A year in review in Minerva Anestesiologica 2009. I critical care. Experimental and clinical studies

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Mechanical ventilation

Ventilating patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) remains a challenge for intensivists. In recent years, thanks to translational research, ventilator-induced lung injury (VILI) was discovered in animals and subsequently the "VILI-protective" ventilatory approach was successfully introduced in clinical practice.[1] However, at least 30-40% of ARDS patients still experience an abnormal repair and remodeling of lung parenchyma (fibro-proliferative phase). Recent studies have identified the extracellular matrix as a novel target of VILI.[2, 3] Mechanical ventilation may affect the macromolecules that constitute the lung extracellular matrix, leading to biophysical changes that profoundly impact the mechanical properties of lung parenchyma. In their elegant review, Rocco *et al*. focused the translational evidences that mechanical ventilation may have on lung extracellular matrix and explored the possible therapeutic issues in the next years.[4] At present time, mechanical ventilation of ARDS patients is targeted to avoid tidal hyperinflation with low end-inspiratory plateau pressures (low stretch) and to re-open and keep opened atelectatic lung parenchyma by adequate levels of positive pressure (open lung).[5] However, recent clinical evidences although confirming classical physiological observations, also suggest that titrating low stretch ventilation and the open lung approach using only the airway pressures may be misleading.[6, 7] Since lung and chest wall are structures "in series", a positive pressure applied to the airway opens both lungs and chest-wall, whereas the "real" lung distending pressure is the transpulmonary pressure.[8] Sarge and Talmor revised the increasing evidences that titrating the lung protective ventilatory strategies based on transpulmonary pressure instead that on airway opening pressure could improve oxygenation and lung mechanics, thus individualizing the ventilator management based on individual patient physiology is quite important.[9]

After the initial outbreak identified in Mexico in late March 2009, influenza A sustained by a modified H1N1 virus rapidly spread to all continents.[10-13] Most patients required mechanical ventilation with high PEEP and frequent use of rescue therapies. Grasselli *et al*. reported the first Italian case of life threatening ARDS associated with H1N1 infection, treated with extracorporeal respiratory assistance (veno-venous extracorporeal membrane oxygenation [ECMO]).[14]

Percutaneous dilational tracheostomy (PDT) has gained the favor of intensivists for managing critically ill patients who require long-term ventilatory support. Carrer *et al*. reported the results of a prospective observational study evaluating the safety and long term consequences of PDT performed over a 6-year period.[15] Few PDT related early complications without clinical consequences were observed. Although late complications were infrequent they presented significant consequences.

However, the preferred techniques and timing

for tracheostomies remains questionable.[16] Peris *et al.* showed that a self-driven control fiberoptic bronchoscopy assistance to PDT procedure, as compared with conventional bronchoscopy, was able to reduce the perioperative complications and shortens the duration of the procedure.[17] It also appears to be a promising tool in didactic applications for physicians and nurses during training. In the accompanying editorial, Guarino *et al.* pointed out that the use of tracheostomy should always be evaluated for each individual patient, as there is likely not a single optimal technique or optimal timing for all patients.[18]

An early tracheostomy (*e.g.*, within 3-5 days) offers concrete advantages over oro- or naso-tracheal intubation, but it must be reserved to patients that are likely to require prolonged invasive ventilation. Waiting for the evidence-based results of adequately powered randomized clinical studies that are currently ongoing, Quintel *et al.* proposed an expert opinion-based flow chart for identifying patients candidate to early tracheostomy.[19] The authors suggested that, based on current knowledge, on day 2 or 3 after onset of mechanical ventilation (>48 hours of mechanical ventilation or need for an artificial airway) tracheostomy should be seriously considered.

