REVIEW ARTICLE

Overview of progresses in critical care medicine 2012

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J Thorac Dis 2013;5(2):184-192. doi: 10.3978/j.issn.2072-1439.2013.02.03

Critical care medicine has not slowed down its pace of development in 2012. The progress and events of key clinical research in this field are summarized as follows.

Initiation of World Sepsis Day (WSD) and new epidemiological data

To improve the public understanding of sepsis and bring global attention to this issue, German doctor Konrad Reinhart co-sponsored the "WSD" campaign with the Global Sepsis Alliance, and put forward the objectives by 2020. The WSD is scheduled for September 13 on a yearly basis, when activities are conducted in various forms around the world to promote the public understanding of sepsis, bring the attention of government agencies and health departments to this condition, and solicit policy support (1).

In response to the establishment of WSD, two epidemiological surveys using data as of 2007 showed significantly increasing hospitalization rates due to severe sepsis in the United States. One of them, spanning from 2003 to 2007, revealed an increase of 71% in the number of severe sepsis patients, an increase of 57% in total hospital costs (from $15.4 billion to $24.3 billion per year), and a more than 1.2-fold increase in patients with ≥3 organ dysfunctions, despite significantly reduced hospital mortality and length of stay (2). The other survey, spanning from 2000 to 2007, showed similar results (3). Not only did the above surveys demonstrate an increasing trend in the incidence of severe sepsis, but they suggested that a large number of patients were being transferred to a long-term care facility after successful treatment (3), exerting a far-reaching impact on the cost structure of social healthcare and allocation of nursing resources. In addition, a survey on readmission of intensive care unit (ICU) patients in the U.S. showed that nearly 2-4% patients discharged from ICU would be readmitted into the same unit within 48 or 120 h, with a median interval of 3.07 d. There was also a significantly higher risk of readmission for patients of the medical wards in a teaching hospital than those in a community hospital (4).

A comparative study of the onset presentations and outcomes of acute respiratory distress syndrome (ARDS) in 1993-1995 versus 2006-2009 (5) showed gradual increase in the age and severity of onset in ARDS patients with the progress of the times, in contrast to significantly shortened length of ICU stay in the survivors, with a downward trend in mortality. While ARDS cases due to trauma and massive blood transfusion gradually reduced, those caused by sepsis have significantly increased. Multiorgan failure (MOF) still remains the most important cause of ARDS.

Hemodynamic optimized therapy in severe sepsis and septic shock

Hemodynamic optimization and choices of crystals and colloids for fluid resuscitation are still the most popular yet controversial area of interest in 2012. In addition, the optimization therapy is by no means confined to the field of critical care medicine; its application can be found in perioperative management and emergency treatment as well. This also involves hemodynamic monitoring, open and restricted transfusion strategies, vasoactive drug selection, transfusion strategies, and other related issues, with every single piece making the situation further complicated.

Early goal-directed therapy (EGDT)

In a multi-center study involving four community and four local hospitals, Cannon *et al.* (6) found that the 6-h resuscitation strategy reduced the mortality of severe sepsis and septic shock by 14.0% (42.8% *vs.* 28.8% P<0.001) and length of stay by 5.1 d (20.7 *vs.* 15.6 d, P<0.001) compared with the control group. The trend of reduced mortality also existed in the concurrent before-after study (43% *vs.* 29%, P<0.001), and in

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Submitted Jan 17, 2013. Accepted for publication Feb 21, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

the comparison between groups where the resuscitation strategy was completed and those where it was not (42.5% *vs.* 27.2%, P<0.001). In view of these findings, the application of early intervention strategies for sepsis should be promoted. In a retrospective analysis, Fuller *et al.* (7) found no improvement in central venous oxygen saturation ($ScvO_2$) or organ function by infusion with blood bags in the EGDT of severe sepsis and septic shock. Hence, further research will be needed to identify the value of blood transfusion in EGDT.

