REVIEW ARTICLE

Critical care medicine 2013: a review and prospect

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The main achievements of clinical researches in the field of critical care medicine have been briefly summarized throughout 2013 in this review, with the purpose of identifying encouraging trend and advocating clinical practices.

Update of international guidelines for management of severe sepsis and septic shock

2012 international guidelines for management of severe sepsis and septic shock were published in the early of 2013 (1). The crucial information was still to advocate the achievement of early restoration of tissue perfusion and elimination of all likely pathogens through bundlelized strategies including Early Goal-Directed Therapy (EGDT). As one of the major revisions, prior 6 h restoration bundle was divided into 3 h Bundle (lactate level, infectious origin, wide-spectrum antimicrobial agents and crystalloids for fluid resuscitation) and 6 h Bundle [vasoactive agents, central venous pressure (CVP), central venous oxygen saturation ($ScvO_2$), retest of blood lactate] and the original 24 h Bundle was removed. Other major revisions have been made on use of antimicrobial agents, fluid resuscitation, acute respiratory distress syndrome (ARDS) and enteral nutrition therapy according to the latest evidences. However, the recommendation levels of many critical interventions have not been substantially updated, and new therapeutic fields and interventions were not involved, such as intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), use of statins and electronic medical cares. Nonetheless, the effectiveness of the guideline will be validated in clinical practice and continuous updates were expected, with its universal implementation and emergence of more evidences.

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Crisis of hydroxyethyl starch and fluid resuscitation

Hydroxyethyl starch (HES) was still a highlighted topic in 2013. Four meta-analyses (2-5) comparing the outcome of critically ill patients receiving HES administration were sequentially published in major medical journals in April 2013. The first article (2) published in BMJ described hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin increased the use of renal replacement therapy and transfusion with red blood cells, and resulted in more serious adverse events in patients with sepsis. Another meta-analysis (3) published in *JAMA* reported use of HES compared with other resuscitation solutions was not associated with a decrease in mortality. The conclusion was compromised seriously due to fraud evidences from German researcher whose investigations have been retracted lately. However, after exclusion of these trials, significant increases of mortality and renal injury were observed. The conclusion of 2013 Cochrane update (4) remained unchanged on the relative effectiveness of colloids compared to crystalloid fluids, and there is no evidence that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. It was highlighted that the use of HES might increase mortality. Moreover, Gattas *et al.* (5) demonstrated in their meta-analysis that the use of HES 130/0.4 and 130/0.42 were associated with significantly increased risk of being treated with RRT. Thus, HES is very disfavored based on current evidences of efficacy, adverse effects and costs. According to the studies mentioned above, U.S.FDA announced a boxed warning on HES products on June 24, and recommended avoid use in patients with critical conditions, renal dysfunction and undergoing open heart surgery. Recently, the Pharmacovigilance Risk Assessment Committee (PRAC) of European Medicines Agency (EMA) announced again that HES should not be used in patients with sepsis, burns or severe conditions and whether to withdraw HES or not still need a final decision.

The controversy between colloids and crystalloid fluids was persistent and the situation became more complicated with the emergence of new evidences. In the latest published CRISTAL study (6), the effects of fluid resuscitation with colloids (gelatin, dextran, HES, 4% albumin or 20% albumin) *vs.* crystalloids

(isotonic or hypertonic saline or Ringer's lactate) on mortality in critically ill patients presenting with hypovolemic shock have been investigated. This multi-center randomized clinical trial enrolled 2,857 patients and the 28-day mortalities were 25.4% and 27.0% [relative risk (RR), 0.96; 95% confidence interval (CI): 0.88-1.04; P=0.26] for colloids and crystalloids respectively. This difference was not statistically significantly. For other secondary endpoints, the 90-day mortalities were 30.7% and 37.2% (RR, 0.92; 95% CI: 0.86-0.99; P=0.03) for colloids and crystalloids respectively, with significant drop of mortality for the colloids group. But there were no significant differences for intensive care unit (ICU), hospital mortality and renal replacement therapy. There were more days alive without mechanical ventilation in the colloids group *vs.* the crystalloids group by 7 days and by 28 days and alive without vasopressor therapy by 7 days and by 28 days. In subgroup analyses, no significant differences in mortality were observed between the colloids group and the crystalloids group for patient receiving fluid resuscitation as monotherapy or with sepsis. Consequently, it is reasonable the unpredicted positive effects of colloids on 90-day mortality require further study before reaching conclusions.

