Massimo Antonelli
Marc Bonten
Jean Chastre
Giuseppe Citerio
Giorgio Conti
J. Randall Curtis
Daniel De Backer
Goran Hedenstierna
Michael Joannidis
Duncan Macrae
Jordi Mancebo
Salvatore M. Maggiore
Alexandre Mebazaa
Jean-Charles Preiser
Patricia Rocco
Jean-François Timsit
Jan Wernerman
Haibo Zhang

Year in review in Intensive Care Medicine 2011. II. Cardiovascular, infections, pneumonia and sepsis, critical care organization and outcome, education, ultrasonography, metabolism and coagulation

M. Antonelli (✉) · G. Conti ·
S. M. Maggiore
Department of Intensive Care and
Anesthesiology, Policlinico Universitario A.
Gemelli, Università Cattolica del Sacro
Cuore, Largo A. Gemelli, 8,
00168 Rome, Italy
e-mail: m.antonelli@rm.unicatt.it
Tel.: +39-06-30153226
Fax: +39-06-30154386

M. Bonten
Department of Medical Microbiology,
Julius Center for Health Sciences,
Primary Care University Medical Center,
Utrecht, The Netherlands

J. Chastre
Reanimation medicale, Hopital Pitié
Salpétrière, Paris, France

G. Citerio
Neurointensive Care Unit, Ospedale S.
Gerardo, Monza, Italy

J. R. Curtis
Division of Pulmonary and Critical Care,
University of Washington,
Seattle, WA, USA

D. De Backer
Service des Soins Intensifs,
Erasme Hospital, Brussels, Belgium

G. Hedenstierna
Department of Clinical Physiology, Uppsala
University, Uppsala, Sweden

M. Joannidis
Department of Internal Medicine,
Medical University of Innsbruck,
Innsbruck, Austria

D. Macrae
Pediatric Intensive Care Unit,
Royal Brompton Hospital, London, UK

J. Mancebo
Intensive Care Medicine Unit, Hospital Sant
Pau, Barcelona, Spain

A. Mebazaa
Department of Anesthesiology
and Critical Care Medicine, Lariboisière
Hospital, Paris, France

J.-C. Preiser
Department of Intensive Care,
Erasme University Hospital,
Brussels, Belgium

P. Rocco
Laboratory of Pulmonary Investigation,
Centro de Ciências da Saúde, Rio de
Janeiro, Brazil

J.-F. Timsit
Intensive Care Medicine Unit,
Hôpital A. Michallon, Grenoble, France

J. Wernerman
Department of Anesthesiology and
Intensive Care Medicine, Karolinska
University Hospital, Stockholm, Sweden

H. Zhang
Interdepartmental Division of Critical Care
Medicine, University of Toronto,
Toronto, ON, Canada

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 differed 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 splanchnic 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.

Bloechlinger 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 starches (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 (StO_2) determined by near-infrared spectroscopy as an index of tissue perfusion, StO_2 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. StO_2 decreased in the forearm (85% from baseline) and also, but more modestly (95% from baseline), in the thenar area. The decrease in StO_2 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, StO_2 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 ($ScvO_2$) is widely used in the ICU to guide treatment and predict outcome. Perz et al. [26] confirmed $ScvO_2$ as a great indicator of outcome in the perioperative period. They first confirmed that low $ScvO_2$ is associated with poor outcome. They further showed, surprisingly, that high $ScvO_2$ also named "supra-normal" $ScvO_2$ 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 antibiotics 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, teicoplanin, 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 antibiotics 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 attainment 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 significant 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 antimicrobials 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 conducted 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. aeruginosa* 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 pandemic (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 infection, 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 obstructive pulmonary disease, and chronic steroid use. Cox regression analysis adjusted for severity and potential confounding factors identified that early use of corticosteroids was not significantly associated with mortality (HR 1.3, 95% CI 0.7–2.4, $p = 0.4$) but was still associated 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) pandemia 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 epidemic'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) (≥ 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 (≥ 1.5 µg/mL) vancomycin MICs, and 36 (51.4%) had low (≤ 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 Minneci 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 (RRI > 1%), 0.76 (RRI > 2%), and 0.70 (RRI > 5%); and for hyperglycemia ($n = 540$), 0.99 (RRI > 1%), 0.97 (RRI > 2%), and 0.94 (RRI > 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

accuracy for the diagnosis of neonatal sepsis; the marked heterogeneity along with the lack of a uniform definition for neonatal sepsis, means that the interpretation of the findings is to be done cautiously.

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 reduced gut citrulline synthesis, leading to a low plasma citrulline concentration. The authors proposed that acute intestinal failure could be defined as 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, Valentin 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%).