Hemodynamic monitoring indicators

French investigators (8) studied the effects of the volume of fluid resuscitation, adjustment of positive inotropic drugs, and vasopressin dosage in the therapy protocol with mechanical ventilation, based on early esophageal ultrasound, for patients with septic shock. They found a lack of consistency in decision making in terms of the liquid load and inotropic drug usage compared with the EGDT strategy. This has demonstrated the complexity of contemporary hemodynamic monitoring in septic shock, which entails more relevant research in future.

Colin *et al.* (9) found in their study that, upon the completion of 6-h fluid resuscitation, significant gradient changes were shown in the tissue oxygen saturation (SO_2) of the thenar, masseter and deltoid muscles in patients with severe sepsis. The receiver operating characteristic (ROC) curve showed that the masseter SO_2 was an effective predictor of $ScvO_2$ >0.70, and the masseter and deltoid SO_2 values could effectively predict the 28-d mortality.

Pierrakos *et al.* (10) evaluated the relationship between the arterial blood pressure and the cardiac index (CI) during fluid challenge in septic shock. The results showed no significant correlation between the mean arterial pressure (MAP) and pulse pressure (PP) or CI in challenge-positive (% CI >10%) patients, indicating a need for caution when interpreting the results of fluid challenge based on MAP.

What is the prognosis of patients with septic shock who have achieved the target lactate clearance rate and $ScvO_2$ following treatment? The Emergency Medicine Shock Research Network (EMSHOCKNET) study, which included 203 patients, showed a mortality rate of 41% for patients who achieved the $ScvO_2$ target (≥0.70) alone, and 8% for those achieving the lactate clearance rate target (≥10%) alone (11). It could be seen that there is no consistent correlation between the two treatment targets, and the clearance rate is apparently associated with a higher prognostic or therapeutic value.

In a prospective observational study, Korean scholars (12) found mortality rates of 41.5% and 35.8% for patients receiving intermittent and continuous $ScvO_2$ monitoring, respectively, during administration of the 6-h EGDT strategy (P=0.550). No significant difference was observed in terms of length of ICU stay, ICU mortality, in-hospital mortality or other indicators between the two groups, suggesting that intermittent $ScvO_2$ monitoring was not superior to the continuous approach.

Choices of crystals and colloids in fluid resuscitation

One of the most important events in the development critical care medicine in 2012 was the release of findings from the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) in New Zealand and Australia (13). In the study, nearly 7,000 ICU patients were randomized to receive 0.6% hydroxyethyl starch (HES130/0.4 group, n=3,315) and normal saline (n=3,336) as fluid resuscitation. Despite the absence of significant difference in mortality (18.0% *vs.* 17.0%, P=0.26) and incidence of kidney failure (10.4% *vs.* 9.2%, P=0.12), significant differences were observed in renal replacement therapy (RRT) (7.0% *vs.* 5.8%, P=0.04), and incidence of renal injury (34.6% *vs.* 38.0%, P=0.005). Hydroxyethyl starch could cause significant side effects (5.3% *vs.* 2.8%, P<0.001). Therefore, although hydroxyethyl starch does not increase mortality, it considerably elevates the risk of kidney dialysis. Coincidentally, a multi-center, parallel, blinded Scandinavian starch for severe sepsis/septic shock trial (6S study) conducted in the Scandinavian region (14) showed a similar conclusion: during the fluid resuscitation for about 800 patients with severe sepsis, the 90-d mortality rates in the HES 130/0.4 group and the Ringer lactate solution group were 51% and 43%, respectively (P=0.03). In the two groups, 12% and 16% patients (P=0.04) needed RRT after 90 days, respectively, and 10% and 6% suffered severe bleeding (P=0.09), respectively. These results associate an increased risk of mortality and kidney damage with the use of hydroxyethyl starch in fluid resuscitation for septic shock or severe sepsis, calling for more caution when prescribing the agent.