Innovation and clinical research in the field of emergency airway management in patients with unexpected difficult intubation has led to the proliferation of techniques and devices in the last 25 years.[20, 21] Besides well-established devices such as laryngeal mask airway (LMA) and combitube, several new extra-glottic devices and videolaryngoscopes have been proposed for the use in clinical practice. Agrò *et al.* revised new devices and techniques for emergency airway management and the algorithms for managing the "failed airway" emergency. However there is no technique found to be effective in every case or that can solve all airway problems.[22]

Loss of airways in case of massive hemoptysis is a rare but life-threatening scenario. Spicek-Macan *et al.* reported an interesting case regarding the use of a bronchial blocker (*i.e.*, a Fogarty catheter) to manage an exanguinating case of tuberculosis related hemoptysis.[23]

Diagnostic imaging is a fundamental part of Intensive Care Unit patient care.[24, 25] The increased sophistication and clinical efficacy of diagnostic imaging of computerized tomography (CT) has resulted in its extensive use over the past quarter century providing a better and more punctual patient management. Soldati *et al.* revised the mainly advantages of lung ultrasound in critical care practice.[26] The authors also described how the non invasive nature of ultrasonography may allow to monitor the disease progression versus the healing process. Although the lung was traditionally not considered as a part of ultrasound in the recent years the acute respiratory failure is become a common situation to apply ultrasound. Lichtenstein suggested an ultrasound approach, "the BLUE protocol", which allow a rapid diagnosis.[27] The "BLUE protocol" by combining three signs with binary answer (anterior lung sliding, anterior lung rockets) with venous analysis allow a 90% of accuracy. The "BLUE protocol" can be achieved in three minutes.

Non-invasive ventilation

In the past 10 years, non-invasive ventilation (NIV) has been increasingly applied to clinically treat acute respiratory insufficiency from different causes.[28] In parallel to a widespread diffusion in our clinical practice, an increasing interest of research has been also focused on this topic.[29] In particular, many are the investigations at the moment available which have studied the clinical feasibility and effectiveness of NIV in different type of acute respiratory failures: patients with exacerbation of chronic obstructive pulmonary disease, patients with hypoxemic respiratory failure due to either cardiopulmonary edema or acute lung injury/acute respiratory distress syndrome, and ventilated patients in their phase of weaning. In our Journal, Nava *et al.* have recently and largely reviewed the topic, mainly on the basis of the evidences available from the literature.[30] The authors, besides discussing the potential clinical role of NIV in common clinical situations (exacerbation of chronic obstructive pulmonary disease, hypoxemic respiratory failure and weaning off from mechanical ventilation), presented the possible clinical effectiveness of this type of ventilation as a useful approach to prevent extubation failure, as well as in patients for which a "do-not-intu-

bate" order has been decided. In their conclusions, the authors clearly highlighted that NIV should primarily be applied as an early approach to acute respiratory insufficiency in order to avoid a further deterioration, thereby avoiding (if possible) intubation and invasive mechanical ventilation. Nonetheless, they clearly warned against a widespread use of NIV in every type of acute respiratory failure without the presence of a skilled-team able to clinically treat such clinical conditions.

Besides the common clinical application, NIV has been increasingly applied outside Intensive Care Units, due to the very diffuse shortage of intensive care beds and the larger diffusion of NIV techniques. In an interesting report, Cabrini *et al.*[31] designed a study aimed at evaluating the perspective about NIV of nurses of general wards in which this type of ventilation has been applied. By distributing a questionnaire in four different general wards, the authors observed a very high percentage of nurses that did not feel involved in the decision-making process regarding NIV application, as well as a very low percentage of nurses that were satisfied with the training received. The conclusions of this article are straightforward: when applied outside Intensive Care Units, the demand for a adequate training on NIV for medical personnel and nurses of the units in which it is applied is very strong. In a further report, Chiumello *et al.*[32] reviewed the same topic from a larger point of view, focusing their attention especially on the different clinical situations in which NIV may be applied (or has been applied) outside Intensive Care Units, such as during acute cardiogenic pulmonary edema,[33-36] acute exacerbation of chronic obstructive pulmonary disease or pneumonia,[37, 38] postoperative patients,[39] and patients with hematological malignancy.[40] Moreover, in the second part of the review, the authors extensively summarized the different typologies of NIV techniques that may be applied outside Intensive Care Units, discussing also the minimum monitoring techniques necessary during the application of NIV, as well as how the organization between the general award and the emergency personnel should be.

