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Cardiovascular

Cardiac failure: epidemiology and treatment

Mebazaa and colleagues in two interesting papers [1, 2] described the clinical presentation, management, and outcomes of acute heart failure (AHF) through the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) on AHF conducted in nine countries in four continents. In the first paper [1] data from 4,953 patients with AHF were collected via questionnaire from 666 hospitals. Clinical presentation included...
decompensated congestive HF (38.6%), pulmonary edema (36.7%), and cardiogenic shock (11.7%). Patients with a de novo episode of AHF (36.2%) were younger, had less comorbidities and lower blood pressure despite greater left ventricular ejection fraction (LVEF), and were more often admitted to ICU. Overall, intravenous (IV) diuretics were given in 89.7%, vasodilators in 41.1%, and inotropic agents (dobutamine, dopamine, adrenaline, noradrenaline, and levosimendan) in 39% of cases. Hospital death rate was 12%, the majority due to cardiogenic shock (43%). More patients with de novo AHF (14.2%) than patients with a pre-existing episode of AHF (10.8%) (p = 0.0007) died. There was graded mortality in intensive care unit (ICU), critical care unit (CCU), and ward patients with mortality in ICU patients being the highest (17.8%) (p < 0.0001). The conclusion stressed the concept that the recognition of subgroups might improve management and outcome by defining specific therapeutic requirements.

The second study [2] identified the risks and benefits of IV drugs in patients hospitalized with acute decompensated heart failure. In this post hoc analysis of ALARM-HF data, the authors used the propensity scoring to identify groups of patients who differ by treatment but had the same multivariate distribution of covariates, allowing the estimations of the effect of specific treatments on the outcome of in-hospital mortality. Unadjusted analysis showed a lower in-hospital mortality rate in AHF patients receiving “diuretics + vasodilators” (n = 1,805) compared with those receiving “diuretics alone” (n = 2,362) (7.6 vs. 14.2%, p < 0.0001). Propensity-based matching (n = 1,007 matched pairs) confirmed the lower mortality of AHF patients receiving diuretics + vasodilators: 7.8 versus 11.0% (p = 0.016). The authors concluded that in terms of in-hospital survival, a vasodilator in combination with a diuretic fared better than treatment with only a diuretic. Catecholamine and inotropes should be used cautiously as it has been seen that they actually increase the risk of in-hospital mortality.

Extracorporeal circulation may assist a failing ventricle: two papers have proposed clever solutions to specific technical problems. Trimlett and co-workers [3] studied a new technique of insertion of double-lumen bicaval cannulas for venovenous extracorporeal membrane oxygenation (ECMO). The rationale is that vascular damage or cardiac perforation may occur during cannulation, but with the new technique this complication seems to have been reduced.

In the study by Endemann and co-workers [4] a different approach was used for coronary artery catheterization in patients during ECMO. The rationale was that an additional puncture of the femoral artery for the angiography carries a risk of complications, whereas their new technique avoided the need for further punctures. Instead they used the arterial lines that were already inserted. They introduced a Y-connector in the arterial cannula of the ECMO setup. At its free end a hemostatic valve was placed, over which the coronary catheters were inserted. This enabled the angiography to be performed and no complications were noted in the limited number of patients they had so far studied.

Cardiogenic shock leads to an inadequate tissue perfusion including a physiological reduction in the splanchic territory. The use of enteral nutrition is associated with an increase in mesenteric arterial output, and thus could be deleterious. On the other hand, mesenteric arterial output may decrease during parenteral nutrition administration, thus having a protective effect. Thibault and colleagues [5] reviewed a number of issues related to the safety of nutrition in patients with cardiogenic shock. The combination of enteral nutrition with supplemental parenteral nutrition during the first days following ICU admission has been proposed to prevent negative energy balance, and such a nutritional strategy could also be beneficial for the mesenteric circulation and may improve the clinical outcome of these patients. This hypothesis needs to be confirmed in future well-designed and conducted studies.

Blochlinger and co-authors [6] reviewed the present knowledge on left ventricular rotation. Such rotation or twisting may be an important mechanism of improving cardiac pumping at reduced oxygen demand. They point to a number of factors that can prevent or impede the systolic twisting and its subsequent release during diastole, factors that will impede the cardiac function. Better understanding of cardiac twisting may guide in preserving or enhancing it in order to improve cardiac pumping.

Impact of type of fluid administration

Fluid administration is a key component of hemodynamic resuscitation. As excessive fluid administration may be deleterious, identification of fluid-responsive patients is desired. Several tests have been developed, mostly based on the variability of stroke volume. Pulse pressure variations are frequently used as a surrogate of stroke volume variations [7], but vascular compliance may distort arterial waveform. Indeed, arterial pressure should ideally be recorded centrally but is for practical reasons recorded in more distal arteries. However, arterial compliance and waveform reflection affect arterial waveform and may thus also affect pulse pressure (and hence pulse pressure variations). Dufour et al. [8] elegantly used an applanation tonometry technique to reconstruct the aortic root waveform and compared central and peripheral pulse pressure variations in 56 patients. This system includes a high-fidelity micromanometer that is applied to the surface of the skin overlying the radial artery, the peripheral arterial waveform is recorded, and central arterial pressure is reconstructed after comparison with brachial artery
pressure (measured noninvasively). Peripheral pulse pressure was higher than central pulse pressure (55 ± 15 vs. 33 ± 14 mmHg), but peripheral and central pulse pressure variations similarly predicted fluid responsiveness.

In addition, there is still an intense debate on the ideal type of fluid that should be used for fluid resuscitation. In the large SAFE trial [9], which randomized 6,997 critically ill patients to receive either 4% albumin or normal saline as resuscitation fluid, there was no difference in outcome in the whole population. In a planned subgroup analysis, the authors focused on the 1,218 patients with severe sepsis at baseline [10]. There were no differences in baseline characteristics, except for mean arterial pressure that was slightly higher in the saline group compared with the albumin group (75 vs. 73, p = 0.03). Mortality at 28 days tended to be lower in the albumin than in the saline group [30.7 vs. 35.3%, odds ratio (OR) 0.87 (0.74–1.02)]. After adjustment for baseline covariates, albumin administration was associated with a significant decrease in the risk of death 0.71 (0.52–0.97). These promising results should be confirmed by a randomized trial in patients with sepsis.