Hemodynamic management

In the field of hemodynamic management, the use of vasoactive medications has long being concerned. Hemandez *et al.* (7) investigated the effects of dobutamine (2.5-h infusion with fixed-dose of 5 mcg/kg/min) on systemic, regional and microcirculatory perfusion parameters in septic shock patients through a randomized, placebo-controlled, double-blind, crossover study. Despite an increasing cardiac index (CI), heart rate and left ventricular ejection fraction, dobutamine exerted no effect on sublingual perfused vessel density or microvascular flow index, as well as metabolic, hepatosplanchnic or peripheral perfusion parameters, compared to placebo. As Mentzelopoulos *et al.* described (8), compared with the control group, the combination of vasopressin (20 IU/CPR cycle) and epinephrine (1 mg/CPR circle) plus methylprednisolone (40 mg) (VSE) could result in improved cerebral function classification at discharge, higher probability for return of spontaneous circulation ≥20 min, improved hemodynamics and $ScvO_2$, and less organ dysfunction.

In recent years, the use of dynamic parameters in the hemodynamic monitoring has become a trend for patients with severe conditions, but it was applicable for mechanically ventilated patients only. Lanspa *et al.* (9) investigated whether dynamic parameters would be predictive for the hemodynamic response in patients with spontaneous breathing after fluid resuscitation. Patients with early septic shock and who were not receiving mechanical ventilation received 10 mL/kg volume expansion after initial resuscitation in the emergency department. Transthoracic echocardiography was used to measure vena cava collapsibility index and CI. Hemodynamic response was defined as an increase in CI 15% or greater. A pulse contour analysis device was used to measure stroke volume variation (SVV). The results indicated that Vena cava collapsibility index and SVV were predictive (area under the curve =0.83, 0.92, respectively). And the optimal thresholds for vena cava collapsibility index and SVV were differ from that in mechanically ventilated patients, as ≥15% and ≥17%, respectively.

In addition, Brazilian researchers reported (10) the effects of an aggressive fluid-restricted (maximum fluid intake, 800 mL/d) and sodium-restricted (maximum dietary intake, 800 mg/d) diet in with ADHF. The results suggested no significant differences in weight loss and clinical congestion score at three days. There were no significant differences between groups in the readmission rate at 30 days. Compared with the control group, treatment group demonstrated a significant increase in perceived thirst. It was concluded that sodium and water restriction in patients admitted for ADHF are unnecessary.

French researchers (11) investigated whether fluid management guided by daily BNP plasma concentrations improves weaning outcomes. In this randomized controlled multicenter study, they enrolled 304 patients. The results suggested furosemide and acetazolamide were given more often and in higher doses in the BNP-driven group than in the control group, resulting in a more negative median fluid balance during weaning [–2,320 (–4,735, 738) *vs.* –180 (–2,556, 2,832) mL; P<0.0001], and shorter time to successful extubation [58.6 (23.3, 139.8) *vs.* 42.4 (20.8, 107.5) h; P=0.034]. The BNP-driven strategy also increased the number of ventilator-free days (VFD) but did not change length of stay or mortality. The complications of electrolyte imbalance, renal failure, or shock did not show significant differences between two strategies.

Mechanical ventilation, extracorporeal membrane oxygenation (ECMO) and tracheotomy

In 2013, two multicenter studies of high frequency oscillatory ventilation (HFOV) in the treatment of ARDS should be concerned (12,13). The OSCILLATE study undertaken in five countries was terminated prematurely after 548 patients were enrolled (12). In-hospital mortality was 47% in the HFOV group, as compared with 35% in the control group (relative risk of death with HFOV, 1.33; 95% CI, 1.09 to 1.64; P=0.005). Patients in the HFOV group received more doses of midazolam and neuromuscular blockers than did patients in the control group. In addition, more patients in the HFOV group received vasoactive drugs and received them for a longer period than did patients in the control group. The OSCAR study (13) conducted in UK also demonstrated no significant inter-group difference in

the primary outcome, with 41.7% in the HFOV group and 41.1% in the conventional-ventilation group (P=0.85). Both studies suggested HFOV might be used with caution for patients with ARDS and individualized regimen should be considered based on the specific condition and ARDS characterization.