In view of an increasing number of evidence against artificial colloids in recent years, both the Cochrane database (15) and the European Society of Critical Care (ESICM) (16) have advised against the use hydroxyethyl starch and gelatin in fluid resuscitation for critically ill patients. Therefore, future studies may focus on the following aspects: the therapeutic efficacy of natural colloids (5% or 20% albumin); comparison across various crystals (saline and Ringer lactate, as well as acetate Ringer's solution); and research and development of other new artificial colloids. For example, in an open prospective study with more than 1,500 ICU patients (17), the authors found that, after calibration, the employment of chlorine-limited infusion strategies reduced the risk of kidney damage or failure [odds ratio (OR): 0.52, 95% confidence interval (95% CI) (0.37, 0.75)], as well as the risk of RRT [OR: 0.52, 95% CI (0.33, 0.81)].

Vasoactive drugs

In 2012, two meta-analyses about norepinephrine (NE) and

dopamine (DA) in the treatment of septic shock were successively published (18,19). In their analysis incorporating five observational studies and six randomized studies with a total of 2,768 patients (1,474 receiving NE and 1,294 DA), Belgium investigators (18) found that DA significantly increased the mortality of patients with septic shock, and was associated with a higher incidence of DA-related arrhythmia in both observational and randomized studies. American investigators (19) included six studies with a total of 2,043 cases of primary or secondary septic shock (995 receiving NE treatment and 1,048 DA). The 28-d mortality rates were 48% and 53% in the two groups, respectively [relative risk (RR): 0.91, 95% CI (0.83, 0.99), P=0.028]. The incidence of arrhythmia was significantly reduced in the NE group [RR: 0.43, 95% CI (0.26, 0.69), P≤0.001]. Subgroup analysis in patients with primary septic shock suggested that NE reduced in-hospital or 28-d mortality, though no significant statistical difference was shown.

In another meta-analysis of vasopressin in the treatment for cardiogenic shock, Greek investigators (20) found that vasopressin failed to show any overall benefit in terms of restoration of spontaneous circulation (ROSC) and neurological prognosis, but it could improve the long-term prognosis of patients whose time from onset to medication was <20 min. ESICM's meta-analysis about vasodilatory shock (21) showed that vasopressin/terlipressin showed no obvious advantage compared with the control group, as the mortality rates were 40.2% and 42.9%, respectively [RR: 0.91, 95% CI (0.79, 1.05), P=0.21], and incidence rates of severe complications 10.6% and 11.8% [RR: 0.90, 95% CI (0.49, 1.67), P=0.75], respectively.

Corticosteroidstherapy

Corticosteroids therapy has always been a hot topic in the field of critical care medicine. A study of the application of hydrocortisone in the treatment of multiple trauma (hydrocortisone polytraumatise, HYPOLYTE) in France (22) showed that stress doses of glucocorticoids could significantly reduce the incidence of 28-d hospital-acquired pneumonia (HAP) in multiple trauma patients [modified ITT analysis, 35.7% in treatment group *vs.* 54.4% in control group, hazard ratio (HR): 0.47, 95% CI (0.25, 0.86), P=0.01]; the duration of mechanical ventilation in the hormone group was increased by 6 d {95% CI [2, 11], P<0.001}. There was no significant difference in mortality [8.2% *vs.* 5.3%, 95% CI (−5%, 11%), P=0.44].

In a Spanish prospective observational study (23), 125 out of 316 ICU HAP patients received hormone therapy during the onset of pneumonia. While hormone therapy reduced the systemic inflammatory response, it also reduced the 28-d survival [corrected HR: 2.503, 95% CI (1.176, 5.330), P=0.017]. Post-hoc analysis showed that hormone therapy could affect the mortality of ICU HAP patients without mechanical ventilation, those with relatively low severity of disease or organ dysfunction, and those with unknown causes or non-septic conditions.