Artificial colloids, and especially hydroxyethyl starch (HES), may be an alternative to albumin. However, HES may be associated with impairment in renal function [11]. However concerns were raised about the use of the old generation of HES in these studies, often in large amounts. Several large-scale randomized trials are currently ongoing in this domain (Clinicaltrials.gov. NCT00962156/NCT00935168). Myburgh et al. [12] published the protocol and analysis plan of the Crystalloid versus Hydroxyethyl Starch Trial (CHEST). CHEST (NCT00935168) aimed to randomize 7,000 critically ill patients to receive either 6% HES (130/0.4) or sodium chloride (0.9%) as sole resuscitation fluid in order to demonstrate an absolute difference of 3.5% in mortality at 90 days. Secondary outcomes include various indices of organ dysfunction and especially renal injury. Inclusion criteria are based on clinical signs (tachycardia, hypotension, oliguria, capillary refill time greater than 1 s) or central venous pressure below 10 mmHg. One may criticize that many of these signs are not specific of hypovolemia. Subgroup analyses will be conducted in four predefined subgroups (trauma, traumatic brain injury, sepsis, and pre-existing renal dysfunction).

A systematic review addressed the influence of HES on hemostasis [13]. HES can reduce von Willebrand factor and interfere with fibrinogen polymerization and platelet function. Newer HES 130/0.4 is said to be safer, but a number of studies dealing with this product have been retracted. Thus, the authors performed a systematic review of studies assessing the effects of HES 130/0.4 on hemostasis by thrombelastography (TEG, ROTEM) or Sonoclot (SCR) in comparison with crystalloid or albumin control fluids. Seventeen in vitro and seven in vivo hemodilution studies were analyzed. Nineteen studies showed a hypocoagulatory effect of HES 130/0.4 on clot formation. Dose effects were apparent in the in vitro studies, which investigated higher dilutions up to 80%. In vivo studies were fewer and did not investigate doses over 40 mL/kg. It was concluded that HES 130/0.4 administration is associated with hypocoagulation and that safer fluids, such as crystalloids, should be chosen for patients at increased risk of bleeding.

Effects of vasoactive agents

The impact of hydrocortisone on vascular hyporeactivity to adrenergic agents has long been recognized [14], but the impact of hydrocortisone on vasopressin hyporesponsiveness is less well defined. In a retrospective cohort of 155 patients with septic shock receiving vasopressin, Torgersen et al. [15] evaluated the impact of combined treatment with hydrocortisone. Hydrocortisone was administered to almost half of the patients (47.8%). Concomitant use of AVP and hydrocortisone was associated with a trend towards lower 28-day mortality [hazard ratio (HR) 0.69, CI 95% 0.43–1.08, p = 0.11]. As patients treated without and with hydrocortisone may not have the same severity, the authors used a propensity score to compare the two groups. This propensity score-based analysis, which included 80 patients only, yielded the same results (28-day mortality OR 0.59, CI 95% 0.27–1.29, p = 0.18). These results are in line with those of a subgroup analysis of the VASST trial [16], which also suggested some potential benefit for the combination of hydrocortisone and vasopressin. This should be tested in future trials.

The microcirculatory effects of terlipressin, another vasopressin derivate, are not well defined and were investigated this year [17]. The sublingual microcirculation was investigated in 20 patients with septic shock just before and 6 h after the administration of a 0.5-mg bolus of terlipressin. Norepinephrine requirements decreased from 0.74 ± 0.73 to 0.42 ± 0.67 µg/(kg min) (p < 0.05), while mean arterial was kept constant (around 70 mmHg). The total number of vessels was not affected but perfusion of microvessels improved. Microcirculatory flow index of small vessels increased at the end of the 6-h study period (from 2.0 ± 0.5 to 2.6 ± 0.6 units, p < 0.05), while heterogeneity index decreased. Given the lack of control group and the time elapsed between measurements, these results need to be confirmed.

Evaluation of microcirculation

Several studies focused on microcirculation. Ait-Oufella et al. [18] investigated whether mottling, a clinical sign indicating impaired tissue perfusion, may be associated with outcome in patients with septic shock. The authors
included 60 consecutive patients and measured hemodynamic variables. They also evaluated mottling around knees, on admission and after 6 h. Mottling was scored from 0 to 5, based on mottling area extension from the knees to the periphery. Mottling score was not related to arterial pressure or cardiac index. High mottling scores were associated with elevated lactate levels, low urine output, and high organ dysfunction scores. In addition, a high mottling score on admission was associated with poor outcome. More importantly, patients experiencing a decrease in mottling score in response to resuscitation had a better prognosis than those with stable or worsening of the score (14-day mortality 12 vs. 77%, p = 0.0005). Unfortunately, it is difficult to determine whether mottling reflects regional or microcirculatory perfusion.

Another trial [19] investigated tissue oxygen saturation (StO2) determined by near-infrared spectroscopy as an index of tissue perfusion. StO2 was measured in two different locations (thenar and forearm) at two different depths (1.5 and 2.5 mm) during simulated hypovolemia. Lower body negative pressure was applied in five steps up to −100 mmHg in 24 healthy volunteers. Hyovolemia induced a progressive decrease in stroke volume down to 45% of baseline. StO2 decreased in the forearm (85% from baseline) and also, but more modestly (95% from baseline), in the thenar area. The decrease in StO2 was similar at both depths, both in thenar and forearm areas. This study shows that the position but not the depth of the probe is relevant for the assessment of tissue perfusion during hypovolemia. Of note, StO2 was less sensitive than stroke volume to detect hypovolemia.

