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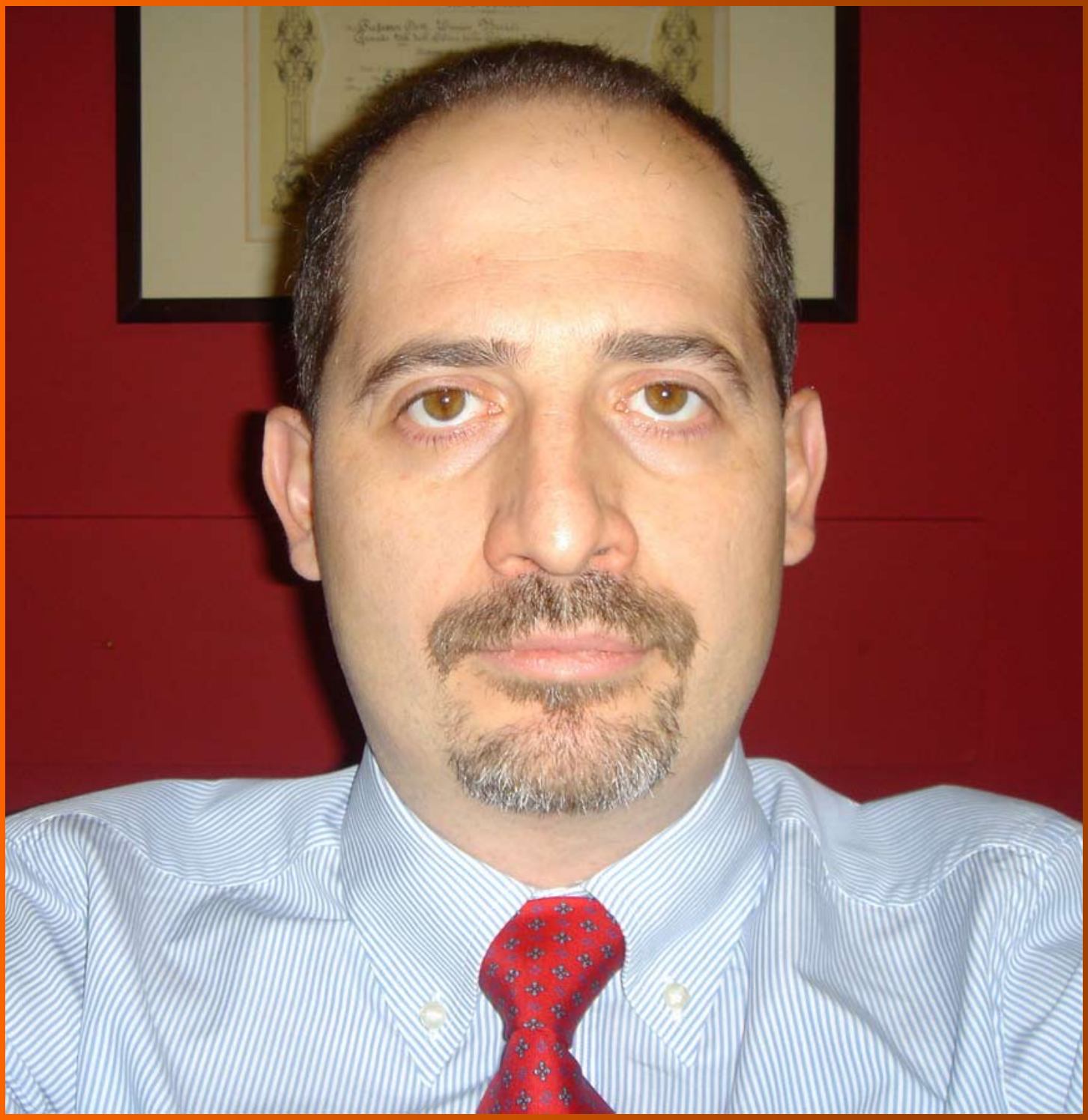

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Xiu-Xia Song, Director
World Journal of Critical Care Medicine
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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PUBLISHER
Baishideng Publishing Group Inc
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REVIEW

Practical strategies for increasing efficiency and effectiveness in critical care education

Maurice F Joyce, Sheri Berg, Edward A Bittner

Maurice F Joyce, Sheri Berg, Edward A Bittner, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, United States

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Correspondence to: Edward A Bittner, MD, PhD, MSEd, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, WHT 437, Boston, MA 02114, United States. ebittner@partners.org
Telephone: +1-617-6435044

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Abstract

Technological advances and evolving demands in medical care have led to challenges in ensuring adequate training for providers of critical care. Reliance on the traditional experience-based training model alone is insufficient for ensuring quality and safety in patient care. This article provides a brief overview of the existing educational practice within the critical care environment. Challenges to education within common daily activities of critical care practice are reviewed. Some practical evidence-based educational approaches are then described which can be incorporated into the daily practice of critical care without disrupting workflow or compromising the quality of patient care. It is hoped that such approaches for improving the efficiency and efficacy of critical care education will be integrated into training programs.

Key words: Medical education; Critical care; Educational efficiency; Educational efficacy; Bedside teaching; Flipped classroom; Patient handover; Multidisciplinary team practice; *In situ* simulation; Procedural training

Core tip: Evidence-based approaches for improving the efficiency and efficacy of critical care education have been developed and should be integrated into training programs. While a variety of such approaches are described in this paper and elsewhere in the medical education literature they share common characteristics. These include utilizing methods to rapidly identify learner needs, teaching directly to those needs, and providing specific feedback on performance. In addition these approaches emphasize active learning activities and integrate educational experiences from the classroom and clinical settings.

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INTRODUCTION

Critical care is a demanding medical specialty in terms of its complexity, the frequency of life threatening situations and the need for rapid decision-making based on incomplete data. The breadth and depth of medical knowledge and technical skill necessary for critical care practice continue to rapidly increase yet the time available for education of trainees has not. Limitations in the duty hours of trainees have reduced clinical exposure and allow less time for traditional methods of education[1]. Increasing clinical volume, administrative responsibilities, and documentation and billing requirements increasingly compete for the time that faculty has available for teaching. It is our mandate as critical care practitioners to educate and ensure that we have competent clinicians able to deliver high quality care to our critically ill patients. It is therefore necessary that we find a solution to the dilemma of providing safe and high-quality care while also providing the necessary education for trainees in clinical settings. Approaches to teaching and learning which account for the exponential growth in medical knowledge, unique learning needs and time constraints of the learners, while adapting to the dynamic and clinically demanding environments of critical care practice are urgently needed[2,3].

In this article, we provide a brief overview of the existing educational practice within the critical care environment. We then discuss challenges to education within common daily activities of critical care practice including bedside care, procedures, handover, and crisis management. Some practical educational approaches are described which can be incorporated into the daily practice of critical care without disrupting workflow or compromising the quality of patient care (Table 1). It is hoped that such approaches will increase the efficiency and efficacy of education that is offered to critical care clinicians, not only during training but throughout their careers.

The intensive care unit learning practice and educational deficiencies

The intensive care unit (ICU) provides unique opportunities for knowledge and skill acquisition in a dynamic and fast-paced clinical environment. There are opportunities to learn technical skills such as airway management, central line placement and ultrasonography, as well as nontechnical skills such as teamwork, communication, and leadership. Surveys suggest that there is no standardized approach to trainee education within critical care medicine, reflecting highly variable ICU environments and practice patterns[4,5]. Such variation in educational practice is noteworthy as it may affect the quality of trainees' education through varied exposure to different patient cases, opportunities to perform procedures, experience with different attending physician practice styles and total teaching time. Despite this lack of a standardized structure, many programs use similar traditional clinical teaching methods. Bedside teaching is the most common format for trainee education and a majority of programs also offer didactic lectures and informal teaching sessions[4]. In addition an increasing number of programs include access to an online "core curriculum" of critical care topics[4]. With these didactic approaches, trainees in critical care acquire knowledge and skills through processes of "active" learning by participating in bedside teaching rounds and by directly administering patient care, while "passive" learning occurs through the use of lectures, conferences and journal clubs.

Bedside teaching, often conducted during ICU rounds, is an essential component of critical care education, as it covers clinical assessment, conduct of the physical exam and decision making. In addition the importance of multidisciplinary communication, bedside manners, professionalism, and other essential clinical skills are emphasized[6]. Involving the entire team in bedside rounds also contributes to multidisciplinary team development and improved patient care[7,8]. Educating during bedside care is not a passive activity; rather it requires skill by the critical care provider. Appropriate tailoring of educational topics to trainee needs in relation to current patients provides the trainee with the satisfaction of having learned something directly relevant to patient care, promoting active learning as well as providing a powerful motivational boost and educational reinforcement. "Conference room" teaching typically consists of a combination of standard "core" lectures (*e.g.,* mechanical ventilation, sepsis and shock) and flexible teaching topics based on current relevance to bedside care. While core lectures ensure that trainees are provided a certain amount of fundamental knowledge, flexible educational activities are designed to complement core lectures in order to tailor learning to the specific needs and interests of current team members and are typically initiated in response to issues identified during the bedside rounding.

Critical care has long had an "apprenticeship style" of training in which long hours and "see one-do one-teach one" were the primary means of fostering learning. However, work-hour restrictions, generational differences and increasing external regulations have altered this traditional approach. While these methods of providing critical care education are longstanding, there is mounting evidence that they are no longer sufficient. Many studies have reported suboptimal education of trainees in areas that are fundamental to critical care practice including deficiencies in medical knowledge, procedural skills, handover, communication and crisis management[9-18]. In addition, there is evidence that methods for education of critical care trainees have changed little since the Accreditation Council for Graduate Medical Education (ACGME) instituted duty hour standards and core competencies[1,19]. These

Table 1 Teaching challenges and strategies for increasing efficiency and effectiveness in critical care education

ICU Activity	Challenges to teaching	Strategies for improvement
Rounding/bedside care	Complexity, unpredictability, rapid pace of clinical care limits time available for teaching Simultaneously instructing trainees while caring for critically ill patients	Use of effective, time efficient methods to identify learner needs, teaching to those specific needs, and providing feedback Examples: Two-minute observation, one-minute preceptor, activated demonstration and teaching scripts
Lecture/didactics	Wide breadth and depth of knowledge required to care for critically ill patients Varying backgrounds and training levels of the learners It is not possible expose trainees to all relevant critical care topics The efficacy of traditional lectures is low	Integrate "in-class" experiences with "out-of-class" learning Practicing clinical decision-making in the classroom allows trainees to learn from their mistakes in a safe environment Example: Flipped classroom
Performing procedures (vascular access, airway management, bronchoscopy, chest tube placement ultrasonography, *etc.*)	Trainees need to acquire procedural competence with a number of diagnostic and therapeutic tools Finding the optimal balance between providing procedural opportunities for trainees and ensuring patient safety	Multifaceted learning strategies with performance assessed and mastery demonstrated away from the clinical setting Examples: Computer-based learning, task trainers, and simulation to provide conceptual and technical understanding Observing and then performing procedures in elective settings, before attempting high risk procedures on critically ill patients Just-in-time training immediately prior to actual performance Use of adjunct technology (*e.g.*, ultrasound, videolaryngoscopy)
Patient handover	Handovers are complex communication tasks The process is often error prone and substandard handovers have been linked to adverse events Critically ill patients are particularly vulnerable to ineffective handovers Limited evidence for a "best" approach Faculty may have limited experience with new handover processes	Develop learning strategies for ensuring information management and collaboration to generate a shared understanding of patients and reduce clinical uncertainty Examples: Discussions of approaches to diagnosis and management of specific conditions promotes learning Providing feedback on clinical actions taken in the preceding shift Providing feedback on clinical actions taken in the preceding shift Direct supervision of the handover process by experienced clinicians to ensure that communication of critical patient information is occurring and to answer clinical questions Supplementing the handover with short educational modules relevant to the patients receiving care Using handovers to evaluate trainee performance and provide formative feedback
Multidisciplinary team practice	High clinical workloads, finding common time to practice, disruption of clinical activities, and cost Training specifically designed to improve team dynamics is new for many critical care clinicians	Multidisciplinary training incorporated into the activities of daily practice (*in situ* simulation) can be inexpensive and less disruptive to staffing Example: Regular repetition of commonly occurring scenarios can be used to reinforce learning and teamwork *In situ* simulation can be used to interrogate departmental and hospital processes in real practice conditions

ICU: Intensive care unit.

deficiencies and an apparent lack of progress in critical care education may have a detrimental effect on patient safety and the quality of care. Perhaps it is because of the apprentice-style educational tradition in critical care that we have been slow to identify and adopt "best practices" of modern education theory for fostering experiential learning. In the age of reduced work hours and increased focus on patient safety, however, we are caught between less experienced clinicians at the bedside and imposed requirements for ensuring clinical competence. To successfully address these challenges requires a different educational experience. The following

sections provide approaches for increasing educational efficiency and efficacy during the daily activities of ICU practice. They are founded in educational theory and meant to be readily integrated into existing critical care practice regardless of the size, practice characteristics or economic resources.

Strategies for teaching with limited time

Educators in the ICU environment face the formidable challenge of simultaneously instructing trainees while caring for critically ill patients in a clinical environment where complexity and the knowledge required for decision making is high, time available for teaching is limited, and interruptions are frequent. Due to increased and competing demands on critical care faculty, the time available for clinical teaching appears to be in decline[20,21]. An even greater barrier to teaching than a heavy clinical workload is the misconception that "real teaching" requires an extended formal lecture. With this teaching misconception in mind, clinicians are understandably reluctant to teach because it interferes with patient care. As clinical educators it is important to recognize that every patient interaction has teachable moments. To maximize learning opportunities, educators must be attentive to identifying these moments and then making them pertinent to a learner's needs. Even small amounts of time focused on teaching can offer important learning opportunities for trainees to acquire new insights and skills. To achieve this efficient and effective teaching approach, a variety of strategies can be successfully employed. These educational strategies share common characteristics including: (1) identifying the learner's needs; (2) teaching directed to meet those specific needs; and (3) providing performance feedback.

Identifying the learner's needs saves time by not teaching what the learner already knows or is not ready for. Assessment of the learner's level of knowledge requires asking good questions as well as the ability to listen and observe. Questions are the educator's "primary diagnostic tool" to ascertain the learner's current level of knowledge and experience with similar situations[21]. Questions that precede a patient encounter can help the educator to ascertain the learner's understanding and experience with the clinical problem at hand-for example, "How do we assess delirium in this patient?". While questions that follow the learner's presentation of a patient can guide the educator's decisions about how and what to teach-for example, "How do you think we should manage this problem?".

A period of brief observation can be an effective means of assessing the learner's abilities instead of making inferences based on a patient presentation alone. The "two-minute observation model" is a well described method in which the teacher observes a patient encounter in order to obtain more specific information about the trainee's learning needs which can be used for providing guidance or feedback[21]. This technique is effective for teaching both history and physical exam skills as well as for teaching communication skills. In advance of the patient encounter, the teacher and learner should agree on which aspect of the interaction will be targeted for the brief observation-such as establishing patient rapport, history taking, physical examination, or discussion with nurse, consultant or family member. As with other learner-centered models, the instructor should set clear expectations, directly observe the learner and provide specific feedback and teaching.

The "one-minute preceptor model" is another focused teaching tool that is easy to implement while engaging in patient care[22]. This method uses a 5 step approach: (1) query the learner about what he/she thinks is going on with the patient; (2) probe for underlying reasoning or alternative explanations; (3) teach a general principle; (4) reinforce what was done well; and (5) correct any errors and make suggestions for improvement. In a mere one minute, the instructor is able to obtain a brief assessment of the trainee, provide an educational pearl, and deliver immediate positive and negative feedback. Research on the one-minute preceptor model suggests that it is an effective and efficient method of engaging learners in high-level case discussions of clinical problems, and its use is associated with strong satisfaction by both learners and teachers[23,24].

"Activated demonstration" is a model in which the learner is asked to observe the clinical teacher performing a skill that is unfamiliar to the learner[25]. After preparing the learner with a preview of the upcoming teaching points, the learner is given a specific assignment to complete while observing, such as "Watch how I perform the laryngoscopy", and provided expectations in terms of participation. After the demonstration, the teacher "activates" the learner by asking him or her to describe what was observed. A brief discussion of relevant learning points then occurs in which the rationale for the actions is examined and further study may be assigned.

"Teaching scripts" are concise, pre-prepared high-yield lessons that the instructor can teach the learner when the appropriate clinical setting arises[26]. To be most effective the script should be adapted to account for the trainee level, the patient's clinical circumstances, and the disease process under consideration[27]. Examples of teaching scripts might include "choosing sedation drugs for an intubated patient" or "fluid management in ARDS". Over time, seasoned clinicians naturally create a portfolio of scripts that they can effortlessly access, but educators at all levels can proactively develop teaching scripts. Limiting the number of learning topics discussed to 2 or 3 per day will increase their significance and the attention paid to each of them[28]. Too many topics can overwhelm the learner, ultimately reducing the educational impact. Finally, it is imperative to briefly review and summarize the important learning topics that were covered and discuss related learning activities. For example, "to review, today we discussed ventilatory management for ARDS. This afternoon, our critical care fellow will share a recent article that is related to our discussion". This summary reinforces prior learning and encourages evidence-based practice as well as peer-to-peer education.

Feedback is a powerful instructional strategy that can be effectively provided with limited time[29]. The key to feedback is providing specific descriptive comments about a learner's performance. The "Ask-Tell-Ask" model is a common model for giving feedback[30]. With this approach the teacher first sets the stage for providing feedback by telling the learner, "I would like to give you feedback". Then, the instructor asks the learner to assess his/her own performance with a question like, "How do you think you did?". Next, the teacher provides his/her own observations (importantly, positive and corrective), addresses the learner's self-assessment and provides an action plan for improvement. This approach incorporates the learner's perspective, avoids judgment and promotes the skill of self-reflection. The timing and location of providing feedback may vary depending on the issue and urgency. On-the-spot feedback based on events occurring at the bedside has the advantage of providing patient-centered in-training evaluations, which are a cornerstone of medical education[31]. In addition trainees highly value feedback related to specific behaviors performed at the bedside, associating high quality teaching with feedback pertaining to specific behaviors such as bedside skills and case presentations[32]. Delaying constructive criticism until a later time might be beneficial in some circumstances to avoid feelings of trainee embarrassment. However it is important to consider that a delay in feedback might also lead to continuation of incorrect and potentially harmful patient care, thus quick context-specific feedback is beneficial in most circumstances with a plan for more extensive discussion in a quiet, "safe" environment at a later time.

Revamping ICU lectures - "flipping" the classroom

Learning within the ICU environment is challenging, not only because of the complexity and rapid pace of patient care but also because of the breadth of knowledge required to care for critically ill patients. A number of critical care organizations have undertaken the task of defining learning objectives for trainees in the critical care setting[33-35]. Given the time constraints associated with clinical practice it is not possible to expose trainees to every topic relevant to critical care. Lectures are a common method of covering a "core curriculum" in critical care yet the efficiency and efficacy of this educational approach is low. It has been shown that learners' attention decreases after only ten minutes and learners only remember approximately 20% of the transmitted content following a lecture[36]. Consequently, there is need for new educational methods that result in more efficient and effective knowledge transmission than provided in traditional conference room lectures. These new methods should not be limited to the transmission of purely factual knowledge, but should provide the opportunity to apply this knowledge to problem solving in practice.

The "flipped classroom" is a novel instructional paradigm designed to increase learning by integrating in-class experience with out-of-class learning[37]. In this paradigm, learners first gain exposure to new material individually, usually *via* reading or watching instructional videos. Formal teaching time is then used for learning-centered activities that build on the pre-class work rather than providing traditional lectures. During the formal teaching time, an instructor facilitates trainee-driven discussion of the material *via* question and answer, discussion, case studies, problem-based learning, and other face-to-face activities. By applying their new knowledge with the guidance of a facilitator, trainees have access to immediate feedback from peers and faculty, which will help them more readily recognize and correct errors in thinking. These "active learning" activities will allow for complex problem solving, peer interaction, and better prepare learners to function independently.

The flipped classroom paradigm is particularly well suited for the ICU learning environment, where acquisition of "core" critical care knowledge is necessary before progressing to the more complex clinical problem solving that is required for patient care[38]. Practicing clinical decision-making in the classroom improves knowledge retention and has the further inherent advantage that the trainees can learn from their mistakes in a safe environment without endangering patients. The flexibility afforded by the flipped classroom allows for learning despite the unpredictability of the ICU environment, as learning materials may be made available to learners regardless of clinical demands or their particular shift schedule. The mechanism used to expose learners to new learning material can vary from simple textbook readings to lecture videos or podcasts. Pre-class assignments can be varied based on differing backgrounds and training levels of the learners. If video-based educational materials are used, they can be paused and replayed, allowing learners to move through the material at their own pace. Using varied formats to present educational content can also support differences in individual learning styles and preferences.

There is no single approach to flipping the classroom in practice. The means of delivering educational content and the ways in which face-to-face activities are used can vary with the subject matter, characteristics of the learners, preferences of the instructor, and available resources. It is essential however that in- and out- of class activities are carefully integrated to optimize the beneficial effects and encourage trainees to be prepared for the in-class activities. Well written objectives that inform the trainees what they are going to learn and how they are going to be assessed should be clearly linked to each individualized learning task.

Some practical tips for flipping the classroom include[39]: (1) learners must be provided resources to acquire factual knowledge prior to the classroom phase. Providing short educational videos, many of which are readily available *via* Open Educational Resources are effective, provided they are matched to the desired learning objectives[40]. The use of other, non-digital material is, however, equally possible; (2) implemented technology should ideally be easily-accessible and ideally already be familiar to the learners; (3) activities both

in the pre-class and classroom phases must be well-structured. Trainees will accept demands for learning more easily when content and time requirements are firmly defined; (4) incentive systems should be implemented to encourage trainees to complete the pre-class activities before the classroom phase. For example, short multiple choice quizzes could be given with correct answers; (5) methods of assessment should be implemented to provide feedback to the trainees on their knowledge acquisition and learning performance achieved through the pre-class and classroom activities; and (6) feedback from trainees is essential to the success of the flipped classroom. Trainees should be encouraged to provide this feedback regularly throughout the learning process including the pre-class activities.

While there is limited literature to date exploring the flipped classroom model in the context of critical care education, evidence of its efficacy from other areas of undergraduate and graduate medical education do appear promising[38,39,41].

Improving procedural training

Critical care trainees must gain procedural competence in a number of technical domains, including vascular access, airway management, bronchoscopy, chest tube placement, and critical care ultrasonography. A fundamental challenge in procedural training is to find the optimal balance between providing educational opportunities for trainees and ensuring safe, efficient patient care. While it can be argued that it is inappropriate to allow an inexperienced trainee to perform a procedure in a high-risk situation, such as in the care of a critically ill patient, it can also be argued that unless trainees are allowed such practice, there will be fewer and fewer clinicians competent to perform life-saving procedures. Since the introduction of the duty-hour limits, concern has arisen that trainees may not be getting as much experience in procedural skills as they once did[42,43]. Given the rapidly changing landscape of critical care practice, with an ever increasing number of diagnostic and therapeutic tools to master, it is necessary that trainees receive high-quality procedural teaching. Although a variety of frameworks for procedural teaching exist in the literature, many training programs continue to rely on an apprenticeship model. The trainers themselves may have varying amounts of expertise with a given procedure which further complicates training. To address these challenges, the literature supports a standardized approach to procedural education with performance assessed and mastery demonstrated away from the clinical setting[44-46]. Multifaceted learning strategies that incorporate computer-based learning, task trainers, and simulation to provide the necessary conceptual and technical understanding of the fundamentals of procedures, followed by observing and then performing procedures on healthy patients in the operating room or other elective situations, have been recommended to facilitate procedural learning before the trainee attempts high risk procedures on critically ill patients[47,48]. Computer-based instruction can provide essential information about a procedure, including its indications, required equipment, and procedural steps. Computer-based learning has been shown to be an effective alternative for providing fundamentals of central line placement, basic ultrasound training and acquisition of knowledge required for difficult airway management[49-52]. After learners receive fundamental information on a procedure, task trainers and simulation can be employed to teach technical skills. Hands-on approaches offer learners physical training in performing procedures and opportunities to rehearse these skills in context without the risk of patient harm. A number of studies have demonstrated that deliberate practice with the use of simulation can improve skills in the clinical environment[53-55]. Use of procedural checklists can be helpful during the technical training to evaluate each step in procedural performance and to appropriately modify behaviors[54]. Adjunct technology can also be utilized to facilitate procedural learning and performance. For example ultrasound use can improve understanding of relevant anatomy and is supported by data demonstrating superiority in overall success and complication reduction for CVL placement, arterial catheter insertion, thoracentesis, and paracentesis[48]. Use of video laryngoscopy, which provides shared views of the airway, improves trainer and trainee collaboration, resulting in more rapid learning curves and increased intubation success rates[55,56].

Even with prior simulation experience, it may be unrealistic to expect trainees to move directly into a dynamic environment such as the ICU and perform procedural skills, especially during crisis situations. Controlled patient encounters that involve performing procedures under elective conditions with supervision by experienced clinicians may help to translate skills that were learned in simulation exercises into the clinical environment in a safe manner. Just-in-time training (JITT) has also been proposed as a training approach to translate learning from the controlled simulation environment into the actual patient setting. With JITT, trainees practice procedural skills and refresh muscle memory immediately prior to performing the procedure on a patient. The JITT concept is based on literature showing that both knowledge and technical skills decay over time and therefore the clinician benefits from training "just-in-time", moments before the procedure[57]. It has also been described in reducing undesirable outcomes in acute procedures, including CPR skills, endotracheal tube placement, central venous catheter insertion and lumbar puncture[58-60]. In addition JITT has been shown to reduce the time to successful completion of procedures, and may even play a role in long-term retention of procedural skills[61].

To facilitate JITT all that is needed is a low-fidelity task trainer that is specific to the chosen procedure. Ideally, this task trainer should be a portable model that can be stored and easily accessed in the critical care practice environment. If possible, authentic equipment should be set aside and dedicated for JITT. Prior to beginning the procedure on a patient, the preceptor instructs the learner to perform the procedure on a task trainer as if it were a real patient using a checklist of critical actions.

For example, in the case of utilizing JITT for endotracheal intubation, skills that can be practiced include: Proper positioning of the patient; effective bag-valve-mask ventilation techniques; correctly maneuvering a laryngoscope; visualizing the vocal cords; inserting the endotracheal tube through the glottic opening; correctly using airway adjuncts, if needed, as rescue airway devices (*e.g.,* laryngeal mask airway or bougie).

The preceptor monitors the learner's performance with each skill and provides continuous formative feedback. The learner is encouraged to ask questions throughout the process and the preceptor is provided the opportunity to correct mistakes in real-time and optimize performance which will be immediately transferrable to the actual procedure moments later. When the preceptor is satisfied with the trainee's demonstrated procedural skills, they can proceed to performing the procedure on the patient. Using this approach, trainee confidence and procedural readiness should improve thereby increasing patient safety.

Facilitating education during handover

Effective handovers allow a team of multiple providers to deliver safe and high quality care by ensuring continuity. Despite its crucial role in ensuring safe and effective patient care, a number of studies have characterized the process as haphazard and error prone and have linked substandard handovers to adverse events[62]. Critically ill patients are particularly vulnerable to ineffective handovers given their complex clinical history and severity of their condition[63]. Patient handover has been identified as a priority to ensure patient safety and the ACGME requires that all training programs monitor handovers[64]. A growing number of studies have proposed educational interventions to improve handovers; however studies that demonstrate improvement in actual patient outcomes based on these interventions are still limited[65]. A recent systematic review found that there were four primary methods for teaching handovers: (1) providing online materials such as videos, texts, and protocols; (2) lectures and group sessions; (3) simulation activities; and (4) role-playing exercises[66]. Common content themes of these educational handover interventions include: (1) information management; (2) team-work, leadership; and communication; and (3) error awareness and professional behavior[66].

In addition to facilitating continuity of care, handovers can also provide an active learning opportunity[67,68]. Handovers, by nature, are associated with clinical uncertainty, making it important for participants to reduce uncertainty through active dialogue[67]. This active dialogue promotes learning through discussions of approaches to diagnosis and management of specific conditions and may also occur through feedback on clinical actions taken in the preceding shift. For example, if a trainee admits a patient and makes a preliminary diagnosis that was confirmed after their shift, he or she should be provided this feedback, thus affirming his or her diagnostic approach. This post-shift feedback can encourage trainees to reflect on the results of their clinical actions even when they are not present to see them unfold. This feedback approach is especially important given current duty hour restrictions.

In addition to relying on the clinical exchange of information and discussions regarding patient care as a way to promote learning, there are more deliberate methods which can be employed to ensure that learning takes place during handovers. The most obvious of these is direct supervision of the handover process by experienced clinicians (faculty, fellows, *etc.*) who can provide guidance to trainees. It is important to recognize that while experienced clinicians can supervise the handover, faculty may have limited experience with new handover processes and faculty development may be required before implementation. Supervision of handovers serves as a way to ensure not only that critical patient information is being communicated, but also as a means to answer the clinical questions that arise during the course of the shift, thereby ensuring that all learners have access to clinical teaching. In addition to direct supervision, another approach to enhance the learning process during handovers is to supplement it with short educational modules tailored to a current case or a set of cases that are commonly encountered. With this approach, the handover is linked to practice-based learning and improvement (an ACGME core competency), allowing learners to integrate new knowledge into their clinical practice.

One way for clinicians to optimize the supervision of handovers and associated teaching is to stratify them according to case complexity[69]. Severity of illness, worsening disease trajectory, or incompleteness of the medical history or diagnostic workup, for example, are factors that increase the importance of an effective handover for ensuring care of a vulnerable patient. In contrast, the handover of a stable or otherwise well-characterized patient, even if the handover is performed poorly, is less likely to lead to an adverse event. Factors that increase the risk of an ineffective handover include the degree of familiarity of the clinicians with the patient, the type of handover, and the level of experience of the clinicians involved[69]. At a minimum the handovers for complex, critically ill patients should be supervised until trainees have demonstrated the ability to perform them effectively and consistently. Even after competency has been demonstrated there also may be benefits to continuing some level of handover supervision. From the standpoint of improving patient safety, a skilled observer can reduce handover errors by providing real-time feedback to the participants, thereby contributing to enhanced accuracy and encouraging experiential learning[69].

Handovers can also be used to evaluate trainee performance and provide formative feedback, as it provides an opportunity to directly observe behaviors related to communication as well as competencies such as professionalism. Evaluations can occur during the handover or as a summary at the end of a rotation. While real-time evaluations have the benefit of providing

immediate feedback, summary evaluations at the end of a rotation have the advantage of enabling trainees to assess improvements in handover performance over time and after repeated interactions. Ideally, handover evaluation should be competency-based and linked to specific, observable behaviors. The quality of the handover content can be assessed using questions such as, "was anticipatory guidance provided and easy to interpret?" or "did 'to-do' items include a rationale?" Evaluating the receivers of handover content may be more difficult, but observable behaviors could include actions indicating active engagement such as asking questions, taking notes and maintaining eye contact[70]. In addition to monitoring the quality of verbal exchange between senders and receivers of the handover, written documentation to facilitate the handover can be assessed for accuracy and readability. Often, a structured template is used to facilitate the transfer of verbal information during handovers. However, documents that are used to support handovers, whether on paper or generated electronically often contain errors, which most often result from a failure to keep these documents up-to-date. Therefore, examining the accuracy of the information in the document, and making certain that key elements such as medications, allergies and code status are updated, will help to ensure the accuracy of information transmission during handover.

Handovers consist of a series of complex communication tasks and it is critical that trainees acquire the specific skills required to both give and receive them. These skills include developing strategies for information management, managing handover dialogue through active listening, asking questions, and collaborating to generate a shared understanding for optimal exchange of information necessary to guide patient care. The skills required for effective handover communication will improve with greater supervision and feedback from experienced clinicians.

In-situ team based training

The management of critically ill patients requires multidisciplinary teams to work collaboratively. Core elements of team performance (*e.g.,* leadership, adaptability, mutual trust, closed-loop communication) impact the quality and safety of patient care[71-73]. Despite the importance of team performance on patient outcomes, providing training specifically designed to improve team dynamics is a relatively new concept for many medical specialties including critical care. Evidence suggests that to improve multidisciplinary team performance it is necessary to train as a multidisciplinary team[73]. *In situ* simulation training has been recognized as a technique to improve multidisciplinary team performance[74,75]. Training within the actual critical care environment allows teams to test their effectiveness in a controlled manner and to interrogate departmental and hospital processes in real time and in real locations[74]. In addition, *in situ* simulation has the advantage that it can be incorporated into the activities of daily practice which is less disruptive to staffing.

Team composition during *in situ* simulation training should reflect normal working practice including different professions and levels of training. Team members should train in their normal roles and at their own skill level and scope of practice-clinicians should not be expected to perform a skill outside of their scope of practice. While it is possible to teach technical skills using multidisciplinary *in situ* simulation, it is arguably better suited to teaching nontechnical skills[74,75]. Although it is possible to spend a large amount of money on high fidelity simulation equipment, it is not essential. A basic platform which is adequate for most critical care simulations only requires a vital sign monitor with adjustable parameters, a clinical bed space, and some clinical consumables. There is little evidence that enhanced fidelity creates a better learning environment[76]. In fact, enhanced fidelity may actually detract from the learning environment depending on the learning objectives. In many cases, real people playing the role of a patient (so called "standardized patient actors") are just as effective and are more realistic especially for scenarios focusing on communication and teamwork. Audiovisual equipment can also be useful for recording the simulation to enhance discussion during debriefing. However, this is not essential. It is feasible to use a phone camera or tablet as a low-cost solution. If video or audio recording is performed, participants must provide consent prior to the session and storage and usage of the electronic media must be controlled.

When initiating an *in situ* simulation program it is generally best to start with simple scenarios aimed at participants' readiness level which will invoke challenge rather than frustration or embarrassment. More complicated or complex scenarios can then be introduced once the program has been established. Regular repetition of commonly occurring scenarios such as cardiac arrest, emergency intubation, and sepsis management can be used to reinforce learning and teamwork by applying a "practice until perfect" approach. Complexity may also be added to simple scenarios through the use of embedded participants who play a role that is intended to add cognitive noise or conflict to the scenario.

It is important to spend time preparing the simulation participants prior to the scenario[77]. This "prebriefing" is a time when the facilitator describes the purpose of the simulation, the learning objectives, the process of debriefing, and clarifies expectations. This prebriefing should also include a confidentiality agreement and an explanation of the rules of simulation engagement, including a description of the simulated "patient", the limitations of the simulation and how they will be overcome, what equipment is available, how drugs and fluids can be "administered," and safety rules (*e.g.,* the use of a live defibrillator). Adopting a "stop word", which will immediately terminate the simulation, is also important to ensure participant safety. It is also essential that an environment of trust is created early on, typically during the prebriefing. If participants feel safe and understand how they are expected to participate as a team prior to

the session, they will have the maximum opportunity for learning within the time available.

Debriefing is an essential, and arguably the most important, element of simulation because it encourages self-reflection which promotes a deeper level of understanding and thereby increases the likelihood of successful transfer of acquired knowledge and skills to the clinical setting[78]. Debriefing should take place immediately after the simulation especially in the critical care environment where participants must return to clinical responsibilities. When allocating time for an *in situ* simulation session, it is important to allocate sufficient time for debriefing. As a simple guideline, the debriefing session should be allocated at least the same amount of time as the duration of the simulation scenario itself[75]. Standardized debriefing formats have been suggested to ensure that key components are covered within the limited time frame[79]. The debriefing session should be designed to achieve the learning objectives and tailored to the specific participant and team characteristics. Learning objectives are often specified beforehand, but may also evolve within the simulation. With pre-specified objectives, such as improving particular team behaviors, the debriefing session affords the opportunity to examine how closely participants' performance approached the goal target, and furthermore, what additional learning is required to bridge the gaps between performance and the target. With evolving objectives, participants may be asked to reflect on the observed evolution of the scenario and to evaluate how the behaviors, attitudes, and choices demonstrated in the simulation relate to real life situations[79,80].

An individual should be designated to facilitate the debriefing process. The facilitator should not "script" the debriefing process but rather should provide sufficient discussion prompts and tools to ensure that participants actively engage in critical analysis, shared reflection and application of the experience to clinical practice. The facilitator is also responsible for ensuring that time and pace is managed effectively. When facilitating a debriefing some simple approaches can be very effective: Start by asking open ended questions such as "how did it go?". As participants respond, rephrase their responses back to them as skills that are part of the learning objectives. Next ask, "what could you do better?". When asked this question, the participants will invariably bring up many management areas that you were going to mention. Finally inquire, "what will you do differently next time?". This will help the trainees focus on making meaningful but simple changes for the next time a similar situation is encountered. The facilitator should close the debriefing by prompting the participants for questions or addressing any specific issues that were not discussed with open ended questions. Debriefing is a time when participants may feel most vulnerable to criticism in front of their peers. This vulnerability may be particularly pronounced with *in situ* simulation since participants work closely with each other. For this reason, creating a friendly and supportive atmosphere is imperative. In summary, *in situ* simulation has the potential to improve patient safety by strengthening skills in teamwork and communication that are essential for well-functioning critical care teams.

CONCLUSION

Technological advances and evolving demands in medical care have led to challenges in ensuring adequate training for providers of critical care. Evidence suggests that reliance on the traditional experience-based model alone is insufficient for ensuring quality and safety in patient care. Evidence-based approaches for improving the efficiency and efficacy of critical care education, have been developed and should be integrated into training programs. While a variety of such approaches are described in this paper they share common characteristics. These include utilizing methods to rapidly identify learner needs, teaching directly to those needs, and providing specific feedback on performance. In addition these approaches emphasize active learning activities and integrate educational experiences from the classroom and clinical settings. Finally such approaches share the advantage that can be incorporated into the daily practice of critical care without substantial cost, workflow disruption or compromise in the quality of patient care. Moving forward, it is imperative that critical care educators keep abreast of emerging educational technologies including personalized learning, mobile technologies and learning analytics[80]. While there is sparse literature describing the benefits and limitations, such technology has the potential to enhance learning and clinical competence within the critical care setting.

REFERENCES

1 **Sabri N**, Sun NZ, Cummings BA, Jayaraman D. The Perceived Effect of Duty Hour Restrictions on Learning Opportunities in the Intensive Care Unit. *J Grad Med Educ* 2015; **7**: 48-52 [PMID: 26217422 DOI: 10.4300/JGME-D-14-00180.1]

2 **Tainter CR**, Wong NL, Bittner EA. Innovative strategies in critical care education. *J Crit Care* 2015; **30**: 550-556 [PMID: 25702843 DOI: 10.1016/j.jcrc.2015.02.001]

3 **Croley WC**, Rothenberg DM. Education of trainees in the intensive care unit. *Crit Care Med* 2007; **35**: S117-S121 [PMID: 17242600 DOI: 10.1097/01.CCM.0000252917.25301.18]

4 **Almoosa KF**, Goldenhar LM, Puchalski J, Ying J, Panos RJ. Critical care education during internal medicine residency: a national survey. *J Grad Med Educ* 2010; **2**: 555-561 [PMID: 22132277 DOI: 10.4300/JGME-D-10-00023.1]

5 **Barrett H**, Bion JF. An international survey of training in adult intensive care medicine. *Intensive Care Med* 2005; **31**: 553-561 [PMID: 15750798 DOI: 10.1007/s00134-005-2583-7]

6 **Peters M**, Ten Cate O. Bedside teaching in medical education: a literature review. *Perspect Med Educ* 2014; **3**: 76-88 [PMID: 24049043 DOI: 10.1007/s40037-013-0083-y]

7 **Kim MM**, Barnato AE, Angus DC, Fleisher LA, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med* 2010; **170**: 369-376 [PMID: 20177041 DOI: 10.1001/archinternmed.2009.521]

8 **Lane D**, Ferri M, Lemaire J, McLaughlin K, Stelfox HT. A systematic review of evidence-informed practices for patient care rounds in the ICU*. *Crit Care Med* 2013; **41**: 2015-2029 [PMID: 23666096 DOI: 10.1097/CCM.0b013e31828a435f]

9 **Cox CE**, Carson SS, Ely EW, Govert JA, Garrett JM, Brower RG, Morris DG, Abraham E, Donnabella V, Spevetz A, Hall

JB. Effectiveness of medical resident education in mechanical ventilation. *Am J Respir Crit Care Med* 2003; **167**: 32-38 [PMID: 12406827 DOI: 10.1164/rccm.200206-624OC]
10 **Wilcox SR**, Seigel TA, Strout TD, Schneider JI, Mitchell PM, Marcolini EG, Cocchi MN, Smithline HA, Lutfy-Clayton L, Mullen M, Ilgen JS, Richards JB. Emergency medicine residents' knowledge of mechanical ventilation. *J Emerg Med* 2015; **48**: 481-491 [PMID: 25497896 DOI: 10.1016/j.jemermed.2014.09.059]
11 **Mueller UW**, Potter JM. Polymerization of human transcortin in plasma. *J Steroid Biochem* 1984; **20**: 1261-1266 [PMID: 6431194 DOI: 10.1016/j.amjmed.2005.08.007]
12 **Boots RJ**, Egerton W, McKeering H, Winter H. They just don't get enough! Variable intern experience in bedside procedural skills. *Intern Med J* 2009; **39**: 222-227 [PMID: 19402860 DOI: 10.1111/j.1445-5994.2009.01699.x]
13 **Marshall JC**, Kwong W, Kommaraju K, Burns KE. Determinants of Citation Impact in Large Clinical Trials in Critical Care: The Role of Investigator-Led Clinical Trials Groups. *Crit Care Med* 2016; **44**: 663-670 [PMID: 26571189 DOI: 10.1186/cc11126]
14 **Cleland JA**, Ross S, Miller SC, Patey R. "There is a chain of Chinese whispers": empirical data support the call to formally teach handover to prequalification doctors. *Qual Saf Health Care* 2009; **18**: 267-271 [PMID: 19651929 DOI: 10.1136/qshc.2008.029983]
15 **Sawatsky AP**, Mikhael JR, Punatar AD, Nassar AA, Agrwal N. The effects of deliberate practice and feedback to teach standardized handoff communication on the knowledge, attitudes, and practices of first-year residents. *Teach Learn Med* 2013; **25**: 279-284 [PMID: 24112195 DOI: 10.1080/10401334.2013.827970]
16 **McCallister JW**, Gustin JL, Wells-Di Gregorio S, Way DP, Mastronarde JG. Communication skills training curriculum for pulmonary and critical care fellows. *Ann Am Thorac Soc* 2015; **12**: 520-525 [PMID: 25734699 DOI: 10.1513/AnnalsATS.201501-039OC]
17 **Hope AA**, Hsieh SJ, Howes JM, Keene AB, Fausto JA, Pinto PA, Gong MN. Let's Talk Critical. Development and Evaluation of a Communication Skills Training Program for Critical Care Fellows. *Ann Am Thorac Soc* 2015; **12**: 505-511 [PMID: 25741996 DOI: 10.1513/AnnalsATS.201501-040OC]
18 **Hayes CW**, Rhee A, Detsky ME, Leblanc VR, Wax RS. Residents feel unprepared and unsupervised as leaders of cardiac arrest teams in teaching hospitals: a survey of internal medicine residents. *Crit Care Med* 2007; **35**: 1668-1672 [PMID: 17507825 DOI: 10.1097/01.CCM.0000268059.42429.39]
19 **Chudgar SM**, Cox CE, Que LG, Andolsek K, Knudsen NW, Clay AS. Current teaching and evaluation methods in critical care medicine: has the Accreditation Council for Graduate Medical Education affected how we practice and teach in the intensive care unit? *Crit Care Med* 2009; **37**: 49-60 [PMID: 19050627 DOI: 10.1097/CCM.0b013e31819265c8]
20 **Colletti JE**, Flottemesch TJ, O'Connell T, Ankel FK, Asplin BR. Teaching and clinical efficiency: competing demands. *West J Emerg Med* 2012; **13**: 186-193 [PMID: 22900111 DOI: 10.5811/westjem.2011.10.6842]
21 **Irby DM**, Wilkerson L. Teaching when time is limited. *BMJ* 2008; **336**: 384-387 [PMID: 18276715 DOI: 10.1136/bmj.39456.727199.AD]
22 **Neher JO**, Gordon KC, Meyer B, Stevens N. A five-step "micro-skills" model of clinical teaching. *J Am Board Fam Pract* 1992; **5**: 419-424 [PMID: 1496899]
23 **Aagaard E**, Teherani A, Irby DM. Effectiveness of the one-minute preceptor model for diagnosing the patient and the learner: proof of concept. *Acad Med* 2004; **79**: 42-49 [PMID: 14690996]
24 **Farrell SE**, Hopson LR, Wolff M, Hemphill RR, Santen SA. What's the Evidence: A Review of the One-Minute Preceptor Model of Clinical Teaching and Implications for Teaching in the Emergency Department. *J Emerg Med* 2016; **51**: 278-283 [PMID: 27377967 DOI: 10.1016/j.jemermed.2016.05.007]
25 **Wilkerson L**, Sarkin RT. Arrows in the Quiver: evaluation of a workshop on ambulatory teaching. *Acad Med* 1998; **73**: S67-S69 [PMID: 9795655]
26 **McGee S**. A piece of my mind. Bedside teaching rounds reconsidered. *JAMA* 2014; **311**: 1971-1972 [PMID: 24846031 DOI: 10.1001/jama.2013.286201]
27 **Gonzalo JD**, Heist BS, Duffy BL, Dyrbye L, Fagan MJ, Ferenchick G, Harrell H, Hemmer PA, Kernan WN, Kogan JR, Rafferty C, Wong R, Elnicki DM. The art of bedside rounds: a multi-center qualitative study of strategies used by experienced bedside teachers. *J Gen Intern Med* 2013; **28**: 412-420 [PMID: 23129164 DOI: 10.1007/s11606-012-2259-2]
28 **Bhave M**, Brzezinski M. Teaching in the ICU: A Comprehensive Review. *ICU Director* 2013; **4**: 270-278 [DOI: 10.1177/1944451613510317]
29 **Rudolph JW**, Simon R, Raemer DB, Eppich WJ. Debriefing as formative assessment: closing performance gaps in medical education. *Acad Emerg Med* 2008; **15**: 1010-1016 [PMID: 18945231 DOI: 10.1111/j.1553-2712.2008.00248.x]
30 **Green GM**, Chen EH. Top 10 ideas to improve your bedside teaching in a busy emergency department. *Emerg Med J* 2015; **32**: 76-77 [PMID: 25239953 DOI: 10.1136/emermed-2014-204211]
31 **Watling CJ**, Lingard L. Toward meaningful evaluation of medical trainees: the influence of participants' perceptions of the process. *Adv Health Sci Educ Theory Pract* 2012; **17**: 183-194 [PMID: 20143260 DOI: 10.1007/s10459-010-9223-x]
32 **Gonzalo JD**, Heist BS, Duffy BL, Dyrbye L, Fagan MJ, Ferenchick G, Harrell H, Hemmer PA, Kernan WN, Kogan JR, Rafferty C, Wong R, Elnicki MD. Content and timing of feedback and reflection: a multi-center qualitative study of experienced bedside teachers. *BMC Med Educ* 2014; **14**: 212 [PMID: 25304386 DOI: 10.1186/1472-6920-14-212]
33 **Bion JF**, Barrett H. Development of core competencies for an international training programme in intensive care medicine. *Intensive Care Med* 2006; **32**: 1371-1383 [PMID: 16841214 DOI: 10.1007/s00134-006-0215-5]
34 **Buckley JD**, Addrizzo-Harris DJ, Clay AS, Curtis JR, Kotloff RM, Lorin SM, Murin S, Sessler CN, Rogers PL, Rosen MJ, Spevetz A, King TE, Malhotra A, Parsons PE. Multisociety task force recommendations of competencies in Pulmonary and Critical Care Medicine. *Am J Respir Crit Care Med* 2009; **180**: 290-295 [PMID: 19661252 DOI: 10.1164/rccm.200904-0521ST]
35 **Fessler HE**, Addrizzo-Harris D, Beck JM, Buckley JD, Pastores SM, Piquette CA, Rowley JA, Spevetz A. Entrustable professional activities and curricular milestones for fellowship training in pulmonary and critical care medicine: executive summary from the Multi-Society Working Group. *Crit Care Med* 2014; **42**: 2290-2291 [PMID: 25226119 DOI: 10.1097/CCM.0000000000000615]
36 **Hartley J**, Cameron A. Some Observations on the Efficiency of Lecturing. *Educ Rev* 1967; **20**: 30-37 [DOI: 10.1080/00131916702000103]
37 **Prober CG**, Khan S. Medical education reimagined: a call to action. *Acad Med* 2013; **88**: 1407-1410 [PMID: 23969367 DOI: 10.1097/ACM.0b013e3182a368bd]
38 **Tainter CR**, Wong NL, Cudemus-Deseda GA, Bittner EA. The "Flipped Classroom" Model for Teaching in the Intensive Care Unit: Rationale, Practical Considerations, and an Example of Successful Implementation. *J Intensive Care Med* 2016; Epub ahead of print [PMID: 26912409 DOI: 10.1177/0885066616632156]
39 **Tolks D**, Schäfer C, Raupach T, Kruse L, Sarikas A, Gerhardt-Szép S, Kllauer G, Lemos M, Fischer MR, Eichner B, Sostmann K, Hege I. An Introduction to the Inverted/Flipped Classroom Model in Education and Advanced Training in Medicine and in the Healthcare Professions. *GMS J Med Educ* 2016; **33**: Doc46 [PMID: 27275511 DOI: 10.3205/zma001045]
40 **Kleinpell R**, Ely EW, Williams G, Liolios A, Ward N, Tisherman SA. Web-based resources for critical care education. *Crit Care Med* 2011; **39**: 541-553 [PMID: 21169819 DOI: 10.1097/CCM.0b013e318206b5b5]
41 **Young TP**, Bailey CJ, Guptill M, Thorp AW, Thomas TL. The flipped classroom: a modality for mixed asynchronous and synchronous learning in a residency program. *West J Emerg Med* 2014; **15**: 938-944 [PMID: 25493157 DOI: 10.5811/westjem.