In another multi-center randomized controlled study on the prophylactic use of high-dose dexamethasone (1 mg/kg) in heart surgery conducted in the Netherlands (24), hormone therapy did not reduce the incidence of major adverse events (death, myocardial infarction (MI), renal failure, or respiratory failure) within 30 days after randomization compared with the control group [RR: 0.83, 95% CI (0.67, 1.01), absolute risk decrease (−1.5%), 95% CI (−3.0%, −0.1%), P=0.07].

Glycemic control

As with hormone therapy, blood glucose control is still an area of great interest in 2012. To identify the relationship between hypoglycemia and mortality, investigators of the famous NICE SUGAR did a secondary analysis using the original data (25). The results showed intensified insulin treatment could lead to medium to severe hypoglycemia in ICU patients, and thus increased mortality, in a dose-response manner. However, that study alone could not determine the causal relationship between hypoglycemia and death.

A large study was designed to evaluate neural development in critically ill children four years after tight glucose control (TGC) in Brussels (26). Over a median follow-up of 3.9 years, it was found that TGC did neither affect IQ evaluation [median interquartile range (IQR): 88.0 (74.0-100.0) in TGC group versus 88.5 (74.3-99.0) in control group, P=0.73] nor increase the incidence of adverse outcomes (death or severe disability). It also significantly increased motor coordination (P<=0.03) and cognitive flexibility (P=0.02). Another large-scale study of TGC in children undergoing cardiac surgery in Boston (27) showed that, although only 3% of the children had severe hypoglycemia (<2.2 mmol/L), TGC did neither significantly reduced the incidence of medical-related infections nor reduce mortality and the number of organ failures. Meanwhile, no significant benefit was observed in high risk children.

Acute lung injury (ALI)/ARDS and respiratory failure

A multi-center randomized controlled study of ALI patients with low calorie diets (n=508) and full diets (n=492) by the National Institutes of Health (NIH) ARDS Network (ARDSNet) (28) showed that, compared with full diets, low caloric intake did neither increase the days of non-mechanical ventilation [14.9 d in low-calorie group, 95% CI (13.9, 15.8), *vs.* 15.0 d in full diet group, 95% CI (14.1, 15.9); difference: 0.1 d, 95% CI (−1.4, −1.2); P=0.89], nor reduce the 60-d mortality [23.2%, 95% CI (19.6%,

26.9%) *vs.* 22.2%, 95% CI (18.5%, 25.8%); difference: 1.0%, 95% CI (−4.1%,−6.3%); P=0.77]. There was no difference in infectious complications between the two groups. Despite an increased amount of gastric motility medication, significant elevation in the incidence of vomiting and constipation, gastric residual volume, glucose level and insulin usage were observed in the full diet group. Based on the above study, low-calorie feeding does not bring noticeable clinical benefits to ALI patients, though it may reduce gastrointestinal intolerance during feeding.

By summarizing animal experiments and clinical data on ALI treatment with inhalation of anticoagulant agents (active protein C, anticoagulant enzyme, heparin, and danaparoid), Dutch investigators (29) found that, while anticoagulant drugs were shown to reduce pulmonary abnormal blood clotting and inflammation in animal experiments, particularly heparin and danaparoid that had effect on systemic coagulation, similar conclusions were supported by very few clinical data. Nonetheless, some studies have shown that nebulized heparin may safely extend the number of days of non-mechanical ventilation for ALI patients.

In a small, single-center study that enrolled 32 patients (30), the addition of ginger extract in high protein enteral nutrition significantly reduced the 5-d and 10-d levels of serum interleukins (IL-1, IL-6) and tumor necrosis factor-α (TNF-α), and increased erythrocyte glutathione levels in ALI patients. Significant improvement was also observed in other indicators, such as oxygenation, static compliance, duration of mechanical ventilation, and length of ICU stay.