Cardiovascular monitoring

*Intensive Care Medicine* first published the need for widespread use of echocardiography in the ICU [20]. Our journal was also the first to publish an “International expert statement on training standards for critical care ultrasonography” endorsed by the European Society of Intensive Care Medicine (ESICM) and 11 other national and international societies of intensive care medicine [21]. Indeed, echocardiography is helpful to assess the diagnosis of a hemodynamic instability. Transesophageal echo can even be used successfully in ARDS patients in prone position [22]. We learned in recent years that tissue Doppler imaging (TDI) is helpful in various conditions such as weaning for either mechanical ventilation or ECMO. Papanikolaou et al. [23] showed, in patients with no history of cardiac failure, that failure to wean from mechanical ventilation was associated with some degree of left ventricular (LV) diastolic dysfunction. Lateral early mitral inflow velocity to peak mitral annulus velocity (E/Em) ratio was a strong independent factor associated with weaning failure. Aissaoui et al. [24] also showed a great interest in the use of TDI to predict ECMO weaning success. Favorable systolic LV parameters assess favorable outcome. Thus, aortic time–velocity integral of at least 10 cm, LV ejection fraction greater than 20–25%, and lateral mitral annulus peak systolic velocity of at least 6 cm/s are associated with ECMO weaning success.

The blood pressure signal provides information which helps physicians to assess hemodynamic status and to guide treatment. Augusto and colleagues [7] summarized the physiological principles on which blood pressure measurements are based. Arterial catheter allows for a continuous and precise monitoring of arterial pressure signal. The analysis of the blood pressure wave provides information that may help the clinician to interpret hemodynamic status, thus guiding fluids and/or vasoactive drugs administration. The physiological mechanisms responsible for arterial pressure generation are explained. In addition, the static and the dynamic indexes generated by heart–lung interactions derived from the arterial pressure wave are discussed. Finally, the recommended target of mean blood pressure value is fully analyzed.

Arterial pressure-based cardiac output is indeed increasingly used in intensive care medicine and in operating rooms in high-risk surgical patients. In a prospective multicentric validation trial, De Backer et al. [25] showed improved validity of the data generated by the third-generation FLoTrac compared with the second generation, in septic patients. Further studies are needed to confirm the validity of those tools in the ICU.

Central venous saturation (ScvO2) is widely used in the ICU to guide treatment and predict outcome. Perz et al. [26] confirmed ScvO2 as a great indicator of outcome in the perioperative period. They first confirmed that low ScvO2 is associated with poor outcome. They further showed, surprisingly, that high ScvO2 also named “supra-normal” ScvO2 is under-recognized as a warning sign of poor outcome. It is likely related to a marked reduction of oxygen consumption as might be seen in sepsis.

**Infections, pneumonia, and sepsis**

**Infections**

Hospital-acquired infections with antibiotic-resistant bacteria are an important problem among critically ill patients. Control of these organisms has largely focused within individual hospitals. Karkada et al. [27] examined the extent to which transfers of critically ill patients could be a vector for the spread of such bacteria and compared the efficiency of different infection control measures in a simulation study of an American hospital network system. Hospitals varied substantially in the importance placed on limiting potential spread, and targeting resources to a
small subset of hospitals on the basis of their position in
the transfer network was 16 times more efficient than
distributing infection control resources uniformly.

Changes in the consumption of MRSA-active antibi-
otics and in the burden of MRSA between 2001 and 2009
were analyzed in a network of 55 German ICUs [28].
“Old MRSA-active antibiotics” included vancomycin,
tecoplanin, and fosfomycin and “new MRSA-active
antibiotics” included quinupristin/dalfopristin, linezolid,
and daptomycin. Both the burden of MRSA and the
pooled mean MRSA resistance proportion did not change
significantly over time. In contrast, MRSA-active antibi-
otics more than doubled from 44 defined daily doses per
1,000 patient-days in 2001 to 92 in 2009. This was due to
the significant increase of new MRSA-active antibiotics
(from 1 to 40), whereas old MRSA antibiotics stayed
stable (43 in 2001 and 52 in 2009).

Crandon and co-workers [29] developed a meropenem
population pharmacokinetic model in critically ill patients
with particular focus on optimizing dosing regimens
based on renal function. Initial modeling was performed
on 21 patients (55 samples) and validation was conducted
with 12 samples from 5 patients. The model was capable
of accurately estimating meropenem concentrations in
critically ill patients over a range of creatinine clearance
values. Compared with 0.5-h infusions, regimens
employing prolonged infusions improved target attain-
ment across all creatinine clearance ranges.

Selective decontamination of the digestive tract (SDD)
has received continued interest for the prevention of
infections. In a randomized trial in a Dutch ICU, SDD and
probiotics were compared [30]. The probiotics contained
*Lactobacillus 299/299v plus fiber, administered two times
daily. The trial was prematurely stopped after a study
reporting increased mortality in critically ill pancreatitis
patients receiving probiotics [31]. There were no signifi-
cant differences in infection rates [31% in the probiotic
group and 24% in the SDD group (OR 1.68, 95% CI
0.91–3.08, p = 0.10)].

Although SDD can significantly decrease infection
rates (and possibly mortality) in ICU patients, it has not
been widely accepted and adopted possibly because of
fear of encouraging bacterial resistance to the antimicro-
bials used. To evaluate the long-term incidence of
carriage of antibiotic-resistant bacteria, its clinical impact
on developing infections, and to explore risk factors for
acquiring resistance, Ochoa-Ardila and colleagues con-
ducted a 5-year cohort study in 1,588 patients given SDD
[32]. Interestingly, long-term use of SDD in that study
was not associated with an increased resistance against
the antimicrobials used as part of the SDD, or with an
increase in the rate in infections caused by resistant
strains; in fact, a reduction in the incidence of *P. aeru-
ginosa* resistant to aminoglycosides was observed. These
findings are in line with those reported by de Smet et al.
[33], showing that the use of SDD was associated with a
reduction in acquired bacteremia and respiratory tract
colonization caused by highly resistant microorganisms
compared with standard care.