Among many different clinical applications, NIV has also been increasingly employed in pediatric patients. In a interesting case report published on our Journal, Doglioni *et al.*[41] described the clinical case of a relatively long-term application of helmet-CPAP on a neonatal affected by severe persistent pulmonary hypertension. The authors reported a successful treatment with discharge from ventilation after 48 hours, with discharge outside the hospital at the 9th postnatal day, in good clinical condition.

Circulation

An increasing interest has been recently given to the dosage of brain natriuretic peptide (BNP) and biologically inactive N-terminal pro-BNP (NT-proBNP) in the diagnosis of congestive heart failure.[42] Increased levels of BNP and NT-proBNP are associated with impaired left ventricular (LV) function and ischemia, pulmonary embolism (PE) and chronic obstructive pulmonary disease.[43] The dosage of BNP is a sensitive and specific test to understand the cardiovascular or the pulmonary origin of breathlessness.[44] Ventricles of the heart can produce BNP after prolonged stretch of cardiac myocytes, but many factors affect left-ventricular filling pressure, influencing the release of BNP in plasma: fluid balance (FB), intrathoracic pressures, inotropical drugs.[45]

Principi *et al.*[46] conducted a prospective study to evaluate the cut-off value of BNP necessary to discriminate patients with congestive heart failure from other patients mechanically ventilated. They enrolled 30 patients needing mechanical ventilation: patients with congestive heart failure had higher values if compared with other patients, but the level of BNP was greater than normal in all patients during mechanical ventilation. The increase of BNP directly correlated with fluid balance and inversely with airway pressure and dobutamine infusion. In addition the plasmatic level of BNP remained higher 24 hours after extubation. The present data suggest that a cut off value of BNP higher than the usual could be necessary to discriminate mechanically ventilated patients without congestive heart failure.

In the editorial Colombo emphasized that plasma BNP is not enough to guide therapeutic decision in patients with heart failure, but it should be used as an adjunct to clinical assessment.[47] However studies should be able to determine the

clinical implications of BNP plasma variations in critically ill patients.

In order to extend monitoring tools, the application of transesophageal echocardiography (TEE) in the operating room and in the Intensive Care Unit has been expanding over the past decades and many studies had been conducted in the last years.[48, 49] Guarracino *et al.* revised the role of TEE in the management of critically ill patients.[50] They defined TEE as a semi-invasive imaging technique that provides a rapid, real-time, bedside assessment of cardiac function and morphology. TEE can also detect anatomical abnormalities and the presence of intracardiac masses or thrombi. In addition the hemodynamic parameters obtained via TEE could be helpful for diagnosis and treatment. The authors concluded that only adequate TEE views and the correct interpretation of the echo data, eventually correlated with other hemodynamic monitoring systems, can be helpful for decision-making, if integrated in the clinical scenario.

Great attention has been recently paid on the use of different vasopressor agents in case of hypotension not responsive to fluid challenge. Decreased vascular tone is a key finding in patients with septic shock.[51] Vasopressor agents are commonly used to correct hypotension and adrenergic agents are classically used for this purpose. Among these agents, norepinephrine is one of the most potent and commonly used, but in some cases dopamine should be preferred. Recently Vincent focused the role of these agents in the treatment of patients with septic shock and hypotension and analyzed the differences between norepinephrine and dopamine.[52] In shock, norepinephrine is more powerful to increase the blood pressure, but dopamine may be useful in patients with compromised cardiac function. Dopamine can also decrease the concentrations of many pituitary hormones, in particular Prolactin, that may cause a transient reduction in T-cell response and lymphocyte count; but the full clinical implications of these endocrine effects in critically ill patients remain unclear.