In the U.K., a multi-center study of intravenous infusion with β2 receptor agonists in ARDS treatment (31) was subject to early termination due to the interim report of increased mortality associated with the 7-d continuous therapy using salbutamol of 15 μg/kg/h [35% *vs.* 23%, RR: 1.47, 95% CI (1.03, 2.08)]. Based on the current evidence, intravenous β2 agonists are not recommended for ARDS patients on mechanical ventilation.

Regarding the treatment of respiratory failure in ARDS patients, Brazilian investigators (32) concluded in a meta-analysis that a ventilation strategy using lower tidal volumes also reduced the progression of lung injury [RR: 0.33, 95% CI (0.23, 0.47), number needed to treat (NNT) 11] and mortality [RR: 0.64, 95% CI (0.46, 0.89), NNT 23]. At the same time, such strategy also reduced the incidence of lung infections and hospital stay.

Enteral and parenteral nutrition

In a prospective, double-blind, randomized controlled trial, Umpierrez *et al.* (33) compared the efficacy of soybean oil or olive oil-based parenteral nutrition formulations for critically ill patients from internal medicine wards. The results showed no difference in the blood sugar level, hospital stay, mortality and nosocomial infection rate, incidence of acute renal failure, inflammatory cytokines, markers of oxidative stress, and leukocyte function between the two groups.

Vanderheyden *et al.* (34) conducted a cost analysis of parenteral nutrition costs at the early (≤1 week) and late (>1 week) stages. Their results showed that 30% of the total hospital costs came from drugs, and early implementation of parenteral nutrition significantly increased the cost (+608.00 EUR/case, P<0.01), particularly the use of anti-infectives (+227.00 EUR/case, P=0.02). Sensitivity analysis suggested that early enteral nutrition brought an average increase of €1210.00/case (P=0.02) in the total cost. Therefore, from the perspective of pharmacoeconomics, early parenteral nutrition is not recommended for critically ill patients.

Pradelli *et al.* (35) conducted a meta-analysis of the efficacy of parenteral nutrition enriched with n-3 polyunsaturated fatty acids for patients after elective surgical and those in ICU, including 23 studies (with 1,502 patients, of which 762 were in ICU). Compared with the standard formula, n-3 polyunsaturated fatty acids rich parenteral nutrition did not improve the mortality [RR: 0.89, 95% CI (0.59, 1.33)], but it significantly reduced the incidence of infection [RR: 0.61, 95% CI (0.45, 0.84)], length of ICU stay [RR: −1.92, 95% CI (−3.27, −0.58)] and the total length of hospital stay [RR: −3.29,95% CI (−5.13, −1.45)]. Other benefits included reduced levels of inflammatory mediators, improved pulmonary gas exchange and lung function, and decreased oxidative stress, plasma phospholipid fatty acid composition and probability of kidney damage.

A multi-center study comparing nasointestinal and nasogastric tubes for mechanically ventilated patients in Australia and New Zealand (36) revealed that 72% and 71% of the two groups achieved the energy target, respectively [mean difference 1%, 95% CI (−3%, −5%), P=0.66], with similar incidence rates of ventilator-associated pneumonia (VAP) (20% *vs.* 21%, P=0.94), vomiting, aspiration, and diarrhea, as well as similar mortality. Mild gastrointestinal bleeding was more common in patients with nasointestinal tube feeding (13% *vs.* 3%, P=0.02).

Acute kidney injury (AKI) and RRT

Pickering *et al.* (37) put forward a hypothesis that a calculated 4-h creatinine clearance rate (Ccr) would be a better indicator for renal function monitoring in critically ill patients, compared with direct measurement of serum creatinine (Cr). By assessment of 484 critically ill patients, the authors found that approximately 24% patients were underdiagnosed based on the Cr level when a diagnosis of AKI was established by an increased Cr level by 50% or decreased 4-h Ccr by >33.3%, and the diagnostic criteria based on Ccr levels within 12 hours was correlated with the increase in the risk of death. Therefore the 4-h Ccr indicator could be extremely valuable for early detection, prognostic

evaluation and intervention of AKI.

