severe sepsis and septic shock in the elderly: An overview

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Abstract

The incidence of severe sepsis and septic shock is increasing in the older population leading to increased admissions to the intensive care units (ICUs). The elderly are predisposed to sepsis due to co-existing co-morbidities, repeated and prolonged hospitalizations, reduced immunity, functional limitations and above all due to the effects of aging itself. A lower threshold and a higher index of suspicion is required to diagnose sepsis in this patient population because the initial clinical picture may be ambiguous, and aging increases the risk of a sudden deterioration in sepsis to severe sepsis and septic shock. Management is largely based on standard international guidelines with a few modifications. Age itself is an independent risk factor for death in patients with severe sepsis, however, many patients respond well to timely and appropriate interventions. The treatment should not be limited or deferred in elderly patients with severe sepsis only on the grounds of physician prejudice, but patient and family preferences should also be taken into account as the outcomes are not dismal. Future investigations in the management of sepsis should not only target good functional recovery but also ensure social independence and quality of life after ICU discharge.

INTRODUCTION

In recent years, the incidence of elderly patients being admitted to intensive care units (ICUs) has increased globally[1]. This process of "demographic transition" can be explained not only by a decrease in fertility, and hence birth rate, but also by a decline in mortality rates leading to increased life expectancy. It has been predicted that in the near future, the elderly will grow more rapidly than any other age group, and by 2050 the world's elderly population will exceed that of the young for the first time in history[2].

Sepsis is an important cause of morbidity and mortality in the older population. Studies on the diagnosis and management of sepsis usually exclude subjects with multiple co-morbidities or those in the very aged group (greater than 80 years); however, as the population becomes increasingly old and ill, this subset of the population will be admitted more frequently into the ICUs and their management will pose a serious challenge to the treating intensivists. Through this review, we have tried to analyze the susceptibility, risk factors, management and outcome of older patients with severe sepsis and septic shock. We have also tried to identify the areas for future investigations that might improve outcomes in this particular patient population.

EPIDEMIOLOGY

Sepsis is defined as an inflammatory body response to infection, with severe sepsis and septic shock being its more severe forms[3]. Despite advances in the management of septic patients, sepsis is still the second leading cause of death among patients in non-coronary ICUs[4]. The incidence and prevalence of sepsis increase with age[5]. Angus *et al*[5] studied discharge records for the year 1995 from 7 hospitals in the United States and found that the annual incidence of severe sepsis was 3.0 cases per 1000 population. However, the incidence of severe sepsis in older patients was 26.2 cases per 1000 population. The mean age of patients with severe sepsis was 63.8 years in this study, which increased to 68.2 years in the latter study[4,5]. The elderly constitute only one fifth of the US population, but they constitute two thirds of the patients admitted to hospital with sepsis[4]. The incidence of severe sepsis per se is also increasing[6,7]. Dombrovskiy *et al*[6] found a 1.7-fold increase in patients admitted with severe sepsis from 1993-2003. In another study by Martin *et al*[4], this increased incidence of sepsis was around 20% more in the elderly population as compared to younger patients. Similar findings of increased incidence of sepsis, with the mean age of patients with severe sepsis being around 60 years, have been reported in studies from the eastern part of the world[8,9]. Mortality rates associated with severe sepsis also increase with increasing age, with the highest mortality in old elderly (patients more than 85 years of age)[9-12]. There is a dearth of data regarding the outcome of elderly patients with sepsis and septic shock. A few studies which have been conducted in this specific patient population and have shown that severe sepsis and septic shock are common in elderly patients and these patients have an increased mortality as compared to their younger counterparts[4,6,9].

RISK FACTORS

There are various risk factors that predispose the elderly to an increased incidence of sepsis.

Preexisting co-morbidities and drugs for these chronic illnesses

The increased risk of sepsis in the elderly can be due to chronic co-morbidities such as cancer, diabetes, obesity, and human immunodeficiency virus, among others[6]. All of these are much more crucial in patients of advanced age. Previous comorbid illnesses like renal or pulmonary disease are commonly associated with increased susceptibility to sepsis[4,13,14]. However co-morbidities alone are not sufficient and other factors such as various drugs, instrumentation and recurrent hospitalization are also responsible for breaching an already compromised immunity[15].

Pre-admission functional status

Pre-admission functional status is much more important than comorbid illness and has been found to be an independent predictor of outcome in elderly patients[16,17]. There are numerous causes of poor functional status including[17,18]: (1) Disuse atrophy due to an inactive lifestyle; (2) Sarcopenia due to accelerated muscle loss; (3) Changes in responsiveness to trophic hormones (growth hormones, androgens, and estrogens); (4) Neurological alterations; (5) Altered cytokine regulation; (6) Changes in protein metabolism; and (7) Changes in dietary intake.

Malnutrition

Malnutrition is also common in the elderly and has been attributed to factors such as inactivity, inadequate funds or resources, mobility and transportation issues, social isolation, functional limitations, poor or restricted diets, chronic disease, dementia, depression, poor dentition, polypharmacy, and alcohol or substance abuse[18].

Endocrine deficiency

Elderly patients also have associated endocrine disorders like hypoadrenalism, hypothyroidism and hypogonadism which alter the response to sepsis, and hence, further predisposes them to increased risk of infection.

Aging

Several studies have found old age itself as an independent risk factor for predisposition to severe sepsis[4,19,20].

Other risk factors

The elderly are also at increased risk for colonization by gram-negative organisms, which may be multi-drug resistant, predisposing the elderly to sepsis[19]. The possible reasons for this increased colonization are nursing home residence, recurrent hospitalization and interventions such as urinary catheterizations, poor functional status or multiple drug use.