Bein *et al.* (14) investigated the effects of a low tidal volume [Vt strategy (Vt ≈3 mL/kg/predicted body weight (PBW)] with extracorporeal CO_2 elimination in established ARDS, compared with the standard strategy (≈6 mL/kg) of the control group. VFD within 60 days were not different between the study group (33.2±20) and the control group (29.2±21, P=0.469), but in more hypoxemic patients (PaO_2/FIO_2 ≤150). It has been demonstrated significant improved 60 d-VFD—in study patients (40.9±12.8) compared to control (28.2±16.4, P=0.033). The mortality rate did not differ between groups.

As shown by the French multicenter trial (15) of prone positioning during mechanical ventilation in patients with ARDS, the 28-day mortality was 16.0% in the prone group and 32.8% in the supine group (P<0.001). The hazard ratio (HR) for death with prone positioning was 0.39 (95% CI, 0.25 to 0.63). Unadjusted 90-day mortality was decreased significantly, with 23.6% in the prone group versus 41.0% in the supine group (P<0.001), and a HR of 0.44 (95% CI, 0.29 to 0.67). The incidence of complications did not differ significantly between the groups, except for the incidence of cardiac arrests, which was higher in the supine group. Comejo *et al.* (16) determined the effects of prone positioning on lung recruitment in patients with ARDS (n=24). Mechanically ventilated patients (Vt 6 mL/kg ideal body weight) underwent whole-lung computed tomography (CT) on a fixed thoracic transverse slice at PEEP 5 and 15 cm H_2O. The results suggested prone positioning further decreased nonaerated tissue and reduced tidal hyperinflation observed at PEEP 15 in supine patients, and cyclic recruitment/de-recruitment decreased only when high PEEP and prone positioning were applied together. Therefore it could be concluded, in patients with ARDS, prone positioning with relative higher PEEP may enhance lung recruitment and decrease alveolar instability and hyperinflation.

In a French study (17), the factors associated with death in ECMO-treated patients with new pandemic influenza A (H1N1) infection and the influence of ECMO on ICU mortality were investigated. The results indicated increasing values of age, lactate, and plateau pressure under ECMO were associated with death by propensity score-matched (1:1) cohort analysis, in disease severity analysis, mortality did not differ between patients receiving ECMO and non-ECMO patients. In addition, the left patients in ECMO group (n=51) who could not be matched were younger, had lower PaO_2/FiO_2 ratio and higher plateau pressure had, however, lower ICU mortality rate.

Jubran *et al.* (18) compared weaning duration with pressure support ventilation *vs.* unassisted breathing through a tracheostomy collar in patients requiring prolonged mechanical ventilation (>21 days). As the results demonstrated, the median weaning time was shorter with tracheostomy collar use than with pressure support (15 *vs.* 19 days, P=0.004). The HR for successful weaning rate was 1.43 for tracheostomy collar use (95% CI, 1.03-1.98; P=0.033) after adjusting for baseline clinical covariates. Use of the tracheostomy collar achieved faster weaning (HR, 3.33; 95% CI, 1.44-7.70; P=0.005). Mortality was equivalent in the pressure-support and tracheostomy collar groups at 6 and at 12 months. Young *et al.* (19) tested the effect of early (within four days) *vs.* late (within ten days) tracheostomy on mortality in adult patients requiring mechanical ventilation. 30-day all-cause mortality after randomization was 30.8% in the early and 31.5% in the late group (absolute risk reduction for early *vs.* late, 0.7%; 95% CI, –5.4% to 6.7%). Two-year mortality was 51.0% in the early and 53.7% in the late group (P=0.74). No significant inter-group differences were observed for median critical care unit length of stay and tracheostomy-related complications.