H1N1

Early use of corticosteroids in patients affected by pan-
demic (H1N1)v influenza A infection, although relatively
common, remains highly debated. In order to assess the
potential usefulness of such a treatment, Martin-Loeches
and colleagues [34] analyzed the chart records of 220
patients admitted to ICU with a confirmed H1N1 infec-
tion, prospectively included in the European Society of
Intensive Care Medicine H1N1 registry. Among these
patients, 126 (57.3%) received corticosteroid therapy on
admission to ICU. They were significantly older and were
more likely to have coexisting asthma, chronic obstruc-
tive pulmonary disease, and chronic steroid use. Cox
regression analysis adjusted for severity and potential
confounding factors identified that early use of cortico-
steroids was not significantly associated with mortality
(HR 1.3, 95% CI 0.7–2.4, p = 0.4) but was still associ-
ated with an increased rate of hospital-acquired
pneumonia (OR 2.2, 95% CI 1.0–4.8, p < 0.05). Very
similar findings were observed in two other large cohort
studies, the first one by Kim et al. [35], and the second
one by Brun-Buisson et al. [36], confirming that early use
of corticosteroids in patients affected by pandemic
(H1N1)v influenza A infection did not result in better
outcomes and was associated with increased risk of
superinfections.

Because some uncertainty about the severity of the
A(H1N1) pandemic persists, particularly regarding its
impact on the healthcare system, Bertolini and colleagues
[37] conducted a prospective observational study in 155
Italian ICUs contributing to the GiViTI national database
during the epidemic phase of the disease. At the epi-
demic’s peak (October–December 2009) the ICU
occupancy rate did not significantly differ from the same
period of the previous year, and was significantly lower
than the 2009 seasonal influenza outbreak (January–
March 2009). Compared with community-acquired
pneumonia (CAP) of other origin (3,678 patients),
A(H1N1) pneumonia was associated with the same risk of
death when potential confounders were taken into account
(OR 0.88, 95% CI 0.59–1.31, p = 0.52). Thus, on the
basis of these data, it seems that the pandemic did not
increase ICU workload compared with other periods, at
least in Italy. However, it is still true that the pandemic
affected many young people, and the burden in terms of
young lives lost cannot be overlooked.

In a retrospective observational study in 23 French
ICUs, Cuquemelle and co-workers [38] investigated
whether procalcitonin (PCT) levels could discriminate
isolated viral from mixed (bacterial and viral) pneumonia
during the A/H1N1v2009 influenza pandemic. Of 103 patients with confirmed A/H1N1 infection and not having received prior antibiotics, 48 had a documented bacterial co-infection (mostly caused by *Streptococcus pneumoniae* or *Staphylococcus aureus*). Median values of PCT were significantly higher in patients with bacterial co-infection: 29.5 (3.9–45.3) versus 0.5 (0.12–2) µg/L ($p < 0.01$). For a cutoff of 0.8 µg/L or more, the sensitivity and specificity of PCT for distinguishing isolated viral from mixed pneumonia were 91 and 68%, respectively.

**MRSA pneumonia**

Although vancomycin has been the mainstay for treatment of MRSA infections, the drug may not be adequate for patients with MRSA pneumonia, particularly when the infection is caused by a strain with a relatively high vancomycin minimal inhibitory concentration (MIC) ($\geq 1.5$ µg/mL). To assess the distribution of vancomycin MICs in MRSA isolates and evaluate the efficacy of vancomycin relative to vancomycin MICs in adult patients with MRSA nosocomial pneumonia, Choi and colleagues [39] analyzed the clinical outcomes of 70 adults with MRSA nosocomial pneumonia treated with vancomycin. Thirty-four (48.6%) isolates had high ($\geq 1.5$ µg/mL) vancomycin MICs, and 36 (51.4%) had low ($\leq 1$ µg/mL) MICs, as determined by $E$ test. Patients infected with high-MIC strains showed slower clinical response and higher relapse rate (29.6 vs. 6.9%, $p = 0.038$) than patients infected with low-MIC vancomycin isolates. Infection caused by high-MIC strains was also an independent predictor of early clinical response failure when tested on multivariate analysis. These results are in accordance with those obtained by other investigators in patients with MRSA bloodstream infections [40].

**Attributable mortality of ventilator-associated pneumonia (VAP)**

Determining the contribution of ICU-acquired pneumonia to patients’ severity of illness and mortality is a major challenge. In order to relate new organ dysfunction/failure (OD/F) occurring during the ICU stay to clinical events, Damas and colleagues [41] measured the SOFA score daily in 453 adult patients with ICU-acquired pneumonia. Although septic shock occurred in 21% of all cases of ICU-acquired pneumonia, infection was responsible for only a minor proportion of organ dysfunctions and/or failures occurring during the ICU stay. Severity of ICU-acquired pneumonia was essentially related to clinical status prior to infection, but not to the type of bacteria. These results are consistent with those recently reported by Nguile-Makao et al. [42] and Bekaert et al. [43] using multistate progressive disability models and causal analysis, detecting a relatively limited attributable ICU mortality of VAP.

**Community-acquired pneumonia**

Emergency and ICU physicians often face the routine challenge of predicting short- to mid-term adverse outcomes for patients with CAP. As biomarkers have significantly improved practices in emergency medicine, it was suggested that they could help management of CAP, particularly when using endothelium-associated peptides, such as precursor peptides of endothelin-1 (proET-1) that correlate closely with endothelial activation. Indeed, emerging evidence points to a critical role of the endothelium in patients with systemic infections [44]. In this context, Schuetz and colleagues [45] evaluated the prognostic information derived from repeated measurements of proET-1 for monitoring patients during the course of disease in a well-defined cohort of 925 CAP patients. They found that both admission proET-1 levels and relative changes between baseline and day 3 provided significant prognostic information in regard to mortality and the need for ICU admission and improved classification of the pneumonia severity index (PSI) score. The results also showed that relative changes in the marker level provided more information compared with absolute marker levels during the follow-up. If verified in intervention studies, monitoring of proET-1 may be helpful for endothelium targeting therapies and for risk stratification complementary to other prohormones.