IMMUNE SYSTEM IN THE ELDERLY

The immune system in older age is abnormal and is in a state of immunosenescence[21]. The pathophysiology of this immunosenescence is complex and multifactorial. There are functional impairments in both cell-mediated immunity and humoral immune responses with age[21]. The thymus, a major organ involved in adaptive cell-mediated immunity, atrophies with age and by 60 years loses most of its activity causing a shift in the T-cell repertoire from naïve T-cells to memory T-cells[21,22]. In response to antigens, these memory cells have limited proliferative capacity, express fewer co-stimulatory molecules like CD40 ligand and CD28, and lead to reduced activation of mitogen-activated protein kinase[22]. B cell and plasma cell populations also gradually decrease with aging[23]. However, polyspecific, low affinity T-cell independent immunoglobulin levels increase with age[23]. Some of these immunoglobulins behave as autoantibodies[24]. Although antibodies against previously exposed antigens are retained, the elderly have a decreased ability

to produce specific opsonophagocytic antibodies against neoantigens[21].

Innate immunity is not spared from the effects of aging, and many functions of innate immunity are affected. Macrophages undergo significant functional alteration, there is reduced antigen processing and expression to T cells, reduced bactericidal activity and altered expression and function of toll like receptors[25]. Besides macrophages, others cells involved in innate immunity like neutrophils and natural killer cells are also impaired causing reduced recognition and destruction of infected cells in the aged[26].

IMPACT OF AGEING ON PATHOPHYSIOLOGY OF SEVERE SEPSIS

In addition to the state of immunosenescence that predisposes the elderly to an increased rate of sepsis, there are also alterations in the body's response to sepsis, hence, leading to the more severe presentation of infection.

Severe sepsis led activation of the coagulation cascade plays a vital role in the pathophysiology of sepsis[21]. An aging led increase in plasma levels of fibrinogen, factor Ⅶ, factor Ⅷ, factor Ⅸ, and other clotting factors which is further potentiated during sepsis explains the increased risk of thrombosis and thromboembolism seen in the elderly[21]. There is also an increased rate of the generation of plasminogen activator inhibitor type 1 in the aged, which contributes to poor clearance of fibrin from the circulation of elderly patients[21]. This combined impact of aging and sepsis on the coagulation cascade partially explains the higher short survival rates with drotrecogin α (activated) in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial[12,27].

There is also an abnormal cytokine response in the elderly[21]. There is a shift from the production of type 1 cytokines [interleukin (IL)-2, tumor necrosis factor (TNF)-α] to type 2 cytokines (IL-4, IL-10)[28]. However, IL-1, IL-3, TNF, interferon-γ, IL-8, and IL-12 production is generally unaffected or increased in the elderly[21]. This predisposes the elderly to systemic infection by microbial pathogens and generally more prolonged proinflammatory responses as compared to younger patients. This also reflects the abnormal response of counter-regulatory cytokines like IL-10 in clearing microbial pathogens[21].

The concept of sepsis-associated myocardial depression is due to several factors including TNF, nitric oxide and probably other inflammatory cytokines like IL-1 and IL-6 which have a negative inotropic effect[29]. This can be further aggravated by aging, leading to a poorer outcome in elderly septic patients[30,31]. The elderly response to endotoxins is also more severe with more profound hypotension, excess epinephrine response, delayed recovery of blood pressure and more profound cytokine response as compared to younger subjects[32].

DIAGNOSIS OF SEPSIS IN THE ELDERLY

The clinical diagnosis of infection in the elderly is challenging and likely to be missed if not anticipated. The presentation of sepsis in the elderly may be more severe and different from that in younger patients[10]. The initial inflammatory response of infection which normally produces symptoms and signs of sepsis are blunted or may be absent in the elderly, while later presentation may be very severe with very rapid progression to septic shock[13,21,26]. It has been shown that the febrile response may be blunted in up to 47% of elderly septic patients[33]. However, nonspecific signs of sepsis like altered mental status, delirium, weakness, anorexia, malaise, falls, and urinary incontinence are common in the elderly[13]. Similar findings can be present in non-infectious diseases in the elderly making the diagnosis difficult[13]. In addition, due to age-related dementia, a clear history may not be available in many patients. Thus, a lower threshold and higher index of suspicion is required to diagnose sepsis in this population[13,34]. Besides the abnormal response to infection, there are challenges in taking adequate diagnostic specimens in elderly patients because of a lack of cooperation in the frail, dehydrated, debilitated, and cognitively impaired[13,34]. Positioning of these patients due to osteoarthritis or other orthopedic problems may prove challenging when performing high-quality imaging studies which may compromise the diagnostic value of these studies[34].

In elderly patients, the most common source of sepsis is respiratory tract followed by genitourinary infections[4]. It is possible that the elderly are at increased risk of infection with multidrug-resistant organisms. In a review of patients treated at hematology and oncology centers in the United States and Canada an increased rate of detection of isolates like methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci* in the elderly was observed. The incidence of Klebsiella species with extended-spectrum β-lactamase phenotyes was also found to be highest among patients older than 65 years and younger than 14 years[35].

The explanation for this disproportionate increased rate of multi-resistant organisms in the elderly is greater exposure to the health care system and cumulative antibiotic exposure, although studies are still lacking in this area to verify these findings.

MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK IN THE ELDERLY

The management of severe sepsis and septic shock in the elderly should be performed as per the International Surviving Sepsis Guidelines[36]. The sepsis resuscitation and management bundles should be started early and have been shown to improve survival with good compliance over different age groups[37,38]. The similar principles of management as used in young adults, including early source control, early goal-directed therapy, use of low tidal volume during mechanical ventilation, should be followed. There are, however, a few specific considerations which should be kept in mind while managing severe sepsis and septic shock in the elderly.