In addition, Alhazzani *et al.* (20) conducted a meta-analysis on neuromuscular blocking agents in ARDS. As the results suggested, short-term infusion of cisatracurium besylate was associated with lower hospital mortality (RR, 0.72; 95% CI, 0.58 to 0.91; P=0.005; I^2=0) and lower risk of barotrauma (RR, 0.43; 95% CI, 0.20 to 0.90; P=0.02; I^2=0), but neuromuscular blockade did not exert positive effect on the duration of mechanical ventilation among survivors or the risk of ICU-acquired weakness.

Difficult intubation in the ICU is always associated with severe life-threatening complications. De Jong *et al.* (21) developed a simplified score (MACOCHA Score) for identifying patients with difficult intubation in the ICU. In this validation cohort of 400 consecutive intubation procedures, the score's AUC was 0.86 (95% CI, 0.76-0.96), with a sensitivity of 73%, a specificity of 89%, a negative predictive value of 98%, and a positive predictive value of 36%. This approach could help to discriminate difficult and non-difficult intubation in the ICU.

Nutrition support therapy

In the field of immunonutrition, Canadian researchers (22) randomly assigned 1,223 critically ill adults in Canada, the United States, and Europe who had multi-organ failure and were receiving mechanical ventilation to receive supplements of glutamine, antioxidants, both, or placebo, in a blinded 2-by-2 factorial trial. As the results demonstrated, There was a trend toward increased mortality at 28 days among patients who received glutamine as compared with those who did not receive glutamine [32.4% *vs.* 27.2%; adjusted odds ratio (OR), 1.28; 95% CI, 1.00 to 1.64; P=0.05]. In-hospital mortality and mortality at six months were significantly higher among those who received glutamine than among those who did not.

Glutamine had no effect on rates of organ failure or infectious complications. Antioxidants had no effect on 28-day mortality or any other secondary end point. No significant interaction between Glutamine versus Antioxidants was observed (P=0.49). Glutamine and Antioxidants had no significant effects on the mortality at 28 days. It was proposed that early provision of glutamine did not improve clinical outcomes of patients with multi-organ failure.

Alhazzani *et al.* (23) conducted a meta-analysis and demonstrated that selenium supplementation in comparison to placebo was associated with lower mortality (OR, 0.73; 95% CI, 0.54, 0.98; P=0.03; I^2=0%). However, among patients receiving and not receiving selenium, there was no difference in ICU length of stay or nosocomial pneumonia. Taiwan researchers (24) also suggested parenteral selenium treatment significantly reduced all-cause mortality in critically ill patients with sepsis (RR 0.83, 95% CI, 0.70-0.99, P=0.04, I^2=0%) in a meta-analysis. Subgroup analyses demonstrated that the administration schedule employing longer duration (RR 0.77, 95% CI, 0.63-0.94, P=0.01, I^2=0%), loading boluses (RR 0.73, 95% CI, 0.58-0.94, P=0.01, I^2=0%) or high-dose selenium treatment (RR 0.77, 95% CI, 0.61-0.99, P=0.04, I^2=0%) might be associated with a lower mortality risk. There was no evidence of adverse events. Palmer *et al.* (25) investigated the efficacy of ω-3 fatty acid supplemented parenteral nutrition in critically ill adult patients in a meta-analysis. Due to poor qualities of the included studies, no differences were found with a risk ratio for death of 0.83 (95% CI, 0.57-1.20; P=0.32). No significant differences were observed in infectious complications and hospital length of stay.

A prospective longitudinal follow-up study (26) evaluating early interventions of low energy permissive underfeeding versus full energy enteral feeding in ALI patients demonstrated patients had substantial physical, psychological, and cognitive impairments, reduced quality of life following acute lung injury, however, initial low energy permissive underfeeding versus full energy enteral feeding did not affect mean SF-36 physical function, survival, or multiple secondary outcomes at 6- and 12-month in survivors.

Casaer *et al.* (27) conducted a secondary analysis on EPaNIC trial (n=4,640) and disclosed none of the subgroups defined by type or severity of illness could benefit from early PN intervention. The analysis also showed the lowest dose of macronutrients was associated with the fastest recovery, and any higher dose, administered parenterally or enterally, was associated with progressively more delayed recovery. And the amount of proteins/amino acids may have more significant effect on delayed recovery with early feeding than that of protein.