Over the last years, most discussion about cardiopulmonary arrest focused on invasive airway techniques, timing of drugs administration and other advanced life support therapies. The recent guidelines for cardiopulmonary resuscitation (CPR) underlined the importance of uninterrupted chest compressions, timing and quality of compressions.[53] Roppolo *et al.* confirmed the need of minimally-interrupted chest compression removing rescue ventilation in cardiac arrest after collapse and that CPR can be prioritized to first restore and maintain better coronary artery perfusion.[54] New adjuncts have been created to augment chest compression and enhance venous return. About the role of automated external defibrillator (AED), Roppolo *et al.* asserts that it became an integral component of basic CPR training and public access to defibrillation has evolved into a popularly encouraged practice.

Renal failure

Intravenous diuretics are frequently used in acute care settings to facilitate fluid management.[55, 56] The rationale behind giving diuretics is that they may protect the kidney from ischemic injury by maintaining a not-oliguric state. There are many classes of diuretics that can be used in acute fluid management, ranging from acetazolamide and spironolactone to the more potent "high ceiling" loop diuretics. Karajala *et al.* revised the role of diuretics in modifying the acute kidney injury (AKI).[57] There was no evidence to suggest that the use of loop diuretics in AKI reduces mortality, the need for dialysis, the number of dialysis or length of intensive care or hospital stay or that diuretic may favour the recovery of renal function. At best diuretics have been shown to decrease the symptoms of pulmonary edema secondary to volume overload.

The intensive care prevalence of AKI is approximately 36%.[58, 59] Sepsis is the leading cause of AKI which often manifests as part of the multiple organ dysfunction syndrome.[60] When AKI is severe enough to require renal replacement therapy (RRT) mortality approaches 60%,[61] consequently an optimal management of patients is essential. Zarbock *et al.* revised the most common RRT considering the timing for initiation, the modality and the dose.[62]

Infections

In 2009, pandemic influenza A (H1N1) represented a challenge for the health care system

worldwide. The World Health Organization (WHO) increased the level of pandemic alert to the highest level (phase 6) on June 2009.[63] Clinical expression of H1N1 infection was mainly represented by mild upper respiratory tract illness and very rarely by lower respiratory tract involvement and pneumonia.[64] Nevertheless, intensivists had to face an exceptionally high number of patients presenting acute respiratory distress syndrome (ARDS) due to primary influenza A (H1N1) viral pneumonia.[65, 66]

In a very precise review De Rosa *et al.*[67] extensively described the characteristics of the initial spread of the infection, with a particular attention to its general epidemiology and methods of diagnosis, as well as clearly discussing the problems related to its clinical treatment. From this point of view, the authors highlighted how the new H1N1 influenza viruses are resistant to amantidine and rimantadine, while they are susceptible to neuraminidase inhibitors (oseltamivir and zanamivir), which may be employed in patients with a progressive and severe lower respiratory tract infections or pneumonia with severe co-morbidities. Moreover, they clearly discussed the importance of employing an empiric antibiotic treatment for community acquired pneumonia, as a bacterial infection may develop in association or as a super-infection. Finally, the authors discussed the critical role of several strategies of infection control, as well as the potential importance of strategies of vaccination. In a further editorial by Fumagalli *et al.*[68] on the presence of H1N1 infection in Intensive Care Unit, the authors mainly focused on the clinical treatment potentially applied to patients affected by H1N1 infection and admitted to Intensive Care Units, with a particular attention to both the antiviral therapy and the associated antibiotic treatment for associated bacterial infections. Of note, the authors largely underline in their editorial the importance of a strict collaboration between an infection disease specialist and the Intensive Care Unit physician, in order to ensure the best chance for patient survival.