Resuscitation

Early goal-directed therapy remains the mainstay of the resuscitation bundle in the management of severe sepsis and septic shock in both young adults and elderly patients[39]. Studies have proven the effectiveness of early goal-directed therapy in adults when used in conjunction with other measures of the sepsis bundles in the management of elderly patients[40]. Various measures which can be taken to improve cardiac output in the elderly should focus on systolic function rather than heart rate as the heart rate response to sepsis is blunted in the elderly[41]. The systolic output of the heart is dependent on left ventricular preload as per Starling's law. Therefore, it is necessary to maintain adequate preload, whenever an aged patient needs to increase his cardiac output, such as during sepsis[26]. However, overzealous fluid administration can also be problematic in patients with aging-associated diastolic dysfunction[41]. Other therapies to improve tissue perfusion like dobutamine can also have variable effects due to relative resistance in the aged and can be arrhythymogenic, especially in patients with a history of coronary artery disease[42]. Blood transfusion triggers should be the same as in young adults with the threshold to transfuse packed red blood cells being kept at a hemoglobin of less than 7 g/dL and a target hemoglobin of 7-9 g/dL[43]. However, the threshold of 7 g/dL contradicts the early goal-directed resuscitation (first 6 h of resuscitation) protocol that targets a hematocrit of 30% in patients with low central venous oxygen saturation, and in patients with active coronary artery disease which may be common in the elderly[40,44]. Vasopressors like dopamine or norepinephrine can be used to maintain perfusion in the face of life-threatening hypotension, despite appropriate fluid challenges[36].

Source control and antibiotics

The dosing of antimicrobials should be based on age-related differences in pharmacokinetic and pharmacodynamic parameters such as decrements in renal function including glomerular filtration rate, tubular secretion, and renal blood flow; reduced lean body mass and increase body fat, and shock-induced reduction in hepatic blood flow[45,46]. There is also an increased incidence of antimicrobial-related adverse effects in the elderly[46,47]. However, the principle of initial bolus dose and overall aggressive dosing to achieve maximal therapeutic dose should not be sacrificed to avoid potential adverse effects[46].

Source control of infection and early appropriate antimicrobials are the two vital components of the management bundle of surviving sepsis guidelines[36,37]. The source of infection should be identified without delay when possible, and appropriate source control measures like removal of infected foreign bodies (intravascular catheters), drainage of abscesses or other infected fluid collections, or definitive management of anatomical derangements sustaining microbial contamination should be contemplated early whenever possible[26,36].

The concept of inadequate initial antibiotic therapy is independently associated with poor outcomes and is valid across all ages[47,48]. The early institution of antimicrobial therapy has been found to significantly decrease mortality even in elderly sepsis patients[47-51]. Broad spectrum empirical antibiotic therapy should be initiated within 1 h of the recognition of sepsis, after samples of blood and other suspected sites of infection have been obtained for culture[36]. The empirical antimicrobial regimens should be based on patient-factors such as underlying co-morbidities or immune-compromised states, site and severity of infection; environmental factors such as residence in nursing homes, history of repeated hospitalizations and local factors like the expected microbiological organism and the antimicrobial susceptibility patterns[45,46]. The strategies of clinical response and culture-based de-escalation and shorter courses of therapy should also be used when appropriate[46].

Corticosteroids

Adrenal insufficiency is common among elderly patients with septic shock[52]. However, the laboratory findings of hyponatremia, hyperkalemia and eosinophilia, which may indicate the presence of adrenal insufficiency, are uncommon in these patients[52,53]. The use of steroids for septic shock has remained a source of controversy because of concerns regarding effectiveness of steroids per se, and on other hand, due to the serious adverse effects of steroids like hyperglycemia, immunosuppression (at high doses), poor wound healing, and exacerbation of myoneuropathy due to critical illness[54,55]. Adding to the controversy, Salgado *et al*[53] showed that advanced age may not be an independent risk factor for relative adrenal insufficiency. Hence, at present, due to lack of definitive evidence, we recommend that low dose intravenous hydrocortisone can be tried in elderly septic shock patients only in such clinical situations where the blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy as recommended by the surviving sepsis guidelines[36].

Activated protein C (Drotrecogin α)

The PROWESS trial in 2001 showed a 6% absolute risk reduction (19.4% relative risk reduction) in the 28-d mortality in patients treated with recombinant human activated protein C (rhAPC) as compared to those who were given placebo[27]. Out of the 850 patients who were randomized in this study to receive rhAPC, 48.6% were more than 65 years of age and 24.1% were more than 75 years of age[27]. On subgroup analysis, in patients more than 75 years (386 patients), there was a 15.5% reduction in the absolute risk of mortality at 28 d and a 15.6% reduction in-hospital mortality in the treatment group as compared to the placebo group, with no detectable increased risk of bleeding[12]. Even long-term survival was significantly higher in the treatment group ($P = 0.02$) among the elderly patient subgroup[12]. Hence, treatment with rhAPC can be safely considered in elderly patients

with septic shock who are at a high risk of death due to severe sepsis, regardless of their age, if there are no contraindications[13,36]. The criteria for giving rhAPC remains the same as in younger patients, which is, Acute Physiology and Chronic Health Evaluation Ⅱ ⩾ 25 and/or patients with septic shock requiring vasopressors despite fluid resuscitation, with sepsis-induced organ dysfunction of more than two organ systems[37].

Respiratory failure and mechanical ventilation

Patients with severe sepsis and septic shock often require mechanical ventilation. The need for mechanical ventilation in the elderly is independently associated with increased mortality[10,56,57]. In the landmark study by the acute respiratory distress syndrome (ARDS) Network, the investigators found an absolute risk reduction in mortality of 9% (40% *vs* 31%) with a relative risk reduction of 22% in the low tidal volume (6 mL/kg) group, when compared with the conventional tidal volume (12 mL/kg) group[58]. On subgroup analysis of the 173 patients aged more than 70 years, ventilation with low tidal volume resulted in an absolute risk reduction of 9.9% in mortality at 28 d[59]. Thus, a tidal volume of 6 mL/kg (predicted) body weight in patients with acute lung injury (ALI)/ARDS is recommended even in elderly patients[60]. In addition, the plateau pressures should be measured in patients with ALI/ARDS and the initial upper limit goal for plateau pressures should be less than 30 cm H_2O. The data regarding weaning in the older population after ARDS are sparse, and general recommendations for younger adults can be followed in the elderly such as using standardized protocols to evaluate patients for weaning and using spontaneous breathing trials[60,61].