In their meta-analysis, Deane *et al.* (28) compared the effects of small bowel and intragastric delivery of enteral nutrients in adult critically ill patients. Small bowel feeding was associated with a reduced risk of ICU-acquired pneumonia (RR 0.75, 95% CI: 0.60-0.93, P=0.01, I^2=11%). Duration of ventilation, length of ICU stay and mortality were unaffected by the route of feeding. There was significantly improved nutrient intake via the small intestinal route. However, there was substantial statistical heterogeneity in studies included.

Immunomodulatory management

In the China multicenter ETASS study (29), thymosin alpha 1 (Tα1) administration was associated with reduced mortalities of patients with severe sepsis from any cause within 28 days (26.0% *vs.* 35.0%, RR 0.74; 95% CI: 0.54-1.02, P=0.049). Greater improvement of monocyte human leukocyte antigen-DR (mHLA-DR) was observed in the Tα1 group on day 3 and 7. No serious drug-related adverse event was recorded.

In a phase II clinical trial (30), the efficacy of talactoferrin (1.5 g, tid, up to 28 days), a recombinant form of human lactoferrin, in the treatment of severe sepsis has been investigated. The difference of all-cause mortality at 28 days between talactoferrin group and placebo group was marginal (14.4% *vs.* 26.9%, two-sided P=0.052), representing a 12.5% absolute and a 46.5% relative reduction in mortality. Reduction in all-cause mortality was sustained at 6 months (P=0.039). Moreover, these reductions in mortality were observed across a wide spectrum of subgroups. The adverse effects of drug were similar to that of placebo. Promisingly, immunomodulatory therapy with talactoferrin will be concerned in focus in the near future.

However, no beneficial outcome was demonstrated for eritoran, an antagonist of MD2-TLR4, against severe sepsis (31). Eritoran is a synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor. There was no significant difference in the primary end point of 28-day and 1-year all-cause mortalities between the eritoran group and the placebo group. No significant differences were observed in any of the pre-specified subgroups.

Japanese researchers (32) evaluated the efficacy of recombinant human thrombomodulin (rhTM) in sepsis-induced DIC. After adjusting for illness imbalances, treatment with rhTM was significantly associated with reduced in-hospital mortality (adjusted HR, 0.45; 95 % CI, 0.26-0.77; P=0.013). An association between rhTM treatment and higher numbers of ICU-free days, VFD, and vasopressor-free days were observed. DIC scores were significantly decreased in the rhTM group compared with the control group in the early period after rhTM treatment, whereas the incidence of bleeding-related adverse events did not differ between the two groups. Meanwhile, in another completed phase-II global multicenter study (33) to evaluate rhTM (ART-123), the mortality was 17.8% in the ART-123 group and 21.6% in the placebo group (P=0.273). There were no statistically significant differences in other endpoints. In post hoc analyses, greatest benefit from ART-123

was seen in patients with at least one organ system dysfunction and an international normalized ratio greater than 1.4 at baseline.

Infection management

Huang *et al.* (34) demonstrated universal decolonization (Daily mupirocin nasal medication + daily chlorhexidine bathing) resulted in a significantly greater reduction in the rate of in-hospital MRSA isolates in ICU and all bloodstream infections than either targeted decolonization (i.e., screening, isolation, and decolonization of MRSA carriers) or screening and isolation in a large clinical trial conducted in 43 U.S. hospitals. Similarly, in another large multicenter trial (35), the overall rate of MDRO (multidrug-resistant organisms) acquisition was 5.10 cases per 1,000 patient-days with chlorhexidine bathing versus 6.60 cases per 1,000 patient-days with nonantimicrobial washcloths (P=0.03), the equivalent of a 23% lower rate with chlorhexidine bathing. The overall rate of hospital-acquired bloodstream infections was 4.78 cases per 1,000 patient-days with chlorhexidine bathing versus 6.60 cases per 1,000 patient-days with nonantimicrobial wash cloths (P=0.007). These results suggested in-hospital infection control strategy based on chlorhexidine was associated with significant effectiveness and its use in such indication is recommended.