Two reviews addressed important issues in the field of CAP. The first analyzed the four different validated rules to help in the decision regarding ICU admission in patients with CAP. Ewig and colleagues [46] critically reviewed these rules: the modified American Thoracic Society (ATS) rule, Infectious Diseases Society of America (IDSA)/ATS rule, España rule, and SMART-COP (systolic blood pressure, multilobar extension of infiltrates, albumin, respiratory rate, tachycardia, confusion, oxygen, and arterial pH). Their performance varies, with sensitivity of around 70% and specificity of around 80–90%. Only negative predictive values are consistently high. Critical methodological issues include the appropriate reference for derivation, the populations studied, the variables included, and the time course of pneumonia. Pneumonia-related complications and decompensated comorbidities may be additional or independent reasons for a severe course. The authors advocate an approach that refers to the evaluation of the need for intensified treatment rather than ICU, based on a set of minor criteria but sensitive to the dynamic nature of pneumonia.

The second review pertained to the assessment of severity to guide ICU admission [47]. Universally
accepted criteria for ICU care in patients with CAP are mechanical ventilation and/or vasopressor support. Chalmers and collaborators aimed to determine if severity assessment tools could be used to guide decisions regarding ICU admission of patients with CAP. To that end, a meta-analysis of 28 studies and five scoring systems was performed. These scoring systems were the PSI, the CURB65 (confusion, urea, respiratory rate, blood pressure, and age ≥65) score, the CRB65 score, the ATS 2001 criteria, and the IDSA/ATS 2007 criteria. The PSI, CURB65, and CRB65 performed similarly in terms of sensitivity and specificity. Patients in CURB65 group zero were at lowest risk of ICU admission (negative likelihood ratio 0.14), whereas the ATS 2001 criteria had the highest positive likelihood ratio (7.05). However, a marked heterogeneity between studies was detected. The authors concluded that scoring systems designed to predict 30-day mortality perform less well in predicting ICU admission.

Sepsis and septic shock

Severe sepsis is associated with high mortality, and the Surviving Sepsis Campaign (SSC) protocol was developed as an international initiative to reduce mortality. Cost-effectiveness of the SSC protocol for the treatment of severe sepsis was determined in 59 Spanish ICUs in an observational prospective before-and-after study after the implementation of an educational program compared with the conventional care of severe sepsis [48]. Patients in the SSC protocol care cohort (n = 1,465) had a lower risk of hospital mortality (44.0 vs. 39.7%, p = 0.04), but mean costs per patient were 1,736 euros higher, largely as a result of increased length of stay. The adjusted incremental cost-effectiveness ratio (ICER) of the SSC protocol was 4,435 euros per life years gained.

An option still debated is the use of steroids for severe sepsis and septic shock. Three recent meta-analyses on the effects of low-dose corticosteroids on mortality reduction in patients with severe sepsis and septic shock gave contradictory results: two showed potential mortality benefit and one showed no mortality benefit. In the March issue Kalil and Sun [49] assessed the efficacy and safety of low-dose steroids for severe sepsis and septic shock by Bayesian methodology. Relative risk reductions (RRR) for 28-day mortality and relative risk increases (RRI) for shock reversal and side effects were estimated. The authors found that in septic shock trials only (Marik meta-analysis), the probability that low-dose steroids decrease mortality by more than 15% (i.e., RRR > 15%) was 0.41 (0.24 for RRR > 20% and 0.14 for RRR > 25%). For severe sepsis and septic shock trials combined, the results were as follows: (1) for the Annane meta-analysis, the probabilities were 0.57 (RRR > 15%), 0.32 (RRR > 20%), and 0.13 (RRR > 25%); (2) for the Minnecci meta-analysis, the probability was 0.57 to achieve mortality RRR > 15%, 0.32 (RRR > 20%), and 0.14 (RRR > 25%). The probability of achieving shock reversal ranged from 65 to 92%. The probability of developing steroid-induced side effects was as follows: for gastrointestinal bleeding (n = 924), there was a 0.73 probability of steroids causing an RRI > 1%, 0.70 for RRI > 2%, and 0.67 for RRI > 5%; for superinfections (n = 964), probabilities were 0.81 (RRR > 1%), 0.76 (RRR > 2%), and 0.70 (RRR > 5%); and for hyperglycemia (n = 540), 0.99 (RRR > 1%), 0.97 (RRR > 2%), and 0.94 (RRR > 5%).

It was concluded that the findings strongly suggest that survival benefit is unlikely to be achieved with low-dose steroids for patients with severe sepsis and/or septic shock. In addition, the probabilities of developing serious drug-induced side effects such as superinfections, bleeding, and hyperglycemia are too high to justify shock reversal as the sole indication for the use of low-dose steroids.

The time course of organ failure in patients with septic shock treated with hydrocortisone was analyzed in a study that was an addendum of the Corticus trial [50]. The authors hypothesized that patients treated with hydrocortisone when compared to placebo would have a faster resolution of organ dysfunction/failure. The authors analyzed the patients who had been enrolled in the Corticus trial: a prospective, randomized, double-blind, placebo-controlled study of 28-day mortality in patients with septic shock for less than 72 h who underwent a short high-dose ACTH test and patients received 11-day treatment with hydrocortisone or placebo. A total of 499 patients were enrolled (hydrocortisone 251, placebo 248). There was no difference in 28-day mortality between the two treatment groups (hydrocortisone 34.3 vs. placebo 31.5%). There was a decrease in the SOFA score of hydrocortisone-treated patients from day 0 to day 7 compared with the placebo-treated patients (p = 0.0027), driven by an improvement in cardiovascular organ dysfunction/failure (p = 0.0005) and in liver failure (p < 0.0001) in the hydrocortisone-treated patients. It was concluded that patients treated with hydrocortisone demonstrated a faster decrease in total organ dysfunction/failure, without being accompanied by a decreased mortality.