Glycemic control

van den Berghe *et al*[62], demonstrated a significant reduction in morbidity and mortality with intensive blood glucose (BG) control of 80 and 110 mg/dL in a primarily surgical ICU patient population. However, the same investigators could not demonstrate reduced mortality with an identical protocol in medical ICU patients, and there was a 6-fold increased rate of hypoglycemia (BG < 40 mg/dL) in the intensive BG control group (18.7% *vs* 3.1%)[63]. The higher rates of severe hypoglycemia associated with intensive insulin therapy were also seen in other trials and in a meta-analysis, thus, any benefit derived from strict glycemic control is partially offset by the serious adverse events of hypoglycemia[63-67]. The surviving sepsis guidelines recommend the maintenance of BG level < 150 mg/dL with the continuous intravenous infusion of insulin and glucose in patients with severe sepsis following stabilization in the ICU[36]. The risk of hypoglycemia is particularly common in elderly septic patients, and therefore, the target of 150 mg/dL seems to be safe in such patients.

Other issues

The other issues concerning the care of elderly patients with severe sepsis may include the use of sedation and analgesia, prophylaxis for deep vein thrombosis, and stress ulcer prophylaxis which should be followed as for the younger adults[37]. The use of protocolized sedation regimes with daily interruption of sedation, to reduce the duration of mechanical ventilation, should be followed[68]. This may include sedative drugs administered as an intermittent bolus rather than by continuous infusion[68]. Low-dose unfractionated heparin, low-molecular-weight heparin, or mechanical prophylactic devices should be used for the prophylaxis of deep vein thrombosis, and H_2-receptor blockers or proton pump inhibitors should be used to prevent stress ulcers[36].

End of life issues

Besides aggressive care of patients with severe sepsis and septic shock, physicians should also be prepared and be equipped to provide quality end-of-life care in elderly patients who have a dismal prognosis. The probability of a decision regarding withholding or withdrawing life-sustaining treatments increases with patient age, however, such decisions should not be based on the futility of treatment, but should be individualized and centered around patient and family wishes[69-71]. This involves advance care planning, including the clear communication of likely outcomes and realistic goals of treatment to the family of the patient or the patient whenever possible. The final decision of limiting or withdrawing treatment may be followed as per the local guidelines. In difficult or more complex situations, the hospital ethical committee or the equivalent teams may provide assistance in decision-making regarding potentially unbeneficial or futile life-sustaining treatments[72].

PROGNOSIS AND OUTCOMES OF SEVERE SEPSIS IN OLDER PATIENTS

There are high mortality rates of around 50%-60% in elderly patients with severe sepsis and septic shock[4,9,73]. The mortality due to severe sepsis in elderly patients is 1.3-1.5 times higher than that in younger cohorts[4,9]. Several studies have found age to be an independent predictor of mortality[4,5,8,9]. Elderly patients with sepsis die earlier during hospitalization and the elderly are more likely to require skilled nursing or rehabilitative care after hospitalization as compared to young adults[4]. Various factors which have been identified as independent predictors of outcome in critically ill patients include[16,73]: (1) Pre-infectious immune or genetic status; (2) Nosocomial events; (3) Co-morbidities; (4) Severity of illness; (5) Age ⩾ 75 years; and (6) Impaired level of consciousness.

The poor prognostic factors in elderly patients with severe sepsis include the presence of shock, elevated serum lactate levels, and presence of organ failure, especially respiratory and cardiac failure[73]. The quality of life after resolution of sepsis is important in formulating health care plans. However, the data regarding subsequent survival and quality of life after an episode of severe

sepsis is limited, especially in the elderly. The elderly are more likely to have poorer functional outcome not only in terms of failure to regain daily living activities, but also in the development of additional functional limitations during the ICU stay[74]. The long-term prognosis of the elderly is chiefly dependent on functional status rather on severity of illness at admission[75]. In a study by Ely *et al*[12], the elderly (≥ 75 years of age) were more likely to be discharged from hospital to a nursing home or alternative health care facility (55%) rather than to home (45%). In another study, age greater than 80 years was found to be an independent predictor of discharge to another healthcare facility rather than to home[76]. Hence, future research in the management of severe sepsis should not only target improved survival, but also good functional outcome in these patients.

HEALTHCARE COSTS AND RATIONING OF RESOURCES

There are huge financial implications in the management of sepsis on limited healthcare resources. Data suggests that the annual cost of sepsis management was $17 billion in the year 2000 alone[5]. Moreover, more than half of this cost was attributable to the care of patients more than 65 years, and around one third to the care of patients more than 75 years of age. The frequency of sepsis is predicted to increase by more than 5% per year along with an increasing elderly population and higher mortality[4]. Hence, management of sepsis in the elderly will have huge financial implications[2,5].

This has led to an intense debate on the rationing of resources, criteria for admission to the ICU and the decision to withdraw or withhold treatment in elderly patients. Denying ICU admission to the elderly has few supporters, however, denying ICU admission and inadequate treatment solely on age is highly controversial[77-82]. There is enough evidence available on the association between increased intensity of treatment and improved survival and good long-term outcome even in the elderly[80,82]. Hence, age only should not be the reason for denying admission or the appropriate management of sepsis in an elderly patient.

AREAS OF FUTURE INVESTIGATIONS

There is a dearth of available data on severe sepsis in the very old, especially regarding factors determining outcome, quality of life and functional outcome after treatment of sepsis. The trials on antisepsis and antimicrobial agents tend to exclude the very elderly, because they are generally believed to be less likely to respond to treatment. However, in order to formulate optimal healthcare policies as the population ages and the number of cases of sepsis increases, future trials should also focus on this age group of patients. Further investigations should also aim to assess the impact of preventive measures and the implementation of bundled strategies in the management of severe sepsis in the elderly.