The investigators at the University of Heidelberg, Germany (38) evaluated the efficacy of sustained low efficiency dialysis (SLED) in the continuous mode against AKI in critically ill patients. In their study, the 90-d mortality rates were similar between the SLED group and the continuous veno-venous hemofiltration (CVVH) group (49.6% in SLED *vs.* 55.6% in CVVH, P=0.43), and no significant difference was shown in hemodynamic parameters. However, SLED significantly reduced the number of days of mechanical ventilation [(17.7±19.4) *vs.* (20.9±19.8) d, P=0.047], length of ICU stay [(19.6±20.1) *vs.* (23.7±21.9) d, P=0.04], blood transfusion [(1,375±2,573) *vs.* (1,976±3,316) mL, P=0.02], and required RRT nursing time (P<0.001). Therefore, attention should be given to the therapeutic potential of SLED.

Bart *et al.* (39) compared the efficacy of drug therapy and ultrafiltration in patients with decompensated heart failure complicated with cardiorenal syndrome, finding that drug therapy provided better renal protection than ultrafiltration beyond 4 d after treatment, with significantly less adverse events. In view of the complicated etiology and long-lasting difficulty in management of AKI in critically ill patients, Chawla *et al.* (40) promoted the "permissive hypofiltration" treatment, a concept derived from the lung protective strategy of "permissive hypoventilation" for ALI/ARDS, in which they believed that early RRT could be employed to revitalize the kidneys, avoid potential adverse damage (such as the capacity overload, hypophosphatemia, and hypothermia) and improve survival, rather than improving renal functions at the cost of increased renal blood flow and glomerular filtration rate. In our opinion, there are valuable considerations in this concept that we can learn from.

Anti-inflammation and antibacterial drugs

Negative conclusions come one after another regarding combined use of antibacterial drugs

A multi-center study in Germany (41) reported that the empirical combination of moxifloxacin and meropenem had comparable efficacy to meropenem alone against severe sepsis in ICU (no significant difference was shown in 28-d and 90-d mortality). Korean investigators (42) found that early use of imipenem/cilastatin and vancomycin combined with the step-down strategy (DE group) did not bring any additional benefit to HAP patients, compared with conventional antibiotic therapy (NDE group) without the strategy (no significant difference was observed in average length of ICU stay and 14-d, 28-d overall mortality). Despite early use of vancomycin in the DE group, significantly increased growth of multi-drug resistant bacteria, especially methicillin-resistant Staphylococcus aureus (MRSA), were observed, as well as MRSA-related mortality, compared with the NDE group.

New antibacterial drugs

A multi-center, double-blind, randomized, non-inferiority trial in the U.S., Canada and Europe (43) demonstrated that oral fidaxomicin (270 cases, 200 mg, once every 12 hours) had similar efficacy and safety against Clostridium difficile infection compared with oral vancomycin (265 cases, 125 mg, once every 6 hours), so it would serve as an alternative to vancomycin. Famous scholar Kollef and colleagues (44) conducted a study to compare doripenem versus imipenem/cilastatin in treatment of late-onset VAP, but it was terminated early. The interim data analysis revealed that doripenem (1 g, continuous intravenous infusion of 4 hrs, every 8 hrs for 7 consecutive days) did not show better efficacy than imipenem/cilastatin (1 g, continuous intravenous infusion of 1 h, every 8 h for 10 consecutive days). It also increased clinical failure and mortality rates, although no significant difference was suggested in either parameter.

Continuous infusion of antibacterial agents

Long-term continuous infusion of time-dependent antibacterial drugs is always a suboptimal but inevitable option in the era of resistant bacteria. Current studies are no longer confined to piperacillin/tazobactam as they once were, and there are quite a few reports of continuous intravenous infusion using meropenem (45), linezolid (46) and vancomycin (47). Studies have confirmed the high safety, blood and tissue concentration (e.g., alveolar epithelial lining fluid), and anti-inflammatory efficacy of continuous infusion, though the specific amount and the need for a loading dose (such as vancomycin) should be further clarified by more investigation.