2014.10.23515]
42 **Dehmer JJ**, Amos KD, Farrell TM, Meyer AA, Newton WP, Meyers MO. Competence and confidence with basic procedural skills: the experience and opinions of fourth-year medical students at a single institution. *Acad Med* 2013; **88**: 682-687 [PMID: 23524922 DOI: 10.1097/ACM.0b013e31828b0007]
43 **Promes SB**, Chudgar SM, Grochowski CO, Shayne P, Isenhour J, Glickman SW, Cairns CB. Gaps in procedural experience and competency in medical school graduates. *Acad Emerg Med* 2009; **16** Suppl 2: S58-S62 [PMID: 20053213 DOI: 10.1111/j.1553-2712.2009.00600.x]
44 **Grantcharov TP**, Reznick RK. Teaching procedural skills. *BMJ* 2008; **336**: 1129-1131 [PMID: 18483056 DOI: 10.1136/bmj.39517.686956.47]
45 **Nestel D**, Groom J, Eikeland-Husebø S, O'Donnell JM. Simulation for learning and teaching procedural skills: the state of the science. *Simul Healthc* 2011; **6** Suppl: S10-S13 [PMID: 21817857 DOI: 10.1097/SIH.0b013e318227ce96]
46 **Huang GC**, McSparron JI, Balk EM, Richards JB, Smith CC, Whelan JS, Newman LR, Smetana GW. Procedural instruction in invasive bedside procedures: a systematic review and meta-analysis of effective teaching approaches. *BMJ Qual Saf* 2016; **25**: 281-294 [PMID: 26543067 DOI: 10.1136/bmjqs-2014-003518]
47 **Lammers RL**, Davenport M, Korley F, Griswold-Theodorson S, Fitch MT, Narang AT, Evans LV, Gross A, Rodriguez E, Dodge KL, Hamann CJ, Robey WC. Teaching and assessing procedural skills using simulation: metrics and methodology. *Acad Emerg Med* 2008; **15**: 1079-1087 [PMID: 18828833 DOI: 10.1111/j.1553-2712.2008.00233.x]
48 **McSparron JI**, Michaud GC, Gordan PL, Channick CL, Wahidi MM, Yarmus LB, Feller-Kopman DJ, Makani SS, Koenig SJ, Mayo PH, Kovitz KL, Thomson CC. Simulation for Skills-based Education in Pulmonary and Critical Care Medicine. *Ann Am Thorac Soc* 2015; **12**: 579-586 [PMID: 25700209 DOI: 10.1513/AnnalsATS.201410-461AR]
49 **Chenkin J**, Lee S, Huynh T, Bandiera G. Procedures can be learned on the Web: a randomized study of ultrasound-guided vascular access training. *Acad Emerg Med* 2008; **15**: 949-954 [PMID: 18778380 DOI: 10.1111/j.1553-2712.2008.00231.x]
50 **Xiao Y**, Seagull FJ, Bochicchio GV, Guzzo JL, Dutton RP, Sisley A, Joshi M, Standiford HC, Hebden JN, Mackenzie CF, Scalea TM. Video-based training increases sterile-technique compliance during central venous catheter insertion. *Crit Care Med* 2007; **35**: 1302-1306 [PMID: 17414726 DOI: 10.1097/01.CCM.0000263457.81998.27]
51 **Platz E**, Liteplo A, Hurwitz S, Hwang J. Are live instructors replaceable? Computer vs. classroom lectures for EFAST training. *J Emerg Med* 2011; **40**: 534-538 [PMID: 19892506 DOI: 10.1016/j.jemermed.2009.08.030]
52 **Bello G**, Pennisi MA, Maviglia R, Maggiore SM, Bocci MG, Montini L, Antonelli M. Online vs live methods for teaching difficult airway management to anesthesiology residents. *Intensive Care Med* 2005; **31**: 547-552 [PMID: 15754200 DOI: 10.1007/s00134-005-2561-0]
53 **Barsuk JH**, McGaghie WC, Cohen ER, O'Leary KJ, Wayne DB. Simulation-based mastery learning reduces complications during central venous catheter insertion in a medical intensive care unit. *Crit Care Med* 2009; **37**: 2697-2701 [PMID: 19885989]
54 **Huang GC**, Newman LR, Schwartzstein RM, Clardy PF, Feller-Kopman D, Irish JT, Smith CC. Procedural competence in internal medicine residents: validity of a central venous catheter insertion assessment instrument. *Acad Med* 2009; **84**: 1127-1134 [PMID: 19638784 DOI: 10.1097/ACM.0b013e3181acf491]
55 **De Jong A**, Molinari N, Conseil M, Coisel Y, Pouzeratte Y, Belafia F, Jung B, Chanques G, Jaber S. Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. *Intensive Care Med* 2014; **40**: 629-639 [PMID: 24556912 DOI: 10.1007/s00134-014-3236-5]
56 **Kory P**, Guevarra K, Mathew JP, Hegde A, Mayo PH. The impact of video laryngoscopy use during urgent endotracheal intubation in the critically ill. *Anesth Analg* 2013; **117**: 144-149 [PMID: 23687228 DOI: 10.1213/ANE.0b013e3182917f2a]
57 **Weaver SJ**, Newman-Toker DE, Rosen MA. Reducing cognitive skill decay and diagnostic error: theory-based practices for continuing education in health care. *J Contin Educ Health Prof* 2012; **32**: 269-278 [PMID: 23280530 DOI: 10.1002/chp.21155]
58 **Cheng A**, Brown LL, Duff JP, Davidson J, Overly F, Tofil NM, Peterson DT, White ML, Bhanji F, Bank I, Gottesman R, Adler M, Zhong J, Grant V, Grant DJ, Sudikoff SN, Marohn K, Charnovich A, Hunt EA, Kessler DO, Wong H, Robertson N, Lin Y, Doan Q, Duval-Arnould JM, Nadkarni VM. Improving cardiopulmonary resuscitation with a CPR feedback device and refresher simulations (CPR CARES Study): a randomized clinical trial. *JAMA Pediatr* 2015; **169**: 137-144 [PMID: 25531167 DOI: 10.1001/jamapediatrics.2014.2616]
59 **Nishisaki A**, Donoghue AJ, Colborn S, Watson C, Meyer A, Brown CA, Helfaer MA, Walls RM, Nadkarni VM. Effect of just-in-time simulation training on tracheal intubation procedure safety in the pediatric intensive care unit. *Anesthesiology* 2010; **113**: 214-223 [PMID: 20526179 DOI: 10.1097/ALN.0b013e3181e19bf2]
60 **Kessler D**, Pusic M, Chang TP, Fein DM, Grossman D, Mehta R, White M, Jang J, Whitfill T, Auerbach M. Impact of Just-in-Time and Just-in-Place Simulation on Intern Success With Infant Lumbar Puncture. *Pediatrics* 2015; **135**: e1237-e1246 [PMID: 25869377 DOI: 10.1542/peds.2014-1911]
61 **Braga MS**, Tyler MD, Rhoads JM, Cacchio MP, Auerbach M, Nishisaki A, Larson RJ. Effect of just-in-time simulation training on provider performance and patient outcomes for clinical procedures: a systematic review. *BMJ Simulation and Technology Enhanced Learning* 2015; **1**: 94-100 [DOI: 10.1136/bmjstel-2015-000058]
62 **Lane-Fall MB**, Collard ML, Turnbull AE, Halpern SD, Shea JA. ICU Attending Handoff Practices: Results From a National Survey of Academic Intensivists. *Crit Care Med* 2016; **44**: 690-698 [PMID: 26588827 DOI: 10.1097/CCM.0000000000001470]
63 **Colvin MO**, Eisen LA, Gong MN. Improving the Patient Handoff Process in the Intensive Care Unit: Keys to Reducing Errors and Improving Outcomes. *Semin Respir Crit Care Med* 2016; **37**: 96-106 [PMID: 26820277]
64 Accreditation Council for Graduate Medical Education. Common Program Requirements. [updated 2011 Dec 6]. Available from: URL: http://www.acgme.org/Portals/0/PFAssets/ProgramRequirements/CPRs_07012016.pdf
65 **Cohen MD**, Hilligoss PB. The published literature on handoffs in hospitals: deficiencies identified in an extensive review. *Qual Saf Health Care* 2010; **19**: 493-497 [PMID: 20378628 DOI: 10.1136/qshc.2009.033480]
66 **Gordon M**, Findley R. Educational interventions to improve handover in health care: a systematic review. *Med Educ* 2011; **45**: 1081-1089 [PMID: 21933243 DOI: 10.1111/j.1365-2923.2011.04049.x]
67 **Arora VM**, Reed DA, Fletcher KE. Building continuity in handovers with shorter residency duty hours. *BMC Med Educ* 2014; **14** Suppl 1: S16 [PMID: 25560954 DOI: 10.1186/1472-6920-14-S1-S16]
68 **Sanfey H**, Stiles B, Hedrick T, Sawyer RG. Morning report: combining education with patient handover. *Surgeon* 2008; **6**: 94-100 [PMID: 18488775]
69 **Wohlauer MV**, Arora VM, Horwitz LI, Bass EJ, Mahar SE, Philibert I. The patient handoff: a comprehensive curricular blueprint for resident education to improve continuity of care. *Acad Med* 2012; **87**: 411-418 [PMID: 22361791 DOI: 10.1097/ACM.0b013e318248e766]
70 **Bhabra G**, Mackeith S, Monteiro P, Pothier DD. An experimental comparison of handover methods. *Ann R Coll Surg Engl* 2007; **89**: 298-300 [PMID: 17394718 DOI: 10.1308/003588407X168352]
71 **Reader TW**, Flin R, Mearns K, Cuthbertson BH. Developing a team performance framework for the intensive care unit. *Crit Care Med* 2009; **37**: 1787-1793 [PMID: 19325474 DOI: 10.1097/CCM.0b013e31819f0451]
72 **Manser T**. Teamwork and patient safety in dynamic domains of healthcare: a review of the literature. *Acta Anaesthesiol Scand*

2009; **53**: 143-151 [PMID: 19032571 DOI: 10.1111/j.1399-6576.2008.01717.x]
73 **Reader TW**, Cuthbertson BH. Teamwork and team training in the ICU: where do the similarities with aviation end? *Crit Care* 2011; **15**: 313 [PMID: 22136283 DOI: 10.1186/cc10353]
74 **Patterson MD**, Geis GL, Falcone RA, LeMaster T, Wears RL. In situ simulation: detection of safety threats and teamwork training in a high risk emergency department. *BMJ Qual Saf* 2013; **22**: 468-477 [PMID: 23258390 DOI: 10.1136/bmjqs-2012-000942]
75 **Spurr J**, Gatward J, Joshi N, Carley SD. Top 10 (+1) tips to get started with in situ simulation in emergency and critical care departments. *Emerg Med J* 2016; **33**: 514-516 [PMID: 26969169 DOI: 10.1136/emermed-2015-204845]
76 **Norman G**, Dore K, Grierson L. The minimal relationship between simulation fidelity and transfer of learning. *Med Educ* 2012; **46**: 636-647 [PMID: 22616789 DOI: 10.1111/j.1365-2923.2012.04243.x]
77 **Rudolph JW**, Raemer DB, Simon R. Establishing a safe container for learning in simulation: the role of the presimulation briefing. *Simul Healthc* 2014; **9**: 339-349 [PMID: 25188485 DOI: 10.1097/SIH.0000000000000047]
78 **Sawyer T**, Eppich W, Brett-Fleegler M, Grant V, Cheng A. More Than One Way to Debrief: A Critical Review of Healthcare Simulation Debriefing Methods. *Simul Healthc* 2016; **11**: 209-217 [PMID: 27254527 DOI: 10.1097/SIH.0000000000000148]
79 **Patterson MD**, Blike GT, Nadkarni VM. EditorsIn: Henriksen K, Battles JB, Keyes MA, Grady ML, editors. SourceAdvances in Patient Safety: New Directions and Alternative Approaches. Rockville (MD): Agency for Healthcare Research and Quality (US); In Situ Simulation: Challenges and Results. 2008 [PMID: 21249938]
80 **Spector JM**. Emerging Educational Technologies and Research Directions. *Educ Technol Soc* 2013; **16**: 21-30

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MINIREVIEWS

Management of parenteral nutrition in critically ill patients

Paolo Cotogni

Paolo Cotogni, Department of Anesthesia and Intensive Care, Pain Management and Palliative Care, S. Giovanni Battista Hospital, University of Turin, 10123 Turin, Italy

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Correspondence to: Paolo Cotogni, MD, MSc, Department of Anesthesia and Intensive Care, Pain Management and Palliative Care, S. Giovanni Battista Hospital, University of Turin, Via Giovanni Giolitti 9, 10123 Turin, Italy. paolo.cotogni@unito.it
Telephone: +39-011-5171634
Fax: +39-011-5171634

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Abstract

Artificial nutrition (AN) is necessary to meet the nutritional requirements of critically ill patients at nutrition risk because undernutrition determines a poorer prognosis in these patients. There is debate over which route of delivery of AN provides better outcomes and lesser complications. This review describes the management of parenteral nutrition (PN) in critically ill patients. The first aim is to discuss what should be done in order that the PN is safe. The second aim is to dispel "myths" about PN-related complications and show how prevention and monitoring are able to reach the goal of "near zero" PN complications. Finally, in this review is discussed the controversial issue of the route for delivering AN in critically ill patients. The fighting against PN complications should consider: (1) an appropriate blood glucose control; (2) the use of olive oil- and fish oil-based lipid emulsions alternative to soybean oil-based ones; (3) the adoption of insertion and care bundles for central venous access devices; and (4) the implementation of a policy of targeting "near zero" catheter-related bloodstream infections. Adopting all these strategies, the goal of "near zero" PN complications is achievable. If accurately managed, PN can be safely provided for most critically ill patients without expecting a relevant incidence of PN-related complications. Moreover, the use of protocols for the management of nutritional support and the presence of nutrition support teams may decrease PN-related complications. In conclusion, the key messages about the management of PN in critically ill patients are two. First, the dangers of PN-related complications have been exaggerated because complications are uncommon; moreover, infectious complications, as mechanical complications, are more properly catheter-related and not PN-related complications. Second, when enteral nutrition is not feasible or tolerated, PN is as effective and safe as enteral nutrition.

Key words: Enteral nutrition; Intensive care; Nutritional support; Vascular access; Artificial nutrition

Core tip: The goal of parenteral nutrition (PN) is to complete the therapy without complications. But the goal of "near zero" PN-related complications is achievable

if appropriate prevention and monitoring procedures for reducing PN complications are instituted. The key message of this review is the strong recommendation for the development and implementation of protocols for the safe management of PN in critically ill patients, in which each healthcare professional will be actively engaged. If accurately managed, PN can be safely provided for most critically ill patients without expecting a relevant incidence of PN-related complications.

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INTRODUCTION

Nowadays, the debate on the use of artificial nutrition (AN) in critically ill patients is a hot topic. In fact, many controversies still remain on several aspects of nutritional support of these patients, *e.g.,* timing, quality of macronutrients, safety, incidence of complications, and route of delivery[1,2].

This review has not the purpose to extensively discuss the indications for parenteral nutrition (PN) that are clearly stated in the guidelines, but describes the management of PN in critically ill patients. The first aim is to discuss what should be done in order that the PN is safe. The second aim is to dispel "myths" about PN-related complications and show how prevention and monitoring are able to reach the goal of "near zero" PN complications. Finally, in this review is discussed the controversial issue of the route for delivering AN in critically ill patients.

INDICATIONS FOR PARENTERAL NUTRITION

Generally speaking, guidelines[3-5] recommend in critically ill patients to initiate enteral nutrition (EN) if oral food intake is insufficient, and PN if EN is not sufficient or feasible. But, the key question is: When to use PN in critically ill patients? Nowadays, the role of PN in critically ill patients is one of the most controversial topic in debate. In fact, there are conflicting recommendations released by the American Society of Parenteral and Enteral Nutrition (ASPEN)[3] and the European Society for Clinical Nutrition and Metabolism (ESPEN)[4] regarding the use of PN in this population. For this reason, the indications for PN in critically ill patients were copied from the guidelines and "pasted" in an Appendix enclosed to this review.

PARENTERAL NUTRITION SAFETY

PN is a complex prescription therapy associated as every other therapy with the potential risk of adverse effects. To prescribe, compound, and dispense PN in critically ill patients are three key components of a multifaceted process involving different healthcare professionals representing the discipline of medicine, nursing, pharmacy, and dietetics, frequently working together in a Nutrition Support Team[6].

Specifically, the physician prescribing PN should have some competences in indications for PN, infection control, peripheral and central vascular access devices (VADs) and all their related complications. As a matter of fact, PN complications can occur both because of the PN itself and as the result of the PN process.

Moreover, lapses, mistakes, and errors may occur during all the phases of PN. Examples of lapses in the verification process include PN administration: (1) to the wrong patient; (2) by the wrong route, infusing a central mixture *via* a peripheral vein or through an incorrect tubing connection; and (3) at the wrong infusion rate. Mistakes concerning wrong infusion rates are among the most frequent errors quoted by literature. These errors pose the risk for patient harm due to potential severe metabolic alterations such as hyperglycemia or fat overload.

A proper management of the PN can get full advantage from its beneficial impact on the patient's condition and lessen the potential adverse effects. Actually, the ASPEN continuously releases clinical guidelines and consensus recommendations about PN safety[7].

The introduction in the daily practice of the "all-in-one" bags (*i.e.,* the commercially available premade multichambered bags) without doubt has improved the PN safety. The ASPEN guidelines[7], comparing the compounded with the multichambered PN formulations, state that the latter have many clinical advantages and better meet the needs of patients. In fact, the "all-in-one" bags allow continuous and stable infusion of all macronutrients. In particular, optimal nitrogen utilization has been found to be achieved when the administration of all macronutrients is performed simultaneously.

Since 2000, Pichard *et al*[8] demonstrated that the use of 3-compartment bags for PN was less expensive than separate bottles and hospital compounded bags. Moreover, these authors demonstrated that standard formulas satisfied the needs of more than 95% of the adult patients. Pontes-Arruda *et al*[9] documented that in critically ill patients the delivery of PN through compounded bags was associated with a significantly higher rate of bloodstream infections (BSIs) and central line-associated bloodstream infections (CLABSIs). These authors suggested that the use of multichamber bags may play a role in decreasing the rate of BSIs in critically ill patients receiving PN.

Another crucial issue about PN safety is the Y-site compatibility of intravenous (IV) drugs with PN. Administering PN and medications at the Y-site is not recommended, but unfortunately cannot be avoided when a large number of IV drugs have to be co-infused

like in critically ill patients. In an interesting study[10], the physicochemical compatibility of the contact 1:1 between many medications and PN was evaluated *in vitro* after 1 and 4 h. The authors found an incompatibility after 1 h among PN and the following medications at the tested concentrations: Albumin (200 mg/mL), esomeprazole (0.8 mg/mL), pantoprazole (0.8 mg/mL), tropisetron (1 mg/mL), and fluorouracil (25 and 50 mg/mL). Moreover, they reported an incompatibility after 4 h among PN and the following antibiotics: Cefepime (100 mg/mL) and amoxicillin (50 mg/mL) plus acid clavulanic (10 mg/mL).

The ASPEN recommends the use of in-line filters for PN delivery to reduce potential harms due to microorganisms, air emboli, particulates, and microprecipitates[7]. In-line filters are required for at increased risk critically ill patients (immune-suppressed or infants, neonates, and children), but their use is controversial in not at-risk ones.

PARENTERAL NUTRITION COMPLICATIONS

To reduce the rate of PN-related complications the first recommendation is to know well them. Every healthcare professional involved in the management of critically ill patient should be prepared to recognize early the onset of a PN complication and intervene for managing it. The PN-related complications can be classified as: (1) metabolic; (2) infectious; and (3) mechanical.

Metabolic complications

The metabolic complications that can occur acutely are altered hydration status, electrolyte disturbances, and hyperglycemia. These complications are common in critically ill patients, but fairly easy to manage. On the contrary, other severe metabolic complications such as PN-associated liver dysfunctions (*i.e.,* steatosis, cholestasis, and gallstones) and metabolic bone disease may be caused by long-term PN use (*i.e.,* years). Indeed, this is not the case for critically ill patients that usually are on PN for weeks and rarely for few months.

To decrease the incidence of metabolic complications is very important to identify them early by monitoring. The latter should be clinical - and laboratory-based. It is strongly recommended the monitoring of fluid balance targeting "near zero", as well as the daily check for edema and fluid retention. Moreover, a well-scheduled laboratory monitoring should be designed for checking electrolytes (particularly, phosphate, magnesium, and calcium), renal (particularly, Estimated Glomerular Filtration Rate) and liver function (transaminases, bilirubin, and gamma-glutamyl transferase). In case of prolonged PN (*i.e.*, weeks or months), the laboratory monitoring should be designed for checking trace elements deficiencies (selenium, zinc, and copper), as well as potential anemia causes (vitamin B12, folic acid, iron, and copper).

However, the most important recommendation to reduce the incidence of metabolic complications is to prevent them. At the beginning of the use of PN, the administration of high doses of glucose frequently caused hyperglycemia. Hyperglycemia (*i.e.,* glucose > 10 mmol/L or > 180 mg/dL) contributes to severe infections, organ dysfunctions, and death in critically ill patients and therefore should be carefully avoided. Currently, glucose-induced abnormalities can be prevented by choosing PN formulations with a reduced glucose amount. In hospitalized patients with hyperglycemia, glycemic control is usually easily achieved by the IV pump-driven infusion of short-acting insulin or by the addition of short-acting insulin into the bag (1-2 U/10 g of dextrose).

In 2001, Van den Berghe *et al*[11] demonstrated in a randomized controlled trial (RCT) in critically ill patients a remarkable positive impact of an intensive insulin therapy on mortality and several other outcomes in case of hyperglycemia. However, many authors subsequently reported that there was a higher incidence of severe hypoglycemia (*i.e.,* 2.2 mmol/L or 40 mg/dL) in patients treated to the tighter limits (*i.e.,* 4.4 mmol/L or 80 mg/dL). Therefore, in our hospital we recommend to use for blood glucose control a cut off of 8.3 mmol/L (or 150 mg/dL). From a practical point of view, an appropriate blood glucose monitoring, based on clinical conditions and infusions scheduled, is able to reduce the risk of both hyperglycemia and hypoglycemia.

Lipid-induced abnormalities arise very rarely in critically ill patients on PN. When these alterations occur generally are more frequent related to liver dysfunction/failure than to PN. When triglyceride levels become greater than 5 mmol/dL (or > 400 mg/dL), we recommend to reduce the fat provision (*e.g.,* reducing the opening of the lipid compartment of the bag). Specifically, we suggest a frequency of lipid administration of 1 to 4 times per week in proportion to the triglyceride levels, although evidence-based data supporting this policy are lacking.

Another hot topic in the debate over the nutritional support of critically ill patients is the issue of the quality of lipid therapy. This issue is still controversial due to, at least in part, inconclusive or contradicting results in several clinical trials using Ⅳ lipid emulsions alternative to soybean oil-based Ⅳ lipid emulsions. In 2013, Manzanares *et al*[12] concluded that alternative oil-based lipid emulsions may be associated with reductions in length of stay in intensive care unit (ICU), duration of mechanical ventilation, and mortality in critically ill patients, but lack of statistical precision prevents any recommendations until further studies confirm these positive effects.

In 2014, in a prospective multicenter study was compared the use of different lipid emulsions (*i.e.,* soybean oil, olive oil, and fish oil) in critically ill patients and found that patients receiving olive oil and fish oil had a shorter time to termination of mechanical ventilation alive and a shorter time to ICU discharge alive[13].

High doses of protein intake may lead to high levels of nitrogen-containing compounds such as urea and creatinine, metabolic acidosis, and hypertonic dehy-

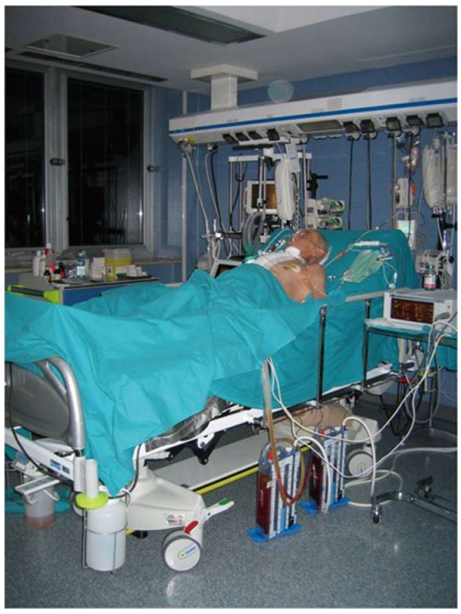

Figure 1 A critically ill patient in intensive care unit (image from Paolo Cotogni, MD, Image used with permission from author).

dration. However, these are very rare PN complications.

Clinical features of deficiencies or excesses of micronutrients (*i.e.,* vitamins and trace elements) during PN can be avoided simply with the addition of these micronutrients according to a time schedule. Specifically, the regular provision through commercial parenteral vitamins and trace elements preparations avoids deficiencies. For example, thiamine supplements (*i.e.,* 100-300 mg/d) should be administered during the first 3 d in patients with possible thiamine deficiency (*i.e.,* in case of severe malnutrition, anorexia nervosa or alcohol abuse) to prevent neurological side effects associated with glucose delivery during PN.

The optimal intake of macronutrients both energy and protein is largely undefined and the prospective trials have given controversial results[2]. The gold standard to avoid overfeeding should be the use of indirect calorimetry for measuring energy expenditure (EE)[1]. The main limit of EE measurements is that caloric needs may change during the ICU stay. If indirect calorimetry is unavailable, a feeding protocol may significantly reduce the risk of overfeeding. In fact, as suggested since many years in ICU where the patient is often metabolic instable, a protocol for management of PN may markedly decrease the incidence of PN-related complications.

The most feared metabolic complication of PN is the refeeding syndrome (RS). This syndrome can occur as a consequence of administration of nutrients to a patient with a severe undernutrition (*i.e.,* with anorexia nervosa or after a long-standing starvation). The clinical picture of RS includes severe and life-threatening electrolyte abnormalities (hypophosphatemia, hypokalemia, and hypomagnesemia), as well as sodium and fluid retention potentially leading to respiratory failure, heart failure, and consequently death. RS can be prevented through a stepwise and patient's tailored feeding protocol[14].

The key points for preventing RS is to provide an optimal management and a daily monitoring of serum electrolyte levels, fluid balance, and organ functions. In patients at risk of RS is of pivotal importance to provide a prophylactic supplement of phosphate, as well as to strictly monitor the serum phosphate levels. Besides, sodium and IV fluids administration should be restricted to maintain zero balance[14].

Infectious complications

In patients receiving PN, the most feared and relevant infectious complications are catheter-related bloodstream infections (CRBSIs) and CLABSIs[15]. However, these infectious complications are not PN-related but more properly catheter-related complications.

The central VAD is of key importance for quite all critically ill patients in different clinical scenarios (ICU, emergency department, and surgical ward) (Figure 1) for the treatment of different disease states (sepsis, shock, organ dysfunction/failure, major trauma, burns, and postoperative complications) and for a variety of purposes (antibiotic therapy, PN, fluids or medications infusion, procedures of dialysis/apheresis, and hemodynamic monitoring)[16].

However, healthcare providers are frequently worried about the potential complications (mainly, BSIs and thrombosis) related to the use of a central VAD, both centrally inserted central catheters (CICCs) and peripherally inserted central catheters (PICCs). The choice between CICCs and PICCs in critically ill patients is a controversial issue, but many authors suggest that PICCs have many advantages over standard CICCs[17,18]. For a complete review on choice of the VAD (indications for PICCs and comparison between CICCs and PICCs), insertion techniques (site of insertion, ultrasound guidance, single *vs* multiple-lumen, stabilization, and tip position), and care of the VAD (dressing of vascular access exit site, administration set replacement, and catheter flushing and locking) in all critically ill patients (adults, neonates, infants, and children)[19].

Since 2006, Pronovost *et al*[20] demonstrated that it is possible to decrease CRBSI in ICU by introducing some interventions and recently seems that the goal of "near zero" CRBSI could become a reality[21]. In 2013, a group of experts included in the top patient safety strategies that can be strongly encouraged for immediate adoption bundles that have checklists to prevent CLASBIs[22].

The first important strategy to decrease the rate of infectious complications is to apply a bundle for the insertion of central VADs, including accurate hand hygiene, skin disinfection with 2% chlorhexidine, maximal sterile barrier precautions, and ultrasound guidance for the catheter insertion[23].

Since 2007, the evidence-based guidelines for preventing healthcare associated infections[24] stated that the use of ultrasound may indirectly reduce infectious complications by facilitating an insertion without immediate mechanical complications[25]. Indeed, nowadays is not justified not using ultrasound guidance for central VAD insertion[26].

The second relevant strategy to decrease the incidence of infectious complications is to apply a bundle for the care of central VADs, including the use of biopatch, semipermeable transparent dressing, 2% chlorhexidine for skin disinfection, and sutureless devices for the catheter care.

Another important strategy to decrease the rate of CRBSI is the selection of the exit site[27]. Many authors suggest the importance to move the exit site of the central VAD from the neck or the supraclavicular area to the infraclavicular area for CICCs or the upper mid-arm for PICCs.

Mechanical complications

The mechanical complications that can more frequently occur are: Lumen occlusion, catheter dislocation, rupture of external tract, and the most feared venous thrombosis. However, these complications, as infectious complications, are catheter-related and not PN-related complications. According to the ESPEN guidelines, central catheter-related venous thrombosis may be prevented by: (1) the use at insertion of the ultrasound guidance; (2) the use of a VAD with the smallest caliber compatible with the patient's need; and (3) the position of the tip of the central VAD between the superior vena cava and the right atrium (at or near the so-called atrio-caval junction)[23].

ENTERAL *VS* PARENTERAL NUTRITION

Based on the experience of Dudrick *et al*[28], the use of PN was introduced in the late 1960s. Since then, without any doubt PN helped greatly many critically ill patients to recover from previously life-limiting clinical conditions. However, the diffuse use of this therapy in all patients, even with extensive indications, brought reservations regarding its benefits and increased the role of EN in the subsequent years.

In the late 1980s emerging evidence from animal studies supported the concept that EN promotes gut function and prevents the translocation of intestinal bacteria. Therefore, total PN was considered to be a "dangerous" form of therapy (*e.g.,* "more harm than good" or "a poison") and this belief resulted in EN becoming the new standard of care in AN.

The PN is also criticized because it is more expensive than EN. Indeed, both EN and PN are relatively cheap treatments, especially if compared to other therapies that the critically ill patients need to survive.

All together, these concerns influenced the decision-making of physicians about the choice between EN and PN for the nutrition support of critically ill patients.

In fact, in 2000 Heyland[29] questioned if PN in critically ill patients was more harm than good because there were studies comparing EN with PN suggesting that PN was associated with increased complications and mortality in some subgroups of these patients. On the contrary, Jeejeebhoy[30] in 2001 had an absolutely opposite judgment regarding PN and stated that the rate of PN-related complications have been overstated.

In critically ill patients, EN is the recommended method of nutritional support when the patient is unable to have an adequate oral intake of nutrients to meet his/her nutritional requirements and the gastrointestinal tract is functional. The enteral route is efficient and cost-effective, however it is not always as easy as it looks.

Also EN may be the cause of complications that can be classified as: (1) metabolic (*e.g.,* RS may occur also with EN); (2) gastrointestinal (*e.g.,* early satiety, nausea, vomiting, and diarrhea); and (3) mechanical or tube-related (*e.g.,* malposition, dislodgement, and clogging, both in case of nasogastric tube and percutaneous endoscopic gastrostomy). Actually, the most feared complication of EN is pulmonary aspiration because it can be a life-threatening condition.

The debate over the topic of the route for delivering AN in critically ill patients are relevant and attractive. Since several years, meta-analysis and RCTs comparing EN and PN found conflicting results as regards the benefits of EN *vs* PN in critically ill patients. In my opinion, there is a great misunderstanding in this debate; in particular, that EN and PN are competitors. On the contrary, the selection of EN or PN for delivering nutritional support should be tailored on an individual basis.

In fact, the route chosen for providing AN should be appropriate to the patient's clinical conditions and should frequently be evaluated for persistent appropriateness, as well as for its adequacy in meeting nutritional requirements of the patient. Not infrequently, in critically ill patients the gastrointestinal tract is not able to tolerate the administration of the prescribed amount of EN formula. If a patient develops intestinal dysfunction/failure due to his/her critical illnesses, PN is more efficient to meet patient's nutritional needs and better tolerated than EN.

In 2014, Harvey *et al*[31] reported the results of a RCT evaluating the route of early nutrition support in 2400 adult critically ill patients. The trial compared early NE with early PN and demonstrated that: (1) the PN and the EN groups did not have significant differences in rates of adverse events, treated infectious complications, and other 14 secondary outcomes; and (2) the target intake was not achieved in most patients although the caloric intake was comparable between the groups. Therefore, the authors concluded that: (1) there was no association between 30-d mortality and the route for delivering the early nutritional support; and (2) early PN, as it is generally administered, is neither more beneficial nor more harmful than EN in critically ill patients.

SUMMARY

The PN-related complications are catheter-related or metabolic complications. In 2005, Beghetto *et al*[32] reported that PN was an independent risk factor for central venous catheter-related infection in nonselected

hospitalized adult patients. In the past years, the rate of catheter-related complications varied from 1.5 to 4.9 episodes per 1000 catheter days, depending on the inhospital patient population, severity of illness, and the type of central VAD[33]. However, after the Pronovost paper[20], the widespread diffusion of guidelines on care, diagnosis, and therapy of complications of central venous catheters access in PN patients[23], and the introduction of nutrition support teams[6], the incidence of PN-related complications is markedly reduced.

In fact, in the RCT of Harvey *et al*[31] the mean number of infectious complications was 0.22 in the parenteral group. Moreover, many studies demonstrated that the goal of "near zero" CRBSI[21] has been achieved; actually, in the recent years the incidence of catheter-related infections in ICU patients varied from 0[18,34-36] to 2.4[37] episodes per 1000 catheter days.

Moreover, the optimization of energy provision with supplemental PN in critically ill patients could reduce nosocomial infections, antibiotic usage, and time on mechanical ventilation, and consequently overall health-care costs[38].

It is well known that hepatic dysfunctions are common PN-related metabolic complications in patients receiving long-term PN[39], but this is not the case for critically ill patients that generally receive PN for weeks.

PN is effective and safe when EN is not feasible or tolerated. However, in these patients receiving PN, endogenous infection is more significant than exogenous infection. Indeed, the lack of EN significantly disrupts the usual gastrointestinal microbiota, leads to mucosal gut atrophy and impaired intestinal barrier function. This may determine an impaired immunity favoring endotoxin absorption, macrophage-mediated and cytokine-mediated inflammation, and dangerous bacterial translocation[33].

The question is: How to decrease the incidence of CRBSIs in this condition? The suggestion is that all patients receiving PN, because of EN was initially not tolerated or feasible, should be assessed every day for tolerance of EN and a combined administration of PN and EN should be initiated as soon as feasible.

An emerging and intriguing issue is the use of probiotics, alone or in combination with prebiotics, in critically ill patients to restore the balance of gastro-intestinal microbiota with a beneficial impact on intestinal permeability and bacterial translocation. However, further studies in this field are needed before a clear recommendation can be released on the possible therapeutic use of pre- and probiotics for the protection of the gut in ICU patients[40].

CONCLUSION

The AN is necessary to meet the nutritional requirements of critically ill patients at nutrition risk because under-nutrition determines a poorer prognosis in these patients. There is debate over which route of delivery of AN provides better outcomes and lesser complications in critically ill patients.

The fighting against PN complications should consider: (1) an appropriate blood glucose control; (2) the use of olive oil- and fish oil-based lipid emulsions alternative to soybean oil-based ones; (3) the adoption of insertion and care central-line bundles; and (4) the implementation of a policy of targeting "near zero" CRBSIs. Adopting all these strategies, the goal of "near zero" PN complications is achievable.

If accurately managed, PN can be safely provided for most critically ill patients without expecting a relevant incidence of PN-related complications. Moreover, the use of protocols for the management of nutritional support and the presence of nutrition support teams may decrease PN-related complications.

In conclusion, the key messages about the management of PN in critically ill patients are two. First, the dangers of PN-related complications have been exaggerated because complications are uncommon; moreover, infectious complications, as mechanical complications, are more properly catheter-related and not PN-related complications. Second, when EN is not feasible or tolerated, PN is as effective and safe as EN.

REFERENCES

1 **Berger MM**, Pichard C. Development and current use of parenteral nutrition in critical care - an opinion paper. *Crit Care* 2014; **18**: 478 [PMID: 25184816 DOI: 10.1186/s13054-014-0478-0]

2 **Preiser JC**, van Zanten AR, Berger MM, Biolo G, Casaer MP, Doig GS, Griffiths RD, Heyland DK, Hiesmayr M, Iapichino G, Laviano A, Pichard C, Singer P, Van den Berghe G, Wernerman J, Wischmeyer P, Vincent JL. Metabolic and nutritional support of critically ill patients: consensus and controversies. *Crit Care* 2015; **19**: 35 [PMID: 25886997 DOI: 10.1186/s13054-015-0737-8]

3 **Taylor BE**, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *Crit Care Med* 2016; **44**: 390-438 [PMID: 26771786 DOI: 10.1097/CCM.0000000000001525]

4 **Singer P**, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Leverve X, Pichard C. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr* 2009; **28**: 387-400 [PMID: 19505748 DOI: 10.1016/j.clnu.2009.04.024]

5 **Kreymann KG**, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, Ebner C, Hartl W, Heymann C, Spies C. ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr* 2006; **25**: 210-223 [PMID: 16697087 DOI: 10.1016/j.clnu.2006.01.021]

6 **Hvas CL**, Farrer K, Donaldson E, Blackett B, Lloyd H, Forde C, Garside G, Paine P, Lal S. Quality and safety impact on the provision of parenteral nutrition through introduction of a nutrition support team. *Eur J Clin Nutr* 2014; **68**: 1294-1299 [PMID: 25248359 DOI: 10.1038/ejcn.2014.186]

7 **Boullata JI**, Gilbert K, Sacks G, Labossiere RJ, Crill C, Goday P, Kumpf VJ, Mattox TW, Plogsted S, Holcombe B. A.S.P.E.N. clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr* 2014; **38**: 334-377 [PMID: 24531708 DOI: 10.1177/0148607114521833]

8 **Pichard C**, Schwarz G, Frei A, Kyle U, Jolliet P, Morel P, Romand JA, Sierro C. Economic investigation of the use of three-

compartment total parenteral nutrition bag: prospective randomized unblinded controlled study. *Clin Nutr* 2000; **19**: 245-251 [PMID: 10952795 DOI: 10.1054/clnu.2000.0106]

9 **Pontes-Arruda A**, Dos Santos MC, Martins LF, González ER, Kliger RG, Maia M, Magnan GB. Influence of parenteral nutrition delivery system on the development of bloodstream infections in critically ill patients: an international, multicenter, prospective, open-label, controlled study--EPICOS study. *JPEN J Parenter Enteral Nutr* 2012; **36**: 574-586 [PMID: 22269899 DOI: 10.1177/0148607111427040]

10 **Bouchoud L**, Fonzo-Christe C, Klingmüller M, Bonnabry P. Compatibility of intravenous medications with parenteral nutrition: in vitro evaluation. *JPEN J Parenter Enteral Nutr* 2013; **37**: 416-424 [PMID: 23112277 DOI: 10.1177/0148607112464239]

11 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367 [PMID: 11794168 DOI: 10.1056/NEJMoa011300]

12 **Manzanares W**, Dhaliwal R, Jurewitsch B, Stapleton RD, Jeejeebhoy KN, Heyland DK. Alternative lipid emulsions in the critically ill: a systematic review of the evidence. *Intensive Care Med* 2013; **39**: 1683-1694 [PMID: 23812404 DOI: 10.1007/s00134-013-2999-4]

13 **Edmunds CE**, Brody RA, Parrott JS, Stankorb SM, Heyland DK. The effects of different IV fat emulsions on clinical outcomes in critically ill patients. *Crit Care Med* 2014; **42**: 1168-1177 [PMID: 24351374 DOI: 10.1097/CCM.0000000000000146]

14 **Khan LU**, Ahmed J, Khan S, Macfie J. Refeeding syndrome: a literature review. *Gastroenterol Res Pract* 2011; **2011**: pii: 410971 [PMID: 20886063 DOI: 10.1155/2011/410971]

15 **Lorente L**, Villegas J, Martín MM, Jiménez A, Mora ML. Catheter-related infection in critically ill patients. *Intensive Care Med* 2004; **30**: 1681-1684 [PMID: 15160239 DOI: 10.1007/s00134-004-2332-3]

16 **Palmer D**, McFie J. Venous access for parenteral nutrition. In: Payne James J, Grimble GK, Silk, DBA. Artificial nutrition support in clinical practice. London, UK, 2001: 379-400

17 **Griffiths VR**, Philpot P. Peripherally inserted central catheters (PICCs): do they have a role in the care of the critically ill patient? *Intensive Crit Care Nurs* 2002; **18**: 37-47 [PMID: 12008876 DOI: 10.1054/iccn.2002.1615]

18 **Pittiruti M**, Brutti A, Celentano D, Pomponi M, Biasucci DG, Annetta MG, Scoppettuolo G. Clinical experience with power-injectable PICCs in intensive care patients. *Crit Care* 2012; **16**: R21 [PMID: 22305301 DOI: 10.1186/cc11181]

19 **Cotogni P**, Pittiruti M. Focus on peripherally inserted central catheters in critically ill patients. *World J Crit Care Med* 2014; **3**: 80-94 [PMID: 25374804 DOI: 10.5492/wjccm.v3.i4.80]

20 **Pronovost P**, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, Sexton B, Hyzy R, Welsh R, Roth G, Bander J, Kepros J, Goeschel C. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006; **355**: 2725-2732 [PMID: 17192537 DOI: 10.1056/NEJMoa061115]

21 **Ruiz-Santana S**, Saavedra P, León C. "Near zero" catheter-related bloodstream infections: turning dreams into reality*. *Crit Care Med* 2012; **40**: 3083-3084 [PMID: 23080438 DOI: 10.1097/CCM.0b013e3182632748]

22 **Shekelle PG**, Pronovost PJ, Wachter RM, McDonald KM, Schoelles K, Dy SM, Shojania K, Reston JT, Adams AS, Angood PB, Bates DW, Bickman L, Carayon P, Donaldson L, Duan N, Farley DO, Greenhalgh T, Haughom JL, Lake E, Lilford R, Lohr KN, Meyer GS, Miller MR, Neuhauser DV, Ryan G, Saint S, Shortell SM, Stevens DP, Walshe K. The top patient safety strategies that can be encouraged for adoption now. *Ann Intern Med* 2013; **158**: 365-368 [PMID: 23460091 DOI: 10.7326/0003-4819-158-5-201303051-00001]

23 **Pittiruti M**, Hamilton H, Biffi R, MacFie J, Pertkiewicz M. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). *Clin Nutr* 2009; **28**: 365-377 [PMID: 19464090 DOI: 10.1016/j.clnu.2009.04.004]

24 **Loveday HP**, Wilson JA, Pratt RJ, Golsorkhi M, Tingle A, Bak A, Browne J, Prieto J, Wilcox M. epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2014; **86** Suppl 1: S1-S70 [PMID: 24330862 DOI: 10.1016/S0195-6701(13)60012-2]

25 **Lamperti M**, Bodenham AR, Pittiruti M, Blaivas M, Augoustides JG, Elbarbary M, Pirotte T, Karakitsos D, Ledonne J, Doniger S, Scoppettuolo G, Feller-Kopman D, Schummer W, Biffi R, Desruennes E, Melniker LA, Verghese ST. International evidence-based recommendations on ultrasound-guided vascular access. *Intensive Care Med* 2012; **38**: 1105-1117 [PMID: 22614241 DOI: 10.1007/s00134-012-2597-x]

26 **Bodenham AR**. Can you justify not using ultrasound guidance for central venous access? *Crit Care* 2006; **10**: 175 [PMID: 17129362 DOI: 10.1186/cc5079]

27 **Pittiruti M**, Migliorini I, Emoli A, Dolcetti L, Pomponi M, Scoppettuolo G, LaGreca A. Preventing central venous catheter related infections: catheter site selection and insertion technique significantly affect the chances of adequate catheter site care. *Intensive Care Med* 2007; **33** Suppl: S13

28 **Dudrick SJ**, Wilmore DW, Vars HM, Rhoads JE. Long-term total parenteral nutrition with growth, development, and positive nitrogen balance. *Surgery* 1968; **64**: 134-142 [PMID: 4968812]

29 **Heyland DK**. Parenteral nutrition in the critically-ill patient: more harm than good? *Proc Nutr Soc* 2000; **59**: 457-466 [PMID: 10997674 DOI: 10.1017/S002966510000063X]

30 **Jeejeebhoy KN**. Total parenteral nutrition: potion or poison? *Am J Clin Nutr* 2001; **74**: 160-163 [PMID: 11470715]

31 **Harvey SE**, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med* 2014; **371**: 1673-1684 [PMID: 25271389 DOI: 10.1056/NEJMoa1409860]

32 **Beghetto MG**, Victorino J, Teixeira L, de Azevedo MJ. Parenteral nutrition as a risk factor for central venous catheter-related infection. *JPEN J Parenter Enteral Nutr* 2005; **29**: 367-373 [PMID: 16107600 DOI: 10.1177/0148607105029005367]

33 **Mundi MS**, Nystrom EM, Hurley DL, McMahon MM. Management of Parenteral Nutrition in Hospitalized Adult Patients. *JPEN J Parenter Enteral Nutr* 2016; Epub ahead of print [PMID: 27587535 DOI: 10.1177/0148607116667060]

34 **Berenholtz SM**, Pronovost PJ, Lipsett PA, Hobson D, Earsing K, Farley JE, Milanovich S, Garrett-Mayer E, Winters BD, Rubin HR, Dorman T, Perl TM. Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med* 2004; **32**: 2014-2020 [PMID: 15483409 DOI: 10.1097/01.CCM.0000142399.70913.2F]

35 **Pronovost PJ**, Goeschel CA, Colantuoni E, Watson S, Lubomski LH, Berenholtz SM, Thompson DA, Sinopoli DJ, Cosgrove S, Sexton JB, Marsteller JA, Hyzy RC, Welsh R, Posa P, Schumacher K, Needham D. Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. *BMJ* 2010; **340**: c309 [PMID: 20133365 DOI: 10.1136/bmj.c309]

36 **DePalo VA**, McNicoll L, Cornell M, Rocha JM, Adams L, Pronovost PJ. The Rhode Island ICU collaborative: a model for reducing central line-associated bloodstream infection and ventilator-associated pneumonia statewide. *Qual Saf Health Care* 2010; **19**: 555-561 [PMID: 21127114 DOI: 10.1136/qshc.2009.038265]

37 **Peredo R**, Sabatier C, Villagrá A, González J, Hernández C, Pérez F, Suárez D, Vallés J. Reduction in catheter-related bloodstream infections in critically ill patients through a multiple system intervention. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 1173-1177 [PMID: 20533071 DOI: 10.1007/s10096-010-0971-6]

38 **Heidegger CP**, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet* 2013; **381**: 385-393 [PMID: 23218813 DOI: 10.1016/S0140-6736(12)61351-8]

39 **Raman M**, Allard JP. Parenteral nutrition related hepato-biliary

disease in adults. *Appl Physiol Nutr Metab* 2007; **32**: 646-654 [PMID: 17622278 DOI: 10.1139/H07-056]
40 **Manzanares W**, Lemieux M, Langlois PL, Wischmeyer PE. Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis. *Crit Care* 2016; **19**: 262 [PMID: 27538711 DOI: 10.1186/s13054-016-1434-y]

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MINIREVIEWS

Exertional rhabdomyolysis and heat stroke: Beware of volatile anesthetic sedation

Karel Heytens, Jan De Bleecker, Walter Verbrugghe, Jonathan Baets, Luc Heytens

Karel Heytens, Department of Anesthesiology, University Hospital Antwerp, 2650 Edegem, Belgium

Jan De Bleecker, Department of Neurology, AZ Sint-Lucas, 9000 Ghent, Belgium

Jan De Bleecker, Department of Neurology, University Hospital Ghent, 9000 Ghent, Belgium

Walter Verbrugghe, Department of Intensive Care, University Hospital Antwerp, 2650 Edegem, Belgium

Jonathan Baets, Department of Neurology, University Hospital Antwerp, 2650 Edegem, Belgium

Jonathan Baets, Laboratory of Neurogenetics and Biobank, Institute Born-Bunge, University of Antwerp, 2610 Wilrijk, Belgium

Luc Heytens, MH Research Unit, University of Antwerp, 2610 Wilrijk, Belgium

Luc Heytens, Departments of Anesthesiology and Neurology, University Hospital Antwerp, 2650 Edegem, Belgium

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Correspondence to: Luc Heytens, MD, PhD, MH Research Unit, University of Antwerp, Campus Drie Eiken, 2610 Wilrijk, Belgium. luc.heytens@uantwerpen.be
Telephone: +32-34-433926

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Abstract

In view of the enormous popularity of mass sporting events such as half-marathons, the number of patients with exertional rhabdomyolysis or exercise-induced heat stroke admitted to intensive care units (ICUs) has increased over the last decade. Because these patients have been reported to be at risk for malignant hyperthermia during general anesthesia, the intensive care community should bear in mind that the same risk of life-threatening rhabdomyolysis is present when these patients are admitted to an ICU, and volatile anesthetic sedation is chosen as the sedative technique. As illustrated by the three case studies we elaborate upon, a thorough diagnostic work-up is needed to clarify the subsequent risk of strenuous exercise, and the anesthetic exposure to volatile agents in these patients and their families. Other contraindications for the use of volatile intensive care sedation consist of known malignant hyperthermia susceptibility, congenital myopathies, Duchenne muscular dystrophy, and intracranial hypertension.

Key words: Exertional rhabdomyolysis; Heat stroke; Intensive care sedation; Inhalational anesthetics; Malignant hyperthermia; Congenital myopathies

Core tip: Recent research has shown that a substantial proportion of patients with exercise-induced heatstroke harbor mutations in the ryanodine-receptor one gene on Chromosome 19 (*RYR1*), encoding for the principal calcium-release channel in striated muscle. These same mutations are known to result in a massively increased calcium-conductivity and life-threatening rhabdomyolysis when malignant hyperthermia (MH) susceptible patients are exposed to volatile anesthetics during general anesthesia. In view of this, exposure to volatile anesthetic sedation - an emerging trend in intensive care units - is contraindicated, not only in patients with known MH susceptibility and other congenital myopathies, but also in patients admitted because of exertional rhabdomyolysis and heatstroke.

Heytens K, De Bleecker J, Verbrugghe W, Baets J, Heytens L. Exertional rhabdomyolysis and heat stroke: Beware of volatile anesthetic sedation. *World J Crit Care Med* 2017; 6(1): 21-27 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i1/21.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i1.21

INTRODUCTION

Exercise-induced rhabdomyolysis (EIR), also known as exertional rhabdomyolysis, is a clinical emergency characterized by extensive post-exercise muscle necrosis and the release of intracellular muscle components into the circulation. The diagnosis is confirmed by a significantly elevated serum creatine kinase (CK) level and/or the presence of myoglobinemia and myoglobinuria. There is no definitive pathological CK cut-off, and therefore, clinical symptoms such as muscle swelling, myalgia, and tenderness occurring with low-intensity exercise, or lasting several days longer than expected, are important clinical signs.

The most severe end of the clinical spectrum-and one of the leading causes of death in young athletes-is known as exertional heat stroke (EHS), a syndrome clinically defined as a body temperature over 40 ℃, with severe rhabdomyolysis and signs of encephalopathy ranging from confusion to convulsions or coma. It is often complicated by multiorgan failure, including acute renal and hepatic failure, and it may result in death if appropriate treatment in an intensive care setting is delayed.

It has been reported for over two decades that a significant part of patients with a history of EIR and/or heat stroke is at increased risk of developing malignant hyperthermia (MH) during general anesthesia[1,2].

MH is well known among anesthetists. It is inherited as an autosomal dominant, genetically heterogeneous trait that manifests as an acute rhabdomyolysis during general anesthesia when susceptible individuals are exposed to volatile anesthetics and/or succinylcholine. The incidence is generally estimated to be approximately 1 in 50000 general anesthesias. In the 1970-1980s, mortality was over 80%, but now, it is fortunately less than 5%[3].

A fulminant MH-crisis is characterized by a combination of clinical and biochemical events: Inappropriate hypercapnia and respiratory acidosis, polypnea, tachyarrhythmia, rapidly increasing body temperature, sweating, generalized muscle rigidity, hemodynamic instability, dark urine due to myoglobinuria, significant CK-increase (often > 10.000 IU/L), and postoperative stiffness and myalgia. Death may result from severe hyperkalemia in combination with respiratory and metabolic acidosis, acute renal failure, hyperthermia > 42 ℃, disseminated intravascular coagulation and fatal cardiac arrhythmias.

Mortality has decreased significantly over the last 20 years because of our better understanding of the syndrome, the use of end-tidal CO_2 ($ETCO_2$) monitoring resulting in earlier diagnosis, and the availability of the antidote dantrolene.

Treatment consists of the immediate discontinuation of volatile anesthetic agents and the administration of dantrolene. The surgical procedure should be terminated as quickly as possible and if the procedure cannot be aborted, the anesthesia technique has to be converted to total intravenous anesthesia. Dantrolene should be administered as a loading bolus of 2.5 mg/kg Ⅳ. Subsequent doses of 1 mg/kg Ⅳ can be repeated up to a maximum dose of 10 mg/kg, and are administered until the clinical signs (hypercapnia, hyperthermia, rigidity) abate. Concomitantly minute volume should be maximized to reduce respiratory acidosis.

Despite adequate treatment, complications still occur in 20% of patients. The most common complication is renal dysfunction and acute renal failure. The complication rate increases to ⩾ 30% when 20 or more minutes elapse between the first clinical sign and dantrolene treatment[4].

This life-threatening anesthesia-related complication is due to the occurrence of point mutations in the genes coding for the calcium-release channel of the sarcoplasmic reticulum, *e.g*., the didyropyridine - ryanodine receptor complex, resulting in a disturbed skeletal muscle calcium homeostasis. The ryanodine receptor (*RYR1* gene on Chromosome 19q) contains the actual "calcium pore". The NH_2-terminal of this protein forms cytosolic protrusions that extend toward, and make contact with, the voltage-gated dihydropyridine receptor located in the T-tubular wall. The corresponding gene for this protein is CACNA1S on Chromosome 1. Depolarization of the sarcolemma and T-tubule first activates the dihydropyridine receptor which in turn activates the ryanodine receptor and opens the calcium-channel as such.

As illustrated in Figure 1, the muscle from patients harboring *RYR1* and/or *DHPR* mutations upon exposure to volatile anesthetics has been shown to exhibit an increased calcium-conductivity and massive calcium release from the SR, in turn resulting in sustained muscle

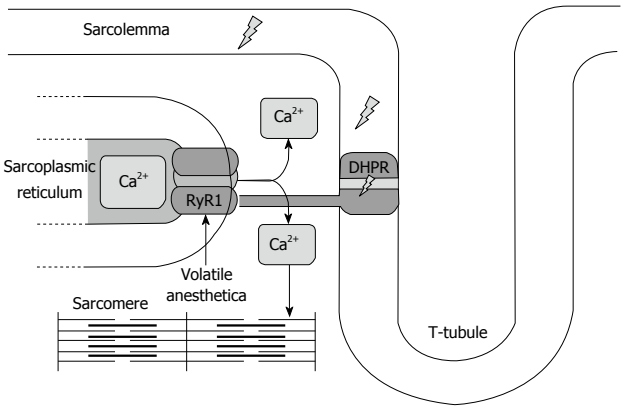

Figure 1 Functional implication of RY1/DHPR receptor mutations after exposure to volatile anesthetics. The action potential generated in the motor endplate is propagated along the sarcolemma and down the T-tubules, to be captured by the voltage sensitive dihydropyridine receptor. The depolarization-induced conformational change in this receptor in turn results in the opening of the RYR1 calcium-channel and calcium release from the SR. Mutations in the ryanodine-dihydropyridine receptor complex upon exposure to inhalational anesthetics lead to a "longer open state" of RYR1, massive calcium release from the SR, and eventually widespread muscle breakdown.

contraction, a catabolic state, and hyperacute muscle breakdown[3].

Susceptibility to MH is diagnosed by in *in vitro* contracture testing (IVCT) in which skeletal muscle fascicles, obtained by biopsy, are exposed to incremental concentrations of caffeine and halothane in a test bath. The muscle contracture obtained in response to the drugs is measured, and is, when above a certain threshold, indicative of MH susceptibility. The test is considered positive [malignant hyperthermia susceptible (MHS)] if a contracture of at least 2 mN is obtained at halothane concentrations of 2 Vol% or less, and/or a caffeine concentration of 2 mmol/L or less. Malignant Hyperthermia negative (MHN) patients do not develop a significant contracture at these concentrations. The European Malignant Hyperthermia Group has standardized this test across Europe. The degree of sensitivity and specificity is 99% and 93.5% respectively[5]. The invasive character of the test however hampers its widespread use as a screening instrument.

Genetically, MH is dominantly inherited. Its estimated prevalence is 1 in 3000[3]. Over the years both chromosomal and allelic heterogeneity have been demonstrated but fortunately, *RYR1* mutations can be found in 50% to 70% of families[3]. Therefore, in an emergency setting, if general anesthesia is required in MHS patients, a trigger free anesthetic technique - avoiding volatile anesthetic agents and/or succinylcholine - is indicated to avoid this potentially lethal complication.