CONCLUSION

The management of elderly patients in the ICU is always challenging in terms of associated clinical co-morbidities and the greater medical, social and financial resources involved. Severe sepsis and septic shock are not only more common, but are also associated with higher morbidity and mortality in elderly patients. A lower threshold and higher index of suspicion is required to diagnose sepsis in this age group. Timely aggressive and balanced management may improve outcomes in these patients. However, more clinical trials including elderly patients will help to decide appropriate management in the future.

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REVIEW

Glycemic control in critically ill patients

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Abstract

Hyperglycemia is common in critically ill patients and can be caused by various mechanisms, including nutrition, medications, and insufficient insulin. In the past, hyperglycemia was thought to be an adaptive response to stress, but hyperglycemia is no longer considered a benign condition in patients with critical illnesses. Indeed, hyperglycemia can increase morbidity and mortality in critically ill patients. Correction of hyperglycemia may improve clinical outcomes. To date, a definite answer with regard to glucose management in general intensive care unit patients, including treatment thresholds and glucose target is undetermined. Meta-analyses of randomized controlled trials suggested no survival benefit of tight glycemic control and a significantly increased incidence of hypoglycemia. Studies have shown a J- or U-shaped relationship between average glucose values and mortality; maintaining glucose levels between 100 and 150 mg/dL was likely to be associated with the lowest mortality rates. Recent studies have shown glycemic control < 180 mg/dL is not inferior to near-normal glycemia in critically ill patients and is clearly safer. Glycemic variability is also an important aspect of glucose management in the critically ill patients. Higher glycemic variability may increase the mortality rate, even in patients with the same mean glucose level. Decreasing glucose variability is an important issue for glycemic control in critically ill patients. Continuous measurements with automatic closed-loop systems could be considered to ensure that blood glucose levels are controlled within a specific range and with minimal variability.

Key words: Critical care; Glycemic control; Hyperglycemia; Hypoglycemia; Insulin

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INTRODUCTION

Hyperglycemia is common in critically ill patients, even those patients who have not been previously diagnosed with diabetes[1,2]. Increasing evidence indicates that the development of hyperglycemia during acute medical or surgical illness is not a physiological or benign condition[3-7]. Alterations in glucose metabolism occur during critical illness and are mediated by various factors, including increased insulin resistance, change in hormone production, and activation of cytokines[8]. In critically ill patients a hypermetabolic state exists[9], with the predominant cause being the intense activation of counter-regulatory hormones and cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6, which may be important mediators of insulin resistance and result in hyperglycemia[10]. Clinicians have increasingly

appreciated the impact of hyperglycemia in patients with diabetes, as well as stress-induced hyperglycemia (SIH) or hospital-related hyperglycemia[11-13]. The vast majority of patients in the intensive care unit (ICU) have SIH, which refers to transient hyperglycemia during illness and is usually restricted to patients without previous evidence of diabetes[14]. Patients without diabetes have a higher mortality risk when admitted to the hospital than do patients with diabetes[15-18].

Hyperglycemia is independently associated with increased ICU mortality[19-23]. Strict control of the blood glucose concentration is considered important because strict control of the blood glucose concentration may reduce mortality and morbidity; however, hypoglycemia is significantly higher in patients with tight glucose control using intensive insulin therapy[24,25]. Glycemic control to a moderately tight range is not inferior to euglycemia and clearly safer in critically ill patients[26,27]. A less than strict approach to managing critical illness-related hyperglycemia while avoiding hypoglycemia is becoming the standard approach in most ICUs.

EPIDEMIOLOGY

The prevalence of hyperglycemia in critically ill patients is difficult to estimate because the diagnosis is variably defined. Approximately 75% of all patients, including diabetics, have blood glucose concentrations > 110 mg/dL at the time of admission, and 12% of all patients have blood glucose concentrations > 200 mg/dL[24]. Another study showed that > 60%, 38% and 23% of patients had blood glucose concentrations > 110 mg/dL, > 150 mg/dL and > 200 mg/dL after admission in the medical ICU of a tertiary care medical center, respectively[28]. Glucose values > 140 mg/dL occur in 51%-58% of patients presenting with acute myocardial infarctions (MIs)[29,30]. Latham *et al*[31] found that 21% of cardiothoracic surgery patients developed post-operative blood glucose levels of > 200 mg/dL. The prevalence rates of hyperglycemia were 86.7%, 61% and 35.2% for pediatric patients with maximal glucose levels of > 110 mg/dL, > 150 mg/dL and > 200 mg/dL, respectively[32]. Faustino *et al*[33] reported prevalence data of 75%, 50.1%, and 26.3% in pediatric patients with cut-off values of 120, 150 and 200 mg/dL, respectively.

CAUSES OF HYPERGLYCEMIA AND PATHOPHYSIOLOGY

The factors contributing to hyperglycemia in patients with critical illnesses include the release of stress hormones and the use of medications (exogenous glucocorticoids, vasopressors, lithium, and β-blockers). Overfeeding, intravenous dextrose, commonly used parenteral nutrition, dialysis solutions, and antibiotic solutions, also contribute to hyperglycemia. Insufficient insulin or volume depletion can cause hyperglycemia[34]. Bed rest, even in the absence of obvious disease, leads to impaired skeletal muscle glucose uptake and promotes peripheral insulin resistance; simple bed rest can further aggravate SIH[35].