Dehmel 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 (I2 = 88% for adrenal insufficiency and I2 = 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 multistep, 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.

References

1. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, Delgado JF, Follath F (2011) Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med 37:290–301

2. Follath F, Yilmaz MB, Delgado JF, Parissis JT, Porcher R, Gayat E, Burrows N, McLean A, Vilas-Boas F, Mebazaa A (2011) Clinical presentation, management and outcomes in the Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF). Intensive Care Med 37:619–626

3. Trimlett RH, Cordingley JJ, Griffiths MJ, Price S, Hunter DN, Finney SJ (2011) A modified technique for insertion of dual lumen bicaval cannulae for venovenous extracorporeal membrane oxygenation. Intensive Care Med 37:1036–1037

4. Endemann DH, Philipp A, Hengstenberg C, Luchner A, Puhler T, Hilker M, Schmid C, Riegger GA, Muller T, Resch M (2011) A simple method of vascular access to perform emergency coronary angiography in patients with veno-arterial extracorporeal membrane oxygenation. Intensive Care Med 37:2046–2049

5. Thibault R, Pichard C, Wernerman J, Bendjelid K (2011) Cardiogenic shock and nutrition: safe? Intensive Care Med 37:35–45

6. Bloechlinger S, Grander W, Bryner J, Dunser MW (2011) Left ventricular rotation: a neglected aspect of the cardiac cycle. Intensive Care Med 37:156–163

7. Augusto JF, Teboul JL, Radermacher P, Asfar P (2011) Interpretation of blood pressure signal: physiological bases, clinical relevance, and objectives during shock states. Intensive Care Med 37:411–419

8. Dufour N, Chemla D, Teboul JL, Monnet X, Richard C, Osman D (2011) Changes in pulse pressure following fluid loading: a comparison between aortic root (non-invasive tonometry) and femoral artery (invasive recordings). Intensive Care Med 37:942–949

9. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256

10. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R (2011) Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 37:86–96

11. Hartog C, Reinhart K (2009) CONTRA: hydroxyethyl starch solutions are unsafe in critically ill patients. Intensive Care Med 35:1337–1342

12. CHEST management committee (2011) The Crystalloid versus Hydroxyethyl Starch Trial: protocol for a multi-centre randomised controlled trial of fluid resuscitation with 6% hydroxyethyl starch (130/0.4) compared to 0.9% sodium chloride (saline) in intensive care patients on mortality. Intensive Care Med 37:816–823

13. Hartog CS, Reuter D, Loesche W, Hofmann M, Reinhart K (2011) Influence of hydroxyethyl starch (HES) 130/0.4 on hemostasis as measured by viscoelastic device analysis: a systematic review. Intensive Care Med 37:1725–1737

14. Annane D, Bellissant E, Sebille V, Lesieur O, Mathieu B, Raphael JC, Gajdos P (1998) Impaired pressor sensitivity to noradrenaline in septic shock patients with and without impaired adrenal function reserve. Br J Clin Pharmacol 46:589–597

15. Torgersen C, Luckner G, Schroder DC, Schmittinger CA, Rex C, Ulmer H, Dunser MW (2011) Concomitant arginine-vasopressin and hydrocortisone therapy in severe septic shock: association with mortality. Intensive Care Med 37:1432–1437

16. Russell JA, Walley KR, Gordon AC, Cooper DJ, Hebert PC, Singer J, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ (2009) Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. Crit Care Med 37:811–818

17. Morelli A, Donati A, Ertmer C, Rehberg S, Orecchioni A, Di Russo A, Pelaia P, Pietropaoli P, Westphal M (2011) Short-term effects of terlipressin bolus infusion on sublingual microcirculatory blood flow during septic shock. Intensive Care Med 37:963–969

18. Ait-Oufella H, Lemoinne S, Boelle PY, Galbois A, Baudel JL, Lemant J, Joffre J, Margetis D, Guidet B, Maury E, Offenstadt G (2011) Mottling score predicts survival in septic shock. Intensive Care Med 37:801–807

19. Bartels SA, Bezemer R, de Vries FJ, Milstein DM, Lima A, Cherpanath TG, van den Meiracker AH, van Bommel J, Heger M, Karemaker JM, Ince C (2011) Multi-site and multi-depth near-infrared spectroscopy in a model of simulated (central) hypovolemia: lower body negative pressure. Intensive Care Med 37:671–677

20. Cholley BP, Vieillard-Baron A, Mebazaa A (2006) Echocardiography in the ICU: time for widespread use! Intensive Care Med 32:9–10

21. Expert round table on ultrasound in ICU(2011) International expert statement on training standards for critical care ultrasonography. Intensive Care Med 37:1077–1083