It is well known that sepsis is also an important cause of morbidity and mortality for neonates, but a rapid and accurate diagnostic is difficult. A group of authors coordinated by Falagas [51] aimed at assessing the value of PCT for the diagnosis of neonatal sepsis by performing a diagnostic test accuracy meta-analysis of relevant studies. Twenty-nine articles were analyzed. The authors found a sensitivity and specificity of 81% (95% CI 74–87%) and 79% (95% CI 69–87%), respectively. The area under the receiver operating characteristic curve (AUC-ROC) was 0.87. However, high statistical heterogeneity was observed for all analyses. It was concluded that although serum PCT at presentation has very good diagnostic
Polymerase chain reaction (PCR)-based techniques allow more rapid and sensitive detection of pathogens compared with conventional blood culture. The current opinion is that PCR can supplement but not replace blood culture in septic patients. A review article published in the July issue [52] deals with these problems. Numerous studies showed that the combined detection rate of both methods (PCR and blood culture) was significantly higher compared with PCR or blood culture alone. An inherent limitation of PCR is that determination of antibiotic resistance can currently be performed only by blood culture. PCR techniques are also costly and involve a significant workload. Except for diagnosis of patients in whom unusual, not cultivable, or fastidious pathogens are of concern, such as immunosuppressed patients with suspected parasitic infection, it might even not be necessary to further increase the spectrum of detectable species. In the authors’ opinion, a narrower assay is more cost effective, may achieve higher accuracy owing to reduced intratest interference, and would better address current and emerging clinical needs.

Phosphorylation pathways may be altered during severe sepsis and septic shock. These pathways play a central role in the development and progression of many other disease states, because they control central biological mechanisms in nearly all cellular functions. In a review published at the beginning of 2011, Martin and Ranieri [53] summarized the function and activity of various phosphorylation mechanisms. The authors discussed the phosphorylation mechanisms in the pathogenesis, diagnosis, and treatment of heart failure, myocardial infarction, stroke, respiratory failure, ventilation-induced lung injury, traumatic brain injury, acute organ failure, systemic sepsis, and shock. It was concluded that a proper understanding of these mechanisms will provide new avenues of treatment by targeting this biological function.

Gastrointestinal dysfunction in critically ill septic patients is common, and probably underestimated. A validated definition of acute intestinal failure is lacking, in the absence of a marker to measure it. A review on gastrointestinal dysfunction in critically ill patients [54] proposed a definition of acute intestinal failure. Small bowel ischemia is related to acute reduction of enterocyte mass and loss of gut barrier. Systemic inflammatory response syndrome and sepsis could be linked to an acute dysfunction of enterocytes without enterocyte reduction. Citrulline is an amino acid mainly synthesized by small bowel enterocytes. Patients with shock have an acute reduction of enterocyte mass and/or acute dysfunction of enterocytes, associated or not with loss of gut barrier function. The authors also stated that the value of plasmatic citrulline as an indicator of acute intestinal failure in critically ill patients must be further evaluated.

### ICU organization and outcome

#### Organization

On behalf of the ESICM working group on quality improvement, Valentini and Ferdinande [55] updated the basic requirement for the planning or renovation of ICUs. A total of 47 ICU physicians from 23 countries reviewed all available literature and reached consensus through an iterative process with several rounds. Although communication and team-working culture are not addressed, this document provides operative guidelines and design recommendations that could help ICU directors ensure the adequate practice of our specialty.

Rapid response teams (RRTs) might be very different in terms of their activity and the characteristics of deteriorating patients in the ward. Jaderling and co-workers [56] compared RRTs, one in a hospital in Austin (Australia) and the other in Stockholm (Sweden). They found that although the number of calls was higher in Austin, the patients’ characteristics were grossly similar and suggested that deteriorating patients are similar all over the world in the hospital ward. Although the rates of limitation of medical treatment decisions was about 30% and not different between centers, the rate of ICU transfer was 9.9% in Austin and 18.7% in Stockholm. The 30-day mortality of both cohorts was high (27.7 vs. 29.4%).

Dehnel and co-workers [57] compared drug concentration of amiodarone, norepinephrine, and hydrocortisone prepared manually and automatically, and measured by high-performance liquid chromatography. They found that more than a half of manually prepared solutions differed from the scheduled concentration by more than 5%. Deviation of more than 15% occurred in 15% of manually prepared solution. Particularly for norepinephrine, the deviation was of at least 10% in 6 of the 30 (20%) manually prepared solutions. Solutions prepared by automated procedure dramatically narrowed the deviation from the desired concentration. The concentration of the machine-made solution was 101.1 ± 4.3% of the desired solution.

#### Outcome

Gayat and co-workers [58] developed a severe post-partum hemorrhage (SPHH) score based on two independent cohorts of parturients in order to predict the need for an advance interventional procedure (AIP) and optimize the
referral of patients at risk to a specialized tertiary care center. AIP was needed in 42 and 43% of the cases. They found that abnormalities of placenta implantation, international normalized ratio greater than 1.64, low fibrinogen (less than 2 g/l), detectable levels of troponin, and heart rate greater than 115 bpm were independent predictors of the need for AIP. They built an SPHH score with one point attributed for the presence of each risk factor. In an external multicenter validation dataset, the AUC-ROC of the score in predicting AIP was 0.818, indicating a good discrimination. The risk of AIP was 11, 39, and 75% for an SPHH score of 0, 1, and 2 or more, respectively.

In a very large cohort of ICU patients from 38 Australian ICUs,Renton et al. [59] found that the rate of readmission was 5.5% (13,598 out of 247,103 patients). Readmissions were associated with a more than fourfold increase in the post-ICU mortality. Discharge from ICU between 6 p.m. and 6 a.m. (OR 1.13, 95% CI 1.13–1.19) was the only factor accessible to improvement. It suggests discharge at night could serve as a process indicator in evaluating structural or organizational aspects of ICUs.