By extension, patients with a history of EIR/EHS are at increased risk of developing an MH event, *e.g*., severe life-threatening rhabdomyolysis when they are exposed to volatile anesthetic sedation, which is an emerging trend in intensive care units (ICUs). Because this fact may not be well known enough among non-anesthetist intensive care specialists, we report three patients with recurrent exertional rhabdomyolysis and/or heat stroke to illustrate the complex relationship with MHS, and we review the literature on this topic.

Patient 1

Male, 43 years of age. Reason for investigation: Recurrent episodes of EIR when participating in half-marathons. During a 2007 half-marathon, he presented with an exercise-induced heat stroke (hyperthermia > 40 ℃). No further clinical details are available. A second episode of ER was noticed 1 year later during a 20-km run. He developed an epileptic insult before finishing the race. At admission, his temperature was 39.8 ℃. More convulsions occurred and his Glasgow coma scale score dropped to 8/15. Sedation with propofol was started, and he was intubated and artificially ventilated. Rhabdomyolysis was diagnosed on the basis of a CK level of 92.000 IU/L, and acute kidney failure occurred (max creatinine level of 3.2 mg/dL), yet with spontaneous recovery and without the need for hemodialysis. The patient could be weaned from mechanical ventilation after 7 d. Further recovery was uneventful. Personal and medical history: Wrist fracture reduction under general anesthesia, active sportsman (handball and squash for years, recent focus on jogging). In between the two episodes of hyperthermia, there were no signs of any myopathy: No myalgias, no cramps, no weakness, and no episodes of cola-colored urines. The family history was negative for myopathies, sudden death, or anesthesia-related complications. His physical examination was normal, as well as Holter monitoring and echocardiography. The resting CK level was 90 IU/L (N < 193 IU/L), lactate 0.68 mmol/L (N < 2 mmol/L). The ischemic exercise test forearm was normal, ruling out glycogen storage disease and myoadenylate deaminase deficiency. The EMG only showed non-specific minor myogenic changes. A 2009 muscle biopsy of the left M. quadriceps revealed a significantly increased number of centrally located nuclei. His IVCT was normal, and not indicative of MHS. A molecular genetic analysis could not reveal any mutation in the carnitine palmitoyl transferase 2 gene *(CPTⅡ),* or *RYR1*.

Patient 2

Male, 34 years of age. Reason for investigation: Recurrent episodes of EIR during cycling. The first major episode occurred during preparation for a cycling event in 2010 when he complained of severe cramping pain in both thighs, and his CK level was found to be 49.536 IU/L and myoglobinuria. Renal failure did not develop. In 2013, after cycle training for 5-6 h, he complained of pronounced muscle weakness with difficulty to walk for a few days. This was accompanied by a CK increase to 9.222 IU/L. He is an avid amateur cyclist, practicing several days a week, most often totaling 400 km/wk, and quite regularly participates in a semi-professional tour of up to 220 km in one day. Retrospective analysis showed similar complaints to have started at the age of 18,

mainly consisting of myalgia with feeling of stiffness, and intermittent myoglobinuria and CK increase. In between the crises, there is normal mobility and power, and no CK increase. He had not yet been exposed to volatile anesthetics. The family history is negative for anesthesia-related events. His father ran marathons, reporting no clinical events. His neurological examination was normal, and functional and biochemical tests showed a basal CK serum level of 293 U/L, a lactate of 0.8 mmol/L, a normal ischemic forearm exercise test and EMG. Muscle biopsy of the left M. quadriceps femoris in 2011 showed an increased number of fibers with internal nuclei and a minor increase of neutral fat drops in some type 1 fibers. These were interpreted as unspecific findings. A repeat muscle biopsy of the left M. quadriceps femoris in 2014 again demonstrated findings of mild myopathic disease: Increased number of fibers with internal nuclei (25%) but also a small number of "cores", which are zones devoid of enzymatic staining. IVCT results: 8 mN contracture at 2 Vol% Halothane, 6 mN contracture with 2 mmol/L Caffeine, indicative of MHS. Molecular genetic analysis did not reveal any mutation in the *CPT II* gene or *RYR1*.

Patient 3

Male, 56 years of age. Reason for investigation: Recurrent myalgia confined to the thigh muscles, described as a sensation of severe tension or cramps, sometimes unilateral, sometimes bilateral. The type of effort appeared not to be related to the complaints: At times a prolonged effort did not provoke any myalgia, whereas at other times, the pain/cramps started after as short an effort of 5-10 min such as descending a staircase. CK values measured during an episode of myalgia rose up to 14.000 IE/L. He is also an amateur cyclist, but complaints were only noticed after the age of 40. There was no previous exposure to volatile anesthetics, and the family history was also negative for anesthesia-related events. His son is not active in sports (his daughter is), but until now has not mentioned any complaints. His clinical examination was normal, but he showed an increase in basal CK value of 269-1771 IU/L at diverse occasions, lactate was 1.2 mmol/L, and the ischemic forearm test was normal. A 2015 muscle biopsy only showed atypical myogenic anomalies. The IVCT was abnormal (5 mN contracture with 2 mmol/L Caffeine, 14 mN contracture with 2 Vol% Halothane), demonstrating MHS. Molecular genetic analysis did not reveal a mutation in the *CPT II* gene, but *RYR1*- mutation analysis demonstrated a base-pair change in exon 43 (p.N2342S; c.7025A > G).

DISCUSSION

There is an emerging trend of using inhalational anesthetics for ICU sedation[6]. The principle motivation is that inhalational anesthetics have an interesting pharmacokinetic profile compared with the usual combination of propofol or benzodiazepine with an analgesic drug. Several practical advantages have been proposed, such as rapid onset and offset of action, low potential for accumulation in fat tissue, drug clearance through the lungs and therefore independent of liver and/or renal function, no tachyphylaxis, an opium sparing effect, bronchodilatory properties, and end-organ protective properties, such as ischemic preconditioning of the heart, although clinical data remain limited on this.

Until about a decade ago, the technical prerequisites for ICU use of volatile anesthetics were not fulfilled, and therefore, their use remained confined to the OR. Technological advances, however, have greatly simplified the application of inhalational anesthetics for ICU sedation. An important milestone was reached in 2005 with the introduction of a volatile anesthetic reflection filter, the anesthetic conserving device (AnaConDa™, Sedana Medical, Uppsala, Sweden), retaining 90% of the volatile anesthetic and thereby enormously reducing the consumption of volatile anesthetic. Since then, other AnaConDa™ competing devices have been produced and tested such as the Mirus™ (Pall Medical, Dreieich, Germany)[7]. Suitable volatile agents are isoflurane, sevoflurane, and desflurane. From a drug delivery point of view, these technical developments have indeed resulted in easy titration to the clinical end-point and the possibility of breath-by-breath bedside monitoring. A 0.3-0.6 minimal alveolar concentration of sevoflurane is most often sufficient in the ICU setting. In view of the increased CO_2 through the systems' enlarged dead space (100 mL), minute volume usually has to be increased by being guided by $ETCO_2$ or blood gas analysis. Desflurane is not commonly used in the ICU in view of its boiling point of 22.8 ℃, requiring a vaporizer heated to 39 ℃, and the higher cost. It can be administered by the Mirus™ device, not the AnaConDa™.

Recent studies have indicated that the currently available scavenger devices that are based on a silica zeolite matrix, adequately adsorb the volatile agents and thereby minimize environmental pollution by volatile anesthetic agents guaranteeing workplace safety[8].

The question still remains to be answered whether volatile anesthetics will really become and stay a player in critical care sedation[6]; however, the technique is being increasingly used in Europe and North-America.

A pilot randomized controlled trial is currently being set up to evaluate the practicability and dangers related to volatile anesthetic agents when used for long-term critical care sedation[9]. This prospective multicenter trial is blinded to the data analyst and aims to recruit 60 adult ICU patients requiring mechanical ventilation and sedation for at least 48 h, in which 40 patients will receive inhaled isoflurane and 20 patients will receive intravenous midazolam and/or propofol, titrated to a targeted Sedation Analgesia Score. Primary outcomes will assess adherence to the particular sedation protocol and atmospheric volatile concentration levels. Secondary outcomes that will be investigated include the quality of sedation, delirium, vasoactive drug support, time to extubation, serum fluoride levels, and mortality.

With an ever-rising concern for adverse events involved in our handling of patients, for any technique to

stand a chance of proving itself, all side-effects have to be clearly identified and communicated to the end users.

In this sense, Purrucker *et al*[10] has issued a warning concerning the use of volatile anesthetic sedation in patients with a high risk of intracranial hypertension. Switching from Ⅳ sedation to sevoflurane decreased MAP and CPP in one-third of the patients studied to such an extent that the early termination of sevoflurane administration was required. The mechanism felt to be responsible was vasodilation in response to a decreasing MAP and a slightly raised partial-pressure carbon dioxide in patients with an already low baseline cerebral compliance.

In this paper, we want to warn about the use of volatile anesthetic sedation in a second subset of ICU patients, in particular those with EIR/EHS in need of intensive care.

Although EIR/EHS is most often encountered in a military setting, the recent worldwide trend to organize mass (semi)marathons has resulted in a significant increase in the frequency of this problem in ICUs worldwide. Indeed, the Centers for Disease Control and Prevention of the United States reported that EHI occurs both during practice and competition, with a disturbing trend of increasing incidence, and mentioning EIR/EHS as one of the leading causes of death in young athletes each year[11].

General anesthesia with volatile anesthetic agents, such as the currently used sevoflurane and desflurane, is known to potentially induce acute rhabdomyolysis in patients with a genetic predisposition to MH. Logically, the same risk is present when genetically MHS patients are exposed to volatile anesthetic sedation in the intensive care setting. A recent publication reported on the development of MH in an ICU patient sedated with sevoflurane[12].

Other groups of patients are also at risk. A link between MHS and EIR has been suggested in the anesthesia literature for over two decades. The earlier reports linked MHS with EIR by demonstrating a positive *in vitro* contracture test. One of the larger series published[2] reports on the IVCT results in 12 unrelated patients with EIR. Ten of the 12 patients had IVCT results indicative of MHS. In the ensuing years, reports occurred providing evidence that "MH-mutations" in RYR1 were being associated with EIR. In 2002, Davis *et al*[13] reported two patients with EIR in which MHS was confirmed through *in-vitro* contracture testing and the presence of a *RYR1* mutation.

Several similar cases were reported, and in 2013, Dlamini *et al*[14] published a large series of 39 unrelated families with rhabdomyolysis and/or exertional myalgia in which nine heterozygous mutations were found in 14 families, several of them recurrent. Five of these mutations had previously been associated with MH. They conclude that *RYR1* mutations account for a substantial proportion of patients presenting with unexplained rhabdomyolysis and/or exertional myalgia, but also that various stressors (*e.g.*, pain, environmental heat, viral infections, drugs) may need to be present to elicit acute rhabdomyolysis. They also suggest that "additional family studies are paramount in order to identify potentially MH susceptible relatives".

In a 2014 paper, Zhao *et al*[15] actually raised the question on whether the two disorders represent one and the same disorder, which they called the Human Stress Syndrome. This hypothesis has gained support, and MH and EIR/EHS are increasingly believed to be different presentations of the "expanding spectrum of RYR1-related myopathies"[16].

In view of the growing evidence that EIR in a substantial portion of the patients admitted to the ICU is a "non-anesthetic RYR1-related rhabdomyolysis"[16], it is of great importance for the patients and families involved to undergo a thorough investigation on the cause of the life-threatening rhabdomyolysis, certainly if the problem has been found to be recurrent. The following reasons substantiate this statement: (1) several "common" underlying causes with significant impact on patients' lives have to be ruled out, such as sickle cell trait, CPTⅡ deficiency, McArdle's disease (glycogen storage disease Ⅴ), myoadenylate deaminase deficiency, and others; (2) to identify potentially MHS individuals as implications for future general anesthesia are important. If a patient is found to be MHS, preventive measures concerning the anesthetic technique have to be taken. Over the last decade, several experts have stated that individuals who have a history of EHS should be screened for MHS[2,16-18]. Even though the IVCT is an invasive test, it is still considered to be the most sensitive and specific test to determine a patient's predisposition to MHS. The estimation of the MH risk in a particular patient is certainly not straightforward, as illustrated by the case presentations. Patient 1 had a negative IVCT and a negative genetic analysis, and is considered to be non-MHS. Therefore, volatile anesthetics can safely be administered in the operating room/ICU to this patient. Patient 2 had a positive IVCT, but no mutation was found upon *RYR1* sequencing. However, it is well known that a *RYR1* mutation is found in only 50%-70% of patients with a positive IVCT[19]. CACNA1S cDNA sequencing was not performed in our patients in view of the cost and the large number of sequence changes reported, most of which are of unclear significance[20]. In this patient, volatile anesthesia has to be avoided in the future, because he is considered MHS by IVCT. Patient 3 had a positive IVCT and a positive *RYR1* mutation (p.N2342S; c.7025A>G - exon 43) that was previously linked to MH, and therefore, this patient is clearly at risk for MH upon exposure to volatile anesthetic agents; and (3) If *RYR1* mutations are found, the condition should be considered to be hereditary, and additional family studies are indicated.

The patient should be seen by a neurologist, because a large number of diverse etiologies have been implicated in acute EIR/EHS, and certain additional clinical features can aid to define the most appropriate investigations. A guideline for a diagnostic EIR/HS workup has been suggested by Capacchione *et al*[21]. Because of the rarity

and heterogeneity of these conditions, however, this EIR/HS workup remains a real diagnostic challenge.

A third group of patients at risk when given volatile anesthetic sedation are patients with congenital myopathies. This is a group of rare genetic muscle disorders (6 in 100000 live births) characterized by different structural abnormalities in skeletal muscle fibers either observable by light- or EM microscopy, and symptoms of hypotonia and muscle weakness present at birth (although the clinical expression may be delayed until childhood or even adult life). These myopathies are genetically heterogeneous, but a substantial subgroup is linked with "gain-of-function" mutations in the *RYR1*-gene, resulting in increased calcium conductance of the calcium-release channel and the potential for acute rhabdomyolysis when exposed to volatile anesthetics. This has been shown to be the case for central core disease, multiminicore disease, centronuclear myopathy, congenital fiber type disproportion, late-onset axial myopathy, and King-Denborough syndrome[22].

The propensity of patients with muscular dystrophies (especially Duchenne muscular dystrophy) to react adversely to volatile anesthetic sedation is well known; however, this does not occur through the presence of *RYR1* mutations but rather is the result of "toxic effects" of these agents as well as succinylcholine on the fragile sarcolemma. Prolonged exposure to volatile anesthetic agents, and certainly the use of succinylcholine, has to be avoided in this group of patients.

If intensive care sedation is needed in these patients, a combination of propofol, benzodiazepines, morphinomimetics, neuraxial block, and, as last resort, non-depolarizing neuromuscular blockers can be used. Dexmedetomidine use for procedural sedation is safe.

CONCLUSION

Dominantly inherited MHS is rare. Therefore, in the general population, life-threatening acute rhabdomyolysis following exposure to volatile anesthetics either in the operating room or the ICU is seldom encountered. However, because a substantial proportion of patients with EIR/EHS and congenital myopathies harbor *RYR1* mutations resulting in an increased calcium-conductivity of the Ca-release channel of the SR, volatile anesthetic sedation should not be used in these high-risk patients.

Contraindications for volatile anesthetic sedation in intensive care consist of: (1) known susceptibility for MH; (2) congenital myopathies (central core disease, multiminicore disease, centronuclear myopathy, congenital fiber type disproportion, late-onset axial myopathy, and King-Denborough syndrome); (3) duchenne muscular dystrophy; (4) exertional rhabdomyolysis; and (5) intracranial hypertension.

REFERENCES

1 **Hopkins PM**, Ellis FR, Halsall PJ. Evidence for related myopathies in exertional heat stroke and malignant hyperthermia. *Lancet* 1991; **338**: 1491-1492 [PMID: 1683922 DOI: 10.1016/0140-6736(91)92304-K]

2 **Wappler F**, Fiege M, Steinfath M, Agarwal K, Scholz J, Singh S, Matschke J, Schulte Am Esch J. Evidence for susceptibility to malignant hyperthermia in patients with exercise-induced rhabdomyolysis. *Anesthesiology* 2001; **94**: 95-100 [PMID: 11135728 DOI: 10.1097/00000542-200101000-00019]

3 **Rosenberg H**, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. *Orphanet J Rare Dis* 2015; **10**: 93 [PMID: 26238698 DOI: 10.1186/s13023-015-0310-1]

4 **Riazi S**, Larach MG, Hu C, Wijeysundera D, Massey C, Kraeva N. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands. *Anesth Analg* 2014; **118**: 381-387 [PMID: 23842196 DOI: 10.1213/ANE.0b013e3182937d8b]

5 **Ording H**, Brancadoro V, Cozzolino S, Ellis FR, Glauber V, Gonano EF, Halsall PJ, Hartung E, Heffron JJ, Heytens L, Kozak-Ribbens G, Kress H, Krivosic-Horber R, Lehmann-Horn F, Mortier W, Nivoche Y, Ranklev-Twetman E, Sigurdsson S, Snoeck M, Stieglitz P, Tegazzin V, Urwyler A, Wappler F. In vitro contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group: results of testing patients surviving fulminant MH and unrelated low-risk subjects. The European Malignant Hyperthermia Group. *Acta Anaesthesiol Scand* 1997; **41**: 955-966 [PMID: 9311391 DOI: 10.1111/j.1399-6576.1997.tb04820.x]

6 **Jerath A**, Parotto M, Wasowicz M, Ferguson ND. Volatile Anesthetics. Is a New Player Emerging in Critical Care Sedation? *Am J Respir Crit Care Med* 2016; **193**: 1202-1212 [PMID: 27002466 DOI: 10.1164/rccm.201512-2435CP]

7 **Bomberg H**, Glas M, Groesdonk VH, Bellgardt M, Schwarz J, Volk T, Meiser A. A novel device for target controlled administration and reflection of desflurane--the Mirus™. *Anaesthesia* 2014; **69**: 1241-1250 [PMID: 25040673 DOI: 10.1111/anae.12798]

8 **Wong K**, Wasowicz M, Grewal D, Fowler T, Ng M, Ferguson ND, Steel A, Jerath A. Efficacy of a simple scavenging system for long-term critical care sedation using volatile agent-based anesthesia. *Can J Anaesth* 2016; **63**: 630-632 [PMID: 26670802 DOI: 10.1007/s12630-015-0562-1]

9 **Jerath A**, Ferguson ND, Steel A, Wijeysundera D, Macdonald J, Wasowicz M. The use of volatile anesthetic agents for long-term critical care sedation (VALTS): study protocol for a pilot randomized controlled trial. *Trials* 2015; **16**: 560 [PMID: 26646404 DOI: 10.1186/s13063-015-1083-5]

10 **Purrucker JC**, Renzland J, Uhlmann L, Bruckner T, Hacke W, Steiner T, Bösel J. Volatile sedation with sevoflurane in intensive care patients with acute stroke or subarachnoid haemorrhage using AnaConDa®: an observational study. *Br J Anaesth* 2015; **114**: 934-943 [PMID: 25823541 DOI: 10.1093/bja/aev070]

11 **Centers for Disease Control and Prevention**. Heat illness among high school athletes --- United States, 2005-2009. *MMWR Morb Mortal Wkly Rep* 2010; **59**: 1009-1013 [PMID: 20724966]

12 **Rosenberg H**, Schuster F, Johannsen S. The introduction of a lightweight mini vaporizer and malignant hyperthermia. *Can J Anaesth* 2015; **62**: 319 [PMID: 25398599]

13 **Davis M**, Brown R, Dickson A, Horton H, James D, Laing N, Marston R, Norgate M, Perlman D, Pollock N, Stowell K. Malignant hyperthermia associated with exercise-induced rhabdomyolysis or congenital abnormalities and a novel RYR1 mutation in New Zealand and Australian pedigrees. *Br J Anaesth* 2002; **88**: 508-515 [PMID: 12066726 DOI: 10.1093/bja/88.4.508]

14 **Dlamini N**, Voermans NC, Lillis S, Stewart K, Kamsteeg EJ, Drost G, Quinlivan R, Snoeck M, Norwood F, Radunovic A, Straub V, Roberts M, Vrancken AF, van der Pol WL, de Coo RI, Manzur AY, Yau S, Abbs S, King A, Lammens M, Hopkins PM, Mohammed S, Treves S, Muntoni F, Wraige E, Davis MR, van Engelen B, Jungbluth H. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. *Neuromuscul Disord* 2013; **23**: 540-548 [PMID: 23628358 DOI: 10.1016/j.nmd.2013.03.008]

15 **Zhao X**, Song Q, Gao Y. Hypothesis: exertional heat stroke-induced myopathy and genetically inherited malignant hyper-

thermia represent the same disorder, the human stress syndrome. *Cell Biochem Biophys* 2014; **70**: 1325-1329 [PMID: 24948473 DOI: 10.1007/s12013-014-0059-5]

16 **Snoeck M**, Treves S, Molenaar JP, Kamsteeg EJ, Jungbluth H, Voermans NC. "Human Stress Syndrome" and the Expanding Spectrum of RYR1-Related Myopathies. *Cell Biochem Biophys* 2016; **74**: 85-87 [PMID: 26972305 DOI: 10.1007/s12013-015-0704-7]

17 **Grogan H**, Hopkins PM. Heat stroke: implications for critical care and anaesthesia. *Br J Anaesth* 2002; **88**: 700-707 [PMID: 12067009 DOI: 10.1093/bja/88.5.700]

18 **Sambuughin N**, Capacchione J, Blokhin A, Bayarsaikhan M, Bina S, Muldoon S. The ryanodine receptor type 1 gene variants in African American men with exertional rhabdomyolysis and malignant hyperthermia susceptibility. *Clin Genet* 2009; **76**: 564-568 [PMID: 19807743 DOI: 10.1111/j.1399-0004.2009.01251.x]

19 **Carpenter D**, Robinson RL, Quinnell RJ, Ringrose C, Hogg M, Casson F, Booms P, Iles DE, Halsall PJ, Steele DS, Shaw MA, Hopkins PM. Genetic variation in RYR1 and malignant hyperthermia phenotypes. *Br J Anaesth* 2009; **103**: 538-548 [PMID: 19648156 DOI: 10.1093/bja/aep204]

20 **Carpenter D**, Ringrose C, Leo V, Morris A, Robinson RL, Halsall PJ, Hopkins PM, Shaw MA. The role of CACNA1S in predisposition to malignant hyperthermia. *BMC Med Genet* 2009; **10**: 104 [PMID: 19825159 DOI: 10.1186/1471-2350-10-104]

21 **Capacchione JF**, Muldoon SM. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. *Anesth Analg* 2009; **109**: 1065-1069 [PMID: 19617585 DOI: 10.1213/ane.0b013e3181a9d8d9]

22 **Snoeck M**, van Engelen BG, Küsters B, Lammens M, Meijer R, Molenaar JP, Raaphorst J, Verschuuren-Bemelmans CC, Straathof CS, Sie LT, de Coo IF, van der Pol WL, de Visser M, Scheffer H, Treves S, Jungbluth H, Voermans NC, Kamsteeg EJ. RYR1-related myopathies: a wide spectrum of phenotypes throughout life. *Eur J Neurol* 2015; **22**: 1094-1112 [PMID: 25960145 DOI: 10.1111/ene.12713]

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MINIREVIEWS

Nutrient stimulation of mesenteric blood flow - implications for older critically ill patients

Thu AN Nguyen, Yasmine Ali Abdelhamid, Liza K Phillips, Leeanne S Chapple, Michael Horowitz, Karen L Jones, Adam M Deane

Thu AN Nguyen, Yasmine Ali Abdelhamid, Leeanne S Chapple, Adam M Deane, Discipline of Acute Care Medicine, University of Adelaide, Adelaide 5005, Australia

Liza K Phillips, Michael Horowitz, Karen L Jones, Adam M Deane, National Health and Medical Research Council Centre for Research Excellence in Translating Nutritional Science to Good Health, Adelaide 5000, Australia

Liza K Phillips, Michael Horowitz, Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide 5000, Australia

Liza K Phillips, Michael Horowitz, Karen L Jones, Discipline of Medicine, University of Adelaide, Adelaide 5005, Australia

Adam M Deane, Intensive Care Unit, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria 3050, Australia

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Correspondence to: Adam M Deane, MBBS, PhD, Intensive Care Unit, Royal Melbourne Hospital, University of Melbourne, 300 Grattan Street, Parkville, Victoria 3050, Australia. adam.deane@adelaide.edu.au
Telephone: +61-3-93429234

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Abstract

Nutrient ingestion induces a substantial increase in mesenteric blood flow. In older persons (aged ⩾ 65 years), particularly those with chronic medical conditions, the cardiovascular compensatory response may be inadequate to maintain systemic blood pressure during mesenteric blood pooling, leading to postprandial hypotension. In older ambulatory persons, postprandial hypotension is an important pathophysiological condition associated with an increased propensity for syncope, falls, coronary vascular events, stroke and death. In older critically ill patients, the administration of enteral nutrition acutely increases mesenteric blood flow, but whether this pathophysiological response is protective, or precipitates mesenteric ischaemia, is unknown. There are an increasing number of older patients surviving admission to intensive care units, who are likely to be at increased risk of postprandial hypotension, both during, and after, their stay in hospital. In this review, we describe the prevalence, impact and mechanisms of postprandial hypotension in older people and provide an overview of the impact of postprandial hypotension on feeding prescriptions in older critically ill patients. Finally, we provide evidence that postprandial hypotension is likely to be an unrecognised problem in older survivors of critical illness and discuss potential options for management.

Key words: Postprandial hypotension; Enteral nutrition; Critical care; Aged; Mesenteric ischaemia

Core tip: In older ambulatory persons, postprandial hypotension is an important pathophysiological condition associated with an increased propensity to coronary vascular events, stroke and death. In older critically ill patients, the administration of enteral nutrition acutely increases mesenteric blood flow, but whether this pathophysiological response is protective, or precipitates mesenteric ischaemia, is unknown. We herein describe the prevalence, impact and mechanisms and management of postprandial hypotension in older people. We finally provide an overview of the impact of postprandial hypotension on feeding prescriptions in and evidence that postprandial hypotension is likely to be an unrecognised problem in older survivors of critical illness.

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INTRODUCTION

Ingestion of nutrients initiates a complex process involving precise coordination between the gastrointestinal tract, autonomic and cardiovascular systems to increase intestinal blood flow, whilst simultaneously maintaining circulatory homeostasis[1,2]. Age and disease-related changes may compromise cardiovascular compensatory mechanisms, which, particularly in older persons, may result in a clinically relevant postprandial fall in blood pressure, known as postprandial hypotension (PPH). PPH is inconsistently defined but is generally regarded as a reduction in systolic blood pressure of $\geqslant$ 20 mmHg, or a decrease to $\leqslant$ 90 mmHg, that occurs within two hours of a meal and persists for at least 30 min[3]. This definition is empiric and derived from the definition of orthostatic hypotension[4]. It is important to recognise that although PPH frequently coexists with orthostatic hypotension, PPH is a distinct entity. However PPH may well occur more frequently, and have more substantive implications, than orthostatic hypotension[5,6].

EPIDEMIOLOGY

A recent meta-analysis reported that PPH occurs in about 20% of "healthy" older persons, about 30%-40% of nursing home residents, 20%-91% of hospitalised patients aged $\geqslant$ 65 years, about 40% of people with diabetes, and 40%-100% of patients with Parkinson's disease[7]. The wide range of reported prevalence in each group reflect the small cohort sizes and the confounding effect of lack of standardisation of methodology between studies; including the definition of PPH, composition of test meal, timing of meal ingestion, technique and duration of blood pressure measurement, and use of concomitant medications. However, it is clear that in each of these groups the prevalence of PPH is high and that the very elderly and patients with diseases associated with autonomic dysfunction are at particular risk. Surprisingly, the prevalence of PPH in elderly survivors of critical illness has not been evaluated.

CLINICAL IMPORTANCE OF POSTPRANDIAL HYPOTENSION

PPH is now recognised as an important pathophysiological condition, not only because of its high prevalence, but also due to the associated substantial morbidity and mortality[3]. In older people in the community, PPH is a strong predictor of syncope, falls, coronary events and stroke - irrespective of whether the individual has symptoms[8]. In a prospective study of 499 nursing home residents, Aronow *et al*[8] reported that the postprandial fall in systolic blood pressure was an independent risk factor for falls, coronary events, stroke and all-cause mortality. Supportive data are also provided by two case-control studies that report that the magnitude and prevalence of PPH are substantially greater in patients with a history of falls or syncope when compared to controls[9,10]. Furthermore, in a five-year study of nursing home residents, PPH was found to be an independent determinant of mortality (RR = 1.79; 95%CI: 1.19-2.68); with a "dose-response", such that all-cause mortality increased 13% for every 10 mmHg decrease in postprandial systolic blood pressure (RR = 1.13; 95%CI: 1.03-1.24)[11].

As indicated, preliminary data suggest that it is important to identify PPH even in those patients who are unaware of the condition. While PPH is associated with adverse outcomes, more than half (about 60%) of patients with PPH may be asymptomatic and, therefore, do not seek treatment[5,6]. For example, Kohara *et al*[12] studied 70 patients hospitalised with essential hypertension and reported that the prevalence of lacunar infarcts was increased two-fold in patients with asymptomatic PPH. The strong association between "asymptomatic" PPH and stroke has also been evident in larger cohorts of older people residing in nursing home facilities and ambulatory older people living in the community[8,13]. While this association does not establish causality, it provides a compelling rationale to diagnose PPH, which is a simple and inexpensive process[7], and to determine whether interventions that attenuate PPH mitigate the risk of adverse outcomes, such as cerebrovascular events[14]. The latter approach is to some extent compromised by the current lack of established effective management strategies[15].

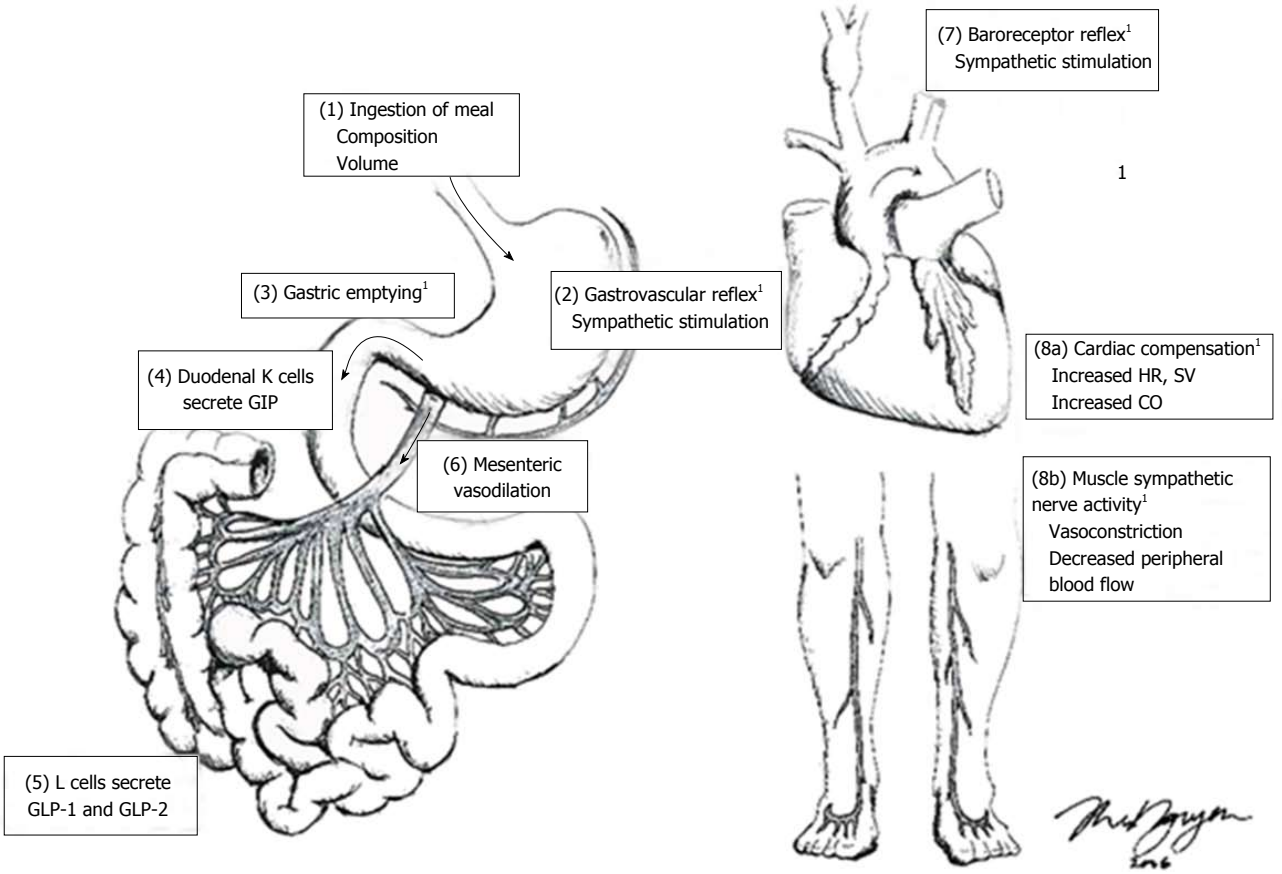

Figure 1 Factors involved in the regulation of postprandial blood pressure. (1) ingestion of a meal, with a greater carbohydrate load results in a greater postprandial hypotensive response; (2) Meal-induced gastric distension from the meal triggers stretch receptors in the stomach wall, increasing sympathetic nerve outflow; (3) gastric content is emptied into the small intestine, and, in response to the nutrient in the small intestine; (4, 5) gastrointestinal peptides are secreted from the small intestine (*e.g.*, GLP-1 and GLP-2, glucagon-like peptide-1 and 2; GIP, glucose insulinotropic polypeptide); (6) gastrointestinal peptides stimulate mesenteric vessel dilation; (7) this results in reduced circulating blood volume and the reduction in blood pressure is detected by baroreceptors; (8a) the "gastrovascular" and baroreceptor reflexes stimulate sympathetic activity to increase heart rate (HR), stroke volume (SV) and thus cardiac output (CO) to maintain postprandial blood pressure; (8b) skeletal vasculature constricts to decrease peripheral blood flow. [1]These factors are affected by age and have been identified as potential pathophysiological mechanisms of postprandial hypotension. Figure drawn by Ms. T. Nguyen. GIP: Glucose-dependent insulinotropic peptide; GLP: Glucagon-like peptide.

EFFECT OF NUTRIENT STIMULATION ON MESENTERIC BLOOD SUPPLY IN HEALTH

The presence of nutrients, particularly glucose and fats[16], in the small intestine stimulates secretion of several vasoactive gastrointestinal hormones that augment intestinal blood flow[17]. In response to direct contact with intraluminal nutrients, intestinal K-cells promptly secrete glucose-dependent insulinotropic peptide, and L-cells secrete glucagon-like peptide-1 and -2 (GLP-1 and GLP-2)[18] (Figure 1). There is a two-fold increase in blood flow through the superior mesenteric artery[3,19], such that up to 20% of total blood volume is diverted to the gastrointestinal tract, which facilitates digestion and absorption of nutrients[17]. The magnitude of this increase in mesenteric blood flow is dependent on meal size and the rate of nutrient delivery from the stomach into the small intestine[20,21]. In the research setting, the potential confounding effect of inter- and intra-individual differences in the rate of gastric emptying on PPH can be regulated by directly infusing nutrient into the small intestine[21,22]. Utilising this technique, it is apparent that mesenteric blood flow increases when nutrient is delivered at a greater rate and, particularly, when carbohydrate or fat are ingested when compared to protein[16,23].

PHYSIOLOGICAL HAEMODYNAMIC RESPONSES TO MEAL-INDUCED MESENTERIC BLOOD FLOW

In health, blood pressure is maintained even in the presence of postprandial mesenteric vasodilation *via* increases in cardiac contractility and peripheral vasoconstriction[3]. Meal-induced splanchnic blood pooling results in a temporary and virtual "hypovolaemia" that stimulates arterial baroreceptors[3], while gastric distension activates the "gastrovascular reflex"[24] (Figure 1). Together, these autonomic reflexes increase sympathetic nerve outflow to the heart and other vascular beds[5,16] to increase both heart rate and stroke volume, thereby, augmenting

cardiac output[3]. In parallel, the increase in muscle sympathetic nerve activity leads to a compensatory vasoconstriction of skeletal vasculature[25].

MECHANISMS UNDERLYING POSTPRANDIAL HYPOTENSION IN AMBULANT OLDER PERSONS

The pathophysiology of PPH reflects multiple factors that impair reflex cardiovascular compensation[3]. Given that mesenteric blood flow appears to be essentially unaffected by age[22], it has been postulated that autonomic dysfunction is the main, albeit not sole contributor, to PPH[7,26,27]. Masuda *et al*[28] estimated that healthy older people require a two to three-fold increase in sympathetic nerve activity to maintain postprandial blood pressure. However, with age, the sensitivity of the gastrovascular and baroreceptor reflexes diminishes[25,29], such that gastric distension may have minimal, or no effect, on plasma noradrenaline concentrations[3]. Consequently, the hypertensive and muscle sympathetic nerve activity responses following ingestion is blunted in apparently "healthy" older people[22,25]. In addition, PPH is common in individuals with autonomic impairment associated with primary autonomic failure, multiple system atrophy, Parkinson's disease or diabetes mellitus, conditions that are all prevalent in older people[30]. In autonomic failure, the postprandial increase in cardiac output is attenuated, indicative of a diminished compensatory response during mesenteric vasodilation[27].

PHYSIOLOGICAL RESPONSES TO ENTERAL NUTRITION IN THE CRITICALLY ILL

Administration of enteral nutrition (EN) is part of standard care of critically ill patients, although the optimal timing for the commencement of EN in patients with shock, and/or who are receiving substantive doses of catecholamines, remains controversial[31]. EN has several theoretical advantages over parenteral nutrition, including the stimulation of mesenteric blood flow and bowel contractility, as well as the release of trophic hormones[31]. In addition, early (within 24-48 h) initiation of EN supports commensal bacteria and favours maintenance of the structural and functional integrity of the gut mucosal barrier, including the gut-associated lymphoid tissue[32,33]. Consequently, feeding *via* the enteral route may limit bacterial overgrowth and attenuate translocation of gastrointestinal organisms and toxins[33,34]. However, in patients with established shock, postprandial nutrient-stimulated demand for mesenteric blood flow may potentially complicate systemic haemodynamics, while the increase in mesenteric blood flow may be deleterious *via* reperfusion injury[35]. The clinical dilemma as to whether EN protects against, or exacerbates, mesenteric ischaemia during critical illness, has been reviewed by several groups[35-37].

SLOWER GASTRIC EMPTYING IN CRITICALLY ILL PATIENTS MAY MITIGATE POSTPRANDIAL HYPOTENSION

Despite EN being a frequently administered intervention, there is a paucity of information regarding its effects on gastrointestinal peptides and mesenteric blood supply in the critically ill[38,39]. However, because of the frequent delay in gastric emptying associated with critical illness[40], the rate of exposure of nutrient to the small intestinal mucosa is diminished in many patients[41] that should, intuitively, attenuate vasoactive gastrointestinal peptide secretion. Our group has, however, reported increases in fasting and postprandial GLP-1 concentrations in the critically ill, particularly in those with feed intolerance[42]. This may represent the effect of undigested carbohydrates and fats remaining in the distal small intestine and colon, resulting in sustained secretion of gastrointestinal peptides. Alternatively, this may be secondary to an increased sensitivity to hormone secretion or decreased hormone clearance during critical illness.

IMPLICATIONS OF CHANGES IN MESENTERIC BLOOD SUPPLY DURING ENTERAL FEEDING

It has been suggested that administration of EN to those patients with haemodynamic compromise or hypoxia could be harmful[35]. According to this concept, fasting mesenteric blood supply is marginal, and the introduction of EN will increase demand beyond oxygen delivery capacity, thereby provoking mesenteric ischaemia[43,44]. While non-occlusive mesenteric ischaemia occurs in < 1% of critically ill patients, it carries substantial mortality (up to 80% in some series)[45].

The pathophysiology of non-occlusive mesenteric ischaemia in the critically ill is incompletely understood, but it is usually preceded by hypotension or hypovolaemia[46]. It has been suggested that during systemic hypotension mesenteric blood supply may be "sacrificed" to preserve systemic blood pressure and, in the presence of artheromatous plaques, which are normally associated with subclinical stenosis, this leads to critical ischaemia[47]. It has also been proposed that disordered autoregulation of mesenteric vasculature causes intense vasospasm of the superior mesenteric artery, even when systemic blood pressure is normal, which may be exacerbated during reperfusion[48]. The tips of the intestinal villi are considered to be especially sensitive to ischaemia, particularly given their reliance on a so-called "counter-current exchanger system" for oxygen delivery[36]. Arterial blood is supplied *via* the central arterial vessel that arborises at the tip of the villus forming a dense subepithelial network of capillaries and

oxygen cross-diffuses from the central supplying vessel to the peripheral limb of the vascular hairpin loop[49]. It has been proposed that when mesenteric blood flow is compromised the velocity of blood flow in the hairpin vascular loops is decreased leading to extravascular oxygen shunting at the base of villi[49], which causes local oxygen deficits at the villi tips, ultimately resulting in ischaemic injury and cell death[36,49].

The tips of intestinal villi are essential for nutrient absorption, and it has been hypothesised that non-specific symptoms of gastrointestinal intolerance represents one of the earliest signs of injury[46]. The presence of unabsorbed nutrient in the bowel lumen results in fluid shifts, bacterial overgrowth and fermentation, potentially causing marked bowel distension[46]. Patients may, therefore, initially present with nausea, diarrhoea, bloating and abdominal distension. According to this theory, as the bowel wall is stretched further, there is a progressive increase in capillary sludging and a reduction in mucosal perfusion[46]. The resultant increased mural and vascular permeability allows translocation of fluid, bacteria and toxins across the bowel wall, which induces third-space fluid shifts and activates a cascade of cytokines and oxidative radicals that exacerbate the ischaemic episode[48]. Furthermore, changes frequently associated with age, such as the presence of congestive heart failure, dysrhythmias or cardiogenic shock, are likely to exacerbate the processes in the development of mucosal ischaemia, thereby identifying older critically ill patients as a high-risk group[46]. However, previous case series of critically ill patients with non-occlusive mesenteric ischaemia include a large proportion of relatively young patients[50,51], which appears inconsistent with the proposed events in this model of pathophysiology.

Moreover, there is conflicting data, which suggest that during a period of systemic hypotension EN is protective and may reduce, or even prevent, non-occlusive mesenteric ischaemia[43]. A number of studies in animal models have demonstrated that small intestinal nutrient stimulates superior mesenteric artery blood flow and mucosal microcirculatory flow[34,43,52-54]. However, it should be recognised that these studies frequently use relatively young animals and an "acute insult" model[55]. Therefore, extrapolation of these data to older critically ill humans, who characteristically have considerable co-morbid illnesses and have been receiving liquid EN for a number of days, should be made highly circumspectly.

There is also a concern that changes in mesenteric blood supply stimulated by EN will lead to redistribution of cardiac output to the mesenteric circulation, thereby, "stealing" blood/oxygen from other organs including the heart and brain[43]. It is well established that PPH is associated with coronary vascular events and stroke in the "healthy" ambulant older persons and hospitalised patients with hypertension potentially due to this "stealing" phenomenon[3]. Whether this phenomenon occurs in the critically ill, and has clinical implications, is unknown.

NUTRIENT STIMULATES MESENTERIC BLOOD FLOW DURING CRITICAL ILLNESS

To improve understanding of mesenteric blood flow during enteral feeding in the critically ill several investigators have "bypassed" the stomach and delivered nutrient directly into the small intestine. Revelley *et al*[38] reported that a standard polymeric nutrient liquid administered *via* a postpyloric tube to nine patients one-day post-cardiopulmonary bypass, who were also receiving catecholamine support, was associated with an approximately 30% increase in postprandial hepatosplanchnic blood flow with minimal impact on systemic haemodynamics. Rokyta *et al*[56] also reported that standard polymeric nutrient liquid infused *via* a postpyloric tube to ten patients with severe sepsis (mean age 61 years and n = 8 receiving catecholamine support) increased hepatosplanchnic blood flow. These investigators found that blood pressure was unaffected by nutrient administration, but that there were modest increases in cardiac output, measured using pulmonary artery thermodilution, when EN was commenced[56]. However, both studies used indocyanine green clearance to measure hepatosplanchnic blood supply, which is dependent on adequate hepatic perfusion and function, and may well be less predictable in the critically ill than in health. Furthermore, both groups utilised a mixed nutrient liquid delivered at a rate (0.75 kcal/min), which is less than normal physiological gastric emptying (1-4 kcal/min)[21] and standard feeding regimens[57,58]. Accordingly, this rate is not known to stimulate changes in mesenteric blood flow in ambulatory older people[22], and is not the rate of gastric emptying in many critically ill patients[59]. Our group evaluated the effect of liquid glucose (2 kcal/min) infused directly into the small intestine in critically ill patients aged $\geqslant$ 65 years[39]. Compared to healthy age-matched persons, we observed that postprandial mesenteric blood flow measured by duplex ultrasound is attenuated in older critically ill patients (n = 11, but only one patient had established shock and required exogenous noradrenaline), which was associated with reduced glucose absorption, while mean arterial pressure was unaffected by nutrient infusion at this rate[39].

In summary, while there are limited data relating to the acute effect of nutrient on mesenteric blood flow, it appears that nutrient does increase macrovascular blood flow. In older critically ill patients with shock, there is no clear evidence that EN precipitates or protects against mesenteric ischaemia, or exacerbates hypotension, in this group. Nonetheless, feeding prescriptions that limit delivery to $\leqslant$ 1.5 kcal/min of a mixed nutrient liquid are likely to be well tolerated.

PREVALENCE AND OUTCOMES OF OLDER PEOPLE IN THE ICU

Given the aging population and improved survival to older age, there is an increasing demand for health care services in older persons, including services provided in the intensive care unit (ICU) for critically ill patients[60,61]. Recent multicentre cohort studies indicate that > 50% of ICU admissions are for patients aged ⩾ 65 years, with 8%-13% of admissions being the very old (aged ⩾ 80 years)[60,62]. Indeed, the prevalence of older critically ill patients admitted to ICUs is projected to rise by 3%-5% annually[60,62]. The increased rate of hospitalisation and admission to ICU in this group is attributable, in part, to the higher prevalence of chronic illness and organ impairment associated with older age[63].

Mortality and health care resource utilisation during, and following, hospital stay in older ICU survivors are substantial[62]. Approximately 16% of ICU patients die in hospital, with older patients being two- to three-fold more likely to die, making up about 70% of ICU non-survivors[60,62]. Six-months after hospital discharge, almost half of ICU survivors have presented to the emergency department and one-third required hospital readmission[62]. Within five years of hospital discharge, one-third of survivors of critical illness die, with about 70% of ICU non-survivors being aged ⩾ 65 years[62]. Those who survive critical illness have a greater reduction in physical function post-ICU requiring more rehabilitation services and utilisation of long-term care facilities[62,64]. Accordingly, it is evident that older survivors of ICU represent a group that may benefit from increased follow-up and novel interventions, particularly when considering the burden associated with health care utilisation following critical illness.

POTENTIAL FOR PPH IN OLDER SURVIVORS OF CRITICAL ILLNESS

All critically ill patients, regardless of age, are at high risk of acute autonomic nerve dysfunction due to the insult critical illness inflicts on organs, which disrupts the inter-organ communication network[65]. Spectral analysis of heart rate variability is frequently used to assess sympathetic-parasympathetic balance and cardiorespiratory interactions non-invasively[65]. While the precise prevalence of autonomic dysfunction in the critically ill is unknown it appears to be is poor prognostic marker for patients within the ICU[65]. Acute autonomic dysfunction, as evidenced as attenuation in heart rate variability, has been reported to be associated with the development of multiple organ dysfunction, cardiac arrhythmias, and death, and it can persist for prolonged periods even after discharge from hospital[66-68]. Schmidt and colleagues prospectively followed 90 critically ill patients with score-defined multiple organ dysfunction (56 patients were on catecholamine support), and reported about 95% of patients had significantly reduced heart rate variability, which was not affected by the administration of sedatives or catecholamines[65]. These investigators also reported that heart rate variability was comparable in young (< 40 years, n = 9), middle aged (40-60 years, n = 31) and older (> 60 years, n = 45), but baroreflex sensitivity declined with age[65]. Given that the baroreceptor reflex and cardiac autonomic function are fundamental to the maintenance of postprandial blood pressure, it is intuitively plausible that older patients who survive critical illness and have autonomic dysfunction represent a group at risk of PPH. However, there is limited data as to the prevalence of PPH in survivors of critical illness and it is also possible that delayed gastric emptying or attenuated superior mesenteric blood flow, which are both observed during critical illness, persist after ICU, and this would mitigate the risk of PPH.

POTENTIAL INTERVENTIONS FOR PATIENTS WITH PPH

Management of PPH can be non-pharmacological, or pharmacological and attenuate PPH by targeting the mechanism(s) involved in the pathophysiology of PPH, as specified in Figure 1[15]. Interventions, such as consuming smaller, more frequent meals, reducing carbohydrate content and protein "pre-loads", to reduce the rate of glucose absorption in the small intestine may be effective, as this has been postulated to reduce the magnitude and duration of increased mesenteric blood flow[23]. The simple task of drinking approximately 350 mL of water immediately prior to nutrient ingestion, to maximise gastric distension, attenuates PPH, probably *via* the gastrovascular reflex[69]. Gastric emptying can be slowed with the use of guar and other "pre-load" stimulants[15]. Inhibition of gastrointestinal peptides may also be achieved *via* the use of alpha-glucosidase inhibitors (*e.g.,* acarbose) or somatostatin analogues (*e.g.,* octreotide)[15,70]. Alternatively, sympathetic nerve activity can be directly stimulated *via* postprandial exercise or caffeine[15]. However, the evidence to support the efficacy of these interventions is limited as studies have, for the main part been acute and limited to small cohorts, often including individuals who do not clearly meet the criteria for diagnosis of PPH. Nevertheless, the use of inexpensive interventions, such as eating smaller meals and drinking water may be sufficient to attenuate PPH.

CONCLUSION

PPH is recognised as an important pathophysiological condition, which is prevalent in older people (aged ⩾ 65 years) living within the community, and is associated with considerable morbidity and mortality. Demographic changes have resulted in an older population within the ICU and this group is likely to be particularly susceptible to PPH due to their co-morbid conditions, as well as the frequent critical illness-associated autonomic dysfunction. While administration of EN will acutely increase me-

senteric blood flow in this group, whether this pathophysiological response is protective, harmful, or has no effect on blood pressure, remains uncertain. Current management strategies for PPH are limited. Further work is required to determine the prevalence of this condition in older survivors of critical illness and evaluate novel interventions in this cohort.