Ventilator associated pneumonia (VAP) is one of the common nosocomial infections which may complicates the course of up to 30% of patients receiving mechanical ventilation.[69] Educational programs designed to maximize compliance with infection control practices have been shown to decrease the rate of VAP.[70, 71]

Timely and appropriate treatment of VAP requires extensive diagnostic efforts. In an original article Lampati *et al.* investigated the hypothesis that routine surveillance samples obtained from tracheal aspirates could help to predict bacterial pathogen if subsequently the patient develops a VAP.[72] Despite the intrinsic weakness of the retrospective-observational design, the study involved 559 patients and results are robust. Positive and negative predictive values of tracheal aspirate surveillance were 92% and 75%, respectively, for Pseudomonas aeruginosa associated VAP and 90% and 89%, respectively, for methicillin resistant *Staphilococcus Aureus* associated VAP. Tracheal aspirates cultures in ventilated patients may help to predict pathogens.

In a stimulating review, Langer *et al.* focused a possible "pragmatic approach" to VAP diagnosis based on the identification of patients with suspected VAP requiring immediate antibiotic treatment *versus* patients with suspected VAP in which antibiotic treatment may be withhold pending the results of diagnostic tests and identification of causative pathogens.[73]

Invasive candidias (candidemia, disseminated candidiasis with deep organ involvement, endocarditis and meningitis) are increasingly reported in the critically ill patients. De Rosa *et al.* synthesized the most recent guidelines for invasive candidiasis treatment in the peculiar ICU perspective.[74] In general, Echinocandins are currently favored for empiric treatment of candidemia, especially in critically ill patients or those with previous azole exposure.

To complete the picture of the reports published in our Journal regarding infections, three interesting clinical cases may deserve our attention.

Bacterial endocarditis represents a rare cause of septicemia in critically ill patients. Gianesello *et al.* reported a case of mitral valve endocarditis in a patient with severe burns, focusing on diagnostic procedures and timing of surgical treatment.[75]

De Gaudio *et al.*[76] described the clinical report of an immunocompetent patient admitted to ICU after the development of a very severe cerebral aspergillosis. After the diagnosis, the patient under-

went the surgical placement of bilateral endoventricular catheters for blood drainage and monitoring of intracranial pressure. Unfortunately, the patient died for the rapid formation and rupture of multiple mycotic aneurysms disseminated in the area of left internal carotid artery and left middle cerebral artery. The authors discussed the uncommon nature of such an infection developed in an immunocompetent patient, thereby hypothesizing the presence of a specific genetic predisposition, which may characterize also the so-rapid lethal course of the infection.

In the third report, Balicco *et al.*[77] discussed the clinical case of a 61 year-old diabetic and obese woman admitted to Intensive Care Unit after the diagnosis of gas gangrene of the left lower limb. After two days of standard clinical treatment, the patient severely deteriorated, and a more extensive radiological imaging approach revealed the presence of bilateral emphysematous pyelonephritis. After extensive antibiotic treatment, supportive intensive therapy and a nephrectomy, the patient died. The authors, highlighting how rare is such a condition [78] and how it is rarely discussed in intensive care journals,[79, 80] elegantly and extensively describe the clinical background, the epidemiology and the possible risk factors for the development of such a condition. They conclude that emphysematous pyelonephritis is a very severe condition which should be considered in the presence of diabetes, ongoing renal failure and unclear development of septic syndrome, with a related presence of emphysema or gas collection at the level of abdomen.

Sepsis

The last decade has seen important changes in the treatment of septic patient.[51] It should be associated with implementation of treatments and strategies tested in clinical trials and reviewed by evidence-based medicine, that uses grading system to classify evidence and provide decision support.[81, 82] Shultz *et al.* published a review [83] that analyzed some therapies and strategies that may have the potential to ameliorate the survival of critically-ill patients, but not supported by all trials. Then authors focused on potential reasons for differences in the results obtained in distinct studies, like the timing of the intervention, the enrolment criteria and the characteristics of population, the trial protocols, the outcomes considered.