Health-related quality of life (HRQoL) after ICU stay is fundamental in assessing the benefits of ICU care. Orwelius and co-workers [60] found that social integration influenced the post-ICU HRQoL, as assessed by SF-36 questionnaire in post-ICU patients, but was not associated with HRQoL in a reference group of people. Therefore social integration needs to be examined in parallel when comprehensive studies of post-ICU HRQoL are undertaken.

Prognostic models have been designed to predict mortality in general ICU populations. It is unclear whether these models serve the same purpose in elderly patients. To answer this question Minne et al. [61] performed a systematic review and identified seven studies. In total, 17 models were found of which six were developed for the general adult ICU population and eleven specifically for elderly patients. Cohorts ranged from 148 to 12,993 patients and only smaller ones were obtained prospectively. The AUC-ROC was most commonly used to measure performance (range 0.71–0.88). The median number of criteria met for clinical credibility was 4.5 out of 7 (range 2.5–5.5) and 17 out of 20 for methodological quality (range 15–20). It was concluded that there is no evidence that elderly-specific models (those developed for elderly or very elderly population) perform better than general models developed for a general adult ICU population.

**Education**

Teaching intensive care medicine

The CoBaTrICE collaboration [62] developed an initial set of 52 possible standards using a modified Delphi process involving experts from 28 European countries. This document might be a basic tool for a dynamic process of quality improvement of the educational environment in intensive care medicine.

Skills and behavior are fundamental in evaluating the quality of a teaching process. Hunziker et al. [63] studied the impact of emotions on the performance of fourth-year medical students before, during, and after a simulated resuscitation. They measured emotion using an 18-item questionnaire. Negative emotions were irritation, disappointment, guilt, shame, and anxiety, and positive emotions of interest were pride, joy, pleasure, and relief. They also measured the perceived stress, feeling of being overwhelmed, and motivation on a ten-point Likert scale. They evaluated the quality of performance on the simulator as duration of uninterrupted chest compressions or defibrillation in the first 180 s after the onset of cardiac arrest. They found that negative emotions during resuscitation were more frequent than before or after. In contrast, positive emotions were less frequent. Students’ stress/overload increased during resuscitation (5.4 before vs. 8.2 during resuscitation, p < 0.0001, WS-ANOVA). Interestingly, the quality of performance was negatively influenced by stress/overload and positively influenced by motivation during the early resuscitation phase. Negative emotions did not remain associated with performance in the final model. The impact of stress coping and increased motivation strategies to improve performance of resuscitation remains to evaluate.

The teaching process by lecture format is widely used at congresses and in medical educational programs. Lautrette et al. [64] wanted to assess the number of take-home messages identified by postgraduate critical care junior doctors (juniors) during lectures. The authors performed a prospective observational study of 13 lectures. Lecturers were not informed. At the end of the lecture, the lecturer and juniors listed the three main take-home messages on a form. Subjective elements of the juniors’ appraisal and objective elements of the lectures were also recorded. Successful knowledge transfer was assessed by matching lecturers’ and juniors’ take-home messages. A total of 367 forms were analyzed. A match equal to 3 (highest match), 2, 1 or 0 was observed in 3.8, 26.7, 48.2, and 21.2% of the forms, respectively. No single subjective or objective element of the lecture was associated with the number of identified take-home messages. It was concluded that two-thirds of critical care junior doctors identified at best only one of the three main take-home messages of a lecture. These results suggest that there is a need to develop strategies to improve the performance of lecture-based learning.

The recognition of intensive care medicine (ICM) as an independent specialty at the European level is a long and difficult process whose end is still far away. In a special article published in December, Rubulotta and colleagues [65] recapitulated the more recent and
important developments in the recognition of ICM as a specialty at both the European and national levels and they also described the impact of the lack of recognition on training schemes throughout Europe and the subsequent ability of trained specialists to then move between different countries. The authors note that there is no harmonization among European countries. Nations providing a national examination for ICM and a national register for specialists in ICM facilitate the free movement of specialists, regardless of European regulations and directives. It was concluded that ICM is currently not a mother specialty and that a long process needs to occur before complete harmonization of training and accreditation and free movement of specialists in Europe will happen.

**Ultrasonography**

Ultrasonography is gaining a growing interest and importance in critical care medicine. This year our journal published several articles on the subject.

A group of 29 experts representing the ESICM and 11 other critical care societies proposed a framework for organizing training in ultrasound techniques adapted to the ICM setting [21]. It was recommended that intensive care physicians should aim to achieve competencies in three main areas: (1) general critical care ultrasound, (2) ‘‘basic’’ critical care echocardiography, and (3) advanced critical care echocardiography. There was 100% agreement among the experts that general critical care ultrasound and ‘‘basic’’ critical care echocardiography should be mandatory in the curriculum of ICM physicians. It was recommended that national intensive care societies play the role of supporting the implementation of training in general critical care ultrasound and basic critical care echocardiography in their own countries.

The use of chest ultrasound is rapidly evolving and it is proposed as a technique to look for pneumothorax. In the February issue, Volpicelli [66] reviewed the current knowledge on lung ultrasound targeted at the diagnosis of pneumothorax and to provide experts’ opinion and personal clinical experience. Ultrasound diagnosis of pneumothorax relies on the recognition of four sonographic artifact signs: the lung sliding, the B lines, the lung point, and the lung pulse. Combining these few signs, it is possible to accurately rule in or rule out pneumothorax at the bedside in several different clinical scenarios. Sensitivity of a lung ultrasound in the detection of pneumothorax is higher than that of conventional anterior-posterior chest radiography (CXR), and similar to that of computed tomography (CT). A major benefit of a lung ultrasound is that it can be used quickly to diagnose pneumothorax at the bedside and does not expose the patient to ionizing radiation. It was concluded that lung ultrasound is the method of choice in several common clinical situations.