In patients with diabetes, the cause of hyperglycemia is a combination of insulin resistance and pancreatic β-cell secretory defects. In patients with SIH, the cause of hyperglycemia is a complex interaction of counter-regulatory hormones, cytokines and insulin resistance[36]. Glucagon, epinephrine, and cortisol increase gluconeogenesis and glycogenolysis. Gluconeogenesis is triggered to a greater extent by glucagon than by epinephrine and cortisol[37-39]. TNF-α may promote gluconeogenesis by stimulating glucagon production[40]. Glycogenolysis is triggered primarily by catecholamines and perpetuated under the influence of epinephrine and cortisol[36].

Insulin resistance may be associated with impaired insulin receptor binding or impairment in the activation of early or intermediate components of the insulin signaling pathway[41] and/or with defects in glucose transporter 4[42]. Epinephrine can inhibit insulin-stimulated glucose transport in skeletal muscle. The action of counter-regulatory hormones on insulin resistance in skeletal muscles may be mediated through an elevation in the circulating free fatty acid level in patients with critical illness, despite hyperinsulinemia[43]. Cytokines such as TNF-α and IL-1, inhibit post-receptor insulin signaling[44,45]. The severity of illness is associated with a proportional rise in serum cytokines and insulin resistance[46,47].

ADVERSE EFFECTS OF HYPERGLYCEMIA

It has been reported that pronounced hyperglycemia might lead to complications or a poor clinical outcome[12]. Elevated blood glucose concentrations are associated with increased morbidity and mortality after burns, surgery, strokes, MIs and head trauma[4,48-54]. In the pediatric ICU, peak blood glucose levels and the duration of hyperglycemia are independently associated with mortality[55]. Hyperglycemia can cause polymorphonuclear neutrophil dysfunction[56], and decreased intracellular bactericidal[57,58] and opsonic activity[56,59] which plays a role in the increased incidence of infections in patients with hyperglycemia. High glucose concentrations in cells can damage mitochondrial protein[60], exacerbate inflammatory pathways, modify the innate immune system, and impair endothelial function[61]. High glucose concentrations also reduce vascular reactivity and endothelial nitric oxide production, which may compromise blood flow to the periphery[62]. In addition, acute hyperglycemia enhances proteolysis[63] and is associated with an increased risk of cardiac complications, hemodynamic and electromyocardial disturbances, acute renal failure, and death[64,65].

INSULIN THERAPY PROTOCOLS

Use of a validated protocol to help maintain the glucose level is effective in critically ill patients. The protocol should be developed by a core group of clinicians, in-

ICU protocol for glycemic management

MD signature_____
Date_____

Goal

The goal of this protocol is to maintain the glucose level between 140 and 160 mg/dL

Monitoring

The initial blood glucose level is monitored every 1-2 h until a stable infusion rate is reached, then decreased to every 4 h while the blood glucose concentration is stable

Management of insulin infusion

Continuous insulin infusion (100 IU of Actrapid HM in 99 mL of 0.9% NaCl) with the use of a pump is started when the blood glucose is > 180 mg/dL on two successive measurements

Blood glucose levels are controlled by the neuro-fuzzy method. The first row at the top of the chart in the appendix displays the range of blood glucose values measured, while the first column on the left displays the range of possible blood glucose values measured 1-4 h previously. The adjusted infusion rate is at the intersection between the perpendicular lines drawn from the present blood glucose values and the blood glucose values found 1-4 h previously

Initial dose: patients received oral hypoglycemic agents or up to 12 U/d of insulin, starting with 0.5 U/h of insulin if patients previously received insulin > 12 U/d, and 0.5 U/h for every 10 U > 12 U/d

Present blood glucose value (mg/dL)

Preceding blood glucose value (mg/dL) (1-4 h before)	≤ 80	81-100	101-120	121-140	141-160	161-180	181-200	201-220	221-240	241-260	> 260
≤ 80	-0.3	-0.2	0.1	0.5	0.8	1.2	1.3	1.4	1.5	1.5	1.5
81-100	-0.5	-0.4	-0.2	0.2	0.6	1	1.2	1.4	1.4	1.5	1.5
101-120	-0.7	-0.7	-0.4	0.0	0.4	0.8	1.1	1.3	1.4	1.4	1.5
121-140	-0.9	-0.8	-0.6	-0.3	0.2	0.6	1	1.2	1.3	1.4	1.4
141-160	-1	-1	-0.6	-0.5	0.0	0.6	0.9	1.1	1.3	1.4	1.4
161-180	-1.2	-1.1	-1	-0.7	-0.2	0.3	0.7	1	1.2	1.3	1.4
181-200	-1.3	-1.3	-1.1	-0.8	-0.4	0.1	0.6	0.9	1.2	1.3	1.4
201-220	-1.4	-1.4	-1.2	-1.0	-0.8	-0.1	0.4	0.8	1.1	1.3	1.4
221-240	-1.4	-1.4	-1.3	-1.1	-0.5	-0.3	0.2	0.7	1	1.2	1.3
241-260	-1.5	-1.5	-1.4	-1.2	-0.6	-0.5	0.1	0.6	0.9	1.2	1.3
> 260	-1.5	-1.5	-1.4	-1.3	-1	-0.6	0	0.5	0.9	1.1	1.3

Management of hypoglycemia

If the blood glucose concentration is ≤ 60 mg/dL, the protocol directs the nurses to stop the insulin infusion, and notifies physicians to administer 50% dextrose immediately, with blood glucose measurements repeated after 30 min

Switch to subcutaneous insulin-injection

If the insulin dose is < below 3 IU/h, a conversion of the intravenous infusion to a subcutaneous insulin injection is considered. The insulin infusion is often discontinued before the patient is discharged from the ICU

Figure 1 Example of glycemic control protocol in an adult intensive care unit. ICU: Intensive care unit.

cluding physicians, nurses, pharmacists, and dietitians with guidelines that provide targeting a specific glucose level, insulin dose adjustment, the interval of glucose monitoring, and time for stopping infusion or decreasing the infusion rate to accommodate changes in patient feeding regimes for tests or medications. The risks of complications, such as hypoglycemia, must be addressed. Intravenous insulin therapy is suggested. The initial blood glucose level is monitored every 1-2 h until a stable infusion rate is reached, then decreased to every 4 h while the blood glucose concentration is stable[66]. A protocol is shown in Figure 1 as an example which can be modified for local needs.