However, in another large multicenter trial (36), although universal glove and gown use were associated with decreased health care worker room entry and increased room-exit hand hygiene compliance, the investigators did not find the difference in the primary outcome of acquisition of MRSA or VRE compared with usual care among patients in medical and surgical ICUs.

Daneman *et al.* (37) assessed the effects of SDD (selective digestive decontamination) and SOD (selective oropharyngeal decontamination) on antimicrobial resistance rates in patients admitted in ICUs in a meta-analysis. When comparing data for patients in intervention groups (those who received SDD or SOD) versus data for those in control groups (who received no intervention), they did not identify difference in the prevalence of colonisation or infection with Gram-positive antimicrobial-resistant pathogens, including meticillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. Among Gram-negative bacilli, no difference in aminoglycoside-resistance or fluoroquinolone-resistance was detected. But they did detect a reduction in polymyxin-resistant Gram-negative bacilli and third-generation cephalosporin-resistant Gram-negative bacilli in recipients of selective decontamination. It was proposed to include a further study to assess the effects of selective decontamination on the long-term development of resistance rates.

In a large multicenter French study, researchers compared the vascular catheters in chlorhexidine dressings, highly adhesive dressings, and standard dressings (38). It was demonstrated that chlorhexidine-gel-impregnated dressings decreased the CRI (catheter-related infections) rate in ICU patients with intravascular catheters. Highly adhesive dressings decreased dressing detachment but increased skin and catheter colonization without influencing CRI or CR-BSI (catheter-related bloodstream infection) rates.

Infection of Clostridium difficile

Infection of Clostridium difficile remains to be a big topic in 2013. van Nood *et al.* (39) demonstrated the administration of a solution of donor feces through a nasoduodenal tube had a success rate of 81% in the treatment of recurrent clostridium difficile infection, which was significantly higher than those receiving vancomycin alone (31%) or vancomycin with bowel lavage (21%). After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, and a decrease in proteobacteria species.

Johnston *et al.* (40) considered twenty trials including 3,818 participants in a systematic review and meta-analysis on the efficacy of probiotics in the treatment of Clostridium difficile-associated diarrhea (CDAD). Probiotics reduced the incidence of CDAD by 66% (HR: 0.34; 95% CI: 0.24-0.49; I^2=0%). No inter-group difference in adverse events was observed. On the contrary, another British multicenter study (41) showed the treatment of preparation of lactobacilli and bifidobacteria was not associated with reduced incidence of antibiotic-associated diarrhea (AAD) (treatment group 10.8% *vs.* placebo group 10.4%) and no inter-group difference was observed in the incidence of C difficile diarrhea (CDD) (0.8% *vs.* 1.2%, P=0.35). This study suggested preparation of lactobacilli and bifidobacteria could not effectively prevent ADD and CDD episodes.

Renal replacement therapy and hemofiltration

In a French multicenter study (42), the efficacies of high-volume hemofiltration (HVHF) at 70 mL/kg/h and standard-volume hemofiltration (SVHF) at 35 mL/kg/h were compared in critically ill patients with septic shock and AKI (acute kidney injury). The trial was stopped prematurely due to slow patient accrual and resources no longer being available. Mortality was not different between groups (HVHF 37.9 % *vs.* SVHF 40.8 %, log-rank test P=0.94). There were also no significant differences in any of the secondary endpoints between treatment groups.

Zhou *et al.* (43) determined the association between various blood purification techniques and all-cause mortality in humans with sepsis in a meta-analysis. Blood purification decreased mortality compared with no blood purification (35.7% *vs.* 50.1%; risk ratio, 0.69; 95% CI, 0.56-0.84; P<0.001). However, it should be caution that these results were driven mainly by the trials

of hemoperfusion and plasma exchange. After excluding trials using polymyxin B hemoperfusion, pooling of all trials of blood purification for treatment of sepsis was no longer associated with lower mortality.