REFERENCES

1 **Oberman AS**, Gagnon MM, Kiely DK, Nelson JC, Lipsitz LA. Autonomic and neurohumoral control of postprandial blood pressure in healthy aging. *J Gerontol A Biol Sci Med Sci* 2000; **55**: M477-M483 [PMID: 10952372]

2 **Takamori M**, Hirayama M, Kobayashi R, Ito H, Mabuchi N, Nakamura T, Hori N, Koike Y, Sobue G. Altered venous capacitance as a cause of postprandial hypotension in multiple system atrophy. *Clin Auton Res* 2007; **17**: 20-25 [PMID: 17139443 DOI: 10.1007/s10286-006-0378-8]

3 **Jansen RW**, Lipsitz LA. Postprandial hypotension: epidemiology, pathophysiology, and clinical management. *Ann Intern Med* 1995; **122**: 286-295 [PMID: 7825766]

4 **Freeman R**, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz IJ, Schondorf R, Stewart JM, van Dijk JG. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Auton Neurosci* 2011; **161**: 46-48 [PMID: 21393070 DOI: 10.1016/j.autneu.2011.02.004]

5 **Imai C**, Muratani H, Kimura Y, Kanzato N, Takishita S, Fukiyama K. Effects of meal ingestion and active standing on blood pressure in patients & gt; or = 60 years of age. *Am J Cardiol* 1998; **81**: 1310-1314 [PMID: 9631968]

6 **Maurer MS**, Karmally W, Rivadeneira H, Parides MK, Bloomfield DM. Upright posture and postprandial hypotension in elderly persons. *Ann Intern Med* 2000; **133**: 533-536 [PMID: 11015166]

7 **Trahair LG**, Horowitz M, Jones KL. Postprandial hypotension: a systematic review. *J Am Med Dir Assoc* 2014; **15**: 394-409 [PMID: 24630686 DOI: 10.1016/j.jamda.2014.01.011]

8 **Aronow WS**, Ahn C. Association of postprandial hypotension with incidence of falls, syncope, coronary events, stroke, and total mortality at 29-month follow-up in 499 older nursing home residents. *J Am Geriatr Soc* 1997; **45**: 1051-1053 [PMID: 9288010]

9 **Puisieux F**, Bulckaen H, Fauchais AL, Drumez S, Salomez-Granier F, Dewailly P. Ambulatory blood pressure monitoring and postprandial hypotension in elderly persons with falls or syncopes. *J Gerontol A Biol Sci Med Sci* 2000; **55**: M535-M540 [PMID: 10995052]

10 **Schoon Y**, Olde Rikkert MG, Rongen S, Lagro J, Schalk B, Claassen JA. Head turning-induced hypotension in elderly people. *PLoS One* 2013; **8**: e72837 [PMID: 23977361 DOI: 10.1371/journal.pone.0072837]

11 **Fisher AA**, Davis MW, Srikusalanukul W, Budge MM. Postprandial hypotension predicts all-cause mortality in older, low-level care residents. *J Am Geriatr Soc* 2005; **53**: 1313-1320 [PMID: 16078956 DOI: 10.1111/j.1532-5415.2005.53415.x]

12 **Kohara K**, Jiang Y, Igase M, Takata Y, Fukuoka T, Okura T, Kitami Y, Hiwada K. Postprandial hypotension is associated with asymptomatic cerebrovascular damage in essential hypertensive patients. *Hypertension* 1999; **33**: 565-568 [PMID: 9931166]

13 **Tabara Y**, Okada Y, Uetani E, Nagai T, Igase M, Kido T, Ochi N, Ohara M, Takita R, Kohara K, Miki T. Postprandial hypotension as a risk marker for asymptomatic lacunar infarction. *J Hypertens* 2014; **32**: 1084-1090; discussion 1090 [PMID: 24695394 DOI: 10.1097/hjh.0000000000000150]

14 **Parati G**, Bilo G. Postprandial blood pressure fall: another dangerous face of blood pressure variability. *J Hypertens* 2014; **32**: 983-985 [PMID: 24695391 DOI: 10.1097/hjh.0000000000000172]

15 **Ong AC**, Myint PK, Potter JF. Pharmacological treatment of postprandial reductions in blood pressure: a systematic review. *J Am Geriatr Soc* 2014; **62**: 649-661 [PMID: 24635650 DOI: 10.1111/jgs.12728]

16 **Gentilcore D**, Hausken T, Meyer JH, Chapman IM, Horowitz M, Jones KL. Effects of intraduodenal glucose, fat, and protein on blood pressure, heart rate, and splanchnic blood flow in healthy older subjects. *Am J Clin Nutr* 2008; **87**: 156-161 [PMID: 18175750]

17 **Fara JW**, Rubinstein EH, Sonnenschein RR. Intestinal hormones in mesenteric vasodilation after intraduodenal agents. *Am J Physiol* 1972; **223**: 1058-1067 [PMID: 4654340]

18 **Kar P**, Cousins CE, Annink CE, Jones KL, Chapman MJ, Meier JJ, Nauck M, Horowitz M, Deane AM. Effects of glucose-dependent insulinotropic polypeptide on gastric emptying, glycaemia and insulinaemia during critical illness: a prospective, double blind, randomised, crossover study. *Crit Care* 2015; **19**: 20 [PMID: 25613747 DOI: 10.1186/s13054-014-0718-3]

19 **Kearney MT**, Cowley AJ, Stubbs TA, Evans A, Macdonald IA. Depressor action of insulin on skeletal muscle vasculature: a novel mechanism for postprandial hypotension in the elderly. *J Am Coll Cardiol* 1998; **31**: 209-216 [PMID: 9426042]

20 **Puvi-Rajasingham S**, Mathias CJ. Effect of meal size on postprandial blood pressure and on postural hypotension in primary autonomic failure. *Clin Auton Res* 1996; **6**: 111-114 [PMID: 8726096]

21 **Vanis L**, Gentilcore D, Rayner CK, Wishart JM, Horowitz M, Feinle-Bisset C, Jones KL. Effects of small intestinal glucose load on blood pressure, splanchnic blood flow, glycemia, and GLP-1 release in healthy older subjects. *Am J Physiol Regul Integr Comp Physiol* 2011; **300**: R1524-R1531 [PMID: 21389332 DOI: 10.1152/ajpregu.00378.2010]

22 **Trahair LG**, Vanis L, Gentilcore D, Lange K, Rayner CK, Horowitz M, Jones KL. Effects of variations in duodenal glucose load on blood pressure, heart rate, superior mesenteric artery blood flow and plasma noradrenaline in healthy young and older subjects. *Clin Sci* (Lond) 2012; **122**: 271-279 [PMID: 21942924 DOI: 10.1042/cs20110270]

23 **O'Donovan D**, Feinle C, Tonkin A, Horowitz M, Jones KL. Postprandial hypotension in response to duodenal glucose delivery in healthy older subjects. *J Physiol* 2002; **540**: 673-679 [PMID: 11956353]

24 **Vanis L**, Gentilcore D, Hausken T, Pilichiewicz AN, Lange K, Rayner CK, Feinle-Bisset C, Meyer JH, Horowitz M, Jones KL. Effects of gastric distension on blood pressure and superior mesenteric artery blood flow responses to intraduodenal glucose in healthy older subjects. *Am J Physiol Regul Integr Comp Physiol* 2010; **299**: R960-R967 [PMID: 20554933 DOI: 10.1152/ajpregu.00235.2010]

25 **Fagius J**, Ellerfelt K, Lithell H, Berne C. Increase in muscle nerve sympathetic activity after glucose intake is blunted in the elderly. *Clin Auton Res* 1996; **6**: 195-203 [PMID: 8902315]

26 **Lagro J**, Meel-van den Abeelen A, de Jong DL, Schalk BW, Olde Rikkert MG, Claassen JA. Geriatric hypotensive syndromes are not explained by cardiovascular autonomic dysfunction alone. *J Gerontol A Biol Sci Med Sci* 2013; **68**: 581-589 [PMID: 23070881 DOI: 10.1093/gerona/gls214]

27 **Kooner JS**, Raimbach S, Watson L, Bannister R, Peart S, Mathias CJ. Relationship between splanchnic vasodilation and postprandial hypotension in patients with primary autonomic failure. *J Hypertens Suppl* 1989; **7**: S40-S41 [PMID: 2632742]

28 **Masuda Y**, Kawamura A. Role of the autonomic nervous system in postprandial hypotension in elderly persons. *J Cardiovasc Pharmacol* 2003; **42** Suppl 1: S23-S26 [PMID: 14871024]

29 **van Orshoven NP**, Oey PL, van Schelven LJ, Roelofs JM, Jansen PA, Akkermans LM. Effect of gastric distension on cardiovascular parameters: gastrovascular reflex is attenuated in the elderly. *J Physiol* 2004; **555**: 573-583 [PMID: 14724212 DOI: 10.1113/

jphysiol.2003.056580]
30 **Trahair LG**, Kimber TE, Flabouris K, Horowitz M, Jones KL. Gastric emptying, postprandial blood pressure, glycaemia and splanchnic flow in Parkinson's disease. *World J Gastroenterol* 2016; **22**: 4860-4867 [PMID: 27239112 DOI: 10.3748/wjg.v22.i20.4860]
31 **McClave SA**, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016; **40**: 159-211 [PMID: 26773077 DOI: 10.1177/0148607115621863]
32 **Jabbar A**, Chang WK, Dryden GW, McClave SA. Gut immunology and the differential response to feeding and starvation. *Nutr Clin Pract* 2003; **18**: 461-482 [PMID: 16215082]
33 **Liew VY**, Chapman MJ, Nguyen NQ, Cousins CE, Plummer MP, Chapple LA, Abdelhamid YA, Manton ND, Swalling A, Sutton-Smith P, Burt AD, Deane AM. A prospective observational study of the effect of critical illness on ultrastructural and microscopic morphology of duodenal mucosa. *Crit Care Resusc* 2016; **18**: 102-108 [PMID: 27242108]
34 **Gianotti L**, Alexander JW, Gennari R, Pyles T, Babcock GF. Oral glutamine decreases bacterial translocation and improves survival in experimental gut-origin sepsis. *JPEN J Parenter Enteral Nutr* 1995; **19**: 69-74 [PMID: 7658604]
35 **McClave SA**, Chang WK. Feeding the hypotensive patient: does enteral feeding precipitate or protect against ischemic bowel? *Nutr Clin Pract* 2003; **18**: 279-284 [PMID: 16215051]
36 **Cresci G**, Cúe J. The patient with circulatory shock: to feed or not to feed? *Nutr Clin Pract* 2008; **23**: 501-509 [PMID: 18849555 DOI: 10.1177/0884533608323431]
37 **Yang S**, Wu X, Yu W, Li J. Early enteral nutrition in critically ill patients with hemodynamic instability: an evidence-based review and practical advice. *Nutr Clin Pract* 2014; **29**: 90-96 [PMID: 24449685 DOI: 10.1177/0884533613516167]
38 **Revelly JP**, Tappy L, Berger MM, Gersbach P, Cayeux C, Chioléro R. Early metabolic and splanchnic responses to enteral nutrition in postoperative cardiac surgery patients with circulatory compromise. *Intensive Care Med* 2001; **27**: 540-547 [PMID: 11355123]
39 **Sim JA**, Horowitz M, Summers MJ, Trahair LG, Goud RS, Zaknic AV, Hausken T, Fraser JD, Chapman MJ, Jones KL, Deane AM. Mesenteric blood flow, glucose absorption and blood pressure responses to small intestinal glucose in critically ill patients older than 65 years. *Intensive Care Med* 2013; **39**: 258-266 [PMID: 23096428 DOI: 10.1007/s00134-012-2719-5]
40 **Kar P**, Jones KL, Horowitz M, Chapman MJ, Deane AM. Measurement of gastric emptying in the critically ill. *Clin Nutr* 2015; **34**: 557-564 [PMID: 25491245 DOI: 10.1016/j.clnu.2014.11.003]
41 **Deane AM**, Rayner CK, Keeshan A, Cvijanovic N, Marino Z, Nguyen NQ, Chia B, Summers MJ, Sim JA, van Beek T, Chapman MJ, Horowitz M, Young RL. The effects of critical illness on intestinal glucose sensing, transporters, and absorption. *Crit Care Med* 2014; **42**: 57-65 [PMID: 23963126 DOI: 10.1097/CCM.0b013e318298a8af]
42 **Summers MJ**, DI Bartolomeo AE, Zaknic AV, Chapman MJ, Nguyen NQ, Zacharakis B, Rayner CK, Horowitz M, Deane AM. Endogenous amylin and glucagon-like peptide-1 concentrations are not associated with gastric emptying in critical illness. *Acta Anaesthesiol Scand* 2014; **58**: 235-242 [PMID: 24410108 DOI: 10.1111/aas.12252]
43 **Kazamias P**, Kotzampassi K, Koufogiannis D, Eleftheriadis E. Influence of enteral nutrition-induced splanchnic hyperemia on the septic origin of splanchnic ischemia. *World J Surg* 1998; **22**: 6-11 [PMID: 9465754]
44 **Kles KA**, Wallig MA, Tappenden KA. Luminal nutrients exacerbate intestinal hypoxia in the hypoperfused jejunum. *JPEN J Parenter Enteral Nutr* 2001; **25**: 246-253 [PMID: 11531215]
45 **Park WM**, Gloviczki P, Cherry KJ, Hallett JW, Bower TC, Panneton JM, Schleck C, Ilstrup D, Harmsen WS, Noel AA. Contemporary management of acute mesenteric ischemia: Factors associated with survival. *J Vasc Surg* 2002; **35**: 445-452 [PMID: 11877691]
46 **Schunn CD**, Daly JM. Small bowel necrosis associated with post-operative jejunal tube feeding. *J Am Coll Surg* 1995; **180**: 410-416 [PMID: 7719544]
47 **Fiddian-Green RG**. Splanchnic ischaemia and multiple organ failure in the critically ill. *Ann R Coll Surg Engl* 1988; **70**: 128-134 [PMID: 3044239]
48 **Bradbury AW**, Brittenden J, McBride K, Ruckley CV. Mesenteric ischaemia: a multidisciplinary approach. *Br J Surg* 1995; **82**: 1446-1459 [PMID: 8535792]
49 **Lundgren O**, Haglund U. The pathophysiology of the intestinal countercurrent exchanger. *Life Sci* 1978; **23**: 1411-1422 [PMID: 362102]
50 **Scaife CL**, Saffle JR, Morris SE. Intestinal obstruction secondary to enteral feedings in burn trauma patients. *J Trauma* 1999; **47**: 859-863 [PMID: 10568712]
51 **Marvin RG**, McKinley BA, McQuiggan M, Cocanour CS, Moore FA. Nonocclusive bowel necrosis occurring in critically ill trauma patients receiving enteral nutrition manifests no reliable clinical signs for early detection. *Am J Surg* 2000; **179**: 7-12 [PMID: 10737569]
52 **Inoue S**, Lukes S, Alexander JW, Trocki O, Silberstein EB. Increased gut blood flow with early enteral feeding in burned guinea pigs. *J Burn Care Rehabil* 1989; **10**: 300-308 [PMID: 2507547]
53 **Gosche JR**, Garrison RN, Harris PD, Cryer HG. Absorptive hyperemia restores intestinal blood flow during Escherichia coli sepsis in the rat. *Arch Surg* 1990; **125**: 1573-1576 [PMID: 2123086]
54 **Bortenschlager L**, Roberts PR, Black KW, Zaloga GP. Enteral feeding minimizes liver injury during hemorrhagic shock. *Shock* 1994; **2**: 351-354 [PMID: 7743361]
55 **Bihari S**, Maiden M, Deane A, Fuchs R, Fraser J, Bersten AD, Bellomo R. Preclinical research in critical care - the Australasian perspective. *Crit Care Resusc* 2015; **17**: 151-152 [PMID: 26282251]
56 **Rokyta R**, Matejovic M, Krouzecky A, Senft V, Trefil L, Novak I. Post-pyloric enteral nutrition in septic patients: effects on hepato-splanchnic hemodynamics and energy status. *Intensive Care Med* 2004; **30**: 714-717 [PMID: 14767586]
57 **Alberda C**, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, Heyland DK. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Med* 2009; **35**: 1728-1737 [PMID: 19572118 DOI: 10.1007/s00134-009-1567-4]
58 **Peake SL**, Davies AR, Deane AM, Lange K, Moran JL, O'Connor SN, Ridley EJ, Williams PJ, Chapman MJ. Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial. *Am J Clin Nutr* 2014; **100**: 616-625 [PMID: 24990423 DOI: 10.3945/ajcn.114.086322]
59 **Kar P**, Plummer MP, Chapman MJ, Cousins CE, Lange K, Horowitz M, Jones KL, Deane AM. Energy-Dense Formulae May Slow Gastric Emptying in the Critically Ill. *JPEN J Parenter Enteral Nutr* 2016; **40**: 1050-1056 [PMID: 26038421 DOI: 10.1177/0148607115588333]
60 **Bagshaw SM**, Webb SA, Delaney A, George C, Pilcher D, Hart GK, Bellomo R. Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Crit Care* (London, England) 2009; **13**: R45 [PMID: 19335921 DOI: 10.1186/cc7768]
61 **Heyland DK**, Stelfox HT, Garland A, Cook D, Dodek P, Kutsogiannis J, Jiang X, Turgeon AF, Day AG. Predicting Performance Status 1 Year After Critical Illness in Patients 80 Years or Older: Development of a Multivariable Clinical Prediction

Model. *Crit Care Med* 2016; **44**: 1718-1726 [PMID: 27075141 DOI: 10.1097/CCM.0000000000001762]
62 **Hill AD**, Fowler RA, Pinto R, Herridge MS, Cuthbertson BH, Scales DC. Long-term outcomes and healthcare utilization following critical illness--a population-based study. *Crit Care* 2016; **20**: 76 [PMID: 27037030 DOI: 10.1186/s13054-016-1248-y]
63 **Haas LE**, Karakus A, Holman R, Cihangir S, Reidinga AC, de Keizer NF. Trends in hospital and intensive care admissions in the Netherlands attributable to the very elderly in an ageing population. *Crit Care* 2015; **19**: 353 [PMID: 26423744 DOI: 10.1186/s13054-015-1061-z]
64 **Campion EW**, Mulley AG, Goldstein RL, Barnett GO, Thibault GE. Medical intensive care for the elderly. A study of current use, costs, and outcomes. *JAMA* 1981; **246**: 2052-2056 [PMID: 6793740]
65 **Schmidt H**, Müller-Werdan U, Hoffmann T, Francis DP, Piepoli MF, Rauchhaus M, Prondzinsky R, Loppnow H, Buerke M, Hoyer D, Werdan K. Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. *Crit Care Med* 2005; **33**: 1994-2002 [PMID: 16148471]
66 **Eick C**, Rizas KD, Meyer-Zürn CS, Groga-Bada P, Hamm W, Kreth F, Overkamp D, Weyrich P, Gawaz M, Bauer A. Autonomic nervous system activity as risk predictor in the medical emergency department: a prospective cohort study. *Crit Care Med* 2015; **43**: 1079-1086 [PMID: 25738854 DOI: 10.1097/ccm.0000000000000922]
67 **Baguley IJ**, Heriseanu RE, Felmingham KL, Cameron ID. Dysautonomia and heart rate variability following severe traumatic brain injury. *Brain Inj* 2006; **20**: 437-444 [PMID: 16716989 DOI: 10.1080/02699050600664715]
68 **Mazzeo AT**, La Monaca E, Di Leo R, Vita G, Santamaria LB. Heart rate variability: a diagnostic and prognostic tool in anesthesia and intensive care. *Acta Anaesthesiol Scand* 2011; **55**: 797-811 [PMID: 21658013 DOI: 10.1111/j.1399-6576.2011.02466.x]
69 **Deguchi K**, Ikeda K, Sasaki I, Shimamura M, Urai Y, Tsukaguchi M, Touge T, Takeuchi H, Kuriyama S. Effects of daily water drinking on orthostatic and postprandial hypotension in patients with multiple system atrophy. *J Neurol* 2007; **254**: 735-740 [PMID: 17420927 DOI: 10.1007/s00415-006-0425-3]
70 **Jansen RW**, Peeters TL, Lenders JW, van Lier HJ, v't Laar A, Hoefnagels WH. Somatostatin analog octreotide (SMS 201-995) prevents the decrease in blood pressure after oral glucose loading in the elderly. *J Clin Endocrinol Metab* 1989; **68**: 752-756 [PMID: 2646315]

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ORIGINAL ARTICLE

Basic Study

Impact of high dose vitamin C on platelet function

Bassem M Mohammed, Kimberly W Sanford, Bernard J Fisher, Erika J Martin, Daniel Contaifer Jr, Urszula Osinska Warncke, Dayanjan S Wijesinghe, Charles E Chalfant, Donald F Brophy, Alpha A Fowler Ⅲ, Ramesh Natarajan

Bassem M Mohammed, Department of Clinical Pharmacy, Faculty of Pharmacy, Cairo University, Cairo 11562, Egypt

Bassem M Mohammed, Erika J Martin, Daniel Contaifer Jr, Urszula Osinska Warncke, Dayanjan S Wijesinghe, Donald F Brophy, Department of Pharmacotherapy and Outcomes Science, Virginia Commonwealth University, Richmond, VA 23298, United States

Kimberly W Sanford, Department of Pathology, Virginia Commonwealth University, Richmond, VA 23298, United States

Bernard J Fisher, Alpha A Fowler Ⅲ, Ramesh Natarajan, Division of Pulmonary Disease and Critical Care Medicine, Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA 23298, United States

Charles E Chalfant, Research and Development, Hunter Holmes McGuire Veterans Administration Medical Center, the Department of Biochemistry and Molecular Biology, the VCU Massey Cancer Center, the VCU Institute of Molecular Medicine and the VCU Johnson Center for Critical Care and Pulmonary Research, Virginia Commonwealth University, Richmond, VA 23298, United States

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Correspondence to: Ramesh Natarajan, PhD, Professor of Medicine, Division of Pulmonary Disease and Critical Care Medicine, Department of Internal Medicine, Virginia Commonwealth University, PO Box 980050, Richmond, VA 23298, United States. ramesh.natarajan@vcuhealth.org
Telephone: +1-804-8271013
Fax: +1-804-6280325

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Abstract

AIM

To examine the effect of high doses of vitamin C (VitC) on *ex vivo* human platelets (PLTs).

METHODS

Platelet concentrates collected for therapeutic or prophylactic transfusions were exposed to: (1) normal saline (control); (2) 0.3 mmol/L VitC (Lo VitC); or (3) 3 mmol/L VitC (Hi VitC, final concentrations) and stored appropriately. The VitC additive was preservative-free buffered ascorbic acid in water, pH 5.5 to 7.0, adjusted with sodium bicarbonate and sodium hydroxide. The doses of VitC used here correspond to plasma VitC levels reported in recently completed clinical trials. Prior to supplementation, a baseline sample was collected for analysis. PLTs were sampled again on days 2, 5 and 8 and assayed for changes in PLT function by: Thromboelastography (TEG), for changes in viscoelastic properties; aggregometry, for PLT aggregation and adenosine triphosphate (ATP) secretion in response to collagen or adenosine diphosphate (ADP); and flow cytometry, for changes in expression of CD-31, CD41a, CD62p and CD63. In addition, PLT intracellular VitC content was measured using a fluorimetric assay for ascorbic acid and PLT poor plasma was used for plasma coagulation tests [prothrombin time (PT), partial thrombplastin time (PTT), functional fibrinogen] and Lipidomics analysis (UPLC ESI-MS/MS).

RESULTS

VitC supplementation significantly increased PLTs intracellular ascorbic acid levels from 1.2 mmol/L at baseline to 3.2 mmol/L (Lo VitC) and 15.7 mmol/L (Hi VitC, $P < 0.05$). VitC supplementation did not significantly change PT and PTT values, or functional fibrinogen levels over the 8 d exposure period ($P > 0.05$). PLT function assayed by TEG, aggregometry and flow cytometry was not significantly altered by Lo or Hi VitC for up to 5 d. However, PLTs exposed to 3 mmol/L VitC for 8 d demonstrated significantly increased R and K times by TEG and a decrease in the α-angle ($P < 0.05$). There was also a fall of 20 mm in maximum amplitude associated with the Hi VitC compared to both baseline and day 8 saline controls. Platelet aggregation studies, showed uniform declines in collagen and ADP-induced platelet aggregations over the 8-d study period in all three groups ($P > 0.05$). Collagen and ADP-induced ATP secretion was also not different between the three groups ($P > 0.05$). Finally, VitC at the higher dose (3 mmol/L) also induced the release of several eicosanoids including thromboxane B_2 and prostaglandin E_2, as well as products of arachidonic acid metabolism *via* the lipoxygenases pathway such as 11-/12-/15-hydroxyicosatetraenoic acid ($P < 0.05$).

CONCLUSION

Alterations in PLT function by exposure to 3 mmol/L VitC for 8 d suggest that caution should be exerted with prolonged use of intravenous high dose VitC.

Key words: Platelet function; Thromboelastography; Flow cytometry; Platelet lipidomics; Vitamin C

Core tip: High dose intravenous vitamin C (VitC) is often used by Complementary and Alternate Medicine practitioners for a variety of ailments. Moreover, use of high dose VitC by mainstream physicians as an adjunct in the treatment of sepsis, sepsis induced acute lung injury, cancer and burns is on the rise. However, there is no information on the impact of these high doses VitC on normal platelet (PLT) function. Prolonged exposure of *ex vivo* PLTs to high doses of VitC altered some PLT functions as assessed by thromboelastography. However, short term exposure (< 8 d) or low dose exposure had almost no impact on PLT function.

Mohammed BM, Sanford KW, Fisher BJ, Martin EJ, Contaifer Jr D, Warncke UO, Wijesinghe DS, Chalfant CE, Brophy DF, Fowler Ⅲ AA, Natarajan R. Impact of high dose vitamin C on platelet function. *World J Crit Care Med* 2017; 6(1): 37-47 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i1/37.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i1.37

INTRODUCTION

Platelets (PLTs) are central to physiologic processes involved in hemostasis and thrombosis[1]. While an immune function of PLTs has been described in the literature[2], recent studies point to an incompletely understood role for PLTs in a myriad of host immune responses. These studies point to altered PLT function in numerous disease states including inflammation, acute respiratory distress syndrome, atherosclerosis and cancer[3-5].

L-ascorbic acid is the reduced form of vitamin C (VitC). It is a water soluble molecule with strong antioxidant properties[6,7]. PLTs possess Na^+-dependent VitC transporters (SVCT2) and this allows them to actively transport VitC intracellularly[8]. Although normal VitC concentrations in plasma are 50-80 μmol/L, PLTs can hold up to 4 mmol/L of intracellular VitC[9]. This is 50-80 fold higher than circulating VitC concentrations in plasma[10]. Studies have shown that VitC plays several roles in platelet functions, including reduction of reactive oxygen species[11], inhibition of expression of the pro-inflammatory CD40 ligand (CD40L)[12], inhibition of thromboxane B_2 formation[13] and stimulation of prostaglandin E_1 production[14]. This underscores the important role of VitC for normal platelet metabolic functions.

While VitC at normal physiological concentrations is critical for PLT function, there is virtually no information on the impact of high concentrations of VitC on PLT function. High dose intravenous VitC was predominantly used by Complementary and Alternate Medicine (CAM) practitioners. However, there has been a recent trend to use high dose intravenous VitC to treat many chronic, untreatable or intractable disease states. At the present time, high dose intravenous VitC is often used as an adjunct in the treatment of sepsis, sepsis induced acute lung injury, cancer, iron deficiency in hemodialysis patients and even in the burn protocol[15-19]. A few studies have reported that high dose intravenous VitC has

complications in those with renal impairment or glucose 6 phosphate dehydrogenase deficiency. But, in general, its use appears relatively safe in multiple published randomized clinical trials. Yet, since the scale of such use is on the rise, it is vital that the safety of high dose VitC be examined in greater detail. To address this need, we examined the effect of exposing human PLTs to high doses of VitC. The doses used in this study were typically those reported in many of the recently completed randomized clinical trials[15-19]. We also used PLTs under *ex vivo* conditions for these studies. These PLTs were primarily collected for therapeutic or prophylactic transfusions and stored appropriately. We examined the effect of high doses VitC on a variety of PLT functions, both at rest and following activation, over an 8 d period.

MATERIALS AND METHODS

Platelet concentrate preparation

Platelet concentrates (PCs) were prepared by Virginia Blood Services (Richmond, VA) following standard operating procedures. Briefly, freshly collected, whole blood was centrifuged at low speed (soft spin 1500 × g) to separate platelet rich plasma (PRP). PRP was subjected to a second centrifugation (hard spin 5000 × g), then all but 50 mL of supernatant plasma was removed to concentrate the PLTs. The PLTs were re-suspended in residual plasma and stored with agitation at 22 ℃-24 ℃ for 8 d at the Virginia Commonwealth University Transfusion Medicine Center.

Experimental design and study groups

PCs were treated with one of three additives: Normal saline (control); 0.3 mmol/L VitC (Lo VitC); or 3 mmol/L VitC (Hi VitC) as final concentrations. We used 6-10 PC's per treatment arm. The VitC additive was preservative-free buffered ascorbic acid in water (Ascor L500, McGuff Pharmaceuticals, Santa Ana, CA), pH 5.5 to 7.0 adjusted with sodium bicarbonate and sodium hydroxide. Prior to supplementation, an initial baseline sample was collected at the blood supplier facility and transported to participating laboratories for analysis. PCs that passed standard screening tests were transported to the Virginia Commonwealth University Transfusion Medicine Center and sampled again on days 2, 5 and 8.

Sample processing

PLT samples were collected using sterile technique and processed. An initial PLT count was obtained and a portion of the sample was used to obtain platelet poor plasma (PPP) by centrifugation at 2000 × g for 10 min. The resultant PPP was then used to adjust the sample platelet concentration to 230-270 × 10^3/ μL (Adj. PRP).

Platelet pH and ascorbate analysis

An aliquot of the unadjusted PC was used for pH determination. For ascorbate determination, Adj. PRP (500 μL) was pelleted by centrifugation; washed with room temperature phosphate buffered saline; deproteinized in 100 μL of cold 20% trichloroacetic acid followed by addition of 100 μL of cold 0.2% dithiothreitol to prevent oxidation. Platelet lysates were vortexed and centrifuged at 10000 g for 10 min 4 ℃. The supernatants were stored at -80 ℃ for batch analysis. Total ascorbate was assessed using a Tempol-OPDA based fluorescence end-point assay as previously described[20].

Plasma coagulation tests

Aliquots of PPP were assayed for prothrombin time (PT), activated partial thromboplastin time, and functional fibrinogen using the Stago STA Compact Coagulation Analyzer (Diagnostica Stago Inc., Parsippany, NJ) according to manufacturer's instructions.

Measurement of platelet function

Viscoelastic properties measurement: The viscoelastic properties of PRP were measured in duplicate on a thromboelastography analyzer [thromboelastography (TEG) 5000, Haemonetics Corp., Braintree, maximum amplitude (MA)] using published methods[21]. Briefly, 30 μL of 0.2 mmol/L $CaCl_2$ and 330 μL of PRP were loaded into the TEG cup sequentially and test parameters (*i.e.*, R, K, α and MA) recorded.

Platelet aggregation and secretion: PLT aggregation in response to 2 μg/mL collagen or 10 μmol/L adenosine diphosphate (ADP) stimulation was measured by optical density using PRP. Simultaneously, the associated PLT adenosine triphosphate (ATP) secretion was measured *via* luminescence using Chrono-Lume™ reagent. Respective PPP aliquots of each sample were used as blanks. All runs were done in duplicate on a Chrono-log Series 500 aggregometer (Chrono-Log Corp., Havertown, PA) according to manufacturer's instructions.

Platelet flow cytometry

Reagents: Human thrombin (T7009), Gly-Pro-Arg-Pro (GPRP) tetra-peptide inhibitor of fibrin polymerization, and serum bovine albumin were all obtained from Sigma-Aldrich (St. Louis, MO); phosphate-buffered saline and formalin from Beckman Coulter (Fullerton, CA); fluorescein isothiocynate conjugated CD41a (CD41a-FITC) and CD-31 (CD31-FITC), and phycoerythrin conjugated CD62p (CD62p-PE) and CD63 (CD63-PE) were obtained from BD Biosciences (San Jose, CA); ADP from Chrono-Log Corp (Havertown, PA).

Procedure: Adj. PRP was diluted (1:10) using sterile saline (0.9% NaCl). Eight tubes were prepared per sample; 1 unstained, 3 CD62p-PE (alone, thrombin 0.5 U/mL, or ADP 10 μmol/L), 3 CD63-PE (alone, thrombin 0.5 U/mL, or ADP 10 μmol/L), and 1 containing the corresponding isotypes-matched monoclonal antibodies mixture (negative control). CD41a-FITC and/or CD31-FITC were used to set the platelets gate for acquisition. GPRP (0.5 mmol/L) was added prior to thrombin

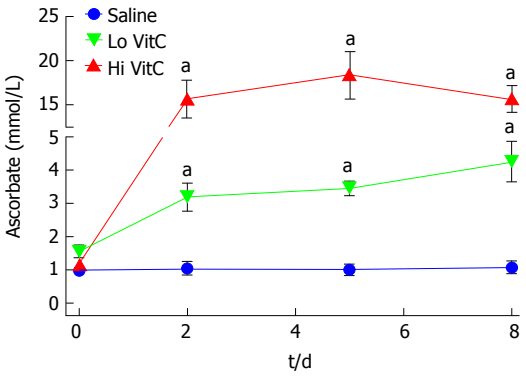

Figure 1 Vitamin C exposure increased intracellular platelet vitamin C concentrations during storage. PLTs supplemented with Lo/Hi VitC had significantly higher intracellular levels of VitC (3.2 mmol/L for Lo VitC and 15.7 mmol/L for Hi VitC) compared to saline controls (1 mmol/L), (n = 10/group, ^{a}P < 0.05). VitC: Vitamin C; PLTs: Platelets.

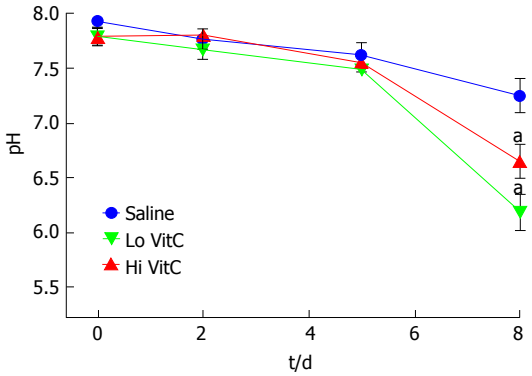

Figure 2 Vitamin C exposure was associated with pH drop on day 8. The addition of Lo/Hi VitC did not alter the pH of the platelet concentrate. Changes in pH were comparable throughout day 5 of storage. Both Lo/Hi VitC were associated with a further significant decrease in pH between day 5 and day 8 (n = 6/group, ^{a}P < 0.05). VitC: Vitamin C; PLTs: Platelets.

activation to inhibit fibrin polymerization. All tubes were processed the same day on the Accuri C6 flow cytometer (BD Biosciences, San Jose, CA). The assay was performed under the following conditions: Fluidics: Medium; forward scatter threshold: 30000; and 20000 events were collected in a preset platelet gate using standard methods including CD41a and/or CD31 as global platelet markers. The collected data were analyzed using FlowJo version 7.6.5. (Ashland, OR). Results were expressed in mean fluorescence intensity units for CD41 and in percentages for other markers of activation.

Lipidomics analysis

Eicosanoids were analyzed as previously described[22-24]. Quantitative analysis of the lipids in the ethanolic extracts was carried out using UPLC ESI-MS/MS as described with minor modifications[25,26]. Briefly, to 200 μL of plasma, LCMS grade ethanol containing 10 ng of each internal standard was added (1 mL). The samples were mixed using a bath sonicator followed by incubation overnight at -20 ℃ for lipid extraction. Following incubation, the insoluble fraction was precipitated by centrifuging at 12000 g for 20 min and the supernatant was transferred into a new glass tube. The lipid extracts were then dried under vacuum and reconstituted in LCMS grade 50:50 EtOH:dH$_2$O (100 μL) for eicosanoid quantitation *via* UPLC ESI-MS/MS analysis.

Statistical analysis

Statistical analysis was performed using SAS 9.3 and GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, United States) by Bernard J Fisher, Division of Pulmonary Disease and Critical Care Medicine, Department of Internal Medicine, Virginia Commonwealth University, Richmond, Virginia and Bassem M. Mohammed, Department of Pharmacotherapy and Outcomes Science, Virginia Commonwealth University, Richmond, Virginia. Data are expressed as mean ± SE. Results were compared by one-way ANOVA and the *post hoc* Tukey test to identify specific differences between groups. Statistical significance was confirmed at a P value of < 0.05.

RESULTS

VitC exposure increased intracellular PLT VitC concentrations during storage

Freshly isolated PLTs contain high concentrations of intracellular VitC (1.23 ± 0.09 mmol/L). These concentrations are about 20 fold higher than the typical plasma levels of 50-80 μmol/L VitC. In freshly isolated PLTs on day 0, intracellular platelet VitC concentrations were not significantly different between the groups (Figure 1). By day 2, PLTs from VitC supplemented bags had significantly higher VitC levels (3.2 mmol/L for Lo VitC and 15.7 mmol/L for Hi VitC) compared to saline (1.2 mmol/L, P < 0.05). VitC content of PLTs observed at day 2 did not significantly change throughout the rest of the storage period in all three groups. This suggests that PLTs, when exposed to high concentrations of VitC, have the capacity to store VitC intracellularly at concentrations that are significantly higher than that observed at normal plasma levels.

VitC exposure was associated with pH drop on day 8

Baseline pH was initially identical between the three groups. There was a slow, but comparable drop in pH in the three groups until day 5. However, in the PC exposed to Lo/Hi VitC supplementation, there was a further significant decrease in pH between day 5 and day 8 (Figure 2, P < 0.05).

VitC exposure did not alter coagulation pathways in PLTs

VitC supplementation did not significantly change PT and PTT values which gradually increased in all three groups (Figure 3A and B). On similar lines, functional fibrinogen levels also did not differ between the groups over the 8 d and remained within a clinically relevant range (Figure 3C).

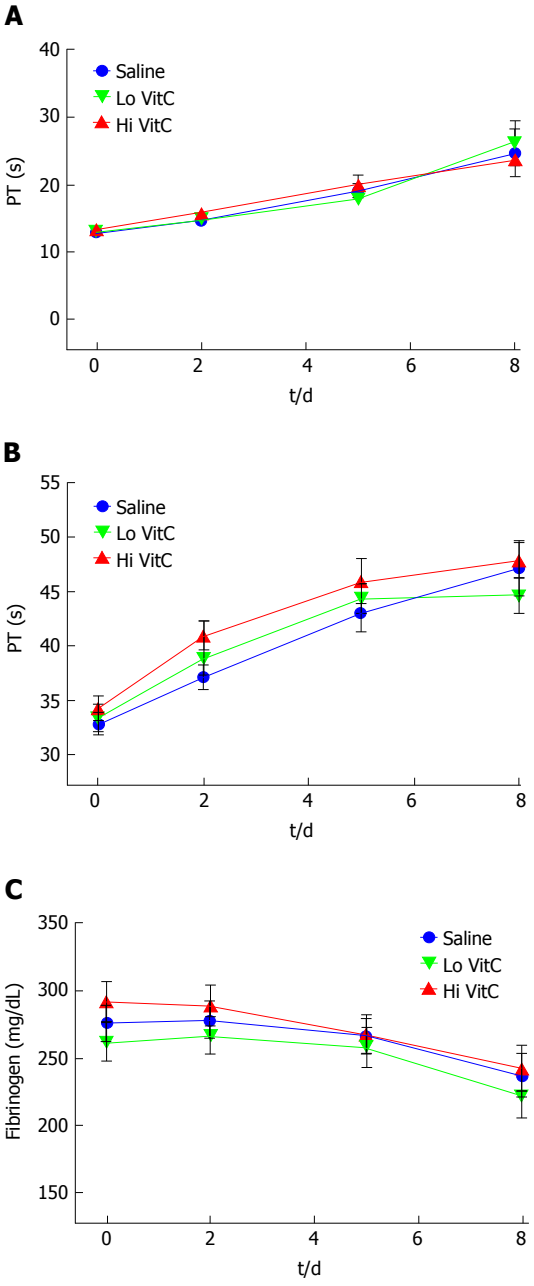

Figure 3 Vitamin C exposure did not alter coagulation pathways in platelets. PT, PTT and Fibrinogen were performed to detect major impacts on the intrinsic, extrinsic and common coagulation pathways. Using platelet poor plasma we observed no significant changes across the saline, Lo- and Hi VitC groups in the PT (A), PTT (B), and Fibrinogen (C) profiles over storage (n =10/group). VitC: Vitamin C; PT: Prothrombin time; PTT: Partial thrombplastin time.

High VitC exposure impacts PLT function on day 8

Over the first 5 d, the addition of Hi or Lo VitC had no deleterious impact on any of the TEG parameters compared to the saline control (Figure 4). However, on day 8 significant differences were associated with extended storage in Hi VitC. Specifically, R and K times were extended in the Hi VitC group when compared to saline group (Figure 4A and B, $P < 0.05$). In agreement with K-time data, a decrease in α-angle was observed in the Hi VitC group on day 8 (Figure 4C, $P < 0.05$). On day 8, there was a fall of 20 mm in MA associated with the Hi VitC compared to both baseline and day 8 saline controls (Figure 4D, $P < 0.05$).

Platelet aggregation studies, showed uniform declines in Collagen and ADP-induced platelet aggregations over the study period in all three groups (Figure 5A and B). In addition, Lo/Hi VitC addition did not alter Collagen and ADP-induced ATP secretion throughout the study (Figure 5C and D). Furthermore, flow cytometric analysis of CD62 and CD63 expression profiles, showed that VitC supplementation had no effect on basal CD62p and CD63 expression during storage (Figure 6A and D). Following ADP (Figure 6B) or thrombin (Figure 6C) stimulation, the CD62 expression showed a steady decrease that was not significantly different across the three groups (except for Hi VitC *vs* saline on day 8, $P < 0.05$). The expression profiles for CD63 differed depending on whether the PC were stimulated with ADP or thrombin (Figure 6E and F). However, the observed flow cytometric analysis changes were not significant across the three groups over 8 d.

Effects of VitC exposure on eicosanoids metabolism in PLTs

Eicosanoids analysis was carried out on days 0, 2, 5 and 8 using aliquots of the PPP fraction of each sample. The levels of the free polyunsaturated fatty acids: Arachidonic acid (AA), eicosapentanoic acid (EPA), and docosahexanoic acid (DHA) did not differ significantly across the three groups throughout the study period (Figure 7A-C). Interestingly, free AA levels showed an initial drop from baseline in the three groups, and then remained unchanged through day 8. Formation of 11-/12-/15-HETE, products of AA metabolism *via* the lipoxygenases pathway showed a gradual increase over storage time (Figure 7D-F). The magnitudes of changes were not significantly different between the Lo VitC and the saline groups. However, levels of 11-HETE was significantly higher at days 5 and 8 in the Hi VitC group when compared to saline (Figure 7D, $P < 0.05$). Hi VitC supplementation significantly augmented 12-HETE levels on days 2, 5 and 8 (Figure 7E, $P < 0.05$). With respect to 15-HETE, only day 8 levels were significantly higher in the Hi VitC group compared to saline (Figure 7F, $P < 0.05$). On similar lines, thromboxane B2 (TXB_2) (the stable metabolite of TXA_2) and prostaglandin E2 (PGE_2), products of AA metabolism *via* the cyclooxygenases pathway were not significantly different between the Lo VitC and saline group. However, Hi VitC supplementation was associated with significantly higher TXB_2 levels on days 5 and 8 (Figure 7G, $P < 0.05$); and significantly higher PGE_2 levels on days 2 and 8 compared to saline (Figure 7H, $P < 0.05$).

DISCUSSION

VitC is one of the most enduring and popular alternative medical treatments sought after. Beyond its oral use to treat scurvy, parenteral VitC has been used by CAM practitioners for more than 6 decades[27-29]. The most

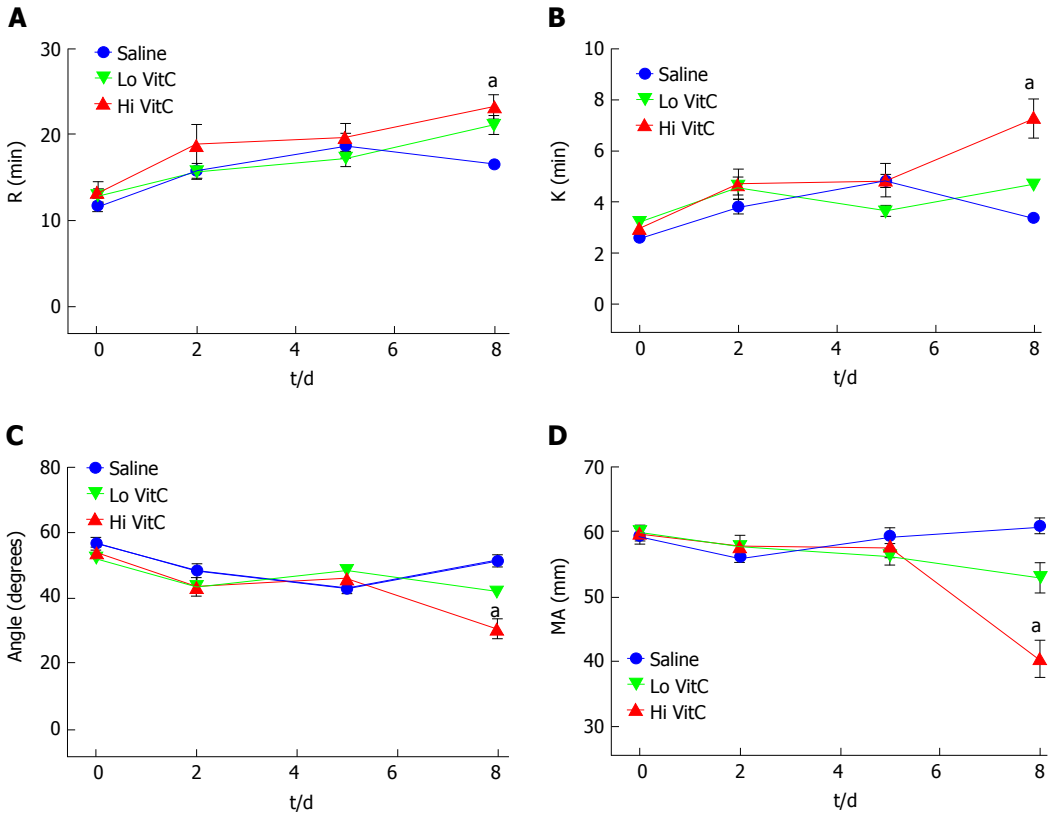

Figure 4 High vitamin C exposure impacts platelet function on day 8. No significant differences were observed between saline, Lo VitC and Hi VitC throughout the standard 5-d storage period in any of the TEG parameters analyzed (n = 10/group). On day-8, R- (A) and K- (B) times were extended in the Hi VitC group compared to saline (n = 10, $^{a}P < 0.05$). Similar changes were observed for the α-angle (C) on day-8 (n = 10, $^{a}P < 0.05$). The Hi VitC group was also associated with a significantly lower MA (D) on day-8 compared to the saline group (n = 10, $^{a}P < 0.05$). VitC: Vitamin C; TEG: Thromboelastography.

controversial use of high dose VitC as a cancer treatment was promoted by the Nobel Laureate, Cameron *et al*[30,31]. Recently published evidence has demonstrated that intravenous, but not oral administration of VitC produces pharmacologic plasma concentrations of VitC[32]. This has elucidated possible mechanisms of action of intravenous VitC and for the first time made therapeutic effects, biologically plausible[33]. In the past few years this therapeutic option has been implemented most often as adjunct therapy in diverse conditions such as sepsis, infections, autoimmune diseases and cancers[15-19]. The basis for use of high dose intravenous VitC has been established in pre-clinical studies in which VitC modulated coagulopathies in disease states. For example, Swarbeck *et al*[34] showed that VitC attenuates plasminogen activator inhibitor-1 expression and release in an *in vitro* model of sepsis. On similar lines Secor *et al*[35] showed that VitC reduces mouse platelet aggregation and surface P-selectin expression in an *ex vivo* model of sepsis. However, to date, no studies have directly examined the effect of high doses of VitC on human PLT function. To address this, we asked the question whether exposure to high doses of VitC, as would normally be observed with high dose intravenous VitC therapy, have any effect on PLT function.

In our study we found that PLTs exposed to VitC rapidly accumulated millimolar quantities of VitC as early as day 2 and maintained these levels throughout the study period (Figure 1). Savini *et al*[8] showed that human PLTs possess the VitC transporter SVCT2, which enable PLTs to increase intracellular levels of VitC. Importantly, while PLTs typically have approximately 4 mmol/L intracellular VitC in normal plasma, exposure to 3 mmol/L VitC increased intracellular VitC levels to > 15 mmol/L. This is significant, especially in cardiovascular pathologies since PLT activation and aggregation are modulated by reactive oxygen species[36]. VitC can alter the oxidative state of PLTs and inhibit the expression of CD40L, a transmembrane protein with pro-inflammatory and pro-thrombotic properties[12]. Indeed, oral administration of VitC has been reported to reduce arterial stiffness and platelet aggregation[37].

VitC did not alter the pH of the PC throughout the standard 5 day storage period when compared to saline controls (Figure 2). Unlike the saline treated PLTs whose pH stayed in the neutral range on day 8, there was a significant drop in pH in the VitC treated PLTs. However, it is unlikely that these pH changes would significantly alter blood pH due to presence of the carbonic acid-bicarbonate buffer, the phosphate buffer system, which consists of phosphoric acid (H_3PO_4) in equilibrium with dihydrogen phosphate ion ($H_2PO_4^-$) and H^+ and hemoglobin that play an important role in regulating the pH of the blood.

Our results show that the changes in PT, PTT and fibrinogen were comparable across the three groups

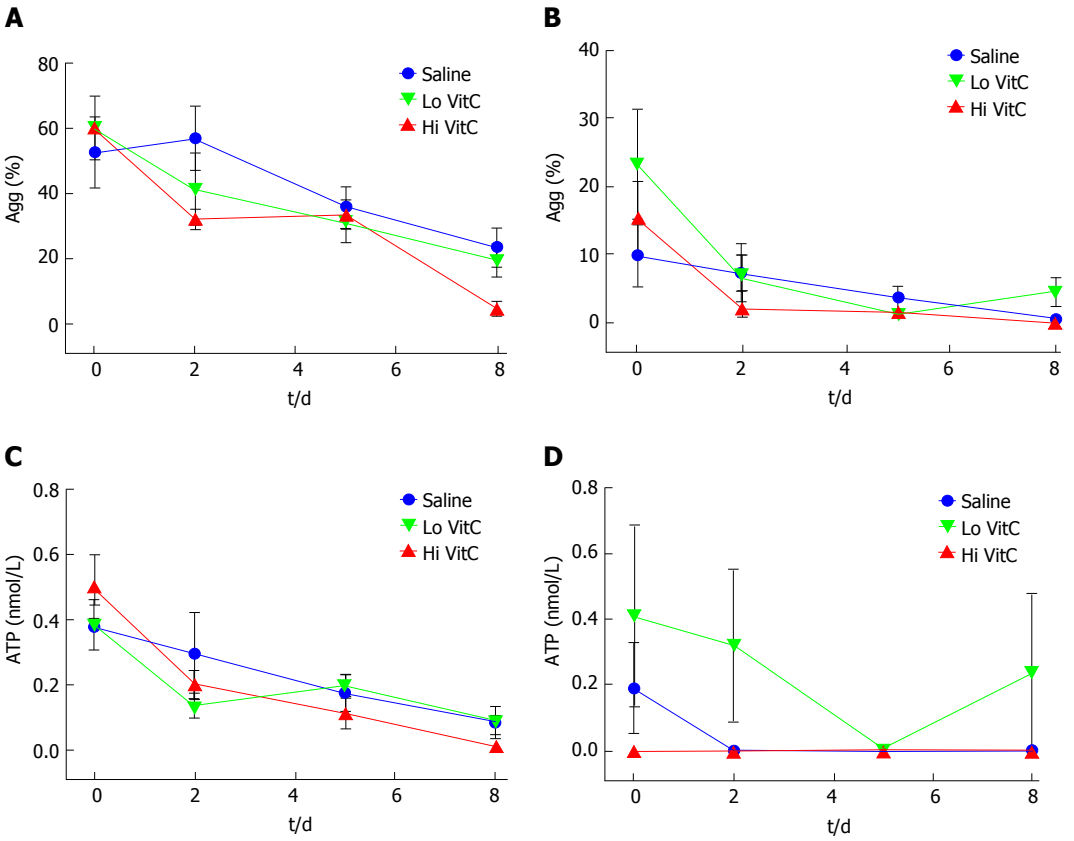

Figure 5 Vitamin C exposure did not affect agonist-stimulated aggregation or adenosine triphosphate secretion by platelets. Using adj. PRP aliquots, addition of Lo/Hi VitC did not alter Collagen-induced PLTs aggregation (A) and ATP secretion (C) as well as ADP-induced PLTs aggregation (B) and ATP secretion (D) when compared to saline controls (n = 10/group). VitC: Vitamin C; PLTs: Platelets; ADP: Adenosine diphosphate; PRP: Platelet rich plasma; ATP: Adenosine triphosphate.

throughout the study period and that exposure to high doses of VitC did not adversely impact these parameters (Figure 3). Only a few studies have employed TEG to evaluate functionality of human PLTs in the PC's[38-41]. However, unlike previous studies that adjusted PRP counts using freshly thawed PPP, we used same sample PPP to make adjustments. While TEG parameters across the three groups were comparable, some critical differences were observed on day 8 in the Hi VitC treated PLTs (Figure 4). The Hi VitC treated group showed a prolonged R-time, and a reduced MA as compared to the saline controls. Also, the Hi VitC groups had significantly delayed kinetics which was evidenced by prolonged K-times and reduced α-angle. It is unclear at this time why these changes occurred and future mechanistic approaches are needed to explain this finding. However, the corollary from these studies is that this inhibitory effect of VitC may have deleterious clinical implications if high dose VitC therapy is instituted for 8 d or more, or if plasma VitC levels are maintained at 3 mmol/L or higher for long periods of time.

Platelet aggregation studies show that Lo/Hi VitC addition did not alter the baseline or collagen and ADP-induced platelet aggregations (Figure 5A and B) and collagen and ADP-induced ATP secretion throughout the study (Figure 5C and D). Flow cytometry showed that VitC supplementation had no effect on basal CD62p and CD63 expression during storage (Figure 6A and D). Following ADP (Figure 6B) or thrombin (Figure 6C) stimulation, the CD62 expression showed a steady decrease that was not significantly different across the three groups (except for Hi VitC). Lo/Hi VitC induced changes in CD63 expression with ADP or thrombin (Figure 6E and F) were not significant over 8 d. These results imply that exposure of normal PLTs to high concentrations of VitC has virtually no impact on agonist induced platelet aggregation under these conditions.