Published glycemic management protocols have been documented to significantly improve glucose levels without a significant increase in the risk of hypoglycemia[67]. The advantages of an algorithm or protocol include more consistent glucose control, less of a trial-and-error pattern of treatment, the ability to maintain glycemic control closer to the target range of near-normal, and earlier intervention for hypoglycemia[68,69]. A lack of protocol-based care might be expected to increase glycemic variability[70].

Regular measurement of blood glucose is a burden for nurses; glycemic control by continuous glucose monitoring with automatic closed-loop systems can reduce the clinical burden[71]. Glycemic management protocols in the ICU should focus more on the variability of glycemic control as the treatment target, because glycemic management is related to patient outcome. Continuous monitoring of glucose would allow for the early identification of rapid fluctuations in status associated with changes in insulin requirements. Continuous monitoring of glucose may help prevent the extremes of glucose variability and can maintain optimal blood levels without causing hypoglycemia, thus decreasing the variability in blood glucose concentrations in patients admitted to the ICU[72]. Conversion of an intravenous infusion to subcutaneous insulin injection therapy is often necessary before or at the time of discharge from the ICU[73].

OUTCOMES

Hyperglycemia has been linked to worse outcomes in critically ill patients[74-76]. The SPRINT study showed that tight glycemic control to a mean of 6.0 mmol/L mitigated organ failure faster than conventional control at a higher mean level of 7.2 mmol/L[77]. In 2001, van den Berghe *et al*[24] published the Leuven study, which demonstrated that tight glycemic control with a target of blood glucose level between 80 and 110 mg/dL had better outcome than conventional control in critically ill surgical patients. ICU mortality, the risk of multi-organ failure, systemic infection and sepsis, the incidence of acute renal failure, critical illness-related polyneuropathy, the need for blood transfusion, and the need for prolonged mechanical ventilator support were reduced from 8% to 4.6%, 34%, 40%, 41%, 44%, 50%, and 50%, respectively. Based on the Leuven study, tight glycemic control was adopted as the standard for critical care patients worldwide. In 2004, Krinsley *et al*[67] demonstrated that patients in whom the blood glucose concentrations were controlled to < 140 mg/dL had superior survival rates than did patients in whom the blood glucose concentrations were controlled to < 200 mg/dL in medical-surgical ICUs. In 2006, Van den Berghe *et al*[25] repeated the Leuven study in a medical ICU, but did not demonstrate a survival benefit with tight glycemic control in all critically ill medical patients; however, better outcomes, including ICU, ventilator, and hospital days were noted. For patients in the ICU > 3 d, a survival benefit was reported in the tight glycemic control group. Other studies in which tight glycemic control in the ICU was achieved did not demonstrate a lower mortality rate, less frequent acute renal failure, decreased need for renal replacement therapy, decreased vasopressors, and a lower number of ventilator-free days in the intensive insulin treatment group[26,78-81]. A significantly higher mortality rate was reported in the NICE-SUGAR study[26]. Furthermore, the NICE-SUGAR study did not demonstrate shorter ventilator, ICU, and hospital days, and a lower rate of renal replacement therapy, positive blood cultures, and red cell transfusions, but significantly higher rates of severe hypoglycemia were noted. Wiener *et al*[82] reviewed 29 randomized controlled trials with a total of 8432 patients in a meta-analysis. Wiener *et al*[82] showed that hospital mortality did not differ between patients with tight glucose control and patients with usual care, and there was also no significant difference in mortality when stratified by glucose goals. Another meta-analysis study showed that intensive insulin therapy may be beneficial in patients admitted to the surgical ICU, but not the medical ICU or a mixed ICU[83].

Patients with SIH had worse outcomes than patients with a known diabetic history. Umpierrez *et al*[2] reported that newly diagnosed hyperglycemia (admission or fasting glucose level > 125 mg/dL or random glucose level > 200 mg/dL) was associated with a 16% mortality rate compared to a mortality rate of 3% among patients with known diabetes and a rate of 1.7% among patients without hyperglycemia. Three cohorts of ICU patients concluded that hyperglycemia during an ICU admission had a more significant impact on the risk of mortality among patients without diabetes than among patients with diabetes[72,84,85].

GLYCEMIC VARIABILITY

Blood glucose levels in critically ill patients fluctuate widely, even when continuous feeding and an insulin infusion are used[69]. Glycemic variability is usually expressed as the standard deviation around the mean glucose value or as the mean amplitude of glycemic excursions[86]. Glycemic variability is also associated with outcome in critically ill patients; specifically, greater glycemic variability is associated with a significantly higher mortality rate[87-89]. Non-survivors of critical illnesses were shown to have a higher standard deviation and coefficient of variation (CV) of glucose (standard deviation/mean glucose level) during the ICU stay. A blood glucose level standard deviation > 20 mg/dL was associated with a 9.6-fold increase in mortality compared with a blood glucose level standard deviation < 20 mg/dL[89]. A deleterious effect resulting from increased glycemic variability was noted among non-diabetic patients, but not among patients with diabetes. The mortality rate among non-diabetic patients with a mean glucose level of 70-99 mg/dL during the ICU stay was 10.2% for patients with a glucose CV of < 15% *vs* 58.3% for patients with a glucose CV above 50%[88]. Increased glycemic variability not only increased the mortality rate, but also morbidities, such as nosocomial infections and hospital length of stay[90]. In a recent retrospective study involving surgical ICU patients, Hermanides and coworkers reported serum glucose variance and combined with high serum glucose levels was associated with the highest mortality, and glucose variability was more important than glucose levels in predicting outcome[91]. Dossett *et al*[92] reported that glucose variability was associated with increased mortality, but the mean blood glucose level was not associated with increased mortality in patients with sepsis.