Several mechanisms give rise to high blood glucose concentrations in critically ill patients: increased concentrations of cortisol, catecholamines and glucagon in the context of hypermetabolic stress response that induces increased gluconeogenesis and glycogenolysis. Normalization of blood glucose by intensive insulin therapy has been shown to reduce morbidity and mortality in one study in surgical intensive care patients,[84] while in a subsequent study in medical intensive care patients [85] resulted in reduced morbidity but not in a reduction in mortality.[85] Merz *et al.* revised the intensive insulin treatment in critically ill patients suggesting that universal treatment guidelines or recommendation that target normoglycemia are premature.[86] The authors recommend that each Intensive Care Unit defines a blood glucose range that can be achieved without causing a significant increase in several hypoglycemia and that fits within the constraints of nursing and economic resources.

In January 2008 have been published the controversial guidelines for management of severe sepsis and septic shock with the intent of providing an update to the original "Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock" published in 2004.[87] The authors used the GRADE system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations.[51] In an expert opinion Antonelli defined this guidelines a large and extraordinary update of the literature offered by current leaders in the field.[88] However as a consensus of experts, most of whom expressed their opinions by voting, the guidelines do not always represent the state of the art. Thus, the guidelines cannot replace the physician's judgments, but should be a starting point for further high quality studies that can add robust evidence to medical practice.

In last years it is has been shown that the recombinant human activated protein C (rh-APC) reduces the sepsis-related activation of inflammatory and coagulation system.[89] Plasminogen activator inhibitor type-1 (PAI-1) levels in plasma are consistently elevated in septic patients and are pre-

dictive of unfavorable outcomes, rh-APC reduces level and activity of PAI-1 and glycemic control was also associated with a reduction of PAI-1 levels.[90]

Polli *et al.*[91] in a post-hoc analysis evaluated the effects on the fibrinolytic system after the administration of rh-APC in septic patients undergoing conventional or tight glycemic control (TGC). The authors observed that rh-APC caused different effects on the fibrinolytic system in patient treated with conventional or TGC strategies and the reduction of inflammatory mediators appeared most evident in patients undergoing conventional glycemic control and treated with rh-APC. In the accompanying editorial, Shultz mentioned some limitation of the study such as the relative small group of patients and that it was left to the attending physicians the possibility to treat patients with rh-APC.[90]

Little is known about the inflammatory phenotype of patients during the evolution of sepsis and its relationship with the severity of organ failure.[92] The innate immune system is the first line of defense against microorganisms and the monocytic lineage involves key cells that act via phagocytosis, antigen presentation to lymphocytis and cytokine release. In their manuscript, Payen *et al.* characterized the inflammatory phenotype using mHLA-DR measurements, plasma levels of pro and anti-inflammatory mediators such as IL-12p40, MIF, IL10, cortisiol in a group of patients presenting severe sepsis or septic shock.[93] The mHLA-DR expression was equally decreased in patients who were treated with immunosuppressive drugs and who were not. Patients with single organ failure showed a similar profound mHLA-DR down-regulation as patients with multiple organ failure (MOF) at day 0. MOF patients presented higher plasma IL-10 and cortisol levels than patients with single organ failure but similar plasma IL-12p40 and MIF levels. However the precise mechanisms and mediators involved remain to be characterized. In the accompanying editorial, Del Sorbo *et al.* highlighted how these results may represent the first step toward a novel functional and molecular definition of groups of septic patients with common pathophysiological mechanisms of disease, more homogeneous clinical characteristics and the highest potential to benefit from specific treatments, determining a more precise prognosis.[94]