Probiotics

There are three meta-analyses of probiotic therapy respectively in patients with severe HAP (48,49) and antimicrobial drug-associated diarrhea (AAD) (50) in 2012 that are worthy of attention. They noted that probiotics could significantly reduce the incidence of HAP or VAP and AAD, and thus mortality. Since the heterogeneity of these study limited their ability to produce sufficient evidence, large-scale multi-center studies are expected on their basis.

Catheter-related blood stream infections (CRBSI)

The association between central venous catheter puncture sites and the risk of CRBSI is another hot issue in 2012, with new perspectives emerging. In a meta-analysis, Marik *et al.* (51) noted

that, although the femoral vein was associated with a higher CRBSI risk compared with the subclavian/internal jugular veins in previous reports, recent studies found no significant difference in terms of the risk and the incidence of thromboembolism across the three sites.

A multi-center randomized controlled study in Greece (52) compared the efficacy of chlorhexidine-impregnated sponge plus chlorophyll catheters versus standard multi-lumen central venous catheters in preventing CRBSI of ICU patients. As shown by the results, short-term use of the chlorhexidine-impregnated sponge plus chlorophyll catheter (median duration of 7 d) as the only preventive measure did not significantly reduce bacterial catheter colonization and the occurrence of CRBSI.

Meanwhile, the evidence-based international recommendations for ultrasound guided vascular puncture (53) have been released in June 2012. In fact, the ultrasound technology has more significant roles in critical care besides the above description. Far-reaching impacts can be expected on the entire medical field and the diagnostic and therapeutic capabilities with the development of this technology.

Delirium and sedation

Delirium screening has become a hot topic in critical care medicine in recent years. In a systematic review, Brazilian investigators (54) compared the screening value of the Confusion Assessment Method for the ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) under ICU settings. Their results were in favor of CAM-ICU, which had a sensitivity of 0.80 [95% CI (0.77, 0.83)], specificity of 0.97 [95% CI (0.95, 0.97)], diagnostic OR value of 103.2 [95% CI (39.6, 268.8)], and area under the ROC curve (AUC) of 0.97. ICDSC had slightly lower sensitivity and specificity and medium diagnostic power, medium: its sensitivity was 0.74 [95% CI (0.65, 0.82)], specificity 0.82 [95% CI (0.77, 0.86)], diagnosis OR value 21.5 [95% CI (8.51, 54.4)], and AUC 0.89. Interestingly, another group of investigators in Brazil (55) concluded opposite results in their meta-analysis: the sensitivity and specificity of CAM-ICU for delirium in ICU patients were 0.76 and 0.97, respectively, while those of ICDSC were 0.80 and 0.75, respectively. However, there was significant heterogeneity across the included studies, and most of them were designed for research purposes only rather than clinical practice. The lower sensitivity of CAM-ICU also limited its potentially wide application.

In a multi-center of daily intermittent sedation in mechanically ventilated patients, Mehta *et al.* (56) noted that, compared with simple sedation protocols, daily intermittent sedation did not shorten the weaning time, length of ICU stay and total hospital days. In addition, it increased daily midazolam and fentanyl dosage, required higher bolus dosage and increased nursing workload. This research added a new controversy to the contemporary sedation practice for critically ill patients.

New findings have been revealed on the efficacy of dexmedetomidine versus midazolam or propofol in sedation of patients on long-term mechanical ventilation in the realm this year. It was noted in an international multi-center study (57) that although dexmedetomidine did not have considerable benefits in terms of maintaining mild-to-moderate sedation levels, it significantly shortened the duration of mechanical ventilation, and improved the patient's expression of pain because of its pharmaceutical feature of "awareness sedation." On the other hand, it was associated with a significantly increased incidence of drug-induced hypotension and bradycardia.