Why is glycemic variability associated with poorer outcomes? Glycemic variability may reflect more attention to detail in medical and nursing care, which may be the real determinants of better outcomes. Less glycemic variability may be associated with severe illness[93]. Induced fluctuation in glycemic levels is more likely to produce apoptosis than sustained hyperglycemia[94,95]. These effects may be mediated *via* wide changes in osmolarity that in turn could affect cellular and organ function[96]. Oxidative stress was produced in much higher concentrations by alterations in glycemic levels than by sustained hyperglycemia[97]. Indeed, increased oxidative stress can result in endothelial dysfunction and contributed to vascular damage. Oxidative stress may be one of the unifying mechanisms underpinning the vasoconstriction, microvascular thrombosis, and inflammation associated

with hyperglycemia and glycemic variability[98,99]. Rapid changes in glucose levels can also induce monocyte adhesion to endothelial cells[100]. Another reason why increased glycemic variability may be associated with poorer ICU outcomes is the fact that significant hypoglycemia could occur undetected[101].

In past trials involving intensive insulin therapy, there were discrepancies in mortality outcomes. All of the data regarding glycemic variability were unavailable in these trials; however, glycemic variability may account for the different mortality rates.

HYPOGLYCEMIA

A plasma glucose concentration < 70 mg/dL is the most common threshold used to define hypoglycemia[102]; however, most of the studies involving glucose control in the ICU have defined severe hypoglycemia arbitrarily as values < 40 mg/dL whether or not the patients had associated symptoms[24,25,67,79,81]. Emerging data suggest that hypoglycemia may have a negative impact on the clinical status and outcome of ICU patients[103,104]. ICU patients may tolerate hypoglycemia poorly and also exhibit impaired counter-regulatory responses or have delayed detection of hypoglycemia. The most severe complications of severe hypoglycemia, such as seizures and death, are easy to measure; more subtle manifestations of neuroglycopenia, such as headaches, fatigue, confusion, dysarthria, or impaired judgment, may be difficult or impossible to diagnose in critically ill patients[105,106]. Hypoglycemia is more common in medical and septic sub-groups of patients[107]. Female gender, a history of diabetes, the APACHE Ⅱ score, mechanical ventilation, continuous veno-venous hemodialysis, and ICU length of stay are independent predictors of hypoglycemia[108]. Spontaneous episodes of severe hypoglycemia are rare and observed mainly in patients with fulminant hepatic failure and adrenal failure secondary to septic shock, and especially in patients with severe co-morbidities, such as liver cirrhosis, chronic renal failure, and malnutrition[26,109].

Based on the Leuven study in 2001, intensive insulin therapy was widely used in many ICUs. Many studies have shown that intensive insulin therapy is associated with significantly more episodes of severe hypoglycemia than conventional insulin therapy[78-81,110]. In the VISEP[80] and Glucocontrol trials[81], the studies were terminated early because of significantly more hypoglycemic episodes in the intensive insulin treatment group. In two meta-analyses studies, intensive insulin therapy also showed a significantly increased risk of hypoglycemia[82,83]. Because intensive insulin therapy has been associated with a significantly higher risk of hypoglycemia, there is increased concern about the safety of intensive insulin therapy, which has become an obstacle to strict glycemic control.

Is the hypoglycemic episode directly responsible for an increased risk of death in patients with critical illnesses? One study revealed the degree of hypoglycemia parallels the increase in the risk of death[111]. Even a single episode of severe hypoglycemia is independently associated with an increased risk of mortality[104]; however, some studies have shown that the occurrence of hypoglycemic is not associated with an increased risk of mortality[108,112].

GLYCEMIC GOAL

Considerable uncertainty remains regarding the optimal target levels of glucose for patients in the ICU. A safe upper limit for blood glucose level during insulin therapy has not been precisely determined in critically ill patients. The Surviving Sepsis Campaign Guidelines advocate a goal of glucose control < 150 mg/dL, in part to limit hypoglycemia[64]. A large body of observational cohort study data from heterogeneous populations strongly suggests that a J- or U-shaped mortality curve exists among acutely and critically ill patients[28,113,114]. Both high and low blood glucose values are independently associated with hospital mortality, with the lowest mortality occurring among those patients with mean glucose levels during their stay in the range of 5.60-8.69 mmol/L and higher rates of mortality for those patients with levels below or above this range[107]. In a recent study, moderate glycemic control was superior to tight glycemic control with decreased mortality and major complications for patients undergoing isolated coronary artery bypass grafting[27]. Patients with a glucose level of 127-179 mg/dL had the lowest mortality and major complications; specifically, sepsis, prolonged ventilation, post-operative renal failure, and the need for new dialysis were highest in the tight glucose control group. Another study also showed that a glucose level of 140-180 mg/dL was associated with the best risk-benefit ratio[103]. The American Association of Clinical Endocrinologists and the American Diabetes Association have increased the treatment threshold to values > 180 mg/dL and a target glucose level between 140 and 180 mg/dL for ICU patients[115].

CONCLUSION

Acute hyperglycemia associated with insulin resistance is common in critically ill patients. Both hyperglycemia and hypoglycemia harm our patients. The appropriate glycemic target has not been established and may indeed be different for different patient populations. At the same mean blood glucose value, the nature of glycemic control can be quite different with respect to glycemic variability. Not only is the blood glucose level important, but glycemic variability is also important. An attempt to minimize glycemic variability might have a significant beneficial impact on the outcomes of patients without diabetes. New strategies should be developed to achieve glycemic control with a minimal risk of hypoglycemia and large glucose variations. More effort should be focused on the quality of blood glucose measurement devices and blood glucose monitoring modalities.

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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,
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Acknowledgments

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

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No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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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Write as mean ± SD or mean ± SE.

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