The role of lung ultrasound in critically ill patients, compared with bedside CXR, was evaluated by Xirouchaki and colleague [67] using thoracic CT as a gold standard. Forty-two mechanically ventilated patients scheduled for CT were prospectively studied with a modified lung ultrasound protocol. Four pathologic entities were evaluated: consolidation, interstitial syndrome, pneumothorax, and pleural effusion. Eighty-four hemithoraces were evaluated by the three imaging techniques. The sensitivity, specificity, and diagnostic accuracy of CXR were 38, 89, and 49% for consolidation, 46, 80, and 58% for interstitial syndrome, 0, 99, and 89% for pneumothorax, and 65, 81, and 69% for pleural effusion, respectively. The corresponding values for lung ultrasound were 100, 78, and 95% for consolidation, 94, 93, and 94% for interstitial syndrome, 75, 93, and 92% for pneumothorax, and 100, 100, and 100% for pleural effusion, respectively, suggesting that lung ultrasound has a considerably better diagnostic performance than CXR for the diagnosis of common pathologic conditions and may be used as an alternative to thoracic CT.

Ultrasonography has been also proposed to detect intracranial hypertension. Invasive intracranial devices are the gold standard for measuring the intracranial pressure, but the technique is not free of risk. The ultrasonography of optic nerve sheath diameter has been suggested as a possible indicator of intracranial hypertension. Dubourg et al. [68] analyzed the data on the accuracy of ultrasonography of optic nerve sheath diameter with invasive measurements of intracranial pressure. They performed a meta-analysis of six studies. No significant heterogeneity was detected. For detection of raised intracranial pressure, the sensitivity was 0.90 and specificity was 0.85. The AUC-ROC was 0.94. It was concluded that ultrasonography of optic nerve sheath diameter shows a good level of diagnostic accuracy for detecting intracranial hypertension in adult patients with traumatic brain injury and intracranial hemorrhage.

Ultrasonography may have the potential to decrease the likelihood of aspiration of gastric contents during urgent endotracheal intubation. An observational study was carried out during 80 urgent endotracheal intubation procedures in which left upper quadrant ultrasonography was performed [69]. If gastric fluid was identified during ultrasonography, it was evacuated using a gastric tube. A subsequent ultrasonography confirmed removal of gastric contents prior to induction. It was found that 19 (24%) patients had gastric fluid content identified and 13 (16%) had sufficient gastric fluid content such that the caregivers proceeded with gastric tube insertion. Gastric fluid volume removed was 553 ± 290 mL and none of the patients had a clinically consequential aspiration event. It was concluded that ultrasonography is useful for the detection of gastric fluid and may reduce the risk of a clinically consequential aspiration event during urgent endotracheal intubation.
**Metabolism and coagulation**

**Metabolism**

**Blood glucose variability might be associated with mortality**

Eslami et al. [70] analyzed 12 studies in a systematic review aiming to identify glucose variability and its association with mortality. The authors found that multiple indicators were used to measure glucose variability, the most common indicators being hypo- and hyperglycemia. All studies reported a statistically significant association between mortality and at least one glucose variability indicator. It was concluded that the independent association between blood glucose level variability and mortality is unsettled. This result was attributed to the variability being analyzed in very disparate ways and because of heterogeneity (in methods, design, and reporting) among the different studies.

**Some drugs currently used in critical care medicine might have detrimental effects**

Among them there is etomidate, an imidazole derivative, is a fast-acting anesthetic agent for rapid sequence intubation, but it is an inhibitor of adrenal 11β-hydroxylase. It may cause adrenal dysfunction after a single bolus lasting for up to 48 h. In a meta-analysis published in the June issue, Albert and coauthors [71] assessed data of etomidate versus comparator anesthetics for mortality and adrenal insufficiency. A total of 19 studies were included. Meta-analysis showed a significant increase in risk ratio for etomidate versus non-etomidate with respect to mortality (risk ratio 1.19, \( p < 0.001 \)) and adrenal insufficiency (risk ratio 1.64, \( p < 0.001 \)). They also found a marked heterogeneity (\( I^2 = 88\% \) for adrenal insufficiency and \( I^2 = 64\% \) for mortality), and studies were of moderate to low quality. It was concluded that the association between etomidate and adrenal insufficiency is strong and it is weak for mortality.

**Coagulation**

Coagulation abnormalities represent a constant danger in the ICM world. For instance, massive bleeding following traumatic injury is the second most common cause of death in industrialized countries. In a systematic review of 230 articles published between January 2000 and August 2009, Lier and colleagues [72] provided recommendations for coagulation management in multiple trauma patients. The authors discuss several diagnostic and therapeutic approaches. It was concluded that for life-threatening hemorrhage, the sole application of fresh frozen plasma may not be sufficient, and that early anticipatory therapy with packed red blood cells, fresh frozen plasma, and purified factor concentrates together with correction of concomitant abnormalities (temperature, pH, ionized calcium) will help rescue more patients.

Some coagulopathies are rare, but intensivists have to be well aware that acquired hemophilia is, for example, a rare condition in which inhibiting antibodies develop against coagulation factors, most often factor VIII, and leads to major bleeding requiring intensive care treatment. Acquired hemophilia also has significant mortality (6–8%). A review article dealt with the diagnosis and management of acquired hemophilia [73]. Recognition of acquired hemophilia presents a clinical challenge, given the rarity of this condition and the potential for confusion with other more common causes of bleeding. An acute onset of bleeding in a patient without history of bleeding should raise suspicion of this disorder, particularly if the patient is elderly or post-partum. The early laboratory diagnosis is a prolongation of activated partial thromboplastin time with normal prothrombin time and platelet count. The treatment of acquired hemophilia is a multi-step, physiologically focused process aimed at controlling both active and recurrent bleeding. It includes administration of human factor VIII concentrate, desmopressin, inhibitor bypassing agents (recombinant activated factor VII and plasma-derived activated prothrombin complex concentrate), and eradication of the inhibitor (plasmapheresis and immunoadsorption, and immunosuppressive treatment). A prompt diagnosis is central to prognosis, and consultation with a hematologist may facilitate efficient diagnosis and management.

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