Brain injury

Chesnut *et al.* (44) randomly assigned 324 patients with severe traumatic brain injury into one of following group: treatment protocol driven by intracranial pressure (ICP)-monitoring group or by imaging-clinical examination group. A targe ICP ≤20 mmHg was specified for the pressure-monitoring group. Investigators did not find significant difference in the primary outcome, a composite measure based on percentile performance across 21 measures of functional and cognitive status (score, 56 in the pressure-monitoring group *vs.* 53 in the imaging-clinical examination group; P=0.49). The other second outcomes, such as Six-month mortality, and median length of stay in the ICU were similar in the two groups. There was also no difference in the distribution of serious adverse events between two groups. Thus, aggressive ICP-decreasing treatment based on ICP monitoring did not demonstrate superiority over those based on imaging and clinical examination.

INTERACT2 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial) study (45) was the largest study in the therapeutic field of acute intra-cerebral hemorrhage (ICH), enrolled 2,839 patients. This study showed aggressive blood-pressure lowering treatment (with a target systolic level of <140 mmHg within one hour), as compared with those receiving guideline-recommended treatment (with a target systolic level of <180 mmHg), had no effect on mortality or major disability in patients with ICH, but it could improve the functional outcomes (OR for greater disability, 0.87; 95% CI, 0.77 to 1.00; P=0.04). Based on the results of INTERACT2, the well-established concept of "antihypertensive therapies might be hazardous to patients with cerebral hemorrhage" might be changed, which will have an important impact on stroke treatment in the near future.

Antipyretic and hypothermia therapies

A French Research Group (46) tested the hypothesis that induced hypothermia improves outcome in patients with severe bacterial meningitis. Patients [Glasgow Coma Scale (GCS) score of ≤8 for <12 hours] with community-acquired bacterial meningitis were enrolled. Hypothermia group received a loading dose of 4 ℃ cold saline and were cooled to 32 to 34 ℃ for 48 hours. In a median analysis, The data and safety monitoring board (DSMB) observed excess mortality in the hypothermia group [25 of 49 patients (51%)] *vs.* the control group [15 of 49 patients (31%)] with statistically significant difference (RR, 1.99; 95% CI: 1.05-3.77, P=0.04). After adjustment for age, score on GCS at inclusion, and the presence of septic shock at inclusion, mortality remained higher (HR, 1.76; 95% CI, 0.89-3.45; P=0.10). The trial was stopped early at the request of the DSMB.

Niven *et al.* (47) studied the efficacy of treating critically ill adults with different fever control strategies. A total of 26 subjects were randomized to the aggressive (n=14, ≥38.3 ℃) or permissive (n=12, ≥40.0 ℃) arm. The aggressive group received a greater dose of acetaminophen (P=0.0001), and more frequently received physical cooling than patients in the permissive group (P=0.01). The mean daily temperature was lower in the aggressive group (37.8 *vs.* 38.0 ℃, P=0.02). There was no difference in the 28-day mortality or in any safety outcome between the treatment groups. Interestingly, same authors determined the effect of antipyretic therapy on critically ill adults in a meta-analysis (48). Five randomized clinical trials in 399 patients were included. The temperature threshold for treatment in the intervention group was commonly 38.3 to 38.5 ℃, whereas it was typically 40.0 ℃ for controls. Fever control did not significantly influence ICU mortality with a pooled risk ratio of 0.98 (95% CI, 0.58-1.63, P=0.90).

H7N9 versus Middle East Respiratory Syndrome (MERS)

At the end of March, 2013, a novel avian influenza A H7N9 virus that infects human beings was identified in Shanghai and Anhui Province in China (49). Although there were no case reports of person-to-person transmission available for H7N9, the clinical presentation and outcome of patients with severe illness were very similar to those of SARS and H1N1, which was concerned seriously. In addition, the spread of human MERS emerging in the Arab region has also become a highlighted topic (50). Although presently there was no evidence supporting pandemic MERS, whether these lethal virus infections will evolve into a threat to global public health should be closely monitored.