Besides several clinical infections may potentially underlying septic syndrome, a further critical problem during the clinical approach of a septic patient is the possibility of monitoring its severity and its time course. During the past years, many efforts have been performed towards this goal. Among many molecules and bio-markers potentially individuated for this purpose, procalcitonin has certainly played an important role. In fact, since the first studies by Assicot *et al.*,[95] its measurement during the course of a bacterial infection has provided an important tool to monitor the overall severity of the infection itself,[96] as well as an apparently critical tool to guide the extent of antibiotic therapy.[97] In his excellent expert opinion on the topic, Dahaba *et al.*[98] extensively reviewed the background of procalcitonin measurements in septic patients, firstly summarizing the biochemical pathway of its production during a bacterial infection, and secondly discussing its role in clinically assessing the severity of sepsis. Most interestingly, the authors discussed whether procalcitonin may be considered a real "mediator" of sepsis or just a "marker" of its development, pointing out that according to the literature now available procalcitonin is likely to be an important mediator of the syndrome, although acting after a different inflammatory "priming". Finally, based upon a series of data derived by their center, the authors reported a high discriminative power in detecting survival of post-operative septic patients by employing a threshold of 3.2 ng/ml of plasmatic concentration of procalcitonin.

Neuro-critical care

Ischemic and traumatic brain injury are characterized by an initial and a secondary insult;the latter one is associated to an up-regulation and release of several mediators that play a role in determining patients' outcome. In models of acute brain injury, hypotermia has proved to be neuroprotective: although the mechanisms are not still known, it is clear that it plays a role in metabolism and secondary ischemic injury reduction, blood-brain barrier protection, intracranial pressure limitation, inhibition of destructing enzyme cascade and apop-

tosis.[99] Regardless these strong evidences, there is still resistance against hypothermic treatment.[100-102] Bianchin *et al.* conducted an Italian survey investigation regarding the indications on methods, monitoring, side effects and avoidance of hypothermia.[103] The study included 448 ICUs and was conducted by phone contact and with a questionnaire sent to the participants. 90% of the questionnaire sent gave answer with about 80% of negative response on use of hypothermia, about 50% of these thought to need more information in order to start using this therapy. Only 20% of the sample used hypothermia and only a little part of them had a written protocol. Principal indication was intra-hospital cardiac arrest and only 10 ICUs gave indications to traumatic brain injury. The results of this survey are similar to other countries, with still a limited use of hypothermia. In the accompanying editorial Longhi *et al.* suggested that more work needs to be done on hypothermia focusing on two different aspects such as the best method of cooling and maintenance, the optimal target temperature, duration, and rate of cooling, the safest rate of re-warming and the optimal management of other concurrent therapies.[99]

Unfortunately brain death is a frequent consequence of traumatic brain injury and cardiac arrest. Mascia *et al.* evaluated a protocol to enhance organ procurement. Only a 20% of potential donors donate organs, and the majority of these die in intensive care after brain death.[104] The brain death is associated to a widespread of complications including hypotension, diabetes insipidus, relative hypothermia, electrolyte imbalance, DIC, arrhythmias, metabolic acidosis, and there is an up-regulation of inflammatory molecules. These complications, if untreated, limit the availability of solid organs transplantable. In this expert opinion authors give recommendations for clinical management.

Pilato *et al.* evaluated the incidence of stroke in critically ill patients.[105] The major pathophysiologic mechanism is thomboembolic with the occlusion of an aterosclerotic plaque with a consequent ischemia. Among the critically ill patient population the main risk factors are represented by the underling pathology at first, coagulation disorders, glucose intolerance/diabetes, while pro-inflammatory state and infections play a minor role. Treatment of the stroke in critically ill patients is the same as the one recommended by international guidelines with rtPA, (ASA, dipyridamole and clopidogrel when contra-indicated).

Childhood meningitis is associated with high mortality and morbidity. In selected cases, the prompt institution of invasive intracranial pressure monitoring and therapy may improve survival, but few studies have evaluated the indications for intracranial pressure monitoring in this specific field.[106] Sala *et al.* reported the case of intracranial pressure monitoring in pediatric bacterial meningitis.[107] An intracranial pressure targeted treatment might be considered in severe cases of bacterial meningitis to optimize brain perfusion and provide relief from severe neurological impairment.