Although we did not observe differences in the levels of free AA, EPA and DHA in the plasma of stored PCs, exposure to Hi VitC was associated with a significant increase in the levels of PGE_2, TXB_2, 11-, 12- and 15-HETE (Figure 7). Some of these free fatty acids (FFAs) have roles in host defense against potential pathogenic or opportunistic microorganisms. Indeed, there is extensive literature demonstrating the antibacterial effects of various free fatty acids from a wide range of biological sources including plants, animals and algae[42]. Whilst their antibacterial mode of action is still poorly understood, studies have shown that their prime target is the cell membrane where FFAs disrupt the electron transport chain and oxidative phosphorylation. Besides interfering with cellular energy production, FFA also inhibit enzyme activity, impair nutrient uptake, and participate in the generation of peroxidation and

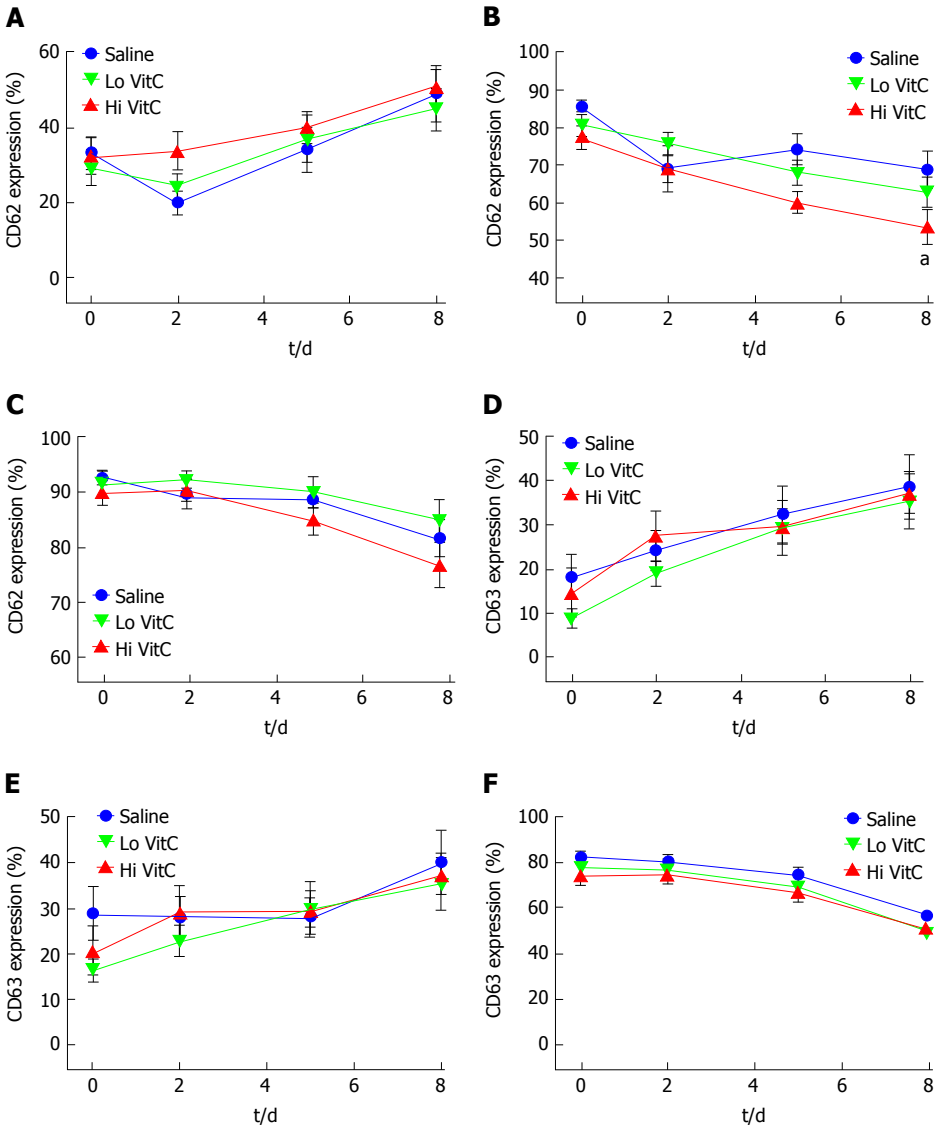

Figure 6 Vitamin C exposure did not significantly alter basal or agonist-stimulated CD62 or CD63 expression profiles. Flow cytometry showed that basal expression of both CD62 (A) and CD63 (D) did not differ with the addition of Lo/Hi VitC. ADP-stimulated CD62 (B) expression was lower on day 8 in the Hi VitC group (n = 10/group, $^{a}P < 0.05$), but CD63 (E) expression was not. Thrombin-stimulated CD62 (C) and CD63 (F) expression also did not differ across the three groups (n = 10/group). VitC: Vitamin C; ADP: Adenosine diphosphate.

auto-oxidation degradation products or direct lysis of bacterial cells. While intravenous VitC has been shown to reduce bacterial burden and improve survival in pre-clinical models of sepsis[43-45] it remains to be determined whether the mechanism involves the induction of these FFAs.

As discussed above, both TXB_2 and PGE_2 levels were significantly higher in PLTs exposed to Hi VitC (Figure 7). Along with possible bacteriostatic effects, there are other potentially beneficial effects associated with induction of these metabolites. For example, a recent study by Bruegel *et al*[46] demonstrated that reduced release of 11-HETE, PGE_2 and TXB_2 was associated with increased disease severity and poor prognosis in septic patients. PGE_2 plays a dual role balancing PLTs response by stimulation or suppression; and is more generally involved in fine tuning the pro-/anti-inflammatory response[47]. While TXA_2 production is associated with PLTs activation, recent data have supported a protective role of TXA_2 *via* its inhibitory regulation of iNOS in the vasculature. In this regard, TXA_2 was found to overcome vascular hypo-responsiveness and help maintaining the vascular tone[48]. The increased production of 12- and 15-HETEs observed in Hi VitC treated bags may also be a protective mechanism against the significantly increased TXA_2[49,50]. In sum, exposure of PLTs to high doses of VitC alters endogenous production of lipid mediators by PLTs. These mediators could have unappreciated, yet far reaching impacts on not just PLTs function but on the entire circulatory system.

We recognize that our studies had a few limitations. PLTs in storage bags are not in their normal physiologic environment. They do not interact with endothelial cells or other cell types in these storage bags; they are highly concentrated; and also have access only to a finite amount of nutrients[51]. Accumulation of products

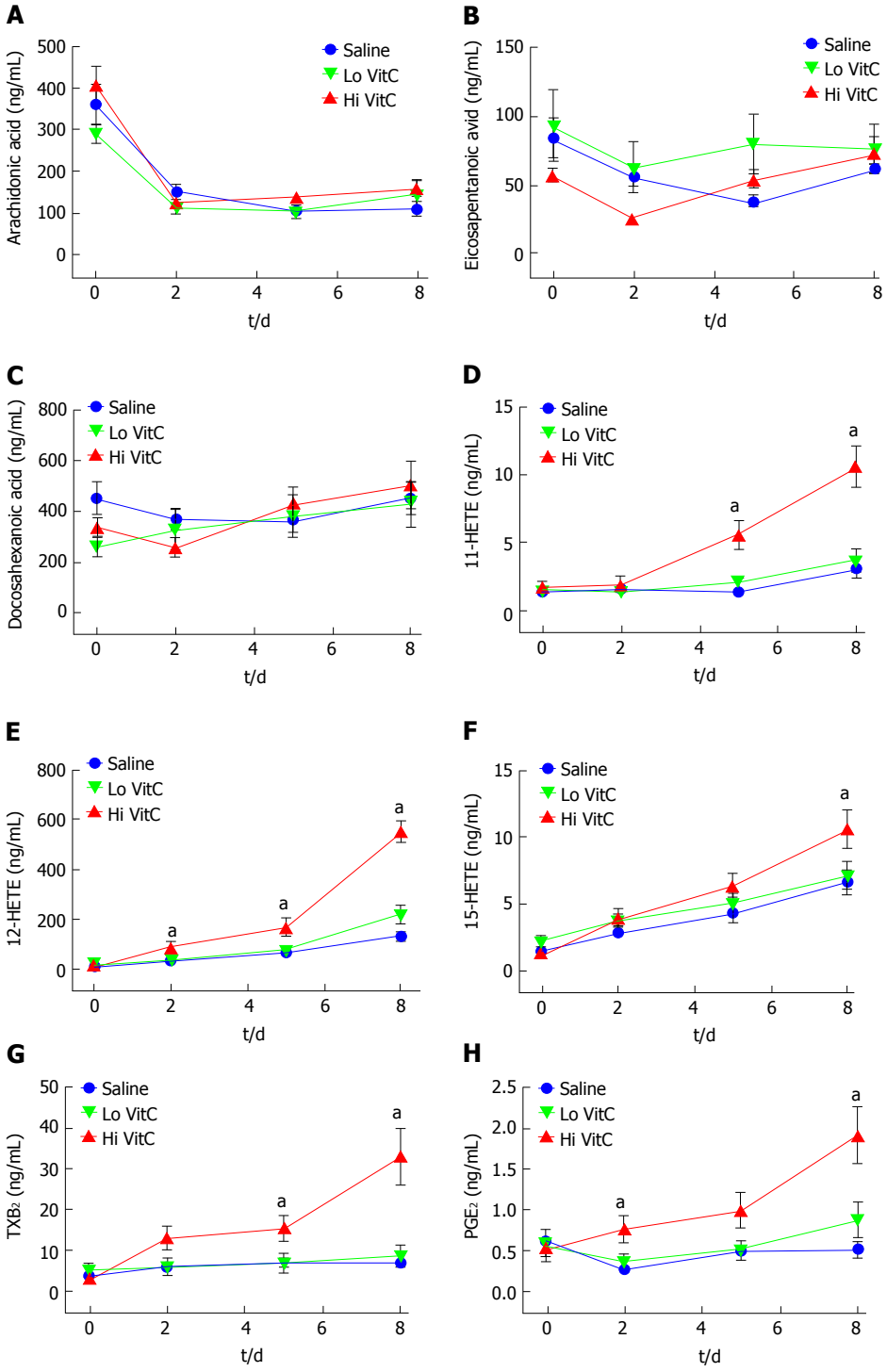

Figure 7 Hi vitamin C, but not Lo vitamin C exposure, was associated with significant changes in the eicosanoid profile over time. Addition of Lo/Hi VitC did not affect the levels of the PUFA: AA (A), EPA (B) and DHA (C) in comparison to saline controls (n = 10/group). Addition of Hi VitC was associated with significantly higher levels of 11-HETE (D) on days 5 and 8 (n = 10/group, $^{a}P < 0.05$); 12-HETE (E) on days 2, 5 and 8 (n = 10/group, $^{a}P < 0.05$); and 15-HETE (F) on day 8 (n = 10/group, $^{a}P < 0.05$). TXB2 (G) was also significantly higher in the Hi VitC group on days 5 and 8 (n = 10/group, $^{a}P < 0.05$). In addition, PGE_2 levels (H) were significantly higher on days 2 and 8 in the Hi VitC group (n = 10/group, $^{a}P < 0.05$). VitC: Vitamin C; PUFA: Polyunsaturated fatty acids; AA: Arachidonic acid; EPA: Eicosapentanoic acid; DHA: Docosahexanoic acid; TXB_2: Thromboxane B2; PGE_2: Prostaglandin E2.

of metabolism in the storage bags and other factors associated with platelets storage beyond 5 d could impact the system buffering capacity leading to the drop in pH observed in our study. This change in pH combined with the closed nature of the *ex vivo* system could also account for the observed effects. A second limitation is that *in vitro* testing of stored PLTs has limitations. While some PLTs functions are lost during storage, others may be recovered *in vivo* following transfusion. As suggested by Cardigan *et al*[51], changes observed in stored PLTs might not necessarily abrogate *in vivo* hemostatic activities. Whether storage of PCs in VitC truly affects hemostatic activities under *in vivo* conditions remains to be determined as a future endeavor.

COMMENTS

Background

Vitamin C (VitC) is a key modulator of platelet (PLT) function. Platelets store high intracellular concentrations of VitC, which then modify its oxidative state and play a role in its ability to aggregate. High dose intravenous VitC is increasingly being used both by Complementary and Alternate Medicine practitioners and by licensed medical practitioners as adjunct therapy for wide ranging diseases including sepsis, sepsis induced acute lung injury, multiple cancers, iron deficiency in hemodialysis patients and burns. However, there is no information on the impact of high dose VitC on normal PLT function. To address this need, the authors examined the effect of exposing *ex vivo* human PLTs to high doses of VitC.

Research frontiers

It is well known that VitC is required for normal platelet function. While pre-clinical studies have examined changes in PLT function in disease and the impact of VitC on these functions, no studies have examined PLT function in the presence of such high doses of VitC.

Innovations and breakthroughs

This is the first study to evaluate *ex vivo* PLT function in the presence of high concentrations of VitC. The innovative approach to use PLT storage bags afforded a reproducible system that allowed for gauging the temporal effects of high doses of VitC on PLT function.

Applications

This study advises moderate levels of caution regarding the extended use of high doses of intravenous VitC. While these high doses have no deleterious impact on PLT function in the short term (up to 5 d), there appear to be unanticipated effects on PLT function as assessed by thromboelastography (TEG) after 8 d of continuous exposure.

Terminology

TEG, is a hemostatic assay that measures the viscoelastic properties (physical) of whole blood clot formation under low shear stress. It shows the interaction of platelets with the coagulation cascade (aggregation, clot strengthening, fibrin cross linking and fibrinolysis).

Peer-review

This is an interesting paper and is worth to be considered for publication.

REFERENCES

1 **Marcus AJ**, Safier LB. Thromboregulation: multicellular modulation of platelet reactivity in hemostasis and thrombosis. *FASEB J* 1993; **7**: 516-522 [PMID: 8472890]

2 **Morrell CN**. Immunomodulatory mediators in platelet transfusion reactions. *Hematology Am Soc Hematol Educ Program* 2011; **2011**: 470-474 [PMID: 22160076 DOI: 10.1182/asheducation-2011.1.470]

3 **Thomas MR**, Storey RF. The role of platelets in inflammation. *Thromb Haemost* 2015; **114**: 449-458 [PMID: 26293514 DOI: 10.1160/TH14-12-1067]

4 **Yadav H**, Kor DJ. Platelets in the pathogenesis of acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 2015; **309**: L915-L923 [PMID: 26320157 DOI: 10.1152/ajplung.00266.2015]

5 **Mezouar S**, Frère C, Darbousset R, Mege D, Crescence L, Dignat-George F, Panicot-Dubois L, Dubois C. Role of platelets in cancer and cancer-associated thrombosis: Experimental and clinical evidences. *Thromb Res* 2016; **139**: 65-76 [PMID: 26916298 DOI: 10.1016/j.thromres.2016.01.006]

6 **Naidu KA**. Vitamin C in human health and disease is still a mystery? An overview. *Nutr J* 2003; **2**: 7 [PMID: 14498993 DOI: 10.1186/1475-2891-2-7]

7 **Figueroa-Méndez R**, Rivas-Arancibia S. Vitamin C in Health and Disease: Its Role in the Metabolism of Cells and Redox State in the Brain. *Front Physiol* 2015; **6**: 397 [PMID: 26779027 DOI: 10.3389/fphys.2015.00397]

8 **Savini I**, Catani MV, Arnone R, Rossi A, Frega G, Del Principe D, Avigliano L. Translational control of the ascorbic acid transporter SVCT2 in human platelets. *Free Radic Biol Med* 2007; **42**: 608-616 [PMID: 17291984 DOI: 10.1016/j.freeradbiomed.2006.11.028]

9 **Padayatty SJ**, Levine M. Vitamin C: the known and the unknown and Goldilocks. *Oral Dis* 2016; **22**: 463-493 [PMID: 26808119 DOI: 10.1111/odi.12446]

10 **Levine M**, Padayatty SJ, Espey MG. Vitamin C: a concentration-function approach yields pharmacology and therapeutic discoveries. *Adv Nutr* 2011; **2**: 78-88 [PMID: 22332036 DOI: 10.3945/an.110.000109]

11 **Olas B**, Wachowicz B. Resveratrol and vitamin C as antioxidants in blood platelets. *Thromb Res* 2002; **106**: 143-148 [PMID: 12182914 DOI: 10.1016/S0049-3848(02)00101-9]

12 **Pignatelli P**, Sanguigni V, Paola SG, Lo Coco E, Lenti L, Violi F. Vitamin C inhibits platelet expression of CD40 ligand. *Free Radic Biol Med* 2005; **38**: 1662-1666 [PMID: 15917194 DOI: 10.1016/j.freeradbiomed.2005.02.032]

13 **Ho PP**, Walters CP, Sullivan HR. Biosynthesis of thromboxane B2: assay, isolation, and properties of the enzyme system in human platelets. *Prostaglandins* 1976; **12**: 951-970 [PMID: 12539 DOI: 10.1016/0090-6980(76)90129-5]

14 **Srivastava KC**. Ascorbic acid enhances the formation of prostaglandin E1 in washed human platelets and prostacyclin in rat aortic rings. *Prostaglandins Leukot Med* 1985; **18**: 227-233 [PMID: 3925463 DOI: 10.1016/0262-1746(85)90022-8]

15 **Tanaka H**, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg* 2000; **135**: 326-331 [PMID: 10722036 DOI: 10.1001/archsurg.135.3.326]

16 **Fowler AA**, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S, Fisher BJ, Natarajan R. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med* 2014; **12**: 32 [PMID: 24484547 DOI: 10.1186/1479-5876-12-32]

17 **Levy TE**. Vitamin C, Infectious Diseases, and Toxins: Curing the Incurable. Philadelphia: Xlibris, 2002

18 **Riordan NH**, Riordan HD, Casciari JJ. Clinical and experimental experiences with intravenous vitamin C. *J Orthomolecular Med* 2000; **15**: 201-203. Available from: URL: http://orthomolecular.org/library/jom/2000/articles/2000-v15n04-p201.shtml

19 **Hoffer LJ**, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller WH. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. *Ann Oncol* 2008; **19**: 1969-1974 [PMID: 18544557 DOI: 10.1093/annonc/mdn377]

20 **Mohammed BM**, Fisher BJ, Huynh QK, Wijesinghe DS, Chalfant CE, Brophy DF, Fowler AA, Natarajan R. Resolution of sterile inflammation: role for vitamin C. *Mediators Inflamm* 2014; **2014**: 173403 [PMID: 25294953 DOI: 10.1155/2014/173403]

21 **White NJ**, Contaifer D, Martin EJ, Newton JC, Mohammed BM, Bostic JL, Brophy GM, Spiess BD, Pusateri AE, Ward KR, Brophy DF. Early hemostatic responses to trauma identified with hierarchical clustering analysis. *J Thromb Haemost* 2015; **13**: 978-988 [PMID: 25816845 DOI: 10.1111/jth.12919]

22 **Wijesinghe DS**, Allegood JC, Gentile LB, Fox TE, Kester M, Chalfant CE. Use of high performance liquid chromatography-electrospray ionization-tandem mass spectrometry for the analysis of ceramide-1-phosphate levels. *J Lipid Res* 2010; **51**: 641-651 [PMID: 19654423 DOI: 10.1194/jlr.D000430]

23 **Wijesinghe DS**, Brentnall M, Mietla JA, Hoeferlin LA, Diegelmann RF, Boise LH, Chalfant CE. Ceramide kinase is required for a normal eicosanoid response and the subsequent orderly migration of fibroblasts. *J Lipid Res* 2014; **55**: 1298-1309 [PMID: 24823941 DOI: 10.1194/jlr.M048207]

24 **Wijesinghe DS**, Chalfant CE. Systems-Level Lipid Analysis Methodologies for Qualitative and Quantitative Investigation of Lipid Signaling Events During Wound Healing. *Adv Wound*

Care (New Rochelle) 2013; **2**: 538-548 [PMID: 24527363 DOI: 10.1089/wound.2012.0402]
25 **Blaho VA**, Buczynski MW, Brown CR, Dennis EA. Lipidomic analysis of dynamic eicosanoid responses during the induction and resolution of Lyme arthritis. *J Biol Chem* 2009; **284**: 21599-21612 [PMID: 19487688 DOI: 10.1074/jbc.M109.003822]
26 **Wijesinghe DS**, Mayton EK, Mietla JA, Mukherjee A, Wu J, Fang X, Chalfant CE. Characterization of lysophosphatidic acid subspecies produced by autotaxin using a modified HPLC ESI-MS/MS method. *Anal Methods* 2011; **3**: 2822-2828 [PMID: 24648853 DOI: 10.1039/C1AY05459G]
27 **Klenner FR**. Observations on the dose and administration of ascorbic acid when employed beyond the range of a vitamin in human pathology. *J App Nutr* 1971; **23**: 61-88
28 **Riordan NH**, Riordan HD, Meng X, Li Y, Jackson JA. Intravenous ascorbate as a tumor cytotoxic chemotherapeutic agent. *Med Hypotheses* 1995; **44**: 207-213 [PMID: 7609676]
29 **Calleja HB**, Brooks RH. Acute hepatitis treated with high doses of vitamin C. Report of a case. *Ohio State Med J* 1960; **56**: 821-823 [PMID: 13806993]
30 **Cameron E**, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: Prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci USA* 1976; **73**: 3685-3689 [PMID: 1068480 DOI: 10.1073/pnas.73.10.3685]
31 **Cameron E**, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci USA* 1978; **75**: 4538-4542 [PMID: 279931 DOI: 10.1073/pnas.75.9.4538]
32 **Padayatty SJ**, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M. Vitamin C pharmacokinetics: implications for oral and intravenous use. *Ann Intern Med* 2004; **140**: 533-537 [PMID: 15068981 DOI: 10.7326/0003-4819-140-7-200404060-00010]
33 **Levine M**, Espey MG, Chen Q. Losing and finding a way at C: new promise for pharmacologic ascorbate in cancer treatment. *Free Radic Biol Med* 2009; **47**: 27-29 [PMID: 19361554 DOI: 10.1016/j.freeradbiomed.2009.04.001]
34 **Swarbreck SB**, Secor D, Ellis CG, Sharpe MD, Wilson JX, Tyml K. Effect of ascorbate on plasminogen activator inhibitor-1 expression and release from platelets and endothelial cells in an in-vitro model of sepsis. *Blood Coagul Fibrinolysis* 2015; **26**: 436-442 [PMID: 25730478 DOI: 10.1097/MBC.0000000000000273]
35 **Secor D**, Swarbreck S, Ellis CG, Sharpe MD, Tyml K. Ascorbate reduces mouse platelet aggregation and surface P-selectin expression in an ex vivo model of sepsis. *Microcirculation* 2013; **20**: 502-510 [PMID: 23402318 DOI: 10.1111/micc.12047]
36 **Iuliano L**, Colavita AR, Leo R, Praticò D, Violi F. Oxygen free radicals and platelet activation. *Free Radic Biol Med* 1997; **22**: 999-1006 [PMID: 9034239 DOI: 10.1016/S0891-5849(96)00488-1]
37 **Wilkinson IB**, Megson IL, MacCallum H, Sogo N, Cockcroft JR, Webb DJ. Oral vitamin C reduces arterial stiffness and platelet aggregation in humans. *J Cardiovasc Pharmacol* 1999; **34**: 690-693 [PMID: 10547085 DOI: 10.1097/00005344-199911000-00010]
38 **Bontekoe IJ**, van der Meer PF, de Korte D. Determination of thromboelastographic responsiveness in stored single-donor platelet concentrates. *Transfusion* 2014; **54**: 1610-1618 [PMID: 24329960 DOI: 10.1111/trf.12515]
39 **Ostrowski SR**, Bochsen L, Windeløv NA, Salado-Jimena JA, Reynaerts I, Goodrich RP, Johansson PI. Hemostatic function of buffy coat platelets in additive solution treated with pathogen reduction technology. *Transfusion* 2011; **51**: 344-356 [PMID: 20723169 DOI: 10.1111/j.1537-2995.2010.02821.x]
40 **Svendsen MS**, Rojkjaer R, Kristensen AT, Salado-Jimena JA, Kjalke M, Johansson PI. Impairment of the hemostatic potential of platelets during storage as evaluated by flow cytometry, thrombin generation, and thrombelastography under conditions promoting formation of coated platelets. *Transfusion* 2007; **47**: 2057-2065 [PMID: 17958535 DOI: 10.1111/j.1537-2995.2007.01430.x]
41 **Reddoch KM**, Pidcoke HF, Montgomery RK, Fedyk CG, Aden JK, Ramasubramanian AK, Cap AP. Hemostatic function of apheresis platelets stored at 4°C and 22°C. *Shock* 2014; **41** Suppl 1: 54-61 [PMID: 24169210 DOI: 10.1097/SHK.0000000000000082]
42 **Desbois AP**, Smith VJ. Antibacterial free fatty acids: activities, mechanisms of action and biotechnological potential. *Appl Microbiol Biotechnol* 2010; **85**: 1629-1642 [PMID: 19956944 DOI: 10.1007/s00253-009-2355-3]
43 **Fisher BJ**, Seropian IM, Kraskauskas D, Thakkar JN, Voelkel NF, Fowler AA, Natarajan R. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Crit Care Med* 2011; **39**: 1454-1460 [PMID: 21358394 DOI: 10.1097/CCM.0b013e3182120cb8]
44 **Fisher BJ**, Kraskauskas D, Martin EJ, Farkas D, Wegelin JA, Brophy D, Ward KR, Voelkel NF, Fowler AA, Natarajan R. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. *Am J Physiol Lung Cell Mol Physiol* 2012; **303**: L20-L32 [PMID: 22523283 DOI: 10.1152/ajplung.00300.2011]
45 **Gaut JP**, Belaaouaj A, Byun J, Roberts LJ, Maeda N, Frei B, Heinecke JW. Vitamin C fails to protect amino acids and lipids from oxidation during acute inflammation. *Free Radic Biol Med* 2006; **40**: 1494-1501 [PMID: 16632110 DOI: 10.1016/j.freeradbiomed.2005.12.013]
46 **Bruegel M**, Ludwig U, Kleinhempel A, Petros S, Kortz L, Ceglarek U, Holdt LM, Thiery J, Fiedler GM. Sepsis-associated changes of the arachidonic acid metabolism and their diagnostic potential in septic patients. *Crit Care Med* 2012; **40**: 1478-1486 [PMID: 22511130 DOI: 10.1097/CCM.0b013e3182416f05]
47 **Dolegowska B**, Lubkowska A, De Girolamo L. Platelet lipidomic. *J Biol Regul Homeost Agents* 2012; **26**: 23S-33S [PMID: 23648196]
48 **Yamada T**, Fujino T, Yuhki K, Hara A, Karibe H, Takahata O, Okada Y, Xiao CY, Takayama K, Kuriyama S, Taniguchi T, Shiokoshi T, Ohsaki Y, Kikuchi K, Narumiya S, Ushikubi F. Thromboxane A2 regulates vascular tone via its inhibitory effect on the expression of inducible nitric oxide synthase. *Circulation* 2003; **108**: 2381-2386 [PMID: 14557367 DOI: 10.1161/01.CIR.0000093194.21109.EC]
49 **Mais DE**, Saussy DL, Magee DE, Bowling NL. Interaction of 5-HETE, 12-HETE, 15-HETE and 5,12-diHETE at the human platelet thromboxane A2/prostaglandin H2 receptor. *Eicosanoids* 1990; **3**: 121-124 [PMID: 2169775]
50 **Fonlupt P**, Croset M, Lagarde M. 12-HETE inhibits the binding of PGH2/TXA2 receptor ligands in human platelets. *Thromb Res* 1991; **63**: 239-248 [PMID: 1837628 DOI: 10.1016/0049-3848(91)90287-7]
51 **Cardigan R**, Turner C, Harrison P. Current methods of assessing platelet function: relevance to transfusion medicine. *Vox Sang* 2005; **88**: 153-163 [PMID: 15787725 DOI: 10.1111/j.1423-0410.2005.00618.x]

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ORIGINAL ARTICLE

Retrospective Study

Risk factors for mortality in postoperative peritonitis in critically ill patients

Yoann Launey, Benjamin Duteurtre, Raphaëlle Larmet, Nicolas Nesseler, Audrey Tawa, Yannick Mallédant, Philippe Seguin

Yoann Launey, Benjamin Duteurtre, Raphaëlle Larmet, Nicolas Nesseler, Audrey Tawa, Yannick Mallédant, Philippe Seguin, Anesthésie Réanimation 1, Centre Hospitalier Universitaire de Rennes, F-35000 Rennes, France

Author contributions: Launey Y, Mallédant Y and Seguin P contributed to study design/planning; Launey Y, Duteurtre B, Nesseler N, Tawa A, Mallédant Y and Seguin P contributed to study conduct; Launey Y, Duteurtre B, Nesseler N, Mallédant Y and Seguin P contributed to data analysis; Launey Y, Duteurtre B, Mallédant Y and Seguin P contributed to writing paper; all authors contributed to revising paper.

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Correspondence to: Philippe Seguin, MD, PhD, Professor, Anesthésie Réanimation 1, Centre Hospitalier Universitaire de Rennes, Inserm U991, F-35000 Rennes, France. philippe.seguin@chu-rennes.fr
Telephone: +33-2-99289371
Fax: +33-2-99282421

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Abstract

AIM

To identify the risk factors for mortality in intensive care patients with postoperative peritonitis (POP).

METHODS

This was a retrospective analysis using a prospective database that includes all patients hospitalized in a surgical intensive care unit for POP from September 2006 to August 2011. The data collected included demographics, comorbidities, postoperative severity parameters, bacteriological findings, adequacy of antimicrobial therapy and surgical treatments. Adequate source control was defined based on a midline laparotomy, infection source control and intraoperative peritoneal lavage. The number of reoperations needed was also recorded.

RESULTS

A total of 201 patients were included. The overall mortality rate was 31%. Three independent risk factors for mortality were identified: The Simplified Acute Physiological Ⅱ Score (OR = 1.03; 95%CI: 1.02-1.05, $P < 0.001$), postoperative medical complications (OR = 6.02; 95%CI: 1.95-18.55, $P < 0.001$) and the number of reoperations (OR = 2.45; 95%CI: 1.16-5.17, $P = 0.015$). Surgery was considered as optimal in 69% of the cases, but without any significant effect on mortality.

CONCLUSION

The results from the large cohort in this study emphasize the role of the initial postoperative severity parameters in

the prognosis of POP. No predefined criteria for optimal surgery were significantly associated with increased mortality, although the number of reoperations appeared as an independent risk factor of mortality.

Key words: Mortality; Postoperative peritonitis; Risk factors; Surgery

Core tip: This retrospective study performed from a prospective data base analysed the risk factor for mortality in 201 patients admitted for postoperative peritonitis (POP) in a surgical intensive care unit. Three independent risk factors for mortality were identified: The Simplified Acute Physiological Ⅱ Score, postoperative medical complications and the number of reoperations. This study emphasizes the role of the initial postoperative severity parameters in the prognosis of POP. No predefined criteria for optimal surgery were significantly associated with increased mortality, although the number of reoperations appeared as an independent risk factor of mortality.

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INTRODUCTION

Postoperative peritonitis (POP), defined as peritonitis occurring after a planned or urgent abdominal surgery, is an infrequent (occurring in approximately equal to the 2%-3% of laparotomies)[1,2], but serious event, with a mortality rate ranging from 30% to 35%[3-5]. The principles of POP management are based on an early diagnosis, optimized surgical source control, adequate antimicrobial therapy and the control of organ failure(s), if necessary[6,7]. Despite clinical, biological and radiological tools, the diagnosis of POP in the postoperative period remains challenging and the surgical source control is not always easy to perform in recently operated abdomens[8-10]. Moreover, multi-drug resistant (MDR) bacteria are frequently isolated in cases of POP, potentially leading to an inadequate antimicrobial therapy and a worsening prognosis[3,5]. Finally, peritonitis is shown to be a frequent condition related to death due to multiple organ failure. In this context, reoperation and postoperative immune depression may favour sepsis and the development of organ failure[11-14].

All of these factors may explain the high mortality observed in association with POP and illustrate the need to evaluate POP separately from other types of intra-abdominal infections. Nevertheless, few studies have evaluated the risk factors for mortality in POP, especially in critically ill patients[8,15,16].

We hypothesized that POP may have specific characteristics and risk factors for mortality that could help physician in the care of the patients with POP. Accordingly, we performed an analysis using a prospective database to determine the risk factors for mortality associated with POP in patients who required intensive care.

MATERIALS AND METHODS

We performed a retrospective analysis from a prospective database that aimed to include all patients with POP. This database was completed from September 2006 to August 2011 in a surgical critical care unit of a university hospital (Rennes - France). All patients older than 18 years of age who were admitted for POP were included. POP was defined as a peritoneal infection developing after intra-abdominal surgery. Only the first episode of POP was taken into account. Patients who had focal abscess(es) drained under computed tomography (CT)-scan guidance and/or who had more than one previous episode of POP before intensive care unit (ICU) admission were excluded. Infections were confirmed macroscopically and/or based on the identification of one or several pathogens in peritoneal sample. Patients were followed up from the first day of hospitalization until their discharge from the hospital or death if it occurred during hospitalization. This study was reviewed and approved by the ethics committee of Rennes University hospital which waived informed consent according to the retrospective design (Avis n° 16-129).

The following data were prospectively collected in the first 24 h: Age, sex, origin of patient (Rennes University hospital or another hospital), hospitalization over the previous 3-mo, antibiotic therapy in the 3 mo previous to the current hospital admission, immunocompromised status (defined based on systemic treatments with corticosteroids or other immunosuppressive drugs, chemotherapy or radiotherapy in the 3 mo previous to the admission), co-morbidities (assessed based on MacCabe score and the following severity scores: Simplified Acute Physiological Score Ⅱ (SAPS Ⅱ), Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) and Sequential Organ Failure Assessment (SOFA)[17-19]. The status (urgent or non-urgent) of the first intra-abdominal surgery was also recorded.

Surgery assessment included the cause of POP and the delay between the first surgery and the reoperation. An optimal surgical treatment was qualified as adequate when the 3 following criteria were met: (1) middle laparotomy; (2) ileostomy or colostomy in cases of injury/perforation below the transverse mesocolon injury or drainage above the transverse mesocolon injury; and (3) careful peritoneal washing of the entire peritoneal cavity with at least 6 L of warm physiological serum and until obtaining a macroscopically clean cavity. Coelioscopy and/or a primary anastomosis were considered as inadequate because their roles in the current recommendations are not well-established[6,7]. The number of

reoperations and the surgical complications, including abdominal wall abscesses, intra-abdominal abscesses, CT-guided drainage of abdominal abscesses and the need for subsequent reoperation, were also reported. Moreover, in our unit, relaparotomies were not planned and were only performed on-demand.

If required, antibiotic prophylaxis for the first surgery was prescribed according to the recommendations of the French Society of Anesthesia and Critical Care (Recommandations pour la pratique de l'antibioprophylaxie en chirurgie. Actualisation 1999. www.sfar.org). Antimicrobial therapies applied between the first surgery and reoperations beginning at least 24 h before the reoperation and lasting more than 24 h were noted. Empirical antimicrobial treatment for the first episode of POP was administered according to the local protocol and included cefotaxime and metronidazole for early POP (< 5 d from the initial surgery) and ticarcillin-clavulanate and amikacin for late POP (≥ 5 d from the initial surgery). Because of the low frequency of methicillin resistant *Staphylococcus aureus* and *Enterococcus faecium*, the use of vancomycin was not considered. Effects of antimicrobial therapy on *Enterococcus* species for ongoing POP and the rates of escalation or de-escalation of antimicrobial therapy were reported. Empirical antimicrobial therapies were re-evaluated based on microbiological data and the susceptibility of the isolated microorganisms. Treatments against fungi were only administered in cases of positive, direct examinations of the peritoneal liquid or positive cultures and included the use of fluconazole or an echinocandin. Bacteremia was recorded and defined based on at least one positive blood culture (2 positive samples in cases of coagulase-negative *Staphylococcus*) and were linked to the intra-abdominal infection if the same microorganisms were recovered in each sample. The duration of antimicrobial therapy ranged from 7 to 10 d.

The isolated microorganisms and the presence of multidrug resistance strains were reported. For each bacterium, the antibiotic sensitivity was determined using the disk-diffusion method. Bacteria were matched into 3 categories: Sensitive, intermediate and resistant. MDR bacteria were defined as follows: Methicillin-resistant *Staphylococcus aureus; Enterococcus* spp. resistant to vancomycin and to high concentrations of gentamycin; *Enterobacteriaceae* producing extended-spectrum beta-lactamase or overexpressing third-generation cephalosporinase; *Pseudomonas aeruginosa* resistant to ticarcillin, ceftazidime, carbapenem or ciprofloxacin; *Acinetobacter* spp. resistant to carbapenem and/or ticarcillin and/or aminoglycosides[5].

Medical complications included septic shock, acute respiratory distress syndrome (ARDS), and acute renal failure. Septic shock was defined based on the Bone criteria[20] and ARDS according to international recommendations[21]. Acute renal failure was defined based on a serum creatinine level and uraemia and/or a urine output and/or a need for dialysis[22]. In cases of chronic renal failure, acute renal failure was defined as an increase of serum creatinine or uraemia and/or urine output and/or the need for dialysis[22]. Lengths of ICU and hospital stays and mortality rates were reported.

Statistical analysis

All statistical analysis were performed with SAS software version 9.2 (SAS Institute, Cary, NC, United States). Mean values and standard deviations were used to describe quantitative data, and a *t*-test or Wilcoxon test were used as needed. Numbers, ranges, and percentages were used to describe qualitative data, and a χ^2 test or Fisher's test was used as needed. The multivariate analysis was designed by selecting variables with a *P*-value < 0.20 in the univariate analysis to build a logistic regression model. The results are expressed with ORs and 95% confidence intervals (95%CI). Results were considered significant at a *P*-value < 0.05.

RESULTS

A total of 201 patients were included in this study. The overall mortality rate was 31% (63/201). The patients' baseline characteristics, severity scores and the determinants of the initial surgery are detailed in Table 1. In a univariate analysis, age, comorbidity evaluated based on McCabe scores and severity at admission in ICU (based on SOFA, APACHE Ⅱ and SAPS Ⅱ scores) were significantly associated with mortality.

The causes of POP were anastomosis leakage (40%), necrosis/ischaemia (20%), traumatic perforation (12%) and miscellaneous (28%) and were not different between the non-survivors and survivors. Surgical procedures were deemed optimal in 69% of the cases (140/201) and the rate did not differ between non-survivors and survivors [71% (45/63) *vs* 69% (95/138); *P* = 0.743]. Details of surgical source control and the number reoperations are provided in Table 2. No significant influence of surgical parameters on the prognoses was found between non-survivors and survivors (Table 2).

Antimicrobial treatment prior to POP (prophylaxis and/or therapy) and changes during the postoperative period (escalation or de-escalation) are provided in Table 3. The microorganisms isolated from the peritoneal fluid (Table 4) and the mean number of microorganisms isolated per patient did not differ between non-survivors and survivors (Table 4). A total of 440 microorganisms were identified in 196 patients [non-survivors, *n* = 139 (61 patients, 2 had no growth) and survivors, *n* = 301 (135 patients, 3 had no growth)]. A total of 46 patients had at least one MDR bacteria recovered from their peritoneal fluid [non-survivors = 28% (17/61) and survivors = 21% (29/135), *P* = 0.378]. Bacteremia did not differ between the 2 groups [non-survivors = 33% (21/63) and survivors = 26% (36/138); *P* = 0.268].

The occurrence of medical complications was identified as a potential risk factor for mortality in the univariate analysis, and the length of hospital stay was significantly shorter for non-survivors (Table 3).

In the multivariate analysis, three independent risk

Table 1 Baseline characteristics, severity scores and initial surgery *n* (%)

	All patients (*n* = 201)	Non-survivors (*n* = 63)	Survivors (*n* = 138)	*P*
Age (yr)	63 ± 15	69 ± 12	61 ± 16	< 0.001
Sex, male	133 (66)	46 (73)	87 (63)	0.199
Origin of patients				
Rennes University Hospital	132 (66)	44 (70)	88 (64)	0.4
Other hospitals	69 (34)	19 (30)	50 (36)	
Hospitalization in the previous 3 mo, yes	78 (39)	24 (38)	54 (39)	1
Immunosuppression, yes	33 (16)	9 (14)	24 (17)	0.581
Antimicrobial therapy in the past 3 mo, yes	54 (26)	16 (25)	38 (28)	0.751
MacCabe score				
Class A	57 (28)	11 (18)	46 (34)	0.036
Class B	107 (53)	36 (57)	71 (51)	
Class C	37 (19)	16 (25)	21 (15)	
SAPS Ⅱ	48 ± 19	60 ± 25	43 ± 14	< 0.001
APACHE Ⅱ	20 ± 8	24 ± 11	18 ± 6	< 0.001
SOFA	7 ± 4	8 ± 5	6 ± 4	< 0.001
Urgent initial surgery	69 (34)	22	47	0.905
Site of the initial surgery				
Colorectal	82 (41)	25 (40)	57 (41)	0.363
Liver - biliary - pancreas	48 (24)	15 (24)	33 (24)	
Oesophagus - gastro-duodenal - small bowel	60 (30)	22 (35)	38 (28)	
Others	11 (5)	1 (1)	10 (7)	

Data are expressed as the mean ± SD or as the number of patients (percentages). SAPS Ⅱ: Simplified acute physiological score Ⅱ; APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; SOFA: Sequential organ failure assessment.

Table 2 Surgical considerations *n* (%)

	Total (*n* = 201)	Non-survivors (*n* = 63)	Survivors (*n* = 138)	*P*
Delay between first operation and surgical reintervention (d)	9.9 ± 7.5	10.4 ± 9.6	9.9 ± 6.2	0.718
Complete surgical source control	140 (69)	45 (71)	95 (69)	0.743
Large way of laparotomy	181 (90)	56 (89)	125 (91)	0.71
Per-operative management of lesions[1]	184 (92)	57 (89)	127 (92)	0.713
Peritoneal washing (at least 6 L) and clear peritoneal cavity	175 (87)	55 (89)	120 (87)	0.946
Reoperation after the first episode of postoperative peritonitis (number)	59 (29)	23 (37)	36 (29)	0.132
No. of reoperations after the first episode of postoperative peritonitis	1.3 ± 0.6	1.4 ± 0.7	1.2 ± 0.5	0.121
Surgical complications				
Parietal abscess	23 (11)	11 (17)	12 (10)	0.095
Intra-abdominal abscess	36 (18)	11 (17)	25 (20)	0.875
Computed tomography-scan guided drainage	30 (15)	7 (11)	23 (19)	0.287

[1]The per-operative management of lesions was defined as the realization of ileostomy or colostomy in cases of injured/perforated infra-mesocolic bowel injury or drainage in cases of supra-mesocolic bowel injury. Data are expressed as the mean ± SD or as the number of patients (percentages).

factors for mortality were identified: SAPS Ⅱ score, the occurrence of medical complications and the number of subsequent reoperations (Table 5).

DISCUSSION

Using a large cohort of ICU patients, we explored the risk factors for mortality associated with POP and found that SAPS Ⅱ score, medical complications and the number of reoperations were independent risk factors for hospital mortality.

Few studies have assessed risk factors for mortality in patients with POP, and most of the studies that have examined this topic included patients hospitalized both in ICUs and surgical wards or included a mix of community and nosocomial peritonitis (including post- and/or non-postoperative) and did not focused on POP in ICU-patients requiring high levels of care[15,16,23]. Mulier *et al*[15] reported a mortality of 30% in 96 POP patients and found that the inability to control the septic source or to clear the abdominal cavity, older age and unconsciousness were independent risk factors for mortality. In this retrospective study, which was not specifically focused on ICU patients, disease severity, measured based on the APACHE Ⅱ score and its acute physiological component, did not appear as an independent risk factor and was only significant when age and unconsciousness were also included in the multivariate model[15]. In another retrospective study performed in 56 POP patients, Torer *et al*[16] found a 32% mortality rate and that sex (female), malignancy, organ failure, a lack of source control and the time period between symptom onset and the 2nd operation were independent risk factors for mortality. Nevertheless, the small cohort of patients in this study

Table 3 Antimicrobial therapies and medical complications *n* (%)

	Total (*n* = 201)	Non-survivors (*n* = 63)	Survivors (*n* = 138)	*P*
Antibiotic prophylaxis for the first surgery	165 (82)	53 (84)	112 (81)	0.38
Antimicrobial treatment prior to the first reintervention	132 (66)	40 (63)	93 (67)	0.564
Empirical antibiotic therapy for POP effective against *Enterococcus* spp.	104 (52)	35 (56)	69 (50)	0.466
Change in empirical antimicrobial POP treatment	130 (65)	33 (52)	97 (70)	0.005
Escalation	60 (46)	20 (32)	40 (29)	
De-escalation	70 (54)	13 (21)	57 (41)	
Medical complications				0.001
Septic shock	125 (62)	58 (92)	67 (49)	
Acute renal failure	79 (39)	39 (62)	40 (29)	
ARDS	54 (27)	28 (44)	26 (19)	
Lengths of stay, d				
ICU	17 ± 17	17 ± 18	17 ± 17	0.2
Hospital	48 ± 44	31 ± 27	57 ± 48	< 0.001

Data are expressed as the mean ± SD or as the number of patients (percentages). POP: Postoperative peritonitis; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit.

Table 4 Microorganisms recovered from the peritoneal liquid and number per patients in which they were found

	Total[1] (*n* = 440)	Non-survivors[1] (*n* = 63)	Survivors[1] (*n* = 138)	*P*
Gram-negative bacilli	206	62	144	0.959
Escherichia coli	97	26	71	0.213
Enterobacter spp.	32	13	19	0.079
Pseudomonas aeruginosa	24	7	17	0.700
Klebsiella spp.	15	3	12	0.066
Proteus spp.	9	3	6	1.000
Citrobacter spp.	8	4	4	0.255
Other gram-negative bacilli	21	6	15	1.000
Gram-positive cocci	161	48	113	0.989
Enterococcus spp.	107	35	72	0.429
E. faecalis	70	25	45	0.328
E. faecium	18	2	16	0.053
Other enterococci	19	8	11	0.279
Streptococcus spp.	23	6	17	0.504
Staphylococcus aureus				
Methicillin sensitive	7	1	6	0.580
Other gram-positive cocci	24	6	18	0.625
Anaerobes	47	17	30	0.979
Bacteroides spp.	39	13	26	0.889
Clostridium spp.	4	2	2	1.000
Other anaerobes	3	2	1	1.000
Fungi	26	12	14	0.938
Candida albicans	17	7	10	0.715
Other fungi	8	4	4	0.317
Number of microorganism types recovered per patient	2.2 ± 1.2	2.2 ± 1.2	2.2 ± 1.2	0.998

[1]Methicillin resistant Staphylococcus aureus was not recovered. Data are expressed as the number of microorganisms (percentage) and the mean ± SD until otherwise.

clearly lacks statistical power, as shown by the wide confidence intervals, and it did not specifically address ICU patients[16]. More recently, in a retrospective study including 102 POP patients, a mortality rate of 39.2% was reported and 4 independent risk factors for mortality were identified (age ⩾ 60, multiple organ failure, inadequate antimicrobial treatment and a stercoral aspect of the peritoneal fluid)[24]. In a selected population of 27 obese patients who required re-operation after initial bariatric surgery and ICU admission, a preoperative BMI > 50 kg/m^2 and multiple reoperations were associated with a poor prognosis and the number of organ failures[8].

Our results generally support the findings of these previous reports. The mortality rate in the cohort studied here was 31%, which is similar to the rates reported in previous related studies, although the patients in the present study were older than those in previous studies. Nevertheless, none of our pre-defined factors for surgical source control were found to significantly impact the mortality rate, and surgical postoperative complications did not appear as a risk factor for mortality. However, the number of reoperations was significantly associated with mortality and, in some patients, surgical source control was not effectively achieved. Indeed, the need

Table 5 Multivariate analysis for the risk factors for mortality

	Odds ratio	95%CI	*P*
Simplified acute physiological score Ⅱ	1.03	1.02-1.05	< 0.0001
Medical postoperative complications	6.02	1.95-18.55	< 0.0001
Number of subsequent reoperations	2.45	1.16-5.17	0.0154

to re-operate after the first episode of POP was 29%, and among these patients, 27% had persistent intra-abdominal infections. Moreover, surgical reoperation under septic peritoneal conditions and inflammation, along with the inherent risk of new bowel injuries, was sometimes associated with difficulties in closing the abdominal wall, which may have played a role in worsening the mortality rate of these patients.

We found a significant influence of the initial severity scores in predicting mortality. Indeed, the SAPS Ⅱ score and medical complications were independently associated with mortality. This confirms the need for the early identification of patients at risk and who have severe symptom to avoid delays in reoperations, which favours the occurrence of organ failure and bacterial growth in the peritoneal cavity and worsens their prognosis for survival[15]. Our results emphasize that the initial hours following POP diagnosis are crucial in the prognosis of POP. Thus, a rapid control of organ failure is required to achieve a better outcome. POP management is based on 3 goals: Supportive care of septic shock, early and adequate antibiotic treatment and the early surgery. Previous reports have shown that a failure to achieve these goals increases the mortality rate[3,25,26].

For initial antimicrobial treatments, we found that patients who survived had a greater rate of secondary adaptation to antibiotics, as reflected by treatment de-escalation. In the cases of antibiotic escalation, the bacteria recovered were resistant and/or not covered by the initial antimicrobial treatment, consequently leading to a potentially higher risk of mortality, although in our study, this parameter was included in the multivariate analysis[3,25,26]. In cases of de-escalation, we assumed that the bacteria recovered were completely targeted by the empirical antimicrobial treatment. In addition, MDR bacteria were found in 23% of patients, which is a lower rate than previously reported, but this did not influence the mortality rate[3,27]. Riché *et al*[28], in a prospective cohort of 68 POP patients admitted to a surgical ICU, found that yeasts recovered in POP patients were associated with an increased risk of death at day 30 after surgery, whereas *Enterococcus* spp. and anaerobes recovered were not. In our study, no bacterial (notably *Enterococcus* spp.) or fungal species were found to impact the mortality rate. The impact of the *Enterococcus* spp. recovered from POP patients on mortality is controversial, and we did not find a relationship between *Enterococcus* spp. and mortality[29-31]. Finally, we did not find that age influenced mortality, but the population we studied was older than that of other studies[15,32,33]. Controversies exist regarding age as a risk factor for mortality in ICUs, and factors other than age itself, such as previous comorbidities and/or frailty, may have a better prognostic significance[34,35]. This issue has been poorly studied in ICU patients with peritonitis. In 163 patients with secondary peritonitis, excluding patients with POP, Hynninen *et al*[32] showed that previous functional status was an independent risk factor for mortality overall but not in the ICU patients.

Several limitations to the interpretation of our data are worth noting. First, this is a retrospective and monocentric study, but data were prospectively collected, and one third of the patients came from another hospital. Moreover, the management of POP was standardized regardless of whether it was for surgical procedures or postoperative ICU management. Second, we assessed only 3 surgical criteria (the type of laparotomy, the intra-operative management of the lesions and the quality of washing), but many other surgical factors not reported in our database may affect outcomes, such as the experience of the surgeon, the duration of the surgery, the quality of the drainage and the stitching of abdominal wall. Third, our inclusion criteria were stringent because we excluded POP that had been operated on using coelioscopy because we believe that the coelioscopy does not have a sufficiently well-defined role in the surgical management of peritonitis[6,7,36]. Fourth, biological markers of inflammation have not been recorded in our database. It might have allowed a better stratification of the peritonitis severity, but were not recommended in usual practice in a recent guideline[36].

This study confirms the negative role of the initial severity criteria and the deleterious role of multiple reoperations, which constitute an indirect sign of inadequate source control, in assessing mortality in patients with POP. An early and successful first surgery is required to increase the chances of a definitive and efficient treatment of POP.

COMMENTS

Background

Postoperative peritonitis (POP) is a rare but severe disease, associated with a challenging diagnosis and a high mortality rate. Multiple organ-failure is a predominant explanation of this burden. But, in addition to supportive care, surgery represents the cornerstone of peritonitis treatment. The timing and adequacy of surgical source control are paramount concerns. Suboptimal surgery may lead to an overwhelmingly negative effect on outcome. In this study, the authors focused on a more refined peritonitis patient's population to better precise the risk factors of mortality especially the impact of surgical parameters.

Research frontiers

Whereas several data exist on the risk factors of mortality in secondary peritonitis, large sample specific studies on POP are scarce. Moreover, surgery has a central role in the management of POP. Identifying more accurately the role of surgical parameters in POP management could affect the way of peritonitis treatment.

Innovations and breakthroughs

This paper is the larger sample size study of selected patients with POP, in which the authors investigated the risk factors of mortality, especially the impact of surgical parameters but also the medical complications. This study confirms

the prominent role of medical complications in the poor outcome of POP, however, it found out no surgical risk factor of mortality.

Applications

These data confirm and recall the prominent negative role of severity parameters in POP outcome. No surgical factor has been found to impact negatively the mortality but larger sample size study with more surgical parameters is needed. Moreover, no patient was treated with laparoscopy but new investigations could be drawn in this perspective.

Terminology

POP belongs to the usual group of secondary peritonitis. More precisely, it includes broadly postoperative abdominal abscesses or diffuse peritoneal infection following abdominal surgery. POP is usually caused by leakage of gut contents, but also by spreading of residual infection or by the occurrence gut ischemia. The severity of POP relies on the associated multiple organ failure.

Peer-review

This is a well written paper with a very relevant topic. It is well researched.