Chinese investigators (58) compared the sedative effects of midazolam and dexmedetomidine for patients with acute cardiogenic pulmonary edema and hypoxemia following failure of non-invasive ventilation (NIV). Based on their results, dexmedetomidine reduced the duration of mechanical ventilation, length of ICU stay and the incidence of hospital-acquired infections by providing an ideal "awareness sedation" level.

New treatment approaches

In a German multi-center study of intra-aortic balloon pump (IABP) in the treatment myocardial infarction with cardiogenic shock (59), IABP did not show significant benefits, as the primary endpoint (30-d mortality) was not noticeably reduced, and no significant difference was observed in other secondary indicators such as hemodynamical stability, length of ICU stay, serum lactate levels, catecholamine dosage and duration, and incidence of renal dysfunction, major bleeding complications, peripheral ischemic events, systemic infection and stroke. In other words, IABP produced no additional benefits when compared with conventional treatment.

Another vitro support equipment, extracorporeal membrane oxygenation (ECMO), which has attracted much attention, is showing a good prospect. According to the study by Fuehner *et al.* (60), ECMO could be used as a transitional treatment option for conscious, non-intubated patients with cardiopulmonary failure who are waiting for lung transplantation. ECMO significantly reduced the post-transplant duration of mechanical ventilation and prolonged post-transplant survival, as compared with intubated patients.

In a large-scale multi-center study (61), French investigators found that, for septic shock patients with fever during the prescription of vasoactive drugs and mechanical ventilation, exogenous measures to maintain their temperature as low as 36.5 to 37.0 ℃ for 48 h would contribute to significant reduction in vasopressor dose and improvement in their condition compared with those not subject to temperature control. More importantly, significantly reduced 14-d mortality was observed when compared with the control group. Regarding therapeutic hypothermia, a

meta-analysis (62) advised that it did not prevent the occurrence of acute AKI or reduce the use of hemofiltration, though regression analysis suggested that it could reduce the mortality.

ICU management

A meta-analysis of intensive care telemedicine by Canadian investigator Wilcox and colleagues (63) showed that remote electronic medicine significantly reduced the length of ICU and hospital stay, and in turn the mortality, compared with traditional standard treatment. However, the effect may be overestimated due to the non-randomized design of some included studies. Obscurity in terms of the specific settings and organizational administration also entails further investigation.

In addition, the joint recommendations for implementation of scientific research and collaboration in critical care medicine (64), as well as recommendations for sepsis treatment in low-resource settings (65), have been issued by many international societies of critical care medicine, which are valuable references.

Other potential treatments

In 2012, the 9th edition of the Antithrombotic Therapy and Prevention of Thrombosis by the Association of American College of Chest Physicians (ACCP) was released, together with the new transfusion guidelines of the American Association of Blood Banks, as well as the management of bleeding following major trauma in Europe. Other potentially valuable options or areas in this regard include: immunoglobulin, statins, levosimendan, labetalol, antioxidants, hypertonic saline, timing of continuous RRT, novel inflammatory factors, and prognostic factor analysis. Owing to space limitations and access, these tools are not detailed in this article.

Conclusions

Compared with the findings last year, we can see that more evidence is emerging for clinical diagnosis and treatment based on systematic reviews or meta-analyses in critical care medicine in 2012. Nonetheless, there are few milestone discoveries derived from a large sample. Meanwhile, a number of inconsistencies and controversies are inherent in regard to blood sugar control, hormone therapy, choices of crystals and colloids, and other aspects. That said, some bright spots are observed in hypothermia treatment, ECMO, thromboprophylaxis, sedation and related fields, which have brought new hope for critical care medicine.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Huang W, Wan X. Overview of progresses in critical care medicine 2012. J Thorac Dis 2013;5(2):184-192. doi: 10.3978/j.issn.2072-1439.2013.02.03