Wernicke's encephalopathy (WE) is a neuropsychiatric syndrome caused by a lack of thiamine associated with acute or chronic gastro-enteric disease. Zangheri *et al.* reported the case of acute necrotic hemorrhagic pancreatitis complicated by WE and stressed the importance of a correct dietetic regimen.[108]

Training

Aside to the development and the different steps achieved by research, "training" should play a major role when considering the overall domain of medicine and clinical practice. In the past years, many different aspects of training have been developed with novel approaches, such as simulation and e-training. In the era of globalization, one of the main critical aspects of training is the possibility of making it uniform among different countries and areas. Regarding this topic, Rubulotta *et al.*[109] reported the results of an international survey: the "Competency-Based Training in Intensive Care Medicine in Europe" (CoBaTrICE).[110] Aim of this survey was specifically to create an internationally recognized competency-based training program for specialists in intensive care medicine, based upon what patients and their relatives express as main and most relevant characteristics. By means of a questionnaire, the authors observed that the priority has been usually given to medical skills and general medical competence, followed by a clear communication to the patient. In contrast,

the involvement of patients and relatives in a decision-making process appeared to be the least considered aspect.

Every day, thousand of manuscripts are submitted worldwide for publications in medical journals. The process of reviewing manuscripts submitted for publication was introduced in England in 17th century and its value for improving scientific knowledge is still widely accepted. The reviewer process is therefore essential, but not sufficiently recognized by the readers and often poorly appreciated by the authors. Cavaliere *et al.* revising the peer review process, suggested that a constructive interaction between editors, reviewers and authors is essential for a real effectiveness of the entire process.[111] The peer review process at the present is the best possible way to ensure quality of scientific publications.

Daily clinical work includes dozen, if not hundreds, decisions. In each case, the clinician has to consider relevant management options, weigh the desirable and undesirable consequences, evaluating patients' decision preferences and at the end make a decision in the best interest of the patient. However the optimal strategy is often not so apparent. Thus in the recent years several clinical practice guidelines have been developed to inform clinical regarding the best option for managing patients. Jaeschke *et al.* revised the correct approach to develop clinical guidelines by using the international grades of recommendation.[112] This approach suggests several steps for guideline development from determine the purpose, scope and intended audience, to formulate recommendations including their strength.

The fundamental goals of medicine are to safeguard and improve community health, quality of life and social welfare. Innovation to reduce morbidity and mortality in critical care medicine, however, often requires research involving human subjects, which has raised considerable concern in the medico-ethical literature.[113, 114] Whetstine synthesized the recent debate regarding the use of human research subjects who are critically ill, undertaked a conceptual analysis of informed consent and its application to such patients and ultimately concluded that research on this vulnerable population could be ethical if specific measures are undertaken.[115]

In emergency and critical care medicine ultrasound can be used as a simple diagnostic toll at the patient's bedside. Breitkreutz *et al.* described a training program for non specialists focused echocardiography in the preresuscitation setting.[116] This program enables novice echocardiographers to be able to perform a focused echocardiogram in a ALS- compliant manner and interpret the findings in the context of the clinical scenario. It is based on the concept of blended learning, incorporating a combination of e-learning, web based teaching and reading selected literature and attendance at a course.

Hyperbaric medicine

In the therapeutic treatment of decompression illness, hyperbaric therapy has a prominent role, therefore the choice of the correct therapeutic table for each case is very important. Several recompression schedules (commonly referred as "treatment tables") have been empirically developed, based on statistics or tests in healthy individuals. Antonelli *et al.* revised the guiding principles in choosing a therapeutic table for decompression illness hyperbaric therapy.[117] However only prospectively randomized trial will permit the proper evaluation of the benefits that each therapeutic option can give. At the present time, much research is focused in this direction. Other approaches besides hyperbaric therapy should not be ruled out, especially in the study of cytotoxic phenomena.

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