Statins

As showed by the Australian multicenter, randomized, double-blind, placebo-controlled trial (51), there was no difference in IL-6 concentrations between the severe sepsis patients assigned to atorvastatin (20 mg daily) or placebo group (P=0.76). There was also no difference in length of stay, change in Sequential Organ Failure Assessment (SOFA) scores or mortality at ICU discharge, hospital discharge, 28- or 90-day, or adverse effects between the two groups, Although cholesterol was lower in patients treated with statins. However, in the predefined group of prior statin users, those randomized to placebo had a greater mortality compared with those who received statins (28% *vs.* 5%; P=0.01). In another multicenter trial (52) performed in 26 ICUs in France, the effect of simvastatin (60 mg, daily)

therapy on prognosis of patients with ventilator-associated pneumonia (VAP) was investigated. Median analysis demonstrated that day 28 mortality was not significant decreased in the simvastatin group than in the placebo group (21.2% *vs.* 15.2%, HR 1.45, 95% CI, 0.83-2.51, P=0.10). There were also no significant differences regarding day-14, ICU, or hospital mortality rates; duration of mechanical ventilation; as well as changes in SOFA score. The study was stopped prematurely after enrollment of 300 patients and the findings do not support the use of statins with the goal of improving VAP outcomes.

Other studies

The "Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit" was revised and published (53). These guidelines used objective assessment tools to evaluate and screen pain, agitation/sedation, and delirium, and recommended the use of opioids, non-opioids, epidural anesthesia against pains of different causes. The guideline suggested dexmedetomidine may be preferred in the management of sedation and delirium. However, another study (54) suggested the prophylactic treatment with low dose (1 mg/8 h) haloperidol in critically ill patients with a high risk for delirium might be associated with lower delirium incidence other than more delirium-free-days.

Spanish researchers determined the hemoglobin threshold for transfusion of red cells in patients with acute gastrointestinal bleeding (55). A total of 921 patients with severe acute upper gastrointestinal bleeding were enrolled and randomly assigned to a restrictive strategy (transfusion when the hemoglobin level fell below 7 g per deciliter) or a liberal strategy (transfusion when the hemoglobin fell below 9 g per deciliter). There was difference in the number of patients who did not receive transfusions between the restrictive strategy (51%) and the liberal strategy (14%), (P<0.001). The probability of survival at six weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95% *vs.* 91%; HR 0.55; 95% CI: 0.33-0.92; P=0.02). Further bleeding rate, adverse events as well as portal-pressure gradient within the first five days in the restrictive-strategy group were promisingly better than that in liberal-strategy group. Meanwhile, the probability of survival was higher with the restrictive strategy than with the liberal strategy in the subgroup of patients who had bleeding associated with a peptic ulcer, cirrhosis and Child-Pugh class A or B disease, but not in those with cirrhosis and Child-Pugh class C disease. Therefore, the restrictive strategy is worthy of recommendation for the treatment of acute upper gastrointestinal bleeding patients.

Chlan *et al.* (56) reported self-initiated patient-directed music (PDM) could reduce anxiety and sedative exposure (intensity and frequency) during ventilatory support in critically ill patients, compared with usual care or noise-canceling headphones.

Intermittent pneumatic compression (IPC) or/and graduated compression stockings (GCS) are often recommended for high risk critically ill patients contraindicated to anticoagulant treatments. As a French multicenter study (57) showed, the incidence of venous thromboembolism was 5.6% in the IPC + GCS group and 9.2% in the GCS group (P=0.19), which was not statistically significantly. Tolerance of IPC was poor and no intergroup difference in mortality rate was observed. These results did not support the superiority of the combination of IPC + GCS to VTE prevention in ICU patients.

Conclusions

In comparison to the 2012 report (58), clarifying of old enigmas and seeking new breakthroughs were the main lines of 2013 global intensive medical community. However, no expected positive clinical outcomes were achieved for those important interventions, such as of high frequency ventilation, fluid resuscitation immunonutritional therapy and so on. There are few milestone discoveries derived from Tα1, fecal transplantation and bedside infection control. Furthermore, it was quiet confusing that, for many specific therapies, significant efficacy were very often demonstrated by a series of meta-analyses, but following large clinical trials only achieved negative outcomes. This paradoxical situation has almost become a universal phenomenon for intensivists. Prospectively, the release of a couple of large studies on EGDT or fluid resuscitation is the most anticipated event (59). Breakthrough conclusions are expected to emerge, which will give new impetus, as well as new hopes, for the progress of Critical Care Medicine.

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