REFERENCES

1 **Pessaux P**, Msika S, Atalla D, Hay JM, Flamant Y. Risk factors for postoperative infectious complications in noncolorectal abdominal surgery: a multivariate analysis based on a prospective multicenter study of 4718 patients. *Arch Surg* 2003; **138**: 314-324 [PMID: 12611581]

2 **Manilich E**, Vogel JD, Kiran RP, Church JM, Seyidova-Khoshknabi D, Remzi FH. Key factors associated with postoperative complications in patients undergoing colorectal surgery. *Dis Colon Rectum* 2013; **56**: 64-71 [PMID: 23222282 DOI: 10.1097/DCR.0b013e31827175f6]

3 **Montravers P**, Gauzit R, Muller C, Marmuse JP, Fichelle A, Desmonts JM. Emergence of antibiotic-resistant bacteria in cases of peritonitis after intraabdominal surgery affects the efficacy of empirical antimicrobial therapy. *Clin Infect Dis* 1996; **23**: 486-494 [PMID: 8879770]

4 **Roehrborn A**, Thomas L, Potreck O, Ebener C, Ohmann C, Goretzki PE, Röher HD. The microbiology of postoperative peritonitis. *Clin Infect Dis* 2001; **33**: 1513-1519 [PMID: 11568851 DOI: 10.1086/323333]

5 **Seguin P**, Fédun Y, Laviolle B, Nesseler N, Donnio PY, Mallédant Y. Risk factors for multidrug-resistant bacteria in patients with post-operative peritonitis requiring intensive care. *J Antimicrob Chemother* 2010; **65**: 342-346 [PMID: 20008043 DOI: 10.1093/jac/dkp439]

6 **Solomkin JS**, Ristagno RL, Das AF, Cone JB, Wilson SE, Rotstein OD, Murphy BS, Severin KS, Bruss JB. Source control review in clinical trials of anti-infective agents in complicated intra-abdominal infections. *Clin Infect Dis* 2013; **56**: 1765-1773 [PMID: 23463643 DOI: 10.1093/cid/cit128]

7 **Bosscha K**, van Vroonhoven TJ, van der Werken C. Surgical management of severe secondary peritonitis. *Br J Surg* 1999; **86**: 1371-1377 [PMID: 10583280 DOI: 10.1046/j.1365-2168.1999.01258.x]

8 **Kermarrec N**, Marmuse JP, Faivre J, Lasocki S, Mognol P, Chosidow D, Muller C, Desmonts JM, Montravers P. High mortality rate for patients requiring intensive care after surgical revision following bariatric surgery. *Obes Surg* 2008; **18**: 171-178 [PMID: 18175195 DOI: 10.1007/s11695-007-9301-1]

9 **Bader FG**, Schröder M, Kujath P, Muhl E, Bruch HP, Eckmann C. Diffuse postoperative peritonitis -- value of diagnostic parameters and impact of early indication for relaparotomy. *Eur J Med Res* 2009; **14**: 491-496 [PMID: 19948445 DOI: 10.1186/2047-783X-14-11-491]

10 **Paugam-Burtz C**, Dupont H, Marmuse JP, Chosidow D, Malek L, Desmonts JM, Mantz J. Daily organ-system failure for diagnosis of persistent intra-abdominal sepsis after postoperative peritonitis. *Intensive Care Med* 2002; **28**: 594-598 [PMID: 12029408 DOI: 10.1007/s00134-002-1250-5]

11 **Guillou PJ**. Biological variation in the development of sepsis after surgery or trauma. *Lancet* 1993; **342**: 217-220 [PMID: 8100934 DOI: 10.1016/0140-6736(93)92303-B]

12 **Unalp HR**, Kamer E, Kar H, Bal A, Peskersoy M, Ali Onal M. Urgent abdominal re-explorations. *World J Emerg Surg* 2006; **1**: 10 [PMID: 16759414 DOI: 10.1186/1749-7922-1-10]

13 **Wakefield CH**, Carey PD, Foulds S, Monson JR, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. *Br J Surg* 1993; **80**: 205-209 [PMID: 8443652 DOI: 10.1002/bjs.1800800224]

14 **Hecker A**, Uhle F, Schwandner T, Padberg W, Weigand MA. Diagnostics, therapy and outcome prediction in abdominal sepsis: current standards and future perspectives. *Langenbecks Arch Surg* 2014; **399**: 11-22 [PMID: 24186147 DOI: 10.1007/s00423-013-1132-z]

15 **Mulier S**, Penninckx F, Verwaest C, Filez L, Aerts R, Fieuws S, Lauwers P. Factors affecting mortality in generalized postoperative peritonitis: multivariate analysis in 96 patients. *World J Surg* 2003; **27**: 379-384 [PMID: 12658477 DOI: 10.1007/s00268-002-6705-x]

16 **Torer N**, Yorganci K, Elker D, Sayek I. Prognostic factors of the mortality of postoperative intraabdominal infections. *Infection* 2010; **38**: 255-260 [PMID: 20393782 DOI: 10.1007/s15010-010-0021-4]

17 **Le Gall JR**, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; **270**: 2957-2963 [PMID: 8254858]

18 **Siro CA**, Bastos PG, Knaus WA, Wagner DP. APACHE II scores in the prediction of multiple organ failure syndrome. *Arch Surg* 1991; **126**: 528-529 [PMID: 2009070 DOI: 10.1001/archsurg.1991.01410280132022]

19 **Vincent JL**, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-710 [PMID: 8844239 DOI: 10.1007/BF01709751]

20 **Bone RC**, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest* 1992; **101**: 1481-1483 [PMID: 1600757 DOI: 10.1378/chest.101.6.1481]

21 **Bernard GR**, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, Lamy M, Legall JR, Morris A, Spragg R. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; **149**: 818-824 [PMID: 7509706 DOI: 10.1164/ajrccm.149.3.7509706]

22 **Bellomo R**, Kellum J, Ronco C. Acute renal failure: time for consensus. *Intensive Care Med* 2001; **27**: 1685-1688 [PMID: 11810109 DOI: 10.1007/s00134-001-1120-6]

23 **Rüttinger D**, Kuppinger D, Hölzwimmer M, Zander S, Vilsmaier M, Küchenhoff H, Jauch KW, Hartl WH. Acute prognosis of critically ill patients with secondary peritonitis: the impact of the number of surgical revisions, and of the duration of surgical therapy. *Am J Surg* 2012; **204**: 28-36 [PMID: 22226144 DOI: 10.1016/j.amjsurg.2011.07.019]

24 **Marzougui Y**, Missaoui K, Hannachi Z, Dhibi Y, Kouka J, Dziri C, Houissa M. [Postoperative peritonitis: pronostic factors of mortality]. *Arch Inst Pasteur Tunis* 2014; **91**: 67-76 [PMID: 26485772]

25 **Schneider CP**, Seyboth C, Vilsmaier M, Küchenhoff H, Hofner B, Jauch KW, Hartl WH. Prognostic factors in critically ill patients suffering from secondary peritonitis: a retrospective, observational, survival time analysis. *World J Surg* 2009; **33**: 34-43 [PMID: 18979129 DOI: 10.1007/s00268-008-9805-4]

26 **Sturkenboom MC**, Goettsch WG, Picelli G, in 't Veld B, Yin DD, de Jong RB, Go PM, Herings RM. Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs. *Br J Clin Pharmacol* 2005; **60**: 438-443

[PMID: 16187977 DOI: 10.1111/j.1365-2125.2005.02443.x]
27 **Augustin P**, Kermarrec N, Muller-Serieys C, Lasocki S, Chosidow D, Marmuse JP, Valin N, Desmonts JM, Montravers P. Risk factors for multidrug resistant bacteria and optimization of empirical antibiotic therapy in postoperative peritonitis. *Crit Care* 2010; **14**: R20 [PMID: 20156360 DOI: 10.1186/cc8877]
28 **Riché FC**, Dray X, Laisné MJ, Matéo J, Raskine L, Sanson-Le Pors MJ, Payen D, Valleur P, Cholley BP. Factors associated with septic shock and mortality in generalized peritonitis: comparison between community-acquired and postoperative peritonitis. *Crit Care* 2009; **13**: R99 [PMID: 19552799 DOI: 10.1186/cc7931]
29 **Seguin P**, Brianchon C, Launey Y, Laviolle B, Nesseler N, Donnio PY, Malledant Y. Are enterococci playing a role in postoperative peritonitis in critically ill patients? *Eur J Clin Microbiol Infect Dis* 2012; **31**: 1479-1485 [PMID: 22076551 DOI: 10.1007/s10096-011-1467-8]
30 **Sotto A**, Lefrant JY, Fabbro-Peray P, Muller L, Tafuri J, Navarro F, Prudhomme M, De La Coussaye JE. Evaluation of antimicrobial therapy management of 120 consecutive patients with secondary peritonitis. *J Antimicrob Chemother* 2002; **50**: 569-576 [PMID: 12356803 DOI: 10.1093/jac/dkf167]
31 **Dupont H**, Vael C, Muller-Serieys C, Chosidow D, Mantz J, Marmuse JP, Andremont A, Goossens H, Desmonts JM. Prospective evaluation of virulence factors of enterococci isolated from patients with peritonitis: impact on outcome. *Diagn Microbiol Infect Dis* 2008; **60**: 247-253 [PMID: 18060725 DOI: 10.1016/j.diagmicrobio.2007.10.006]
32 **Hynninen M**, Wennervirta J, Leppäniemi A, Pettilä V. Organ dysfunction and long term outcome in secondary peritonitis. *Langenbecks Arch Surg* 2008; **393**: 81-86 [PMID: 17372753 DOI: 10.1007/s00423-007-0160-y]
33 **Neri A**, Marrelli D, Scheiterle M, Di Mare G, Sforza S, Roviello F. Re-evaluation of Mannheim prognostic index in perforative peritonitis: prognostic role of advanced age. A prospective cohort study. *Int J Surg* 2015; **13**: 54-59 [PMID: 25475872 DOI: 10.1016/j.ijsu.2014.11.035]
34 **Le Maguet P**, Roquilly A, Lasocki S, Asehnoune K, Carise E, Saint Martin M, Mimoz O, Le Gac G, Somme D, Cattenoz C, Feuillet F, Malledant Y, Seguin P. Prevalence and impact of frailty on mortality in elderly ICU patients: a prospective, multicenter, observational study. *Intensive Care Med* 2014; **40**: 674-682 [PMID: 24651884 DOI: 10.1007/s00134-014-3253-4]
35 **Bagshaw SM**, Stelfox HT, McDermid RC, Rolfson DB, Tsuyuki RT, Baig N, Artiuch B, Ibrahim Q, Stollery DE, Rokosh E, Majumdar SR. Association between frailty and short- and long-term outcomes among critically ill patients: a multicentre prospective cohort study. *CMAJ* 2014; **186**: E95-102 [PMID: 24277703 DOI: 10.1503/cmaj.130639]
36 **Montravers P**, Dupont H, Leone M, Constantin JM, Mertes PM, Laterre PF, Misset B, Bru JP, Gauzit R, Sotto A, Brigand C, Hamy A, Tuech JJ. Guidelines for management of intra-abdominal infections. *Anaesth Crit Care Pain Med* 2015; **34**: 117-130 [PMID: 25922057 DOI: 10.1016/j.accpm.2015.03.005]

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ORIGINAL ARTICLE

Observational Study

Implementation of enteral feeding protocol in an intensive care unit: Before-and-after study

Martin Padar, Gerli Uusvel, Liis Starkopf, Joel Starkopf, Annika Reintam Blaser

Martin Padar, Gerli Uusvel, Joel Starkopf, Department of Anaesthesiology and Intensive Care, Tartu University Hospital, 51014 Tartu, Estonia

Liis Starkopf, Department of Public Health, Section of Biostatistics, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen, Denmark

Joel Starkopf, Annika Reintam Blaser, Department of Anaesthesiology and Intensive Care, University of Tartu, 51014 Tartu, Estonia

Annika Reintam Blaser, Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, Lucerne Cantonal Hospital, 6000 Lucerne, Switzerland

Author contributions: Padar M, Starkopf J and Reintam Blaser A designed the study; Uusvel G and Starkopf L participated in the data collection and analysis; Padar M, Starkopf J and Reintam Blaser A participated in the interpretation of the results and drafted the manuscript; all the co-authors participated in the development of the final version of the manuscript.

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Correspondence to: Annika Reintam Blaser, MD, PhD, Researcher, Department of Anaesthesiology and Intensive Care, University of Tartu, L. Puusepa 8, 51014 Tartu, Estonia. annika.reintam.blaser@ut.ee
Telephone: +372-5142281

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Abstract

AIM

To determine the effects of implementing an enteral feeding protocol on the nutritional delivery and outcomes of intensive care patients.

METHODS

An uncontrolled, observational before-and-after study was performed in a tertiary mixed medical-surgical intensive care unit (ICU). In 2013, a nurse-driven enteral feeding protocol was developed and implemented in the ICU. Nutrition and outcome-related data from patients who were treated in the study unit from 2011-2012 (the Before group) and 2014-2015 (the After group) were obtained from a local electronic database, the national Population Registry and the hospital's Infection Control

Service. Data from adult patients, readmissions excluded, who were treated for at least 7 d in the study unit were analysed.

RESULTS

In total, 231 patients were enrolled in the Before and 249 in the After group. The groups were comparable regarding demographics, patient profile, and severity of illness. Fewer patients were mechanically ventilated on admission in the After group (86.7% *vs* 93.1% in the Before group, $P = 0.021$). The prevalence of hospital-acquired infections, length of ICU stay and ICU, 30- and 60-d mortality did not differ between the groups. Patients in the After group had a lower 90-d ($P = 0.026$) and 120-d ($P = 0.033$) mortality. In the After group, enteral nutrition was prescribed less frequently ($P = 0.039$) on day 1 but significantly more frequently on all days from day 3. Implementation of the feeding protocol resulted in a higher cumulative amount of enterally ($P = 0.049$) and a lower cumulative amount of parenterally ($P < 0.001$) provided calories by day 7, with an overall reduction in caloric provision ($P < 0.001$). The prevalence of gastrointestinal symptoms was comparable in both groups, as was the frequency of prokinetic use. Underfeeding (total calories < 80% of caloric needs, independent of route) was observed in 59.4% of the study days Before *vs* 76.9% After ($P < 0.001$). Inclusion in the Before group, previous abdominal surgery, intra-abdominal hypertension and the sum of gastrointestinal symptoms were found to be independent predictors of insufficient enteral nutrition.

CONCLUSION

The use of a nurse-driven feeding protocol improves the delivery of enteral nutrition in ICU patients without concomitant increases in gastrointestinal symptoms or intra-abdominal hypertension.

Key words: Gastrointestinal symptoms; Underfeeding; Nutrition protocol; Feeding protocol; Enteral feeding; Enteral nutrition; Parenteral nutrition; Critical care

Core tip: Following implementation of a nurse-driven enteral feeding protocol in a mixed medical-surgical intensive care unit (ICU) with a high baseline underfeeding rate, caloric intake *via* the enteral route was significantly increased during the first week in the ICU without concomitant increases in the frequency of gastrointestinal symptoms, intra-abdominal hypertension or use of prokinetic medication.

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INTRODUCTION

Enteral feeding (EN) is currently considered the best option for providing nutrition to critically ill patients. The use of the enteral route may specifically reduce disease severity by attenuating the stress response[1] while avoiding the increased infectious morbidity observed with the use of parenteral nutrition (PN)[2]. Starting EN early after admission to an intensive care unit (ICU) is favoured over a delayed approach, as it reduces morbidity and mortality[3,4]. The best clinical outcomes are achieved when over 85% of the prescribed caloric intake is provided[5]. However, inadequate enteral feeding continues to exist in ICUs worldwide[6]; indeed, a previous study[7] conducted in our ICU demonstrated that insufficient enteral feeding occurred in more than half of the patients.

Guidelines issued by the American Society for Parenteral and Enteral Nutrition and the Society of Critical Care Medicine suggest the use of a feeding protocol to improve nutritional outcomes[2]. These protocols aim to standardize and automate the provision of EN, enabling bedside nurses to initiate, monitor and alter the administration of feeds without direct orders from the attending physician[8]. Several studies[9-12] have shown an increase in nutritional provision with the use of enteral feeding protocols, but the effect of these protocols on relevant patient outcomes has been shown in only a few studies[13-15].

The aim of this study was to evaluate the effect of a nurse-driven enteral feeding protocol on the amount of nutrition provided and on patient outcomes. An observational before-and-after study was conducted.

MATERIALS AND METHODS

Ethical considerations

The study was approved by the Research Ethics Committee of the University of Tartu with waived informed consent (permit no. 258/T-6).

Statistical review statement

The statistical methods of this study were reviewed by a co-author Liis Starkopf from the Department of Public Health, Section of Biostatistics, Faculty of Health and Medical Sciences, University of Copenhagen.

Patient population

The 1st Intensive Care Unit of Tartu University Hospital is a 10-bed tertiary level mixed medical-surgical ICU in a regional hospital. Data from patients treated in this department before and after the implementation of a nurse-driven feeding protocol were compared. Included in this study were adult patients (at least 18 years of age) who were treated in the ICU for at least 7 consecutive days. Readmissions were excluded.

Design of the study

An uncontrolled, observational before-and-after study

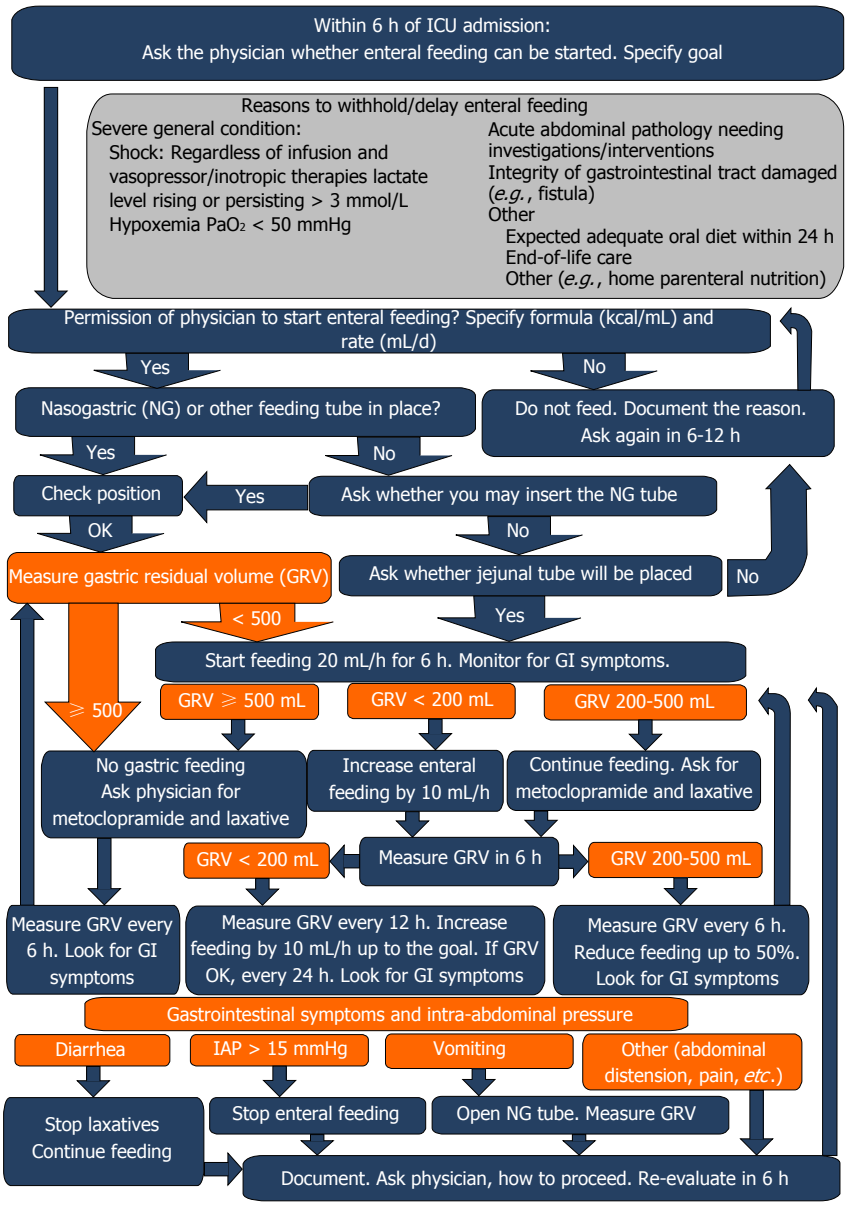

Figure 1 Feeding protocol. ICU: Intensive care unit; GI: Gastrointestinal.

was performed. In 2013, a nurse-driven feeding protocol was implemented in the study unit. The study period comprised three phases: Pre-intervention (Before), intervention and post-intervention (After). No dieticians were involved in any of the study phases.

In 2011 and 2012, an enteral feeding protocol was not in use. Decisions regarding nutrition were made daily by the attending physician, while the nursing staff was responsible for the provision of feedings. Adult patients, not including readmissions, who were treated for at least 7 d in the ICU in 2011 and 2012 were included in the Before group.

The enteral feeding protocol was implemented in 2013 (Figure 1). In our study, the year 2013 served as a learning and adaptation period, and thus patients in this period were not included in our analysis.

In 2014 and 2015, the use of the enteral feeding protocol was routine. Eligible patients admitted during this period composed the After group.

In the post-intervention phase, physicians were not required to follow the feeding protocol for nutrition-related decisions. Adherence to the protocol was not assessed in the present study.

Data collection

Admission characteristics, nutritional information and outcome data were extracted from an electronic database used in the ICU, while data concerning hospital-acquired infections were provided by the Hospital Infection Control Service. Mortality data were retrieved from the national Population Register.

Enteral feeding protocol

The study authors developed the feeding protocol according to available examples in the scientific literature in 2012. The ultimate purpose was to support bedside

nurses with a structural decision tree for independent decision making in enteral feeding.

Variables

Patient characteristics included age, sex, body mass index (BMI), diagnostic category, occurrence of abdominal surgery, Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ)[16] and Sequential Organ Failure Assessment (SOFA)[17] scores, vasopressor or inotrope treatment and mechanical ventilation (MV) on admission to the ICU. The diagnostic category was defined as surgical or medical according to the diagnoses at ICU admission. Outcome variables were length of ICU stay and MV, prevalence of hospital-acquired infections (ventilator-associated pneumonia, urinary tract infection, blood stream infection, *Clostridium difficile* enterocolitis), ICU mortality and 30-, 60-, 90- and 120-d mortality. Hospital-acquired infections were defined as a diagnosis by the Hospital Infection Control Service.

Nutritional support variables included the amount of calories administered daily *via* enteral and parenteral routes during a patient's ICU stay. Only data from the first 7 days were included in the analysis. Insufficient EN was defined as the provision of less than 50% of caloric needs *via* the enteral route and was assessed on day 4 and day 7.

Overfeeding was defined as receiving more than 110% of daily caloric needs *via* any route, and underfeeding as less than 80%; these variables were analysed as the total incidence during 7 d.

Dextrose-based maintenance infusions were included in the calculations of parenteral calories, whereas the nutritional value of propofol was not taken into account.

Gastrointestinal (GI) symptoms and management variables were recorded daily and were defined and calculated as follows. Absence or presence of bowel sounds was determined daily by a senior intensive care physician using auscultation in a non-protocolized manner. To measure gastric residual volume (GRV), enteral feeding was stopped, and the nasogastric tube was held closed for 30 min. The tube was then opened and remained open for 30 min with a collection bag mounted to the bed well under the level of the stomach, allowing for the free flow of gastric content. Evacuated content was discarded. Initially, after starting EN, GRV measurements were performed every 6 h. Further measurements were made every 12 h, if two consecutive measurements had yielded less than 200 mL. A large GRV was defined as a total daily volume greater than 500 mL. Bowel distension was defined when confirmed radiologically. Vomiting and GI bleeding were defined as a visible amount of vomit or the presence of a visible amount of blood in stomach contents or stool, respectively. Diarrhoea was defined as the occurrence of liquid stools more than 3 times in a day. Intra-abdominal pressure (IAP) was recorded daily in select patients who were considered at risk for intra-abdominal hypertension (IAH) according to departmental routine. In those patients, IAP was measured intermittently every 6 to 12 h (more frequently if the previous IAP was increased - 12 mmHg or higher) with a transvesical pressure measurement technique in accordance with the clinical practice guidelines of the World Society of the Abdominal Compartment Syndrome[18]. The sum of GI symptoms was defined as the sum of the daily prevalence (1) or absence (0) of previously described GI symptoms. Prescription of metoclopramide was defined as a standing order of the drug.

Statistical analysis

Categorical variables are described as the number of patients and proportions and were compared using χ^2 or Fisher's exact test. The normality of the distribution of continuous variables was evaluated by Kolmogorov-Smirnov test. Continuous variables are described as the median and inter-quartile range if not stated otherwise. Comparisons of continuous variables were performed using an independent samples median test.

Logistic regression analyses were performed to identify the independent predictors of insufficient EN by day 4 and day 7. All admission day variables that positively predicted outcomes in the univariate analysis with $P < 0.2$ were entered stepwise into a multiple logistic regression model. Coupling variables were added and removed with a stepwise approach to obtain a final optimal model for predicting insufficient EN. Nagelkerke R Square test was used to evaluate the power of the prediction models. The data were analysed using SPSS software (version 23.0, IBM).

RESULTS

Patient characteristics and outcome data

In total, 665 and 683 patients, respectively, were admitted to the ICU before and after the implementation of the feeding protocol. After excluding patients under 18 years of age, readmissions and patients who stayed less than 7 d in the ICU, the study population consisted of 231 patients in the Before and 249 patients in the After group.

The groups did not differ regarding patient age, sex, BMI, case-mix, APACHE Ⅱ or SOFA scores nor in the frequency of vasopressor/inotrope therapy at admission. Around half of the patients had a surgical profile, and the majority of them had received abdominal surgery. The proportion of patients who were mechanically ventilated on admission was significantly smaller in the After group. No significant changes between the two groups were found in length of ICU stay, duration of mechanical ventilation, frequency of hospital-acquired infections or ICU, 30-d and 60-d mortality. However, 90-d and 120-d mortality were significantly lower in the After group (Table 1).

Nutritional support

EN was not initiated during the ICU stay of 19 patients. After implementation of the feeding protocol, significantly

Table 1 Admission characteristics and outcome data

	All	Before	After	*P*-value (before *vs* after)
Admission characteristics				
n of pt	480	231	249	
Male gender, *n* (%)	298 (62.1)	151 (65.4)	147 (59.0)	0.159
Surgical profile, *n* (%)	256 (53.3)	120 (51.9)	136 (54.6)	0.311
Abdominal surgery, *n* (%)	141 (29.4)	72 (31.2)	69 (27.7)	0.232
Age, mean (range)	61.7 (18-96)	61.5 (18-96)	62.0 (20-93)	0.684
BMI	27.8 (24.3-31.6)	27.7 (24.5-31.5)	27.8 (24.3-32.0)	0.791
APACHE Ⅱ, points	16 (11.0-22.0)	16 (11.0-21.0)	16 (12.0-22.0)	0.948
SOFA, points	8 (6.0-10.0)	8 (6.0-10.0)	8 (7.0-10.0)	0.504
Vasopressor/inotrope, *n* (%)	407 (84.8)	195 (84.4)	212 (85.1)	0.462
Mechanical ventilation, *n* (%)	431 (89.8)	215 (93.1)	216 (86.7)	0.021
Outcomes				
ICU stay (d)	13 (9-21)	13 (9-22)	13 (8-21)	0.978
Mechanical ventilation (d)	10 (6-17)	9 (6-18)	10 (6-17)	0.796
Ventilator pneumonia, *n* (%)	16 (3.3)	7 (3.0)	9 (3.6)	0.461
Urinary tract infection, *n* (%)	31 (6.5)	16 (6.9)	15 (6.0)	0.582
Bloodstream infection, *n* (%)	16 (3.3)	6 (2.6)	10 (4.0)	0.404
Cl difficile colitis, *n* (%)	14 (2.9)	6 (2.6)	8 (3.2)	0.450
ICU mortality	51 (10.6)	28 (12.1)	23 (9.2)	0.190
30-d mortality	121 (25.2)	64 (27.7)	52 (22.9)	0.134
60-d mortality	136 (28.3)	73 (31.6)	63 (25.3)	0.076
90-d mortality	157 (32.7)	86 (37.2)	71 (28.5)	0.026
120-d mortality	164 (34.2)	89 (38.5)	75 (30.1)	0.033

BMI: Body mass index; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ; SOFA: Sequential Organ Failure Assessment; ICU: Intensive care unit.

Table 2 Daily enteral caloric intake

Daily enteral caloric intake	Before Median (IQR), kcal	After Median (IQR), kcal	*P*-value
Day 1	0 (0-100)	0 (0-0)	0.016
Day 2	0 (0-480)	100 (0-480)	0.409
Day 3	160 (0-700)	370 (0-767)	0.031
Day 4	340 (0-800)	500 (10-960)	0.003
Day 5	400 (0-1000)	580 (176-1100)	0.142
Day 6	500 (53-1000)	695 (240-1138)	0.003
Day 7	500 (108-1000)	720 (200-1155)	0.018

fewer patients received enteral feeding on day 1 (27.7% Before *vs* 18.1% After; $P = 0.039$). On day 2, EN was administered to approximately half of the patients in both groups (48.5% Before *vs* 53% After; $P = 0.593$). The median time to EN initiation was similar between the groups [day 2 (1-5) Before *vs* day 2 (2-4) After ($P = 0.73$)]. After implementation of the feeding protocol, a larger proportion of patients received EN from day 3 onwards (Figure 2), and the median daily caloric intake *via* the enteral route was significantly higher on days 3, 4, 6 and 7 (Table 2).

After implementation of the feeding protocol, the cumulative amount of enterally provided calories during patients' first week in the ICU was significantly higher ($P = 0.049$), while the amount of calories provided from parenteral nutrition was significantly lower ($P < 0.001$, Table 3). Overall, fewer calories (enteral plus parenteral) were provided during the first 7 d ($P < 0.001$) after the feeding protocol was implemented. The median percentage of calories administered enterally of the calculated caloric needs day-by-day is presented in Figure 3.

The incidence of overfeeding in all analysed days was 8.4% in the Before and 4.5% in the After group ($P < 0.001$), whereas underfeeding occurred on 59.4% and 76.9% of the days in the Before and After group, respectively ($P < 0.001$).

The results of the regression analysis with variables predicting insufficient EN by day 4 and day 7 are shown in Table 4. The risk of insufficient EN both on day 4 and day 7 was increased in patients in the Before group.

Gastrointestinal symptoms and treatment

We found no significant differences between the groups regarding the daily occurrence of vomiting, radiologically confirmed bowel distension, GI bleeding or large GRV (> 500 mL/d). The incidence of diarrhoea was similar and below 10% in both groups, with the only exception of day 4, when more cases were observed in the After group (19/249 *vs* 6/213, $P < 0.05$). No difference was noted in the maximal sum of GI symptoms per day [median 1 (1-2) in both groups, $P = 0.112$].

Half of the patients in both groups developed intra-abdominal hypertension in their first week in the ICU (51.2% Before *vs* 55.9% After, $P = 0.218$). A difference was observed only on day 5, when 29.5% of the patients in the After group had IAH compared to 20.5% in the Before group ($P = 0.043$).

After implementation of the feeding protocol, the prescription of metoclopramide did not increase, and on day 2, it was significantly lower (9.1% Before *vs* 3.6% After, $P = 0.011$).

Table 3 Seven-day cumulative enteral and parenteral caloric intake

Cumulative caloric intake	All	Before	After	*P*-value
	Median (IQR), kcal	Median (IQR), kcal	Median (IQR), kcal	(before *vs* after)
Cumulative EN calories day 7	2870 (803-5163)	2300 (380-5030)	3210 (1280-5215)	0.049
Cumulative PN calories day 7	3100 (1338-5225)	3977 (1775-6646)	2600 (825-4287)	< 0.001
Cumulative total calories day 7	6531 (5035-8140)	7030 (5667-8970)	6000 (4715-7498)	< 0.001

EN: Enteral feeding; PN: Parenteral nutrition.

Table 4 Regression analysis with day of admission variables predicting insufficient enteral feeding by day 4 and day 7

Variables predicting insufficient EN	Day 4		Day 7	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Before group	4.02 (1.55-10.40)	0.004	2.09 (1.35-3.22)	0.001
Abdominal surgery	3.97 (1.26-12.46)	0.018	3.09 (1.82-5.27)	< 0.001
Sum of GI symptoms	6.01 (2.55-14.14)	< 0.001	2.35 (1.60-3.44)	< 0.001
IAH	4.20 (1.32-13.34)	0.015	-	-
Nagelkerke R Square	0.349		0.19	

EN: Enteral feeding; GI: Gastrointestinal; IAH: Intra-abdominal hypertensio.

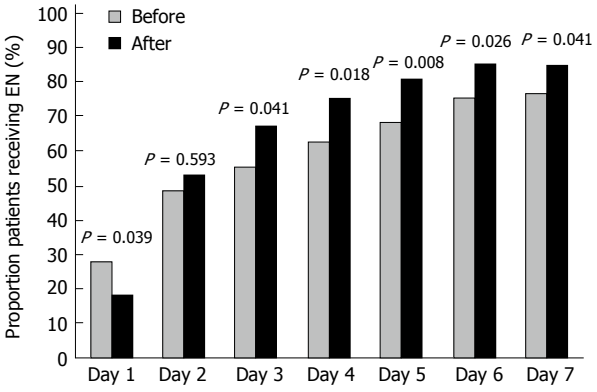

Figure 2 Daily proportion of patients receiving enteral nutrition. EN: Enteral feeding.

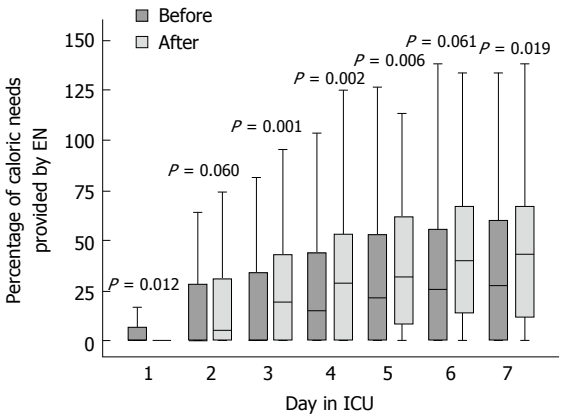

Figure 3 Percentage of caloric needs provided by enteral feeding before and after implementation of feeding protocol. The boxes represent interquartile range (a median value is marked with a line) and error bars 95%CI. EN: Enteral feeding.

DISCUSSION

This before-and-after study was designed to evaluate the effects of the implementation of a nurse-driven feeding protocol on feeding practices and on the outcomes of long-term adult patients in a mixed ICU. The amount of enterally given calories was higher after implementing the feeding protocol, without a concomitant increase in the use of a prokinetic nor in the prevalence of GI symptoms or IAH.

Our findings are in accordance with previous before-and-after studies using nurse-driven rate-based enteral feeding protocols. Studies by Arabi *et al*[10] and Spain *et al*[19] have shown an increase in the cumulative enteral caloric intake on days 7 and 3 in the ICU, respectively, while a greater proportion of patients receiving enteral nutrition after implementation of a feeding protocol was reported by Barr *et al*[20] and Compton *et al*[11]. More frequent and earlier achievement of nutritional goals have been described[11,12], as well as a reduction in the use of parenteral nutrition[12]. These were small, mostly single-centre studies and therefore lacked generalizability. A cluster randomized controlled trial (RCT) by Martin *et al*[13] (the ACCEPT trial) showed that evidence-based nutrition algorithms focusing on the early provision of enteral feeding and on frequent re-evaluations increased the number of days when EN was delivered and reduced both hospital length of stay and mortality. A large cluster RCT conducted by Doig *et al*[9] with 1118 patients and 27 enrolled ICUs showed an earlier start of both enteral and parenteral feeding and greater nutritional adequacy occurred after implementing evidence-based guidelines with a versatile practice change strategy; however, their study failed to demonstrate effects on patient outcomes. Finally, improved nutritional adequacy and reductions in infectious morbidity have been shown in studies by Heyland *et al*[14], using a volume-based, top-down feeding algorithm, and by Taylor *et al*[15], using an enhanced EN approach. The RCTs demonstrating positive effects on nutrition and clinical

outcomes included a variety of interventions, meaning the effects of the feeding protocols were inseparable from those of the whole strategy. In our study, only long-term patients were included, a third of whom had abdominal surgery. Patients with complicated abdominal surgery, requiring a prolonged stay in the ICU, are undoubtedly the most challenging group of patients in terms of successful EN. This aspect needs to be taken into account when interpreting our results, which showed largely insufficient EN both before and after implementation of the feeding protocol. During the time the study was conducted, some changes in the understanding of nutrition in the acute phase of critical illness emerged, including the concept of autophagy and non-inferiority or even possible benefits of underfeeding in the early phase[21-26]. These changes may explain why EN was started less frequently on the day of admission (in most cases not the full 24-h day) in the After group compared to the Before group.

Interestingly, while the cumulative amount of enteral calories in the first week in the ICU increased, the amount of parenterally given calories decreased by a greater amount. The decreased incidence of overfeeding (considering total calories) after implementation of the feeding protocol did not explain the magnitude of the observed change. Accordingly, implementation of the enteral feeding protocol resulted in decreased total caloric intake. There are some possible explanations for this finding. Shortly before the feeding protocol was implemented, the results of the EPaNIC trial[27] were acknowledged and were potentially interpreted as an argument against early parenteral nutrition. This might have led to a reduction in PN independent of the feeding protocol. Additionally, decisions regarding the initiation of PN continued to be made by physicians in a non-protocolized way. Therefore, because more patients received EN in the After group, the physicians may have been more likely to withhold supplemental PN in these patients, whereas (full) PN was more likely to be prescribed in patients who remained without EN (larger proportion in the Before group). However, these interactions led to a negative result regarding total caloric intake. Even if significantly increased amounts of enteral calories were administered after implementation of the feeding protocol, they remained far from reaching the caloric targets. As the end-effect, the more pronounced reduction in PN resulted in an even larger caloric deficit in the After group. This is an important finding, indicating the need to plan complex nutritional interventions including EN and PN without the risk of increases in enterally provided calories resulting in an increased total caloric deficit. The presence of a dietician in the ICU would probably also help eliminate this problem. Although the optimal timing of supplemental PN is not known, a cumulative caloric deficit above 4000 kcal should likely be avoided[28-30].

It should, however, be noted that the nutritional value of propofol was not included in the caloric calculations in the present study, whereas the awareness regarding the appropriate amounts of calories provided with propofol infusions and regarding the negative impact of overfeeding[31,32] is increasing. It is not clear whether the propofol dosage influenced physicians' decisions about the nutrition prescribed in the study period, and furthermore, whether this potential effect varied between the pre- and post-intervention phases.

The prevalence of GI symptoms is high in critically ill patients[33], and any increases in their prevalence due to more aggressive EN should be avoided. The identified differences in some of the symptoms on single days during the first week in the ICU seemed random and related to the low total number of events. However, the safety of using standard feeding protocols in certain patient groups (*e.g.*, those at increased risk for aspiration or severe bowel distension) was not established in the current study.

The main strengths of our study are the relatively constant patient population in the study unit over the years and the daily documented data on GI symptoms. However, our study has several limitations. The single-centre design with a limited number of select (stay > 7 d) patients in a mixed ICU, with a significant proportion of patients receiving abdominal surgery, decreases the generalizability of our results. Furthermore, we studied a relatively long time span and it is possible that other non-protocolized changes in clinical routines might have occurred and influenced the outcomes. Some of the documented GI symptoms occurred very rarely, and therefore the significance of the difference in their prevalence may have changed more or less with each case.

We believe that in addition to describing the magnitude of the effect of a feeding protocol on the delivery of EN and patient-related outcomes, our study notes a possible pitfall regarding the implications of a nurse-driven feeding protocol without standardizing the use of supplemental PN.

The use of a nurse-driven feeding protocol is associated with an improved delivery of enteral nutrition without a concomitant increase in the use of prokinetics nor in the prevalence of GI symptoms or IAH in adult ICU patients with an ICU stay of at least 7 d. Increased, but still insufficient, EN may lead to the withholding of PN, resulting in an even larger total caloric deficit. Therefore, the use of an enteral nutrition protocol alone without the presence of a dietician and in absence of a standard for supplemental parenteral nutrition may not prevent severe underfeeding.

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COMMENTS

Background

Enteral feeding is the method of choice for providing nutrition to critically ill patients, yet underfeeding continues to be a problem in intensive care units (ICUs) worldwide. This also holds true to their study unit - a mixed ICU with a

high proportion of long-staying patients admitted after complicated abdominal surgery. The use of an enteral feeding protocol has been consistently shown to improve the delivery of enteral nutrition (EN) in several studies, however, only a few have reported an effect on relevant patient outcomes.

Research frontiers

Early EN has recently become a hotspot in research of nutritional support for critically ill. Yet not clearly proven, there is some data suggesting that early EN improves important patient-centred outcomes of intensive care. Implementation of a feeding protocol would be the first pragmatic step for any ICU aiming to facilitate EN. This study confirms that with protocol based approach, enteral delivery of nutrients can be significantly enhanced without an increase in gastrointestinal symptoms.

Innovations and breakthroughs

In ICU long-stayers, implementation of the enteral feeding protocol significantly improved the delivery of EN. Unlike most similar studies, the authors reported on gastrointestinal symptoms, intra-abdominal hypertension and the use of prokinetic medications and demonstrated that this improvement in EN did not increase the frequency of aforementioned problems. Importantly, after introduction of the feeding protocol, the use of parenteral nutrition decreased significantly, resulting in a reduction in both parenterally administered and total calories. Accordingly, the prevalence of underfeeding did not decrease despite implementation of the enteral feeding protocol.

Applications

This study demonstrated that use of an enteral feeding protocol was safe in terms of nutrition-related complications. However, in a nutritionally challenging patient population, it also brought along a reduction in overall caloric intake. This finding may warrant implementing a strategy of supplemental parenteral nutrition to help reduce the caloric debt seen in long-staying ICU patients.

Terminology

A nurse-driven enteral feeding protocol refers to an algorithm enabling the bedside nurse to start, monitor and adjust the delivery of enteral tube feedings to patients not capable of oral food intake.

Peer-review

This study was well conducted and nicely written. It has enough quality to be published in this journal.

REFERENCES

1 **Windsor AC**, Kanwar S, Li AG, Barnes E, Guthrie JA, Spark JI, Welsh F, Guillou PJ, Reynolds JV. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut* 1998; **42**: 431-435 [PMID: 9577354 DOI: 10.1136/gut.42.3.431]

2 **McClave SA**, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016; **40**: 159-211 [PMID: 26773077 DOI: 10.1177/0148607115621863]

3 **Marik PE**, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* 2001; **29**: 2264-2270 [PMID: 11801821 DOI: 10.1097/00003246-200112000-00005]

4 **Doig GS**, Heighes PT, Simpson F, Sweetman EA, Davies AR. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Med* 2009; **35**: 2018-2027 [PMID: 19777207 DOI: 10.1007/s00134-009-1664-4]

5 **Heyland DK**, Cahill N, Day AG. Optimal amount of calories for critically ill patients: depends on how you slice the cake! *Crit Care Med* 2011; **39**: 2619-2626 [PMID: 21705881 DOI: 10.1097/CCM.0b013e318226641d]

6 **Heyland DK**, Dhaliwal R, Wang M, Day AG. The prevalence of iatrogenic underfeeding in the nutritionally 'at-risk' critically ill patient: Results of an international, multicenter, prospective study. *Clin Nutr* 2015; **34**: 659-666 [PMID: 25086472 DOI: 10.1016/j.clnu.2014.07.008]

7 **Kuslapuu M**, Jõgela K, Starkopf J, Reintam Blaser A. The reasons for insufficient enteral feeding in an intensive care unit: A prospective observational study. *Intensive Crit Care Nurs* 2015; **31**: 309-314 [PMID: 25864368 DOI: 10.1016/j.iccn.2015.03.001]

8 **Heyland DK**, Cahill NE, Dhaliwal R, Sun X, Day AG, McClave SA. Impact of enteral feeding protocols on enteral nutrition delivery: results of a multicenter observational study. *JPEN J Parenter Enteral Nutr* 2010; **34**: 675-684 [PMID: 21097768 DOI: 10.1177/0148607110364843]

9 **Doig GS**, Simpson F, Finfer S, Delaney A, Davies AR, Mitchell I, Dobb G. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. *JAMA* 2008; **300**: 2731-2741 [PMID: 19088351 DOI: 10.1001/jama.2008.826]

10 **Arabi Y**, Haddad S, Sakkijha M, Al Shimemeri A. The impact of implementing an enteral tube feeding protocol on caloric and protein delivery in intensive care unit patients. *Nutr Clin Pract* 2004; **19**: 523-530 [PMID: 16215149 DOI: 10.1177/0115426504019005523]

11 **Compton F**, Bojarski C, Siegmund B, van der Giet M. Use of a nutrition support protocol to increase enteral nutrition delivery in critically ill patients. *Am J Crit Care* 2014; **23**: 396-403 [PMID: 25179035 DOI: 10.4037/ajcc2014140]

12 **Mackenzie SL**, Zygun DA, Whitmore BL, Doig CJ, Hameed SM. Implementation of a nutrition support protocol increases the proportion of mechanically ventilated patients reaching enteral nutrition targets in the adult intensive care unit. *JPEN J Parenter Enteral Nutr* 2005; **29**: 74-80 [PMID: 15772383 DOI: 10.1177/014860710502900274]

13 **Martin CM**, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *CMAJ* 2004; **170**: 197-204 [PMID: 14734433 DOI: 10.1177/0115426504019003309]

14 **Heyland DK**, Murch L, Cahill N, McCall M, Muscedere J, Stelfox HT, Bray T, Tanguay T, Jiang X, Day AG. Enhanced protein-energy provision via the enteral route feeding protocol in critically ill patients: results of a cluster randomized trial. *Crit Care Med* 2013; **41**: 2743-2753 [PMID: 23982032 DOI: 10.1097/CCM.0b013e31829efef5]

15 **Taylor SJ**, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med* 1999; **27**: 2525-2531 [PMID: 10579275 DOI: 10.1097/00003246-199911000-00033]

16 **Knaus WA**, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818-829 [PMID: 3928249 DOI: 10.1097/00003246-198510000-00009]

17 **Vincent JL**, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, Sprung CL, Colardyn F, Blecher S. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998; **26**: 1793-1800 [PMID: 9824069 DOI: 10.1097/00003246-199811000-00016]

18 **Kirkpatrick AW**, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med* 2013; **39**: 1190-1206

[PMID: 23673399 DOI: 10.1007/s00134-013-2906-z]
19 **Spain DA**, McClave SA, Sexton LK, Adams JL, Blanford BS, Sullins ME, Owens NA, Snider HL. Infusion protocol improves delivery of enteral tube feeding in the critical care unit. *JPEN J Parenter Enteral Nutr* 1999; **23**: 288-292 [PMID: 10485441 DOI: 10.1177/0148607199023005288]
20 **Barr J**, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. *Chest* 2004; **125**: 1446-1457 [PMID: 15078758 DOI: 10.1378/chest.125.4.1446]
21 **Casaer MP**, Van den Berghe G. Nutrition in the acute phase of critical illness. *N Engl J Med* 2014; **370**: 1227-1236 [PMID: 24670169 DOI: 10.1056/NEJMra1304623]
22 **Rice TW**, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, Morris A, Dong N, Rock P. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012; **307**: 795-803 [PMID: 22307571 DOI: 10.1001/jama.2012.137]
23 **Arabi YM**, Aldawood AS, Haddad SH, Al-Dorzi HM, Tamim HM, Jones G, Mehta S, McIntyre L, Solaiman O, Sakkijha MH, Sadat M, Afesh L. Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults. *N Engl J Med* 2015; **372**: 2398-2408 [PMID: 25992505 DOI: 10.1056/NEJMoa1502826]
24 **Casaer MP**, Van den Berghe G. Editorial on the original article entitled "Permissive underfeeding of standard enteral feeding in critically ill adults" published in the New England Journal of Medicine on June 18, 2015. *Ann Transl Med* 2015; **3**: 226 [PMID: 26539443 DOI: 10.3978/j.issn.2305-5839.2015.07.22]
25 **Hermans G**, Casaer MP, Clerckx B, Güiza F, Vanhullebusch T, Derde S, Meersseman P, Derese I, Mesotten D, Wouters PJ, Van Cromphaut S, Debaveye Y, Gosselink R, Gunst J, Wilmer A, Van den Berghe G, Vanhorebeek I. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. *Lancet Respir Med* 2013; **1**: 621-629 [PMID: 24461665 DOI: 10.1016/S2213-2600(13)70183-8]
26 **Braunschweig CA**, Sheean PM, Peterson SJ, Gomez Perez S, Freels S, Lateef O, Gurka D, Fantuzzi G. Intensive nutrition in acute lung injury: a clinical trial (INTACT). *JPEN J Parenter Enteral Nutr* 2015; **39**: 13-20 [PMID: 24722769 DOI: 10.1177/0148607114528541]
27 **Casaer MP**, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011; **365**: 506-517 [PMID: 21714640 DOI: 10.1056/NEJMoa1102662]
28 **Heidegger CP**, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet* 2013; **381**: 385-393 [PMID: 23218813 DOI: 10.1016/S0140-6736(12)61351-8]
29 **Villet S**, Chiolero RL, Bollmann MD, Revelly JP, Cayeux R N MC, Delarue J, Berger MM. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr* 2005; **24**: 502-509 [PMID: 15899538 DOI: 10.1016/j.clnu.2005.03.006]
30 **Dvir D**, Cohen J, Singer P. Computerized energy balance and complications in critically ill patients: an observational study. *Clin Nutr* 2006; **25**: 37-44 [PMID: 16321459 DOI: 10.1016/j.clnu.2005.10.010]
31 **Grau T**, Bonet A, Rubio M, Mateo D, Farré M, Acosta JA, Blesa A, Montejo JC, de Lorenzo AG, Mesejo A. Liver dysfunction associated with artificial nutrition in critically ill patients. *Crit Care* 2007; **11**: R10 [PMID: 17254321 DOI: 10.1186/cc5670]
32 **Schulman RC**, Mechanick JI. Can nutrition support interfere with recovery from acute critical illness? *World Rev Nutr Diet* 2013; **105**: 69-81 [PMID: 23075588 DOI: 10.1159/000341272]
33 **Reintam A**, Parm P, Kitus R, Kern H, Starkopf J. Gastrointestinal symptoms in intensive care patients. *Acta Anaesthesiol Scand* 2009; **53**: 318-324 [PMID: 19243317 DOI: 10.1111/j.1399-6576.2008.01860.x]

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ORIGINAL ARTICLE

Observational Study

Timing, method and discontinuation of hydrocortisone administration for septic shock patients

Miguel A Ibarra-Estrada, Quetzalcóatl Chávez-Peña, Claudia I Reynoso-Estrella, Jorge Rios-Zermeño, Pável E Aguilera-González, Miguel A García-Soto, Guadalupe Aguirre-Avalos

Miguel A Ibarra-Estrada, Pável E Aguilera-González, Critical Care Unit, Instituto Jalisciense de Cancerología, Guadalajara Jalisco 44280, Mexico

Miguel A Ibarra-Estrada, Pável E Aguilera-González, Critical Care Unit, Hospital General Regional #180, Instituto Mexicano del Seguro Social, Tlajomulco de Zúñiga Jalisco 45655, Mexico

Quetzalcóatl Chávez-Peña, Miguel A García-Soto, Transplant Care Unit, Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social, Guadalajara Jalisco 44340, Mexico

Quetzalcóatl Chávez-Peña, Guadalupe Aguirre-Avalos, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara Jalisco 44340, Mexico

Claudia I Reynoso-Estrella, Jorge Rios-Zermeño, Guadalupe Aguirre-Avalos, Critical Care Unit, Hospital Civil Fray Antonio Alcalde, Guadalajara Jalisco 44280, Mexico

Author contributions: Ibarra-Estrada MA designed the study, performed data collection, statistical analysis, interpretation of data, and drafted the manuscript; Chávez-Peña Q and Reynoso-Estrella CI performed data collection and helped draft the manuscript; Rios-Zermeño J, Aguilera-González PE, García-Soto MA and Aguirre-Avalos G performed data collection; all authors were involved and approved the final manuscript.

Institutional review board statement: This study has been approved by the scientific and ethics committees at Instituto Jalisciense de Cancerología (INV-01/16), and Hospital Civil Fray Antonio Alcalde (HCG/CEI-0321/16). A copy of approval can be provided on request.

Informed consent statement: All study participants, or their next of kin, provided informed written consent prior to study enrollment.

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Data sharing statement: Data presented in the manuscript is anonymized, and the risk of identifying individual patients is very low. No additional data is available from the study other than the data stated in this manuscript.

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Correspondence to: Dr. Miguel A Ibarra-Estrada, Critical Care Unit, Instituto Jalisciense de Cancerología, Coronel Calderón 715, Guadalajara Jalisco 44280, Mexico. drmiguelibarra@hotmail.com
Telephone: +52-33-40401508

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Abstract

AIM

To characterize the prescribing patterns for hydrocortisone for patients with septic shock and perform an exploratory analysis in order to identify the variables associated with better outcomes.

METHODS

This prospective cohort study included 59 patients with septic shock who received stress-dose hydrocortisone.

It was performed at 2 critical care units in academic hospitals from June 1st, 2015, to July 31st, 2016. Demographic data, comorbidities, medical management details, adverse effects related to corticosteroids, and outcomes were collected after the critical care physician indicated initiation of hydrocortisone. Univariate comparison between continuous and bolus administration of hydrocortisone was performed, including multivariate analysis, as well as Kaplan-Meier analysis to compare the proportion of shock reversal at 7 d after presentation. Receiver operating characteristic (ROC) curves determined the best cut-off criteria for initiation of hydrocortisone associated with the highest probability of shock reversal. We addressed the effects of the taper strategy for discontinuation of hydrocortisone, noting risk of shock relapse and adverse effects.

RESULTS

All-cause 30-d mortality was 42%. Hydrocortisone was administered as a continuous infusion in 54.2% of patients; time to reversal of shock was 49 h longer in patients who were given a bolus administration [59 h (range, 47.5-90.5) *vs* 108 h (range, 63.2-189); $P = 0.001$]. The maximal dose of norepinephrine after initiation of hydrocortisone was lower in patients on continuous infusion [0.19 μg/kg per minute (range, 0.11-0.28 μg)] compared with patients who were given bolus [0.34 μg/kg per minute (range, 0.16-0.49); $P = 0.004$]. Kaplan-Meier analysis revealed a higher proportion of shock reversal at 7 d in patients with continuous infusion compared to those given bolus (83% *vs* 63%; $P = 0.004$). There was a good correlation between time to initiation of hydrocortisone and time to reversal of shock ($r = 0.80$; $P < 0.0001$); ROC curve analysis revealed that the best criteria for prediction of shock reversal was a time to initiation of hydrocortisone of ⩽ 13 h after administration of norepinephrine, with an area under the curve of 0.81 ($P < 0.001$). The maximal dose of norepinephrine at initiation of hydrocortisone with the highest association with shock reversal was ⩽ 0.28 μg/kg per minute, with an area under the curve of 0.75 ($P = 0.0002$). On a logistic regression model, hydrocortisone taper was not associated with a lower risk of shock relapse (RR = 1.29; $P = 0.17$) but was related to a higher probability of hyperglycemia [odds ratio (OR), 5.3; $P = 0.04$] and hypokalemia (OR = 10.6; $P = 0.01$).

CONCLUSION

Continuous infusion of hydrocortisone could hasten the resolution of septic shock compared to bolus administration. Earlier initiation corresponds with a higher probability of shock reversal. Tapering strategy is unnecessary.

Key words: Corticosteroids; Hydrocortisone; Timing; Administration; Discontinuation; Septic shock

Core tip: Until now, the indications, timing, administration, and discontinuation of hydrocortisone for septic shock patients have been widely variable. Our study found that continuous infusion was the most effective method compared to bolus administration; we also identified a time from vasopressor administration of ⩽ 13 h and/or a norepinephrine dose of ⩽ 0.28 μg/kg per minute as the best clinical criteria for initiation of hydrocortisone. We found no benefit from the tapering strategy, which was only associated with a higher incidence of hyperglycemia and hypokalemia.

Ibarra-Estrada MA, Chávez-Peña Q, Reynoso-Estrella CI, Rios-Zermeño J, Aguilera-González PE, García-Soto MA, Aguirre-Avalos G. Timing, method and discontinuation of hydrocortisone administration for septic shock patients. *World J Crit Care Med* 2017; 6(1): 65-73 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i1/65.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i1.65

INTRODUCTION

Since William Schumer stated in the mid-1970s that early administration of adjunctive steroids could be helpful in the management of patients with septic shock[1], investigators have developed experimental animal and human trials to study the role of corticosteroid therapy; however, this benefit remains controversial[2,3]. The controversy may exist because the studies have varied in their design, steroid preparation, dose, strategy of administration (intermittent bolus or continuous infusion), length of therapy, time of initiation, and patterns of discontinuation[4].

Corticosteroids had been shown to be associated with a faster reversal of shock compared to placebo[5-9]. For that reason, the 2012 Surviving Sepsis Campaign Guidelines recommended administration of hydrocortisone (200 mg/d) if hemodynamic stability is not achievable after fluid resuscitation and vasopressor therapy[2]. Nevertheless, the patterns in clinical practice remain widely heterogeneous because of differing interpretations of the definition of poor responsiveness of shock to fluid and vasopressor therapy, discrepancy between clinicians' interpretation of guidelines, discrepancy in clinical practice, and unfamiliarity with existing evidence[10].

The aim of this observational study was to characterize the use of hydrocortisone in septic shock patients in order to identify the most effective method of administration and withdrawal, and to find the best clinical criteria for initiation of corticosteroid therapy to increase the probability of shock reversal.

MATERIALS AND METHODS

Setting

This was a prospective cohort study conducted in 2 medical/surgical intensive care units at tertiary academic hospitals from June 1st, 2015, through July 31st, 2016. All patients recruited in Instituto Jalisciense de Cancerología had oncologic disease; there were no

oncologic patients recruited at Hospital Civil Fray Antonio Alcalde. Inclusion criteria for patients were a diagnosis of septic shock, defined as sepsis induced hypotension persisting despite adequate fluid resuscitation[2], for which the attending intensivist determined the need for adjunct hydrocortisone therapy at a stress dose (no more than 200 mg/d), regardless of the timing and method of administration. Shock reversal was considered when the arterial pressure remained stable (SAP > 90 mmHg or MAP > 70 mmHg without requirement of new vasopressor infusion) for more than 24 h. Relapse was defined as recurrence of septic shock, requiring norepinephrine resumption within first 7-d after reversal. Patients with a previous diagnosis of adrenal insufficiency, who received hydrocortisone at a dose more than 200 mg/d, and who died within the first 48 h after intensive care unit (ICU) admission were excluded. The scientific and ethics committees at Instituto Jalisciense de Cancerología (INV-01/16) and Hospital Civil Fray Antonio Alcalde (HCG/CEI-0321/16) approved this investigation.

Data collection

After patients with septic shock were deemed candidates for initiation of hydrocortisone, informed consent was obtained from patient or their next of kin, and data were prospectively collected. Recorded information included demographic data, comorbidities, maximal dose (calculated to ideal body weight) and length of vasopressor requirement, timing, method of administration and discontinuation of hydrocortisone, adverse effects of corticosteroids, ICU length of stay, time to death, and 30-d mortality. The Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ) score and the Sequential Organ Failure Assessment score were calculated within the first day of ICU admission.

Statistical analysis

Continuous variables were reported as the mean [standard deviation (SD)] if they were normally distributed, or the median [interquartile range (IQR)] if they were not normally distributed, according to the Shapiro-Wilk test. A Mann-Whitney or *t*-test was used for comparison between groups as appropriate. We used a two-way mixed ANOVA test for comparison between pre- and post- hydrocortisone maximal doses of norepinephrine. Categorical variables were expressed as the number of measurements (%) and were compared by χ^2 test. We constructed receiver-operating characteristic (ROC) curves for time to initiation of hydrocortisone and dosage of norepinephrine at initiation of hydrocortisone to determine the ability for prediction of shock reversal; optimal cut-off values were obtained with the greatest sum of sensitivity and specificity using the Youden index[11]. The relationship between time to initiation of hydrocortisone and total duration of shock was estimated with the Spearman correlation coefficient test. We performed a Kaplan-Meier analysis to compare the shock reversal rate at 7 d between continuous and bolus administration. Multivariate logistic regression was performed to identify factors associated with shock reversal and adverse effects. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test, considered as adequate if $P > 0.05$[12]. Based on vasopressor dosages in a previous study of septic shock patients with our same settings[13], we determined that 26 patients with continuous infusion and 26 with bolus administration of hydrocortisone would be needed to detect a difference of 0.10 μg/kg per minute in norepinephrine maximal dosage from 12 h after initiation of corticosteroid with a 90% statistical power and type Ⅰ error of 5%. For all tests, *P*-values were two-sided, and a value lower than 0.05 was considered statistically significant. We used MedCalc (Ver 16.4.3, Ostend, Belgium) for calculating sample size and for the statistical analysis.

The statistical methods of this study were reviewed by Miguel A. Ibarra-Estrada, clinical investigator and biomedical statistics analysis expert from Critical Care Unit, Instituto Jalisciense de Cancerología, Guadalajara Jalisco 44280, Mexico; Critical Care Unit, Hospital General Regional #180, Instituto Mexicano del Seguro Social, Tlajomulco de Zúñiga Jalisco 45655, Mexico.

RESULTS

Throughout the study period, 826 patients were admitted to both ICUs, of which 66 (7.9%) had a diagnosis of septic shock; 59 patients met the inclusion criteria because 7 subjects died within the first 48 h (Figure S1, supplementary material). The median age was 57 years (IQR, 38-65), 26 patients (44.1%) were men, 25 patients (42.4%) were oncologic, and 42 patients (71.2%) were surgical patients. The most common source of infection was pneumonia, which presented in 26 patients (44.1%). The mean APACHE Ⅱ score was 21.5 (SD ± 5.8). Hydrocortisone was administered as a continuous infusion in 54.2% of patients; the median dose of norepinephrine at initiation of hydrocortisone was 0.3 μg/kg per minute (IQR, 0.18-0.39), there were no systemic steroids administered other than hydrocortisone, time from norepinephrine to initiation of hydrocortisone was 12 h (IQR, 6-27), and length of vasopressor requirement was 83 h (IQR, 49-120). Among survivors, hydrocortisone was tapered in 23 patients (53.5%). Overall 30-d mortality was 42.4%.

Method of administration

There were no significant differences in demographic and baseline clinical characteristics between patients in the continuous infusion and bolus groups (Table 1). We found no differences in these characteristics between recruitment centers (Table S1, supplementary material). Patients in the bolus group received hydrocortisone 6 h later than patients with continuous infusion ($P = 0.01$), and time to shock reversal was 49 h longer ($P = 0.001$). Concerning adverse affects, bolus administration was significantly associated with higher incidence of new

Table 1 Univariate analysis of demographic, clinical characteristics and outcomes of the study population according to method of administration of hydrocortisone

Characteristics	Continuous infusion (n = 32)	IV bolus (n = 32)	P value
Age, median (IQR)	50 (37-64)	61 (39-70)	0.19
Male gender, n (%)	12 (37.5)	14 (51.9)	0.27
Oncologic disease, n (%)	15 (46.9)	10 (37)	0.45
Surgical patients, n (%)	25 (78.1)	17 (63)	0.2
Infection source, n (%)			
Pneumonia	13 (40.6)	13 (48.1)	0.56
Ventilator associated	7 (21.8)	6 (22.2)	0.87
Health care associated	3 (9.3)	4 (12.5)	0.66
Community acquired	3 (9.3)	3 (11.1)	0.52
Abdomen	14 (43.7)	10 (37)	0.6
Soft tissue	4 (12.5)	1 (3.7)	0.23
Urinary tract	1 (3.1)	2 (7.4)	0.45
Other	0 (0)	1 (3.7)	0.27
Diabetes, n (%)	8 (25)	4 (14.8)	0.33
Acute kidney injury, n (%)	14 (43.7)	17 (63)	0.14
Baseline creatinine, mg/dL, median (IQR)	0.8 (0.7-1.4)	1.1 (0.7-1.5)	0.32
ARDS, n (%)	10 (31.2)	11 (40.7)	0.45
APACHE Ⅱ score (SD)	21 ± 6	21.7 ± 5.6	0.76
SOFA score (SD)	10 ± 2.9	11 ± 2.7	0.16
Vasopressin use, n (%)	12 (37.5)	4 (14.8)	0.5
Maximum NE dose (mcg/kg per minute), median (IQR)	0.25 (0.17-0.36)	0.33 (0.20-0.39)	0.55
Hydrocortisone dose (mg/kg per day), median (IQR)	2.63 ± 0.27	2.75 ± 0.31	0.13
NE to hydrocortisone (h), median (IQR)	8 (4-19.5)	14 (8-31.5)	0.01
Time to shock reversal (h), median (IQR)	59 (47.5-90.5)	108 (63.2-189)	0.001
Shock relapse, n (%)	4 (18.2)	7 (38.9)	0.14
Hydrocortisone tapered, n (%)	10 (41.7)	13 (68.4)	0.08
Diuretic use, n (%)	19 (59.4)	11 (40.7)	0.15
New onset hypernatremia, n (%)	17 (53.1)	18 (66.7)	0.29
New onset hypokalemia, n (%)	12 (37.5)	18 (66.7)	0.02
New onset hyperglycemia, n (%)	19 (59.4)	23 (85.2)	0.03
Superinfection, n (%)	3 (9.4)	5 (18.5)	0.31
Wound dehiscence, n (%)	3 (9.4)	2 (7.4)	0.78
UGIB, n (%)	1 (3.1)	0 (0)	0.35
ICU-AW, n (%)	8 (25)	9 (33.3)	0.48
Vasopressor-free days, median (IQR)	3 (2-5)	2 (0-3.7)	0.12
ICU LOS, median (IQR)	8.5 (6-13)	9 (5-13)	0.81
30-d mortality, n (%)	10 (31.2)	15 (55.6)	0.06

APACHE Ⅱ: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome; ICU-AW: Intensive care unit acquired weakness; ICU LOS: Intensive care unit length of stay; IQR: Interquartile range; NE: Norepinephrine; SOFA: Sequential Organ Failure Assessment; UGIB: Upper gastrointestinal bleeding.

onset hyperglycemia, with a relative risk (RR) of 2.7 (P = 0.03); hypokalemia was also more common with bolus administration, with a RR of 1.8 (P = 0.03). There was a trend to higher mortality in the bolus group, but this was not statistically significant (RR = 1.5; P = 0.06).

Regarding efficacy, continuous infusion was associated with a lower norepinephrine maximal dose requirement, from 12 h after hydrocortisone initiation. At two-way mixed ANOVA test, the maximal dose of norepinephrine for patients with continuous infusion after initiation of hydrocortisone was 0.19 μg/kg per minute, compared to 0.34 μg/kg per minute for patients on bolus administration, with a significant interaction between groups (P = 0.04; Figure 1). At Kaplan-Meier analysis, continuous infusion was also significantly associated with a higher proportion of shock reversal at 7 d after presentation of shock (83% *vs* 63%; P = 0.004; Figure 2); this difference remained significant after adjustment for vasopressin use with Cox proportional hazards regression (P = 0.02).

At survival analysis, there was a trend to higher survival in patients on continuous infusion, with a hazard ratio for death of 0.47; however, this was not significant after adjustment for time to initiation of hydrocortisone (P = 0.06).

Initiation

We found a significant correlation between time to initiation of hydrocortisone and time to shock reversal, with a Spearman correlation coefficient of 0.80 ($P \leqslant$ 0.001; Figure 3). Moreover, we built a ROC curve for this variable and obtained the best cut-off at ⩽ 13 h, with a significant area under the curve (AUC) at 0.81 ($P \leqslant$ 0.0001), obtaining a sensitivity of 70% and specificity of 88% for prediction of shock reversal (Figure 4). Taking the dose of norepinephrine as a potential criterion for prompting initiation of hydrocortisone, ROC curve analysis revealed the best cut-off at ⩽ 0.28 μg/kg per minute,

Table 2 Univariate and multivariate logistic regression analysis for relevant factors associated with new-onset hyperglycemia

Variable	Univariate		*P* value	Multivariate	*P* value
	NO-H (*n* = 42)	No NO-H (*n* = 17)		Adjusted OR (95%CI)	
Bolus hydrocortisone, *n* (%)	19 (45.2)	13 (76.5)	0.04	3.2 (0.5-26.5)	0.99
Hydrocortisone taper, *n* (%)	20 (64.5)	3 (27.3)	0.03	5.3 (1.8-34.5)	0.04
Diabetes, *n* (%)	11 (26.2)	1 (5.9)	0.08	6.2 (0.4-79.0)	0.95

Goodness-of-fit (Hosmer-Lemeshow). χ^2 = 0.019, *P* = 1.00; AUC, 0.88 (0.75-0.96), *P* = 0.0001. NO-H: New-onset hyperglycemia; OR: Odds ratio.

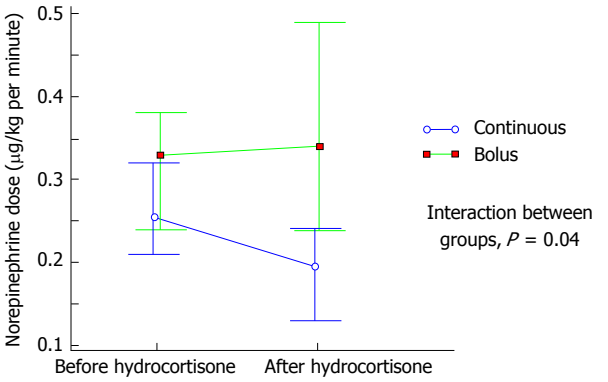

Figure 1 Change in maximal norepinephrine dose from 12 h after initiation of hydrocortisone. Comparison between continuous and bolus administration groups, with two-way mixed ANOVA test, *P* = 0.04.

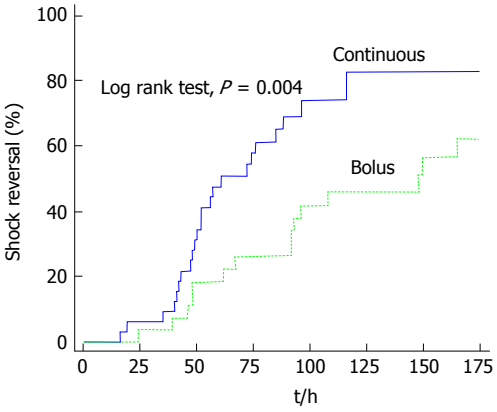

Figure 2 Kaplan-Meier analysis comparing the rate of septic shock reversal, according to administration of hydrocortisone. At 7 d (168 h), 83% of continuous infusion patients were vasopressor-free compared to 63% of patients who were in the bolus administration group, *P* = 0.004.

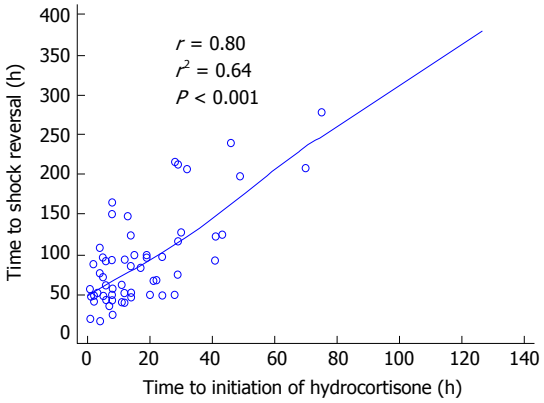

Figure 3 Correlation between time to initiation of hydrocortisone and total time to shock reversal. Spearman correlation coefficient 0.80, *P* < 0.001.

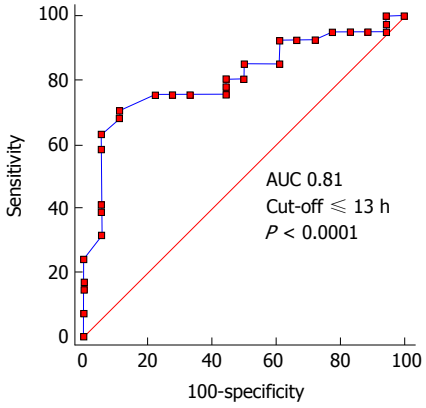

Figure 4 Receiver operating characteristic curve analysis of time to initiation of hydrocortisone for prediction of shock reversal. AUC, 0.81, *P* < 0.0001. Cut-off obtained with Youden index. AUC: Area under the curve.

with an AUC of 0.75 (*P* = 0.0002), a sensitivity of 65%, and a specificity of 88% for shock reversal.

Discontinuation and adverse effects

As expected for patients with shock reversal, length of hydrocortisone administration was significantly longer for patients with the tapering strategy than for patients with sudden discontinuation [121 h (IQR, 81-245) *vs* 50 h (IQR, 44-101); *P* = 0.001]. Taper strategy was independently associated with a higher risk of hyperglycemia (RR = 3.2; *P* = 0.042), and hypokalemia (RR = 2.8; *P* = 0.005). Because bolus administration was also independently associated with higher risk of hyperglycemia and hypokalemia at univariate analysis, we performed logistic regression models adjusting for potential confounding variables; only the taper strategy maintained statistical significance for higher risk of hyperglycemia (Table 2) and had the highest OR for hypokalemia (Table 3).

Hydrocortisone taper was not associated with a lower risk of shock relapse (RR = 1.29; *P* = 0.17).

Shock reversal

In order to identify the variables associated with a higher probability of shock reversal, we performed a logistic regression model, adjusting for relevant covariables. As shown in Table 4, only the initiation of hydrocortisone ⩽

Table 3 Univariate and multivariate logistic regression analysis for relevant factors associated with new-onset hypokalemia

Variable	Univariate		*P* value	Multivariate	*P* value
	NO-HK (*n* = 30)	No NO-HK (*n* = 29)		Adjusted OR (95%CI)	
Bolus hydrocortisone, *n* (%)	12 (40)	20 (69)	0.02	8.5 (1.2-59.9)	0.03
Hydrocortisone taper, *n* (%)	17 (77.3)	6 (30)	0.002	10.6 (1.5-73.3)	0.01
AKI, *n* (%)	13 (43.3)	18 (62.1)	0.08	0.1 (0.01-0.8)	0.03
Diuretic use, *n* (%)	20 (66.7)	10 (34.5)	0.01	6.3 (0.95-42.0)	0.05

Goodness-of-fit (Hosmer-Lemeshow). χ^2 = 5.52, *P* = 0.59; AUC, 0.88 (0.74-0.95), *P* = 0.0001. AKI: Acute kidney injury; HK: Hypokalemia; OR: Odds ratio.

Table 4 Univariate and multivariate logistic regression analysis for relevant factors associated with shock reversal

Variable	Univariate		*P* value	Multivariate	*P* value
	Shock reversal (*n* = 30)	No-reversal (*n* = 29)		Adjusted OR (95%CI)	
Age (yr), SD	53 ± 16.3	50 ± 16.3	0.46		
Male gender, *n* (%)	15 (36.6)	11 (61.1)	0.08	1.4 (0.21-10.1)	0.68
Medical disease, *n* (%)	11 (26.8)	6 (33.3)	0.61		
Oncologic disease, *n* (%)	20 (48.8)	5 (27.8)	0.13	1.0 (0.18-6.3)	0.92
AKI, *n* (%)	17 (41.5)	14 (77.8)	0.01	0.3 (0.05-2.0)	0.23
ARDS, *n* (%)	12 (29.3)	9 (50)	0.12	2.7 (0.4-16.9)	0.27
Superinfection, *n* (%)	5 (12.2)	3 (16.7)	0.68		
APACHE Ⅱ score (SD)	20 ± 5.4	23 ± 6.4	0.16	1.1 (0.9-1.3)	0.18
SOFA score (SD)	10 ± 3.0	10 ± 2.4	0.69		
Vasopressin use, *n* (%)	10 (24.4)	6 (33.3)	0.48	2.5 (0.4-15.4)	0.31
Early hydrocortisone (≤ 13 h from NE), *n* (%)	28 (68.3)	2 (11.1)	0.0001	13.8 (1.4-129)	0.02
NE dose at hydrocortisone initiation ≤ 0.28 μg/kg per minute, *n* (%)	28 (68.3)	2 (11.1)	0.0001	32.4 (2.7-382)	0.005

Goodness-of-fit (Hosmer-Lemeshow). χ^2 = 7.01, *P* = 0.53; AUC, 0.91 (0.80-0.96), *P* ≤ 0.0001. AKI: Acute kidney injury: APACHE Ⅱ: Acute physiology and chronic health evaluation; ARDS: Acute respiratory distress syndrome; NE: Norepinephrine; SOFA: Sequential organ failure assessment.

13 h from vasopressor administration and initiation of norepinephrine at a dose ≤ 28 μg/kg per minute were statistically significant.

DISCUSSION

The main finding in our study is that, compared to bolus strategy, the administration of hydrocortisone by continuous infusion may lead to a faster reversal of shock and is associated with a higher proportion of vasopressor-free patients at 7 d. Furthermore, we identified optimal cut-off criteria for initiation of hydrocortisone, either based on the time from initiation of vasopressor, or the current maximal dose of norepinephrine. This study also suggests there is no benefit of the tapering strategy because it does not lower the risk of shock relapse but is only associated with a higher incidence of adverse effects.

The current Surviving Sepsis Campaign Guidelines[2] suggest using continuous infusion, rather than a repetitive bolus of hydrocortisone. This recommendation is only based on the results of an observational study in which bolus hydrocortisone was associated with increased blood glucose levels and more variable peak values compared to continuous infusion[14]. This assumption was confirmed by univariate analysis in our study, and the findings strengthen this recommendation's effectiveness because the vasopressor requirement was 2 d shorter for patients on continuous infusion.

Most current studies, including meta-analyses, only focus on the association between corticosteroids and mortality in septic shock patients[6-10,15-20]; therefore, information related to the hemodynamic effects of both methods of administration is limited. In a recent Chinese study of septic shock patients, the continuous infusion strategy was correlated with a slight improvement in mean arterial pressure but only at 6 h after corticosteroid treatment, and the response was not sustained[21]. To our knowledge, this is the first study comparing both methods in which continuous infusion was found to hasten shock reversal. A possible explanation is the noted high variability in glucocorticoid sensitivity among septic shock patients with severe disease, as measured by suppression of inflammatory cytokine production[22]. Moreover, it has been found that a common genetic variation in the promoter of NF-KB1 (insertion-deletion polymorphism - 94ins/delATTG) is, in fact, associated with nonresponse and a 3-fold increase in risk of death in patients receiving hydrocortisone[23]. As these factors were not included in our study, the distribution of this potential bias in our population is unknown.

The primary change in practice reported after the publication of the Corticosteroid Therapy of Septic Shock study[9] and the updated Surviving Sepsis Campaign Guidelines was that physicians no longer used the cosyntropin stimulation test to identify which patients would benefit from corticosteroids[24]. However, since there are no specific criteria for definition of poorly responsive shock, a major discrepancy between clinicians' interpretation guidelines and clinical practice is the trigger for initiation of hydrocortisone. In a recent study[10], the most common

clinical threshold for prescribing corticosteroids was the presence of 2 or more vasopressors in 64% of patients. We believe that there should be a global agreement according to variables associated with the higher probability of shock reversal. Based on our results at ROC curve analysis and correlation with time to shock reversal, we suggest initiation of hydrocortisone at ⩽ 13 h after vasopressor administration. This conclusion agrees with a recent study of severely shocked patients in which the early administration of hydrocortisone (< 9 h) was associated with a significantly lower total time of vasopressors and mortality[25].

In a retrospective review addressing norepinephrine as a trigger for initiation of corticosteroids, the dose was arbitrarily defined as non-weight-based low, moderate, or high[10]. Through a more objective approach, we found a dose of ⩽ 0.28 μg/kg per minute to be the best predictor for shock reversal, a lower threshold than what has been used in most studies[9,25,26], reinforcing the recommendation of an earlier initiation of hydrocortisone also based on vasopressor dose[27,28].

Another interesting finding of this study is the apparent lack of benefits to the tapering strategy for discontinuation of hydrocortisone. The Surviving Sepsis Campaign Guidelines suggest tapering from steroids when they are no longer required; therefore, this strategy is the most commonly used (in up to 74% of patients), depending on the duration of hydrocortisone therapy[10]. Unfortunately, there has been no comparative study between tapering and abrupt cessation, and the main argument for this suggestion is a small crossover study in which shock relapse occurred in 30% of patients with sudden discontinuation[29]; however, the study was underpowered to reach that conclusion, because the data arose from a subgroup analysis of 20 patients. Therefore, tapering has a 2D recommendation (the weakest possible) on the GRADE system. Furthermore, there have been other randomized controlled studies in which corticosteroids were abruptly discontinued without reported increased risk of shock relapse[7,8]. In the current study, tapering was only associated with adverse effects; therefore, we suggest this should be avoided, especially for patients with ongoing hyperglycemia and/or hypokalemia.

The main strength of this study is that it was specifically designed to compare the efficacy between both methods of administration of hydrocortisone, according to vasopressor requirement, indirectly assessing their effects on immunomodulation and vasomotor tone improvement.

This study has some limitations; we did not address the effects of the use of some drugs known to affect adrenal function (*e.g.,* etomidate, antifungals, benzodiazepines, and opioids)[30]. Medical management for septic shock patients is always based on the current Surviving Sepsis Campaign Guidelines and are very similar at both hospitals; however, due to the observational and nonrandomized design of the study, we cannot ensure completely homogeneous treatment regarding other relevant variables associated with improving outcomes (*e.g.,* appropriateness and type of fluid resuscitation and correct and timely use of antibiotics). This study was powered to detect differences in short-term vasopressor requirements and to find the best cut-offs for initiation of hydrocortisone only; therefore, results concerning analysis between groups should be interpreted cautiously, and should be taken as hypothesis-generating data for the design of future clinical randomized controlled trials.

In conclusion, we found that continuous infusion of hydrocortisone could hasten resolution of septic shock compared with bolus administration, and that earlier initiation based on time and/or norepinephrine dose is related with a higher probability of shock reversal. The tapering strategy appears unnecessary and may be only related to additional adverse effects.

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COMMENTS

Background

The latest Surviving Sepsis Campaign Guidelines recommend administration of low-dose hydrocortisone (200 mg/d) when hemodynamic stability is not achievable after fluid resuscitation and vasopressor therapy. Although the benefits of hydrocortisone are increasingly being recognized, several issues concerning its specific indications, clinical criteria for initiation, adequate method of administration, and strategy of discontinuation are unresolved, which leads to widely heterogeneous prescribing practices among critical care physicians. Studies addressing those issues are lacking.

Research frontiers

The reported prescribing patterns of hydrocortisone for patients with septic shock come from studies performed only in the United States and describe a wide variability of clinical practices. In Mexico, this kind of information is scarce.

Innovations and breakthroughs

Continuous infusion of hydrocortisone leads to faster resolution of shock than bolus administration. Initiation of hydrocortisone at ⩽ 13 h after starting norepinephrine and/or a maximal dose of ⩽ 28 μg/kg per minute is associated with a higher probability of shock reversal. There is no benefit from a tapering strategy because this was only shown to lead to additional adverse effects.

Applications

The results of the study add valuable information, which could contribute to the initiation of a widespread agreement regarding specific indications on the correct use of hydrocortisone in septic shock patients.

Peer-review

It is a well design study, though performed in a small group of patients.

REFERENCES

1 **Schumer W**. Steroids in the treatment of clinical septic shock. *Ann Surg* 1976; **184**: 333-341 [PMID: 786190 DOI: 10.1097/00000658

-197609000-00011]
2 **Dellinger RP**, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41**: 580-637 [PMID: 23353941 DOI: 10.1097/CCM.0b013e31827e83af]
3 **Dellinger RP**. Steroid therapy of septic shock: the decision is in the eye of the beholder. *Crit Care Med* 2008; **36**: 1987-1989 [PMID: 18520670 DOI: 10.1097/CCM.0b013e31817d7ee4]
4 **Patel GP**, Balk RA. Systemic steroids in severe sepsis and septic shock. *Am J Respir Crit Care Med* 2012; **185**: 133-139 [PMID: 21680949 DOI: 10.1164/rccm.201011-1897CI]
5 **Bollaert PE**, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; **26**: 645-650 [PMID: 9559600 DOI: 10.1097/00003246-199804000-00010]
6 **Briegel J**, Forst H, Haller M, Schelling G, Kilger E, Kuprat G, Hemmer B, Hummel T, Lenhart A, Heyduck M, Stoll C, Peter K. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; **27**: 723-732 [PMID: 10321661 DOI: 10.1097/00003246-199904000-00025]
7 **Yildiz O**, Doganay M, Aygen B, Güven M, Keleştimur F, Tutuû A. Physiological-dose steroid therapy in sepsis [ISRCTN36253388]. *Crit Care* 2002; **6**: 251-259 [PMID: 12133187 DOI: 10.1186/cc1498]
8 **Annane D**, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaud P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; **288**: 862-871 [PMID: 12186604 DOI: 10.1001/jama.288.7.862]
9 **Sprung CL**, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; **358**: 111-124 [PMID: 18184957 DOI: 10.1056/NEJMoa071366]
10 **Contrael KM**, Killian AJ, Gregg SR, Buchman TG, Coopersmith CM. Prescribing patterns of hydrocortisone in septic shock: a single-center experience of how surviving sepsis guidelines are interpreted and translated into bedside practice. *Crit Care Med* 2013; **41**: 2310-2317 [PMID: 23787398 DOI: 10.1097/CCM.0b013e31828cef29]
11 **Youden WJ**. Index for rating diagnostic tests. *Cancer* 1950; **3**: 32-35 [PMID: 15405679 DOI: 10.1002/1097-0142(1950)3:1<32::AID-CNCR2820030106>3.0.CO;2-3]
12 **Hosmer DW**, Taber S, Lemeshow S. The importance of assessing the fit of logistic regression models: a case study. *Am J Public Health* 1991; **81**: 1630-1635 [PMID: 1746660 DOI: 10.2105/AJPH.81.12.1630]
13 **Ibarra-Estrada MÁ**, López-Pulgarín JA, Mijangos-Méndez JC, Díaz-Gómez JL, Aguirre-Avalos G. Respiratory variation in carotid peak systolic velocity predicts volume responsiveness in mechanically ventilated patients with septic shock: a prospective cohort study. *Crit Ultrasound J* 2015; **7**: 29 [PMID: 26123610 DOI: 10.1186/s13089-015-0029-1]
14 **Weber-Carstens S**, Deja M, Bercker S, Dimroth A, Ahlers O, Kaisers U, Keh D. Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients. *Intensive Care Med* 2007; **33**: 730-733 [PMID: 17325831 DOI: 10.1007/s00134-007-0540-3]
15 **Annane D**, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA* 2009; **301**: 2362-2375 [PMID: 19509383 DOI: 10.1001/jama.2009.815]
16 **Annane D**, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. *Cochrane Database Syst Rev* 2015; (**12**): CD002243 [PMID: 26633262 DOI: 10.1002/14651858.CD002243.pub3]
17 **Arabi YM**, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, Knawy BA, Hajeer AH, Tamimi W, Cherfan A. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ* 2010; **182**: 1971-1977 [PMID: 21059778 DOI: 10.1503/cmaj.090707]
18 **Huh JW**, Choi HS, Lim CM, Koh Y, Oh YM, Shim TS, Lee SD, Kim WS, Kim DS, Hong SB. Low-dose hydrocortisone treatment for patients with septic shock: a pilot study comparing 3days with 7days. *Respirology* 2011; **16**: 1088-1095 [PMID: 21726354 DOI: 10.1111/j.1440-1843.2011.02018.x]
19 **Tagami T**, Matsui H, Fushimi K, Yasunaga H. Low-dose corticosteroid treatment and mortality in refractory abdominal septic shock after emergency laparotomy. *Ann Intensive Care* 2015; **5**: 32 [PMID: 26514125 DOI: 10.1186/s13613-015-0074-8]
20 **Wang C**, Sun J, Zheng J, Guo L, Ma H, Zhang Y, Zhang F, Li E. Low-dose hydrocortisone therapy attenuates septic shock in adult patients but does not reduce 28-day mortality: a meta-analysis of randomized controlled trials. *Anesth Analg* 2014; **118**: 346-357 [PMID: 24445635 DOI: 10.1213/ANE.0000000000000050]
21 **Chen Z**, Yang C, He H, He Z. [The impacts of low-dose corticosteroids infusion given in different manners on refractory septic shock patients]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2015; **27**: 443-447 [PMID: 26049181 DOI: 10.3760/cma.j.issn.2095-4352.2015.06.006]
22 **Cohen J**, Pretorius CJ, Ungerer JP, Cardinal J, Blumenthal A, Presneill J, Gatica-Andrades M, Jarrett P, Lassig-Smith M, Stuart J, Dunlop R, Starr T, Venkatesh B. Glucocorticoid Sensitivity Is Highly Variable in Critically Ill Patients With Septic Shock and Is Associated With Disease Severity. *Crit Care Med* 2016; **44**: 1034-1041 [PMID: 26963327 DOI: 10.1097/CCM.0000000000001633]
23 **Schäfer ST**, Gessner S, Scherag A, Rump K, Frey UH, Siffert W, Westendorf AM, Steinmann J, Peters J, Adamzik M. Hydrocortisone fails to abolish NF-κB1 protein nuclear translocation in deletion allele carriers of the NFKB1 promoter polymorphism (-94ins/delATTG) and is associated with increased 30-day mortality in septic shock. *PLoS One* 2014; **9**: e104953 [PMID: 25133403 DOI: 10.1371/journal.pone.0104953]
24 **Bruno JJ**, Dee BM, Anderegg BA, Hernandez M, Pravinkumar SE. US practitioner opinions and prescribing practices regarding corticosteroid therapy for severe sepsis and septic shock. *J Crit Care* 2012; **27**: 351-361 [PMID: 22341726 DOI: 10.1016/j.jcrc.2011.12.011]
25 **Katsenos CS**, Antonopoulou AN, Apostolidou EN, Ioakeimidou A, Kalpakou GT, Papanikolaou MN, Pistiki AC, Mpalla MC, Paraschos MD, Patrani MA, Pratikaki ME, Retsas TA, Savva AA, Vassiliagkou SD, Lekkou AA, Dimopoulou I, Routsi C, Mandragos KE. Early administration of hydrocortisone replacement after the advent of septic shock: impact on survival and immune response*. *Crit Care Med* 2014; **42**: 1651-1657 [PMID: 24674923 DOI: 10.1097/CCM.0000000000000318]
26 **Torgersen C**, Luckner G, Schröder DC, Schmittinger CA, Rex C, Ulmer H, Dünser MW. Concomitant arginine-vasopressin and hydrocortisone therapy in severe septic shock: association with mortality. *Intensive Care Med* 2011; **37**: 1432-1437 [PMID: 21779849 DOI: 10.1007/s00134-011-2312-3]
27 **Bentzer P**, Fjell C, Walley KR, Boyd J, Russell JA. Plasma cytokine levels predict response to corticosteroids in septic shock. *Intensive Care Med* 2016; **42**: 1970-1979 [PMID: 27071387 DOI: 10.1007/s00134-016-4338-z]
28 **Gordon AC**, Mason AJ, Perkins GD, Stotz M, Terblanche M, Ashby D, Brett SJ. The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. *Crit Care Med* 2014; **42**: 1325-1333 [PMID: 24557425 DOI: 10.1097/CCM.0000000000000212]
29 **Keh D**, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, Volk HD, Doecke WD, Falke KJ, Gerlach H. Immunologic

and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; **167**: 512-520 [PMID: 12426230 DOI: 10.1164/rccm.200205-446OC]

30 **Greenberg SB**, Coursin DB. Timing of corticosteroids in refractory septic shock: a key or wishful thinking?*. *Crit Care Med* 2014; **42**: 1733-1735 [PMID: 24933052 DOI: 10.1097/CCM.0000000000000361]

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ORIGINAL ARTICLE

Prospective Study

Comparison of inhaled milrinone, nitric oxide and prostacyclin in acute respiratory distress syndrome

Martin Albert, Daniel Corsilli, David R Williamson, Marc Brosseau, Patrick Bellemare, Stéphane Delisle, Anne QN Nguyen, France Varin

Martin Albert, Departments of Intensive Care and Medicine, Hôpital du Sacré-Coeur, de Montréal Research Center, Université de Montréal, Montréal H4J 1C5, Canada

Daniel Corsilli, Marc Brosseau, Patrick Bellemare, Department of Intensive Care, Centre Hospitalier Universitaire de Montréal, Université de Montréal, Montréal H2W 1T8, Canada

David R Williamson, Anne QN Nguyen, France Varin, Department of Pharmacy, Université de Montréal, Hôpital du Sacré-Coeur de Montréal Research Center, Montréal H4J 1C5, Canada

Patrick Bellemare, Department of Respiratory Care, Hôpital du Sacré-Coeur de, Montréal H4J 1C5, Canada

Stéphane Delisle, Hôpital du Sacré-Coeur, de Montréal Research Center, Université de Montréal, Montréal H4J 1C5, Canada

Author contributions: All the authors contributed to the manuscript.

Institutional review board statement: The protocol was approved by the Hôpital du Sacré-Coeur de Montréal ethics committee and consent was obtained from patients or their next of kin. The protocol was submitted to and approved by Health Canada.

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Correspondence to: Martin Albert, MD, Departments of Intensive Care and Medicine, Hôpital du Sacré-Coeur, de Montréal Research Center, Université de Montréal, 5400 boul, Gouin Ouest, Montréal H4J 1C5, Canada. m.albert@umontreal.ca
Telephone: +1-514-3382050
Fax: +1-514-3383557

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Abstract

AIM

To evaluate the safety and efficacy of inhaled milrinone in acute respiratory distress syndrome (ARDS).

METHODS

Open-label prospective cross-over pilot study where fifteen adult patients with hypoxemic failure meeting standard ARDS criteria and monitored with a pulmonary artery catheter were recruited in an academic 24-bed medico-surgical intensive care unit. Random sequential administration of iNO (20 ppm) or nebulized epoprostenol (10 μg/mL) was done in all patients. Thereafter, inhaled milrinone (1 mg/mL) alone followed by inhaled milrinone in association with inhaled nitric oxide (iNO) was administered. A jet nebulization device synchronized with the mechanical ventilation was use to administrate the epoprostenol and the milrinone. Hemodynamic measurements and partial pressure of arterial oxygen (PaO_2) were recorded before and after each inhaled therapy

administration.

RESULTS

The majority of ARDS were of pulmonary cause (n = 13) and pneumonia (n = 7) was the leading underlying initial disease. Other pulmonary causes of ARDS were: Post cardiopulmonary bypass (n = 2), smoke inhalation injury (n = 1), thoracic trauma and pulmonary contusions (n = 2) and aspiration (n = 1). Two patients had an extra pulmonary cause of ARDS: A polytrauma patient and an intra-abdominal abscess Inhaled nitric oxide, epoprostenol, inhaled milrinone and the combination of inhaled milrinone and iNO had no impact on systemic hemodynamics. No significant adverse events related to study medications were observed. The median increase of PaO_2 from baseline was 8.8 mmHg [interquartile range (IQR) = 16.3], 6.0 mmHg (IQR = 18.4), 6 mmHg (IQR = 15.8) and 9.2 mmHg (IQR = 20.2) respectively with iNO, epoprostenol, inhaled milrinone, and iNO added to milrinone. Only iNO and the combination of inhaled milrinone and iNO had a statistically significant effect on PaO_2.

CONCLUSION

When comparing the effects of inhaled NO, milrinone and epoprostenol, only NO significantly improved oxygenation. Inhaled milrinone appeared safe but failed to improve oxygenation in ARDS.

Key words: Inhaled milrinone; Nitric oxide; Pulmonary hypertension; Hypoxemia; Acute respiratory distress syndrome; Prostacyclin

Core tip: To our knowledge, this is the first study testing inhaled milrinone as a therapy in acute respiratory distress syndrome and comparing it to more frequently used inhaled therapies. It shows that inhaled milrinone is safe but is not efficacious.

Albert M, Corsilli D, Williamson DR, Brosseau M, Bellemare P, Delisle S, Nguyen AQN, Varin F. Comparison of inhaled milrinone, nitric oxide and prostacyclin in acute respiratory distress syndrome. *World J Crit Care Med* 2017; 6(1): 74-78 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i1/74.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i1.74

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is unfortunately a common problem in intensive care units (ICU) and has been associated with significant morbidity and mortality[1]. Hypoxemia and hypercapnia are the primary manifestations of the ventilation-perfusion mismatch observed in ARDS patients. Despite several advances in mechanical ventilation, treatment of severe hypoxemia has remained one of the greatest challenges in the ICU. Among these therapies, inhaled nitric oxide (iNO) is commonly used for the treatment of hypoxemia in ARDS because it allows for selective vasodilation of ventilated units, transforming relative dead space into adequate ventilation-perfusion units[1,2]. Regardless of the well documented failure to improve survival, iNO is still of common use because of the oxygenation gain it allows. However, it has substantial cost, has been associated with potential serious side effects such as renal failure and needs a special device for its delivery[2,3]. Inhaled prostacyclin has also been used in ARDS and has been shown to significantly reduce pulmonary artery pressure and increase oxygenation[4-6]. However, prostacyclin administration is technically challenging given its short half-life and susceptibility to photo-degradation[7]. The phosphodiesterase type Ⅲ inhibitor milrinone is a potent pulmonary vasodilator that has been used with success as an inhaled therapy for pulmonary hypertension in cardiac surgery and may be a potential alternative to actual treatment strategies[8,9]. Animal studies have suggested a response to milirinone in acute lung injury[10].

The primary objective of this study was to assess the tolerability and safety of inhaled milrinone in ARDS patients. The secondary objectives included: Evaluation of the efficacy of inhaled milrinone in improving hypoxemia compared to baseline; comparison of the effects of inhaled milrinone, iNO and inhaled epoprostenol in improving hypoxemia and secondary pulmonary hypertension compared to baseline; evaluation of the efficacy of combining inhaled milrinone with iNO on hypoxemia and pulmonary hypertension.

MATERIALS AND METHODS

In an academic 24-bed medico-surgical intensive care unit, patients were screened over a 2-year period. Adult patients were enrolled if they had hypoxemic respiratory failure meeting standard moderate to severe ARDS criteria: Ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) of 200 or less, pulmonary capillary wedge pressure (Pcwp) $\leqslant$ 18 mmHg and bilateral infiltrates on frontal chest radiograph. Recruited patients also had a pulmonary artery catheter and an arterial line. Patients with severe hemodynamic instability (defined as the need for more than one vasopressor or the use of more than 0.5 μg/kg per minute of norepinephrine), on intravenous milrinone or nitrate derivatives that could not be weaned for study purposes and patients on high frequency oscillatory ventilation were excluded. Patients with a history of hypersensitivity to study medications, pregnant patients and those who participated in another study involving oxymetric values or pulmonary hemodynamics were also excluded.

Patients were randomly administered sequential nebulization of iNO (20 ppm) or epoprostenol (10 μg/mL for a total volume of 5 mL). Thereafter, milrinone (1 mg/mL for a total volume of 5 mL at each nebulisation)

Table 1 Baseline characteristics of the patients (n = 15)

Age (yr)	57 (IQR = 22)
Gender	12 men, 3 women
SOFA score (ICU admission)	7.5 (IQR = 7)
SOFA score (day of protocol)	10.0 (IQR = 5)
APACHE-Ⅱ (ICU admission)	23 (IQR = 7)
APACHE-Ⅱ (day of protocol)	23.5 (IQR = 7.0)
PaO_2 (mmHg)	80 (IQR = 39)
FiO_2 (%)	80 (IQR = 30)
PaO_2/FiO_2	138 (IQR = 68)
PEEP (cm H_2O)	10 (IQR = 2)
MAP (mm Hg)	75 (IQR = 16)
mPAP (mm Hg)	28 (IQR = 7)
Cardiac index (L/min per square metre)	3.7 (IQR = 2.6)

IQR: Interquartile range; SOFA: Sequential organ failure assessment; APACHE: Acute physiological and chronic health evaluation; PEEP: Positive end-expiratory pressure; MAP: Mean arterial pressure; mPAP: Mean pulmonary arterial pressure.

alone and in association with iNO was administered. Each drug was nebulized for 20 min and a 30 min washout was allowed between each drug. We used a jet nebulization device ventilator synchronized to nebulize epoprostenol and milrinone (MicroMist® Nebulizer model 1880; Hudson RCI, Temecula, CA, United States). The nebulizer was attached to the inspiratory limb of the ventilator near the endotracheal tube. The mass median diameter obtain with this nebulizer is 2.1 μm and the nebulization flow is between 0.25 and 0.3 mL/min. The ventilatory circuit humidification was stopped during the nebulization. Adjustment of the tidal volume was done during nebulization to obtain the same minute ventilation. The iNO was administered using a standard iNO Delivery system (INOvent®, Ohmeda, Madison, WI, United States) attached to the inspiratory limb of the ventilator. A constant dose of 20 ppm of iNO was used and monitored by the injection device. Blood pressure and oxygenation status were continuously monitored. If hemodynamic instability occurred, defined as a lowering of systolic arterial pressure ⩾ 10 mmHg or lowering of mean arterial pressure (MAP) ⩾ 5 mmHg, the study medication was stopped. If oxygenation status worsened, defined as a lowering of arterial oxygen saturation ⩾ 10% (measured with continuous pulse oximetry and confirmed by arterial gas), the study medication was stopped. Adverse events potentially related to study medications such as increase hemodynamic instability and renal failure was prospectively evaluated. Using a previously published milrinone assay[11], we determined the plasma level of milrinone at the end of the administration of inhaled milrinone or the combination of iNo and inhaled milrinone in eight samples from our last four patients.

Demographic data, APACHE Ⅱ and SOFA scores were collected. The following parameters were measured before and during each specific drug nebulization: MAP, mean pulmonary arterial pressure, thermodilution cardiac output, PaO_2, heart rate, central venous pressure and Pcwp. The following parameters were calculated: Systemic and pulmonary vascular resistances (SVR and PVR), PVR/SVR Ratio, indexed pulmonary vascular resistance, transpulmonary gradient, PaO_2/FiO_2, cardiac index, shunt and oxygenation index. A patient was considered a responder to study medications if is PaO_2 increased of more than 20% from the pre-inhalation value[2].

As the primary goal of this pilot study was safety and feasibility and no preliminary data existed in this population, a convenience sample of 15 patients was chosen. Given a within patient standard deviation of 11%, the sample size enabled the detection of a 12% difference in PaO_2 between baseline and post-milrinone PaO_2. Given the small sample-size, demographic and baseline data were described as medians and interquartile range. Continuous data were analysed using Wilcoxon signed rank tests.

The study was performed at Hôpital du Sacré-Coeur de Montréal, Canada. The local ethics committee approved the protocol and consent was obtained from patients or their next of kin. The protocol was submitted to and approved by Health Canada.

RESULTS

Fifteen consecutive patients were included in the study (Table 1). The majority of ARDS cases were of pulmonary origin (n = 13) and pneumonia (n = 7) was the leading underlying initial disease. Other pulmonary causes of ARDS were: Post cardiopulmonary bypass (n = 2), smoke inhalation injury (n = 1), thoracic trauma and pulmonary contusions (n = 2) and aspiration (n = 1). Two patients had an extra pulmonary cause of ARDS: A polytrauma patient and an intra-abdominal abscess. The main hemodynamic responses are summarized in Table 2. INO, epoprostenol, inhaled milrinone and the combination of inhaled milrinone and iNO did not have any significant impact on measured hemodynamics when compared to baseline (all P > 0.1).

We observed for the oxygenation measurement a median increase of PaO_2 from baseline of 8.8 mmHg [interquartile range (IQR) = 16.3], 6.0 mmHg (IQR = 18.4), 6 mmHg (IQR = 15.8) and 9.2 mmHg (IQR = 20.2) respectively with iNO, epoprostenol, inhaled milrinone, and iNO added to milrinone. When compared to baseline, the combination of inhaled milrinone and iNO (P = 0.004) and only iNO had a statistically significant effect (P = 0.036). The median percent response to iNO, epoprostenol, inhaled milrinone and the combination of milrinone and iNO was 11.2% (IQR = 25%), 5.3% (IQR = 24%), 7.9% (IQR = 19%) and 11.8% (IQR = 26%), respectively. The response rate to study medications, defined as an increase of more than 20% from the pre-inhalation value, were 33.3%, 20.0%, 13.3% and 33.3% respectively with iNO, epoprostenol, inhaled milrinone and the combination of inhaled milrinone and iNO. The median PaO_2 response of 39.0 mmHg in responders was higher with iNO than with epoprostenol (26.5 mmHg) or milrinone (10 mmHg).

No significant adverse events related to study medi-

Table 2 Hemodynamic parameter variations (n = 15)

	iNO	Epoprostenol	Milrinone	Milrinone + NO
MAP (mmHg)	-2.0 (11.0)	1.0 (8.0)	3.0 (6.0)	3.0 (7.0)
HR (bpm)	-2.0 (6.0)	0.0 (4.0)	0.0 (4.0)	0.0 (6.0)[1]
CVP (mmHg)	0.0 (1.4)	0.0 (4.0)	0.0 (1.0)	-1.0 (2.0)
PAOP (mmHg)	0.0 (3.0)	1.0 (4.0)	0.0(2.0)	-1.0(3.0)
mPAP (mmHg)	-2.0 (4.0)	-1.0 (3.0)	0.0 (3.0)	-2.0 (3.0)[1]
CI (L/min per square metre)	0.1 (0.6)	0.0 (0.7)	0.6 (0.9)	-0.1 (0.4)
iPVR	-30.6 (130.9)	-51.7 (165.2)	-9.4 (103.1)	0.0 (91.2)

[1]No hemodynamic variation reached statistical significance (P > 0.1 for any value) except for the median mPAP variations in the Milrinone + NO group (P = 0.47). MAP: Mean arterial pressure; HR: Heart rate; CVP: Central venous pressure; PAOP: Pulmonary artery occlusion pressure; mPAP: Mean pulmonary arterial pressure; CI: Cardiac index; iPVR: Indexed pulmonary vascular resistance; iNO: Inhaled nitric oxide.

cations were observed. The milrinone concentrations of all samples were very low (average 8.68 ng/mL) and two samples showed a level below the lower limit of quantification (1.25 ng/mL).

DISCUSSION

In this pilot study, we demonstrated that it is feasible and safe to administer inhaled milrinone and the combination of inhaled milrinone and iNO to patients with moderate to severe ARDS over a short period of time. However, inhaled milrinone had no significant effects on oxygenation and hemodynamic parameters in these patients.

These results are surprising given the beneficial effects of inhaled milrinone in other patient population such as cardiac surgery. Trying to understand these discrepancies, we hypothesized that systemic recirculation of absorbed milrinone and therefore increase pulmonary shunt could potentially explain the lack of oxygenation improvement, though then we should expect pulmonary arterial pressure fluctuations. However, low milrinone plasmatic levels suggest underdosing rather than recirculation. Physiological changes in ARDS may also counteract milrinone effect in such patient populations[12]. The dosing itself or inadequacy of our nebulising technique might be related to the relative inefficacy of milrinone.

Our study has many limitations such as the small sample size and a monocentric design. Given the half-life of milrinone it would have been impossible to begin with milrinone and certify lack of residual effect potentially inducing bias in our results including studying use of the combination of milrinone and eproprostenol. The deposition and absorption of nebulized drugs is very variable in mechanically ventilated patients, it would have been interesting to generate a dose-response curve for each drug and then to study the safety of the lowest dose of each drug that gave the maximal response.

In summary, it appeared safe to administrate inhaled milrinone and a combination of inhaled milrinone and iNO to ARDS patients over a short period of time. When comparing the effects of the three inhaled vasodilators (NO, milrinone and epoprostenol), inhaled NO was the only medication significantly improving gas exchanges. Inhaled milrinone appeared safe but failed to improve oxygenation in ARDS. Further studies are needed in order to confirm usefulness of inhaled milrinone in ARDS and its appropriate administration regimen and nebulising technique.

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COMMENTS

Background

Treatment of severe hypoxemia has remained one of the greatest challenges in the intensive care units. Inhaled therapies such as inhaled nitric oxide allow for selective vasodilation of ventilated units, transforming relative dead space into adequate ventilation-perfusion units. The phosphodiesterase type Ⅲ inhibitor milrinone is a potent pulmonary vasodilator may be a potential alternative to actual costly treatment strategies. Animal studies have suggested a response to milrinone in acute lung injury.

Research frontiers

Despite several advances in mechanical ventilation, acute respiratory distress syndrome remains a condition with high mortality. New therapies to improve oxygenation and outcomes need to be investigated.

Innovations and breakthroughs

To their knowledge, this is the first study testing inhaled milrinone as a therapy in acute respiratory distress syndrome and comparing it to more frequently used inhaled therapies. It shows that inhaled milrinone is safe but is not efficacious.

Applications

Inhaled milrinone was shown to be safe in acute respiratory distress syndrome in our study. Although not efficacious in our trial, it could be further studied in a larger study or with more selected populations to see if an effect can be found.

Terminology

Milrinone: A phosphodiesterase type Ⅲ inhibitor that is a potent pulmonary vasodilator that has been used with success as an inhaled therapy for pulmonary hypertension in cardiac surgery.

Peer-review

This is a case of Acute Respiratory Distress Syndrome, with both methodologically and therapeutically impeccable evolution, as it can be seen in its radiographic progression. The semiotic paradigm is one of the canonical forms of scientific thought that allows to authorize the progression of medical knowledge from particular deductions to general applications. It must be considered the above distinction for this work and it useful effectiveness proposed by their authors.

REFERENCES

1 **Rossaint R**, Falke KJ, López F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med* 1993; **328**: 399-405 [PMID: 8357359 DOI: 10.1056/NEJM199302113280605]

2 **Griffiths MJ**, Evans TW. Inhaled nitric oxide therapy in adults. *N Engl J Med* 2005; **353**: 2683-2695 [PMID: 16371634 DOI: 10.1056/NEJMra051884]

3 **Afshari A**, Brok J, Møller AM, Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. *Anesth Analg* 2011; **112**: 1411-1421 [PMID: 21372277 DOI: 10.1213/ANE.0b013e31820bd185]

4 **Pappert D**, Busch T, Gerlach H, Lewandowski K, Radermacher P, Rossaint R. Aerosolized prostacyclin versus inhaled nitric oxide in children with severe acute respiratory distress syndrome. *Anesthesiology* 1995; **82**: 1507-1511 [PMID: 7793662]

5 **Walmrath D**, Schneider T, Schermuly R, Olschewski H, Grimminger F, Seeger W. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **153**: 991-996 [PMID: 8630585 DOI: 10.1164/ajrccm.153.3.8630585]

6 **Zwissler B**, Kemming G, Habler O, Kleen M, Merkel M, Haller M, Briegel J, Welte M, Peter K. Inhaled prostacyclin (PGI2) versus inhaled nitric oxide in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; **154**: 1671-1677 [PMID: 8970353 DOI: 10.1164/ajrccm.154.6.8970353]

7 **Lowson SM**. Inhaled alternatives to nitric oxide. *Anesthesiology* 2002; **96**: 1504-1513 [PMID: 12170067]

8 **Haraldsson s A**, Kieler-Jensen N, Ricksten SE. The additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in postcardiac surgical patients with pulmonary hypertension. *Anesth Analg* 2001; **93**: 1439-1445, table of contents [PMID: 11726420]

9 **Sablotzki A**, Starzmann W, Scheubel R, Grond S, Czeslick EG. Selective pulmonary vasodilation with inhaled aerosolized milrinone in heart transplant candidates. *Can J Anaesth* 2005; **52**: 1076-1082 [PMID: 16326679 DOI: 10.1007/BF03021608]

10 **Bueltmann M**, Kong X, Mertens M, Yin N, Yin J, Liu Z, Koster A, Kuppe H, Kuebler WM. Inhaled milrinone attenuates experimental acute lung injury. *Intensive Care Med* 2009; **35**: 171-178 [PMID: 18972099 DOI: 10.1007/s00134-008-1344-9]

11 **Nguyen AQ**, Théorêt Y, Chen C, Denault A, Varin F. High performance liquid chromatography using UV detection for the quantification of milrinone in plasma: improved sensitivity for inhalation. *J Chromatogr B Analyt Technol Biomed Life Sci* 2009; **877**: 657-660 [PMID: 19201666 DOI: 10.1016/j.jchromb.2009.01.024]

12 **Cepkova M**, Matthay MA. Pharmacotherapy of acute lung injury and the acute respiratory distress syndrome. *J Intensive Care Med* 2006; **21**: 119-143 [PMID: 16672636 DOI: 10.1177/0885066606287045]

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Prospective Study

Attributable cost of a nosocomial infection in the intensive care unit: A prospective cohort study

Binila Chacko, Kurien Thomas, Thambu David, Hema Paul, Lakshmanan Jeyaseelan, John Victor Peter

Binila Chacko, John Victor Peter, Medical ICU, Division of Critical Care, Christian Medical College, Vellore 632004, Tamil Nadu, India

Kurien Thomas, Department of Medicine, Pondicherry Institute of Medical Sciences, Puducherry 605014, India

Thambu David, Department of Medicine Ⅱ, Christian Medical College, Vellore 632004, Tamil Nadu, India

Hema Paul, Hospital Infection Control Committee, Christian Medical College, Vellore 632004, Tamil Nadu, India

Lakshmanan Jeyaseelan, Department of Biostatistics, Christian Medical College, Vellore 632004, Tamil Nadu, India

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Correspondence to: John Victor Peter, MD, DNB, MAMS, FRACP, FJFICM, FCICM, FICCM, Professor and Head, Medical ICU, Division of Critical Care, Christian Medical College, Ida Scudder Road, Vellore 632004, Tamil Nadu, India. peterjohnvictor@yahoo.com.au
Telephone: +91-416-2282693
Fax: +91-416-2282035

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Abstract

AIM

To study the impact of hospital-acquired infections (HAIs) on cost and outcome from intensive care units (ICU) in India.

METHODS

Adult patients (> 18 years) admitted over 1-year, to a 24-bed medical critical care unit in India, were enrolled prospectively. Treatment cost and outcome data were collected. This cost data was merged with HAI data collected prospectively by the Hospital Infection Control Committee. Only infections occurring during ICU stay were included. The impact of HAI on treatment cost and mortality was assessed.

RESULTS

The mean (± SD) age of the cohort (n = 499) was

42.3 ± 16.5 years. Acute physiology and chronic health evaluation-Ⅱ score was 13.9 (95%CI: 13.3-14.5); 86% were ventilated. ICU and hospital length of stay were 7.8 ± 5.5 and 13.9 ± 10 d respectively. Hospital mortality was 27.9%. During ICU stay, 76 (15.3%) patients developed an infection (ventilator-associated pneumonia 50; bloodstream infection 35; urinary tract infections 3), translating to 19.7 infections/1000 ICU days. When compared with those who did not develop an infection, an infection occurring during ICU stay was associated with significantly higher treatment cost [median (inter-quartile range, IQR) INR 92893 (USD 1523) (IQR 57168-140286) *vs* INR 180469 (USD 2958) (IQR 140030-237525); $P < 0.001$ and longer duration of ICU (6.7 ± 4.5 d *vs* 13.4 ± 7.0 d; $P < 0.01$) and hospital stay (12.4 ± 8.2 d *vs* 21.8 ± 13.9 d; $P < 0.001$)]. However ICU acquired infections did not impact hospital mortality (31.6% *vs* 27.2%; $P = 0.49$).

CONCLUSION

An infection acquired during ICU stay was associated with doubling of treatment cost and prolonged hospitalization but did not significantly increase mortality.

Key words: Attributable cost; Nosocomial infection; Length of stay; Mortality; Intensive care

Core tip: There is paucity of data on the impact of hospital acquired infections (HAIs) on cost and outcome from intensive care units (ICU) in developing countries. In this prospective study of 499 patients admitted over 1-year to a medical ICU in India, there were 19.7 HAIs per 1000 ICU days. Occurrence of infection was associated with significantly higher treatment cost ($P < 0.001$); the median attributable cost of an infection was 87594 Rupees (USD 1436). Although ICU acquired infections increased ICU length of stay (6.7 ± 4.5 d *vs* 13.4 ± 7.0 d; $P < 0.01$), it did not impact mortality (31.6% *vs* 27.2%; $P = 0.49$).

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INTRODUCTION

Health care associated infection (HAI) is a major preventable complication in critically ill patients across the world[1,2]. Whilst there is a significant body of information and evidence on the cost of these infections from developed countries, primary research from developing countries, in this area, is limited[3,4]. Translation of results of studies from developed countries on the impact and cost of infections to situations in developing countries may not be appropriate for several reasons: (1) different microbiological profile of HAIs[5,6]; (2) perceived reluctance among physicians regarding treatment of HAIs that is probably based on the impression that these infections are associated with poor survival[7,8]; and (3) limited resources and affordability which argues that resource allocation for the treatment of HAI would steal opportunities away from other potentially treatable patients, waiting for an intensive care unit (ICU) bed. The affordability issue is compounded by the fact that only about 10% of the estimated 70000 ICU beds in India are available in the public sector, where treatment is provided free of cost[9]. This poses a major problem of demand-supply mismatch, not only in the public sector, but also in the private sector since the population that needs to be covered in India is over 1 billion. Minimal subscription to private health insurance and resource pooling being in its infancy results in significant out-of-pocket expenses that push several families below the poverty line[10].

In the light of the above, a study was undertaken to evaluate the "cost" (in terms of money) and "impact" (in terms of clinical outcomes) of HAIs in developing countries. Such studies would facilitate investment on interventions that reduce infection as well as help plan appropriate allocation of the scarce resources of materials (ICU beds and equipment), manpower and money to address this problem in the ICU setting.

MATERIALS AND METHODS

In this study spanning 1-year, prospectively collected ICU cost data was merged with HAI data collected prospectively by the Hospital Infection Control Committee (HICC). ICU cost data was obtained from a study that looked at cost-utility as well as willingness-to-pay in patients admitted to the medical ICU[11].

Patients and setting

The study was undertaken in a 24-bed medical critical care unit in a 2500-bed, university-affiliated, private teaching hospital in semi-urban India. In this hospital, other than the very few covered by private health insurance, the entire treatment cost is expected to be paid for by the patient.

During a 1-year period (January-December 2011), adult patients (> 18 years) admitted to the 24-bed medical critical care unit were enrolled if they stayed beyond 24-h in the ICU. Patients not consenting to participate, patients not admitted under internal medicine (*e.g.*, hematological malignancies, chronic liver disease), or patients with surgical problems were excluded. A diagnosis of HAI was made only when a new infection occurred 48-h after hospital admission. The study was approved by the Institutional Review Board and Ethics committee (IRB No. 10011) and consent was obtained from patient or next-of-kin.

Costs

"Treatment cost", obtained from the hospital electronic

Table 1 Demographic data of the groups with and without hospital acquired infections

Features	HAI (n = 76)	No HAI (n = 420)	P value
Age, mean (SD), (yr)	39.4 (16.2)	42.9 (16.5)	0.04
Male:female	46:30	241:179	0.70
APACHE Ⅱ score, mean (SD)	14.01 (4.7)	13.9 (6.0)	0.58
Diagnosis n (%)			
Sepsis (including scrub typhus)	27 (35.5)	195 (46.4)	
Deliberate self-harm	30 (39.4)	99 (23.6)	
Cardiac	4 (5.3)	34 (8.1)	0.11
Acute respiratory distress syndrome	5 (6.6)	28 (6.7)	
Neurological	6 (7.9)	43 (10.2)	
Others	4 (5.3)	21 (5.0)	

Data not available for 3 patients. HAI: Hospital acquired infection; APACHE: Acute physiology and chronic health evaluation; SD: Standard deviation.

system, was taken as the direct medical cost incurred from the time of admission to hospital until discharge from hospital (including ICU cost). This included bed and nursing charges, professional fees, equipment charges, investigations, oxygen charges, and medication costs[12].

Infections

Infection data was obtained from the HICC that does daily active surveillance. Only infections occurring during ICU stay were included. Ventilator associated pneumonia (VAP), blood stream infections (BSI) and urinary tract infections (UTI) developing 48-h after hospital admission were the infections that were analysed. VAP and UTI were defined as per the CDC guidelines[13]. BSI was defined as a positive blood culture with a recognized pathogen or the combination of clinical symptoms (fever > 38 ℃, chills, hypotension) and two positive blood cultures for a common skin commensal from two separate blood samples drawn within 48 h[14].

Outcome data

The impact of infections on outcomes was explored. This included its effect on length of stay (ICU and hospital) and hospital mortality. We also assessed the impact of individual infections (VAP, UTI and BSI) on mortality.

Statistical analysis

Frequencies and percentages were used to describe baseline data, overall hospital and ICU mortality. Continuous variables [Acute physiology and chronic health evaluation (APACHE) Ⅱ score, cost and ICU and hospital length of stay] were expressed as mean [standard deviation (SD)] if data was normally distributed. Where data was not normally distributed (*e.g.*, treatment cost), it was expressed as median with interquartile range (IQR). Hospital mortality and length of stay (ICU and hospital) for the two groups, with HAI and without HAI, were calculated. χ^2 tests were used to compare proportions. In order to study the impact of HAI on mortality, it was decided to adjust for disease severity and other potential confounders if mortality was significantly different between those who developed infection *vs* those who did not develop infection.

RESULTS

Baseline demographic data

During the study period, 1599 patients were admitted to medical critical care. A total of 499 patients were enrolled. Exclusion criteria were admission under other specialty units (n = 434), deaths or discharges within 24 h (n = 105), refusal of consent (n = 58) and those not recruited during public holidays or weekends (n = 503)[11].

Demographic data are summarized in Table 1. The diagnosis included 122 different International Classification of Diseases (ICD) code entities and comprised predominantly of acute febrile illness including scrub typhus (44.4%), deliberate self-harm (26%), neurological illnesses (9.8%) and cardiac problems (7.6%).

The study cohort (n = 499) was relatively young with a mean (SD) age of 42.3 ± 16.5 years and mean APACHE-Ⅱ of 13.9 (95%CI: 13.3-14.5); 86% of patients were invasively ventilated. The mean (SD) ICU length of stay was 7.8 ± 5.5 d.

Infection data

Infection data was available in 496 (99.4%) patients. During ICU stay, 76 patients (15.2%) developed an infection, translating to 19.7 infections/1000 ICU days. Patients who developed a HAI were significantly younger (P = 0.04) than those who did not develop a HAI (Table 1). However the gender distribution and APACHE-Ⅱ score were not different between the groups. There were 50 episodes of VAP, 35 episodes of BSI and 3 episodes of UTI; 10 patients had more than one episode of infection. The median time to develop the infection followed an interesting pattern; VAP tended to occur in the first week of ICU stay (8 ± 5 d) while BSI occurred in the second week (11.4 ± 7 d) and UTI in the third week (18.7 ± 12.4 d).

Microbiological data

Overall, non-fermenting gram-negative carbapenem resistant organisms were isolated from 51 of the 88 episodes (36 VAP, 14 BSI and 1 UTI). There were 4 infections with colistin resistant organisms (3 VAP and 1 BSI). Twelve BSI isolates were susceptible gram-negative organisms. There was no Methicillin resistant staphylococcus aureus (MRSA) isolate in our cohort.

Outcome and cost data

Overall, infections were associated with doubling of length of stay (Table 2). However, mortality was similar in those who developed a HAI and those who did not develop it (Table 2). A logistic regression analysis was

Table 2 Impact of hospital-acquired infections on outcomes

Outcome	HAI (n = 76)	No HAI (n = 420)	P value
ICU length of stay, mean (SD), (d)	13.4 (7.0)	6.7 (4.5)	< 0.01
Hospital stay, mean (SD), (d)	21.8 (13.9)	12.4 (8.2)	< 0.001
In-hospital mortality	31.60%	27.20%	0.49
Mortality with VAP[1]	26%	27.2%[2]	1.0
Mortality due to BSI[1]	37%	27.2%[2]	0.24
CAUTI mortality[1]	33%	27.2%[2]	1.0

[1]Total number of patients with VAP was 50, BSI 35 and CAUTI 3; the total number of patients with individual infections exceed 76 since 10 patients had more than one infection source; [2]Indicates patients who had no HAI during the entire course of intensive care stay; thus in the analysis for VAP, those with BSI or CAUTI were excluded from the no HAI group and for BSI those with VAP and CAUTI were excluded from the no HAI group. Data available only on 496 patients. VAP: Ventilator associated pneumonia; BSI: Blood stream infection; CAUTI: Catheter associated urinary tract infection; SD: Standard deviation; HAI: Hospital acquired infection.

Table 3 Comparison of overall cost between those with infection and those without infection

Type	HAI (n = 76)	No HAI[1] (n = 420)	Cost difference	P value
Mean (SD) cost (INR)				
Any infection	226398 (226268)	115058 (93754)	111340	< 0.0001
VAP	235350 (253421)	115058 (93754)	120292	< 0.001
BSI	283887 (341916)	115058 (93754)	168829	< 0.001
CAUTI	190059 (34096)	115058 (93754)	155963	0.05
Median (IQR) cost (INR)				
Any infection	180469 (140030-237525)	92875 (57243-139104)	87594	< 0.0001
VAP	182991 (133038-238952)	92875 (57243-139104)	90116	< 0.0001
BSI	170753 (141788-238650)	92875 (57243-139104)	77878	< 0.0001
CAUTI	173085 (155818-190352)	92875 (57243-139104)	80210	0.06

[1]The cost of no HAI is the same for all sub-categories of analysis based on source of infection since patients who developed any infection were not included in the "no HAI" group. At the time of the study, 1 USD = INR 61. Values in parenthesis indicate standard deviation. INR: Indian rupees; HAI: Hospital acquired infection; VAP: Ventilator associated pneumonia; BSI: Blood stream infection; CAUTI: Catheter associated urinary tract infection; SD: Standard deviation; IQR: Inter-quartile range.

not performed in view of the lack of effect of infection on mortality. Additionally, when individual infections were considered separately, there was no mortality difference between those who developed a specific infection [*i.e.*, VAP, BSI or catheter associated urinary tract infection (CAUTI)] *vs* those who did not develop any infection during ICU stay (Table 2).

An infection acquired in the ICU was associated with doubling of overall cost when compared with patients who did not develop an infection during hospitalization. When VAP, BSI and UTI were analysed independently, the overall cost (median IQR) of each infection was almost similar (Table 3). The median attributable cost of an infection worked out to INR 87594 (USD 1436).

DISCUSSION

This study provides insight and information on the burden (economic and otherwise) of common HAIs in the medical ICU of a developing country. While it could be argued that there is data from developed countries to this effect, our data with the different spectrum of infections (predominant VAP and few UTI) and microbiology (over 60% of the isolates carbapenem resistant) merit reporting and discussion.

Nosocomial infections, individually and overall in our study, were associated with doubling of cost without any impact on mortality. The acquisition of infection was also associated with the need for an additional 7-10 d in the ICU, resulting in further constraining the already limited ICU resources in our setting. Although the increased length of ICU stay is consistent with the limited evidence available for VAP in other countries[15], this has significant hospital infrastructure and public health implications in our setting.

These findings beg a response to the following questions. First, given the lack of impact of infections on mortality despite the antimicrobial resistance patterns, it is worth treating these infections. Second, should there be a focused approach to looking at measures to decrease infections and improving quality of patient care in ICU? On the face of it, the appropriate response to the above questions would be a resounding yes. However as alluded to, in view of the limited resources, treatment of patients with ICU acquired infections is likely to impact bed allocation to a patient with a more reversible problem. This, coupled with the inability to pay for the entire cost of treatment[11], places an additional

economic burden on institutions that provide subsidy or charity. Denying on-going care for a potentially reversible problem (in this case a HAI) would violate ethical and moral principles of healthcare. Thus, the response to the second question assumes greater importance.

In India, ICU infrastructure and staffing are varied across hospitals[16]. It is also known that nosocomial infection rates in developing countries are far higher than that in developing countries. Focusing on reducing the incidence of nosocomial infections would translate to better utilization of ICU beds and economic resources. In addition to rigid enforcement of hand hygiene measures, micromanaging central line handling and optimizing pneumonia prevention strategies may help reduce infection rates. In addition, hospital administrators need to consider optimizing staff-patient ratio and spacing between ICU beds, a problem that probably potentiates infection risk[17,18]. The latter strategy would involve a cost shift from the patient (who bears the cost of an infection) to the hospital (in improving nursing ratio and bed spacing) that may be beyond the reach of many institutions.

This study, in the setting of a developing country, establishes the fact that an ICU acquired infection is associated with a significant increase in cost. The perception of poor survival is misplaced and patients who develop a HAI should be treated with cautious optimism. The utilitarian philosophy and steal phenomenon remains, since infections are associated with doubling of hospital stay and costs and are likely to prevent other patients from being treated in ICU. Efforts should be maximized on improving infection control practices since additional resource allocation in this setting may be challenging to the majority of health care settings.

COMMENTS

Background

Intensive care units (ICU) acquired infections are generally viewed with skepticism for several reasons. First, is a fact that treatment of ICU acquired infections would increase cost significantly and add pressure on the already stretched ICU resources second, is a perception that such infections would be associated with poor survival and third is an utilitarian philosophy that argues that such resource allocation would "steal" opportunities away from potentially treatable patients waiting for an ICU bed. This study aimed to explore the impact of ICU acquired infections on overall cost and mortality in a tertiary care hospital in a developing country. In this study spanning 1-year, prospectively collected ICU cost data incorporating direct and indirect cost was merged with nosocomial infection data collected by the hospital infection control committee.

Research frontiers

Health care associated infection (HAI) is a major preventable complication in critically ill patients across the world. Whilst there is a significant body of information and evidence on the cost of these infections from developed countries, primary research from developing countries, in this area, is limited. Additionally, translation of data from developed countries on the impact and cost of infections to situations in developing countries may not be appropriate given the different microbiological profile of HAIs.

Innovations and breakthroughs

This study has provided important information that suggests that paying attention to reducing nosocomial infections would not only translate to lower costs, but also make more intensive care beds available for other patients needing them.

Applications

This study provides insight and information on the burden (economic and otherwise) of common HAIs in the medical ICU of a developing country. While we were not surprised with the finding that HAIs were associated with doubling of cost as compared to those without HAIs, it was reassuring to know that there was no evidence of association of increased mortality despite the antimicrobial resistance patterns. It is thus worth treating this infections and there should be an aggressive focused approach to decrease infections and improve quality of patient care in ICU.

Terminology

HAIs are defined as new infections that develop in the hospital after 48 h of admission. In this study, cost and impact on outcomes (death and length of stay) of common ICU acquired infections, ventilator associated pneumonia, blood stream infections and urinary tract infections were analysed.

Peer-review

The work is novel and good.

REFERENCES

1 **Dudeck MA**, Weiner LM, Allen-Bridson K, Malpiedi PJ, Peterson KD, Pollock DA, Sievert DM, Edwards JR. National Healthcare Safety Network (NHSN) report, data summary for 2012, Device-associated module. *Am J Infect Control* 2013; **41**: 1148-1166 [PMID: 24274911 DOI: 10.1016/j.ajic.2013.09.002]

2 **Rosenthal VD**, Maki DG, Mehta Y, Leblebicioglu H, Memish ZA, Al-Mousa HH, Balkhy H, Hu B, Alvarez-Moreno C, Medeiros EA, Apisarnthanarak A, Raka L, Cuellar LE, Ahmed A, Navoa-Ng JA, El-Kholy AA, Kanj SS, Bat-Erdene I, Duszynska W, Van Truong N, Pazmino LN, See-Lum LC, Fernández-Hidalgo R, Di-Silvestre G, Zand F, Hlinkova S, Belskiy V, Al-Rahma H, Luque-Torres MT, Bayraktar N, Mitrev Z, Gurskis V, Fisher D, Abu-Khader IB, Berechid K, Rodríguez-Sánchez A, Horhat FG, Requejo-Pino O, Hadjieva N, Ben-Jaballah N, García-Mayorca E, Kushner-Dávalos L, Pasic S, Pedrozo-Ortiz LE, Apostolopoulou E, Mejía N, Gamar-Elanbya MO, Jayatilleke K, de Lourdes-Dueñas M, Aguirre-Avalos G. International Nosocomial Infection Control Consortium (INICC) report, data summary of 43 countries for 2007-2012. Device-associated module. *Am J Infect Control* 2014; **42**: 942-956 [PMID: 25179325 DOI: 10.1016/j.ajic.2014.05.029]

3 **Zimlichman E**, Henderson D, Tamir O, Franz C, Song P, Yamin CK, Keohane C, Denham CR, Bates DW. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013; **173**: 2039-2046 [PMID: 23999949 DOI: 10.1001/jamainternmed.2013.9763]

4 **Nangino Gde O**, Oliveira CD, Correia PC, Machado Nde M, Dias AT. Financial impact of nosocomial infections in the intensive care units of a charitable hospital in Minas Gerais, Brazil. *Rev Bras Ter Intensiva* 2012; **24**: 357-361 [PMID: 23917933 DOI: 10.1590/S0103-507X2012000400011]

5 **Vincent JL**, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; **302**: 2323-2329 [PMID: 19952319 DOI: 10.1001/jama.2009.1754]

6 **Pradhan NP**, Bhat SM, Ghadage DP. Nosocomial infections in the medical ICU: a retrospective study highlighting their prevalence, microbiological profile and impact on ICU stay and mortality. *J Assoc Physicians India* 2014; **62**: 18-21 [PMID: 25906516]

7 **Pittet D**, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA* 1994; **271**: 1598-1601 [PMID: 8182812 DOI: 10.1001/jama.271.20.1598]

8 **Smith RL**, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infections.

Chest 1991; **100**: 164-167 [PMID: 2060337 DOI: 10.1378/chest.100.1.164]

9 **Divatia JV**, Iyer S. Ten major priorities for intensive care in India. *Intensive Care Med* 2015; **41**: 1468-1471 [PMID: 25573499 DOI: 10.1007/s00134-014-3618-8]

10 **Jayaram R**, Ramakrishnan N. Cost of intensive care in India. *Indian J Crit Care Med* 2008; **12**: 55-61 [PMID: 19742248 DOI: 10.4103/0972-5229.42558]

11 **Thomas K**, Peter JV, Christina J, Jagadish AR, Rajan A, Lionel P, Jeyaseelan L, Yadav B, John G, Pichamuthu K, Chacko B, Pari P, Murugesan T, Rajendran K, John A, Sathyendra S, Iyyadurai R, Jasmine S, Karthik R, Mathuram A, Hansdak SG, Abhilash KP, Kumar S, John KR, Sudarsanam TD. Cost-utility in medical intensive care patients. Rationalizing ongoing care and timing of discharge from intensive care. *Ann Am Thorac Soc* 2015; **12**: 1058-1065 [PMID: 26011090 DOI: 10.1513/AnnalsATS.201411-527OC]

12 **Peter JV**, Thomas K, Jeyaseelan L, Yadav B, Sudarsan TI, Christina J, Revathi A, John KR, Sudarsanam TD. COST OF INTENSIVE CARE IN INDIA. *Int J Technol Assess Health Care* 2016: 1-5 [PMID: 27608529 DOI: 10.1017/S0266462316000398]

13 **Horan TC**, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; **36**: 309-332 [PMID: 18538699 DOI: 10.1016/j.ajic.2008.03.002]

14 **Suetens C**, Morales I, Savey A, Palomar M, Hiesmayr M, Lepape A, Gastmeier P, Schmit JC, Valinteliene R, Fabry J. European surveillance of ICU-acquired infections (HELICS-ICU): methods and main results. *J Hosp Infect* 2007; **65** Suppl 2: 171-173 [PMID: 17540265 DOI: 10.1016/S0195-6701(07)60038-3]

15 **Safdar N**, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med* 2005; **33**: 2184-2193 [PMID: 16215368 DOI: 10.1097/01.CCM.0000181731.53912.D9]

16 **Yeolekar ME**, Mehta S. ICU care in India--status and challenges. *J Assoc Physicians India* 2008; **56**: 221-222 [PMID: 18702381]

17 **Schwab F**, Meyer E, Geffers C, Gastmeier P. Understaffing, overcrowding, inappropriate nurse: ventilated patient ratio and nosocomial infections: which parameter is the best reflection of deficits? *J Hosp Infect* 2012; **80**: 133-139 [PMID: 22188631 DOI: 10.1016/j.jhin.2011.11.014]

18 **Stone PW**, Pogorzelska M, Kunches L, Hirschhorn LR. Hospital staffing and health care-associated infections: a systematic review of the literature. *Clin Infect Dis* 2008; **47**: 937-944 [PMID: 18767987 DOI: 10.1086/591696]

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CASE REPORT

Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome

Alpha A Fowler Ⅲ, Christin Kim, Lawrence Lepler, Rajiv Malhotra, Orlando Debesa, Ramesh Natarajan, Bernard J Fisher, Aamer Syed, Christine DeWilde, Anna Priday, Vigneshwar Kasirajan

Alpha A Fowler Ⅲ, Rajiv Malhotra, Orlando Debesa, Ramesh Natarajan, Bernard J Fisher, Aamer Syed, Christine DeWilde, Anna Priday, Division of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA 23298, United States

Christin Kim, Department of Anesthesia Critical Care, Virginia Commonwealth University School of Medicine, Richmond, VA 23298, United States

Lawrence Lepler, Division of Critical Care Medicine, INOVA Fair Oaks Hospital, INOVA Health Care System, Fairfax, VA 22042, United States

Vigneshwar Kasirajan, Division of Cardiothoracic Surgery, Virginia Commonwealth University School of Medicine, Richmond, VA 23298, United States

Author contributions: Fowler Ⅲ AA is principal investigator, corresponding author, and contributed to study concept, basic and translational research; Kim C and Lepler L contributed to patient's clinical care, patient follow-up and manuscript review; Malhotra R contributed to patient's clinical care; Debesa O contributed to patient's clinical care and manuscript review; Natarajan R and Fisher BJ contributed to manuscript creation, basic research leading to clinical use; Syed A and Kasirajan V contributed to clinical care and manuscript creation; DeWilde C contributed to clinical care and laboratory coordination; Priday A contributed to FDA regulatory coordinator for IND used for study.

Institutional review board statement: The use of intravenous vitamin C in humans has been approved by the Virginia Commonwealth University Institutional Review Board (HM20000917).

Informed consent statement: Permission for the patient to receive intravenous vitamin C as described in this case report was granted by the patient's legal next of kin. All patient health information was de-identified and held in strictest confidentiality.

Conflict-of-interest statement: All authors have no conflicts of interests to declare.

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Correspondence to: Alpha A Fowler Ⅲ, MD, William Taliaferro Thompson Professor of Medicine, Division of Pulmonary Disease and Critical Care Medicine, Virginia Commonwealth University School of Medicine, 1200 East Broad Street, PO Box 980050, Richmond, VA 23298,
United States. alpha.fowler@vcuhealth.org
Telephone: +1-804-8289071
Fax: +1-804-8282578

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Abstract

We report a case of virus-induced acute respiratory distress syndrome (ARDS) treated with parenteral vitamin C in a patient testing positive for enterovirus/rhinovirus on viral screening. This report outlines the first use of high dose intravenous vitamin C as an interventional therapy for ARDS, resulting from enterovirus/rhinovirus respiratory infection. From very significant preclinical research performed at Virginia Commonwealth University

with vitamin C and with the very positive results of a previously performed phase Ⅰ safety trial infusing high dose vitamin C intravenously into patients with severe sepsis, we reasoned that infusing identical dosing to a patient with ARDS from viral infection would be therapeutic. We report here the case of a 20-year-old, previously healthy, female who contracted respiratory enterovirus/rhinovirus infection that led to acute lung injury and rapidly to ARDS. She contracted the infection in central Italy while on an 8-d spring break from college. During a return flight to the United States, she developed increasing dyspnea and hypoxemia that rapidly developed into acute lung injury that led to ARDS. When support with mechanical ventilation failed, extracorporeal membrane oxygenation (ECMO) was initiated. Twelve hours following ECMO initiation, high dose intravenous vitamin C was begun. The patient's recovery was rapid. ECMO and mechanical ventilation were discontinued by day-7 and the patient recovered with no long-term ARDS sequelae. Infusing high dose intravenous vitamin C into this patient with virus-induced ARDS was associated with rapid resolution of lung injury with no evidence of post-ARDS fibroproliferative sequelae. Intravenous vitamin C as a treatment for ARDS may open a new era of therapy for ARDS from many causes.

Key words: Intravenous vitamin C; Acute respiratory distress syndrome; Enterovirus/rhinovirus; Acute lung injury; Extracorporeal membrane oxygenation

Core tip: Enterovirus/rhinovirus has been reported to cause devastating acute lung injury. We report here the first use of high dose intravenous vitamin C to attenuate the acute respiratory distress syndrome that was caused by this viral infection. We have previously reported that vitamin C used in this interventional fashion is a potent anti-inflammatory agent.

Fowler Ⅲ AA, Kim C, Lepler L, Malhotra R, Debesa O, Natarajan R, Fisher BJ, Syed A, DeWilde C, Priday A, Kasirajan V. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. *World J Crit Care Med* 2017; 6(1): 85-90 Available from: URL: http://www.wjgnet.com/2220-3141/full/v6/i1/85.htm DOI: http://dx.doi.org/10.5492/wjccm.v6.i1.85

INTRODUCTION

Viral diseases can produce the acute respiratory distress syndrome (ARDS)[1]. Pandemic viruses are the most common viruses that produce lung injury. Influenza viruses and coronaviruses (*e.g.*, H5N1, H1N1 2009, severe acute respiratory syndrome coronavirus, and middle east respiratory syndrome coronavirus) are potentially lethal pathogens known to produce lung injury and death from ARDS[2-5]. At the tissue level, lung injury results from increased permeability of the alveolar-capillary membrane that leads to hypoxia, pulmonary edema, and intense cellular infiltration, particularly neutrophilic infiltration. The exact pathogenesis of virus-induced ARDS is slowly becoming understood. Unlike the "cytokine storm" occurring in bacterial sepsis that leads to up-regulation of pro-inflammatory cytokines [*e.g.*, interleukin-1β (IL-1β), IL-8, IL-6] and generation of reactive nitrogen and oxygen species in the vascular space, viruses such as the influenza virus target alveolar epithelium, disabling sodium pump activity, damaging tight junctions, and inducing cell death in infected cells. Cytokines produced by virally infected alveolar epithelial cells activate adjacent lung capillary endothelial cells which then leads to neutrophil infiltration. Subsequent production of reactive oxygen and nitrogen species by infiltrating neutrophils further damages lung barrier function[1]. Apart from pandemic viruses other viruses, are increasingly reported to produce severe ARDS. While most of the approximately 100 strains of enterovirus primarily infect the gastrointestinal tract, enterovirus-D68 (EV-D68) has tropism for the respiratory tract. EV-D68 produces acute respiratory disease ranging from mild upper respiratory tract symptoms to severe pneumonia and lung injury as in the case we describe here. In an outpatient setting, EV-D68 disease has manifested most commonly among persons younger than 20 years and adults aged 50-59 years[6]. In August 2014, EV-D68 emerged as a cause of severe respiratory infections with hospitals in Illinois and Missouri reporting an increased incidence of rhinovirus and enterovirus infection[7]. In this report, 30 of 36 isolates from the nasopharyngeal secretions of patients with severe respiratory illness were identified as EV-D68. Following these reports, an unusually high number of patients with severe respiratory illness were admitted to these facilities, presumably with EV-D68 infection. Enterovirus-D68 leading to ARDS has been reported in China, Japan, and in the United States[8-11]. The report by Farrell *et al*[11], describes a previously healthy 26-year-old woman who developed severe ARDS following an enterovirus-D68 infection. Despite all critical care support measures, the patient required protracted mechanical ventilation for 32-d, necessitating tracheostomy and endoscopic gastrostomy tube placement. She was discharged alive 55 d following admission. Enterovirus and rhinovirus were recovered from the respiratory secretions of the patient we report here. Extracorporeal membrane oxygenation was rapidly required in our patient's care following failure of conventional mechanical ventilation. The patient reported by Farrell *et al*[11] is the full extent of support required for patients with ARDS who ultimately develop a fibroproliferative course as described by Burnham *et al*[12]. Karhu *et al*[13] and Choi *et al*[14] recently reported finding rhinovirus as the etiology of severe community acquired pneumonia and respiratory failure

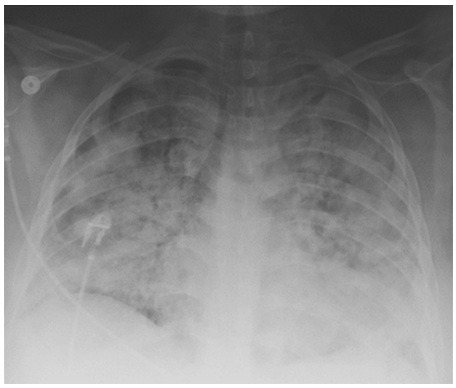

Figure 1 Patient's anterior-posterior chest X-ray film prior to intubation.

in mechanically ventilated adults who had a proven viral etiology of respiratory failure.

We report here the first application of high dose intravenous vitamin C employed as an interventional drug treatment for virus-induced ARDS. Very few studies in critically ill patients with ARDS have reported the use of intravenous vitamin C. The use of vitamin C to treat lung injury is still investigational. Nathens *et al*[15] infused ascorbic acid at 1 g every 8 h combined with oral vitamin E for 28 d in 594 surgically critically ill patients and found a significantly lower incidence of acute lung injury and multiple organ failure. Tanaka *et al*[16] infused ascorbic acid continuously at 66 mg/kg per hour for the first 24 h in patients with greater than 50% surface area burns and showed significantly reduced burn capillary permeability. A single report (published as abstract only) of a clinical study of large intravenous doses of ascorbic acid, and other antioxidants (tocopherol, N-acetyl-cysteine, selenium), in patients with established ARDS showed reduction in mortality of 50%[17]. Clinical protocols currently in use for hospitalized septic patients fail to normalize ascorbic acid levels. Vitamin C dosages utilized in the treatment of the patient we describe in this case report arose from our previous human studies, infusing high dose intravenous vitamin C into critically ill patients with severe sepsis[18] and in our preclinical studies[19-21]. Our work thus far shows vitamin C to exert potent "pleotropic effects" when used as described in this report. We showed that septic patients receiving high dose intravenous vitamin C exhibit significant reduction in multiple organ injury and reduced inflammatory biomarker levels[18]. Our preclinical work in septic lung-injured animals shows that vitamin C down-regulates pro-inflammatory genes that are driven by transcription factor NF-κB. Furthermore, vitamin C significantly increases alveolar fluid clearance in septic lung-injured animals[21]. Finally, infused vitamin C's capability to down-regulate liberated reactive oxygen and nitrogen species appears to be critical for attenuating lung injury[22].

CASE REPORT

A 20-year-old white female presented to urgent care with 24 h of increasing dyspnea after returning from a 7-d trip to Italy. While in Italy she was exposed to several members of the family with whom she was visiting who had symptoms of upper tract respiratory infection. One family member had recently traveled to Morocco. While in Italy, the patient had visited a buffalo farm and ate unpasteurized cheese. There were no other unusual exposures. She noted cough and yellow sputum for 3 d with intermittent fever and night sweats.

DISCUSSION

A chest X-ray revealed diffuse bilateral opacities (Figure 1). Arterial blood gas testing revealed severe hypoxemia while receiving 100% oxygen by non-rebreather mask. Antibiotics were initiated and she was admitted to intensive care unit (ICU) with a diagnosis of community acquired pneumonia. She denied GI symptoms, rash or arthralgia. She denied any history of thromboembolic disease, chest or leg pain or swelling. Her only medication was oral contraceptive for migraines associated with her menstrual cycle. Non-invasive positive pressure ventilation failed to support hypoxemic respiratory failure and intubation was required on hospital day 3. An echocardiogram revealed normal cardiac function. Respiratory cultures were negative, but a molecular detection viral respiratory panel was positive for enterovirus/rhinovirus (FilmArray, BioFire Diagnostics, LLC, Salt Lake City, Utah). Despite high PEEP and low tidal volume ventilation, hypoxemia (PaO_2/FiO_2 = 75) and hypercapnia remained severe. Chest imaging on hospital day 3 revealed dense bilateral opacities with central air bronchograms (Figure 2). Due to failure of conventional ventilatory strategies, veno-venous extracorporeal membrane oxygenation (ECMO) was initiated on hospital day 3. Low tidal volume assist-control, pressure-control ventilatory strategy was continued. Vancomycin, piperacillin-tazobactam and levofloxacin started at ICU admission were continued. High-dose intravenous vitamin C (200 mg/kg per 24 h) was initiated on ECMO day 1 with the total daily vitamin C dosage divided equally into four doses and infused every 6 h. AP chest X-ray imaging on ECMO day 2 following institution of vitamin C infusion revealed significant improvement in bilateral lung opacities (Figure 3). Given the patient's hemodynamic instability and vasopressor requirements, the critical care physician staff and nursing staff were very careful to keep the patient's intake and output fluid balance even, being careful not to volume load a patient who was suffering from permeability pulmonary edema. Bronchoscopy on ECMO day 3 was negative for bacterial or fungal respiratory pathogens. Histoplasma, Blastomyces, Aspergillus, and Legionella antigen studies were negative. Furosemide was used to achieve a daily negative fluid balance. Daily chest imaging with AP chest X-rays documented continued resolution of bilateral opacities. Importantly, lung gas exchange significantly improved following institution of vitamin C infusions. Chest imaging on ECMO day 6 revealed significant further reduction in lung opacities. ECMO decannulation and extubation from

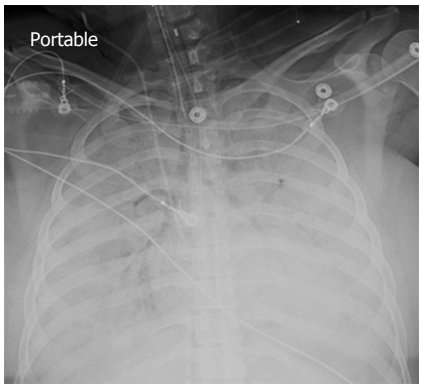

Figure 2 Patient's anterior-posterior chest X-ray film on extracorporeal membrane oxygenation day 1.

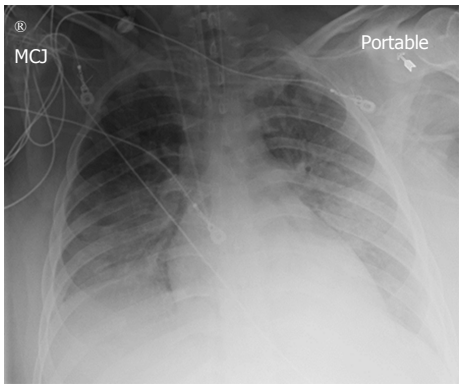

Figure 3 Patient's anterior-posterior chest X-ray film on extracorporeal membrane oxygenation day 2.

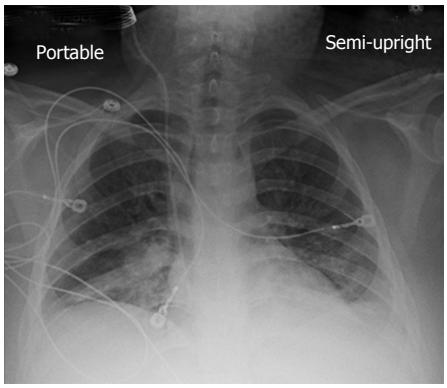

Figure 4 Patient's anterior-posterior chest X-ray film on extracorporeal membrane oxygenation decannulation, extubation day 7.

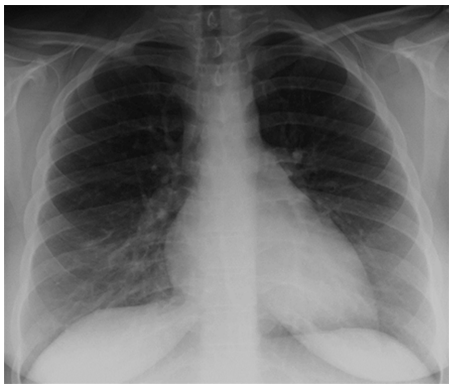

Figure 5 Patient's posterior-anterior chest X-ray film two weeks following hospital discharge.

ventilation occurred on ECMO day 7 (Figure 4). Vitamin C dosing was continued while the patient remained on ECMO. Vitamin C dosing was reduced by half (100 mg/kg per 24 h) for one day following decannulation from ECMO then reduced by half again (50 mg/kg per 24 h) for an additional day. Post-extubation the patient required 4 L/min nasal oxygen for 48 h and then was discharged home on room air. She was discharged home on hospital day 12. Although we did not quantify the plasma ascorbic acid levels in the patient we report here, we have previously reported that critically ill patients with severe sepsis treated with the identical vitamin C infusion protocol achieved plasma ascorbic acid levels of 3.2 mmol, values which are 60 fold higher than normal plasma ascorbic acid levels[18].

In conclusion, we report here the first use of vitamin C as an interventional drug to attenuate lung injury produced by viral infection. The patient described here was discharged home 12 d following hospitalization, requiring no oxygen therapy. Follow-up exam at 1 mo following the patient's initial hospitalization revealed her to have completely recovered. Figure 5 displays her follow-up chest X-ray film. Importantly, it should be noted that this is a single case report. The role of Vitamin C in this patient's recovery is not certain, and clearly additional investigation will be required before this can be recommended as a therapy for ARDS.

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COMMENTS

Case characteristics

A 20-year-old female with no significant medical history presented with acute respiratory failure following a spring break in central Italy. While in Italy she was exposed to a sick contact who was a member of the family she was staying with.

Clinical diagnosis

The clinical diagnosis of severe acute respiratory distress syndrome (ARDS) in this case was established by the extent of respiratory failure present, the radiographic findings, and the need for extracorporeal membrane oxygenator support required. The patient's exposure to the sick contact in Italy suggested the diagnosis of a viral etiology.

Differential diagnosis
ARDS, viral pneumonia, sepsis from unknown etiology.

Laboratory diagnosis
The diagnosis of the etiology of the patient's respiratory failure was obtained by a panel that uses real-time polymerase chain reaction technology to identify respiratory viral pathogens. FilmArray Respiratory panel is manufactured by BioFire Diagnostics, LLC, Salt Lake City, Utah.

Imaging diagnosis
Standard Anterior-Posterior chest X-ray films confirmed the diagnosis of ARDS.

Pathological diagnosis
No lung tissue was obtained from the patient. The diagnosis of ARDS was established by the extent of respiratory failure and the imaging required during the patients hospital stay.

Treatment
In this case report, the authors describe the first use of high dosage intravenous vitamin C as adjunctive therapy for viral induced ARDS.

Related reports
At this point in time, there are no other case reports specifically referencing vitamin C as a treatment for ARDS. The authors have previously reported (ref. [18]) the use of high dose vitamin C as an adjunctive therapy for severe sepsis. Many patients in that trial likely could be considered to have had ARDS.

Experiences and lessons
For many years multiple investigators have conducted clinical treatment trials, searching for effective therapies to assist in the treatment for ARDS. In this case report, the authors may have shed new light on a treatment which may ultimately be effective. The successful outcome described in this case report would suggest that larger trials must be conducted with high dosage intravenous vitamin C.

Peer-review
This is an interesting report of use of high dose intravenous vitamin C in ARDS.

REFERENCES

1 **Short KR**, Kroeze EJ, Fouchier RA, Kuiken T. Pathogenesis of influenza-induced acute respiratory distress syndrome. *Lancet Infect Dis* 2014; **14**: 57-69 [PMID: 24239327 DOI: 10.1016/S1473-3099(13)70286-X]

2 **Zaki AM**, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; **367**: 1814-1820 [PMID: 23075143 DOI: 10.1056/NEJMoa1211721]

3 **Guery B**, Poissy J, el Mansouf L, Séjourné C, Ettahar N, Lemaire X, Vuotto F, Goffard A, Behillil S, Enouf V, Caro V, Mailles A, Che D, Manuguerra JC, Mathieu D, Fontanet A, van der Werf S. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. *Lancet* 2013; **381**: 2265-2272 [PMID: 23727167 DOI: 10.1016/S0140-6736(13)60982-4]

4 **Drosten C**, Seilmaier M, Corman VM, Hartmann W, Scheible G, Sack S, Guggemos W, Kallies R, Muth D, Junglen S, Müller MA, Haas W, Guberina H, Röhnisch T, Schmid-Wendtner M, Aldabbagh S, Dittmer U, Gold H, Graf P, Bonin F, Rambaut A, Wendtner CM. Clinical features and virological analysis of a case of Middle East respiratory syndrome coronavirus infection. *Lancet Infect Dis* 2013; **13**: 745-751 [PMID: 23782859 DOI: 10.1016/S1473-3099(13)70154-3]

5 **de Jong MD**, Simmons CP, Thanh TT, Hien VM, Smith GJ, Chau TN, Hoang DM, Chau NV, Khanh TH, Dong VC, Qui PT, Cam BV, Ha do Q, Guan Y, Peiris JS, Chinh NT, Hien TT, Farrar J. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat Med* 2006; **12**: 1203-1207 [PMID: 16964257 DOI: 10.1038/nm1477]

6 **Meijer A**, van der Sanden S, Snijders BE, Jaramillo-Gutierrez G, Bont L, van der Ent CK, Overduin P, Jenny SL, Jusic E, van der Avoort HG, Smith GJ, Donker GA, Koopmans MP. Emergence and epidemic occurrence of enterovirus 68 respiratory infections in The Netherlands in 2010. *Virology* 2012; **423**: 49-57 [PMID: 22177700 DOI: 10.1016/j.virol.2011.11.021]

7 **Midgley CM**, Jackson MA, Selvarangan R, Turabelidze G, Obringer E, Johnson D, Giles BL, Patel A, Echols F, Oberste MS, Nix WA, Watson JT, Gerber SI. Severe respiratory illness associated with enterovirus D68 - Missouri and Illinois, 2014. *MMWR Morb Mortal Wkly Rep* 2014; **63**: 798-799 [PMID: 25211545]

8 **Xiang Z**, Gonzalez R, Wang Z, Ren L, Xiao Y, Li J, Li Y, Vernet G, Paranhos-Baccalà G, Jin Q, Wang J. Coxsackievirus A21, enterovirus 68, and acute respiratory tract infection, China. *Emerg Infect Dis* 2012; **18**: 821-824 [PMID: 22516379 DOI: 10.3201/eid1805.111376]

9 **Zhang T**, Ren L, Luo M, Li A, Gong C, Chen M, Yu X, Wu J, Deng Y, Huang F. Enterovirus D68-associated severe pneumonia, China, 2014. *Emerg Infect Dis* 2015; **21**: 916-918 [PMID: 25897574 DOI: 10.3201/eid2105.150036]

10 **Kaida A**, Kubo H, Sekiguchi J, Kohdera U, Togawa M, Shiomi M, Nishigaki T, Iritani N. Enterovirus 68 in children with acute respiratory tract infections, Osaka, Japan. *Emerg Infect Dis* 2011; **17**: 1494-1497 [PMID: 21801632 DOI: 10.3201/eid1708.110028]

11 **Farrell JJ**, Ikladios O, Wylie KM, O'Rourke LM, Lowery KS, Cromwell JS, Wylie TN, Melendez EL, Makhoul Y, Sampath R, Bonomo RA, Storch GA. Enterovirus D68-associated acute respiratory distress syndrome in adult, United States, 2014. *Emerg Infect Dis* 2015; **21**: 914-916 [PMID: 25897542 DOI: 10.3201/eid2105.142033]

12 **Burnham EL**, Janssen WJ, Riches DW, Moss M, Downey GP. The fibroproliferative response in acute respiratory distress syndrome: mechanisms and clinical significance. *Eur Respir J* 2014; **43**: 276-285 [PMID: 23520315 DOI: 10.1183/09031936.00196412]

13 **Karhu J**, Ala-Kokko TI, Vuorinen T, Ohtonen P, Syrjälä H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. *Clin Infect Dis* 2014; **59**: 62-70 [PMID: 24729498 DOI: 10.1093/cid/ciu237]

14 **Choi SH**, Hong SB, Ko GB, Lee Y, Park HJ, Park SY, Moon SM, Cho OH, Park KH, Chong YP, Kim SH, Huh JW, Sung H, Do KH, Lee SO, Kim MN, Jeong JY, Lim CM, Kim YS, Woo JH, Koh Y. Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med* 2012; **186**: 325-332 [PMID: 22700859 DOI: 10.1164/rccm.201112-2240OC]

15 **Nathens AB**, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, Radella F, Garcia I, Maier RV. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Ann Surg* 2002; **236**: 814-822 [PMID: 12454520]

16 **Tanaka H**, Matsuda T, Miyagantani Y, Yukioka T, Matsuda H, Shimazaki S. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg* 2000; **135**: 326-331 [PMID: 10722036]

17 **Sawyer MAJ**, Mike JJ, Chavin K. Antioxidant therapy and survival in ARDS (abstract). *Crit Care Med* 1989; **17**: S153

18 **Fowler AA**, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, Farthing CA, Larus TL, Martin E, Brophy DF, Gupta S, Fisher BJ, Natarajan R. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med* 2014; **12**: 32 [PMID: 24484547 DOI: 10.1186/1479-5876-12-32]

19 **Fisher BJ**, Seropian IM, Kraskauskas D, Thakkar JN, Voelkel NF, Fowler AA, Natarajan R. Ascorbic acid attenuates lipopolysaccharide-induced acute lung injury. *Crit Care Med* 2011; **39**: 1454-1460 [PMID: 21358394 DOI: 10.1097/CCM.0b013e3182120cb8]

20 **Fisher BJ**, Kraskauskas D, Martin EJ, Farkas D, Puri P, Massey HD, Idowu MO, Brophy DF, Voelkel NF, Fowler AA, Natarajan R. Attenuation of sepsis-induced organ injury in mice by vitamin C. *JPEN J Parenter Enteral Nutr* 2014; **38**: 825-839 [PMID: 23917525 DOI: 10.1177/0148607113497760]

21 **Fisher BJ**, Kraskauskas D, Martin EJ, Farkas D, Wegelin JA, Brophy D, Ward KR, Voelkel NF, Fowler AA, Natarajan R. Mechanisms of attenuation of abdominal sepsis induced acute lung injury by ascorbic acid. *Am J Physiol Lung Cell Mol Physiol* 2012; **303**: L20-L32 [PMID: 22523283 DOI: 10.1152/ajplung.00300.2011]

22 **Berger MM**, Oudemans-van Straaten HM. Vitamin C supplementation in the critically ill patient. *Curr Opin Clin Nutr Metab Care* 2015; **18**: 193-201 [PMID: 25635594 DOI: 10.1097/MCO.0000000000000148]

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