22. Mekontso Dessap A, Proost O, Boissier F, Louis B, Roche Campo F, Brochard L (2011) Transesophageal echocardiography in prone position during severe acute respiratory distress syndrome. Intensive Care Med 37:430–434

23. Papanikolaou J, Makris D, Saranteas T, Karakitsos D, Zintzaras E, Karabinis A, Kostopanagiotou G, Zakynthinos E (2011) New insights into weaning from mechanical ventilation: left ventricular diastolic dysfunction is a key player. Intensive Care Med 37:1976–1985

24. Aissaoui N, Luyt CE, Leprince P, Trouillet JL, Leger P, Pavie A, Diebold B, Chastre J, Combes A (2011) Predictors of successful extracorporeal membrane oxygenation (ECMO) weaning after assistance for refractory cardiogenic shock. Intensive Care Med 37:1738–1745

25. De Backer D, Marx G, Tan A, Junker C, Van Nuffelen M, Huter L, Ching W, Michard F, Vincent JL (2011) Arterial pressure-based cardiac output monitoring: a multicenter validation of the third-generation software in septic patients. Intensive Care Med 37:233–240

26. Perz S, Uhlig T, Kohl M, Bredle DL, Reinhart K, Bauer M, Kortgen A (2011) Low and "supranormal" central venous oxygen saturation and markers of tissue hypoxia in cardiac surgery patients: a prospective observational study. Intensive Care Med 37:52–59

27. Karkada UH, Adamic LA, Kahn JM, Iwashyna TJ (2011) Limiting the spread of highly resistant hospital-acquired microorganisms via critical care transfers: a simulation study. Intensive Care Med 37:1633–1640

28. Meyer E, Schwab F, Schroeren-Boersch B, Gastmeier P (2011) Increasing consumption of MRSA-active drugs without increasing MRSA in German ICUs. Intensive Care Med 37:1628–1632

29. Crandon JL, Ariano RE, Zelenitsky SA, Nicasio AM, Kuti JL, Nicolau DP (2011) Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Med 37:632–638

30. Oudhuis GJ, Bergmans DC, Dormans T, Zwaveling JH, Kessels A, Prins MH, Stobberingh EE, Verbon A (2011) Probiotics versus antibiotic decontamination of the digestive tract: infection and mortality. Intensive Care Med 37:110–117

31. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG (2008) Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet 371:651–659

32. Ochoa-Ardila ME, Garcia-Canas A, Gomez-Mediavilla K, Gonzalez-Torralba A, Alia I, Garcia-Hierro P, Taylor N, van Saene HK, de la Cal MA (2011) Long-term use of selective decontamination of the digestive tract does not increase antibiotic resistance: a 5-year prospective cohort study. Intensive Care Med 37:1458–1465

33. de Smet AM, Kluytmans JA, Blok HE, Mascini EM, Benus RF, Bernards AT, Kuijper EJ, Leverstein-van Hall MA, Jansz AR, de Jongh BM, van Asselt GJ, Frenay IH, Thijsen SF, Conijn SN, Kaan JA, Arends JP, Sturm PD, Bootsma MC, Bonten MJ (2011) Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. Lancet Infect Dis 11:372–380

34. Martin-Loeches I, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, Chiche JD, Barahona D, Villabon M, Balasini C, Pearse RM, Matos R, Rello J (2011) Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. Intensive Care Med 37:272–283

35. Kim SH, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, Lee HB, Lim CM, Koh Y (2011) Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 183:1207–1214

36. Brun-Buisson C, Richard JC, Mercat A, Thiebaut AC, Brochard L (2011) Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med 183:1200–1206

37. Bertolini G, Rossi C, Crespi D, Finazzi S, Morandotti M, Rossi S, Peta M, Langer M, Poole D (2011) Is influenza A(H1N1) pneumonia more severe than other community-acquired pneumonias? Results of the GiViTI survey of 155 Italian ICUs. Intensive Care Med 37:1746–1755

38. Cuquemelle E, Soulis F, Villers D, Roche-Campo F, Ara Somohano C, Fartoukh M, Kouatchet A, Mourvillier B, Dellamonica J, Picard W, Schmidt M, Boulain T, Brun-Buisson C (2011) Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. Intensive Care Med 37:796–800

39. Choi EY, Huh JW, Lim CM, Koh Y, Kim SH, Choi SH, Kim YS, Kim MN, Hong SB (2011) Relationship between the MIC of vancomycin and clinical outcome in patients with MRSA nosocomial pneumonia. Intensive Care Med 37:639–647

40. Kullar R, Davis SL, Levine DP, Rybak MJ (2011) Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis 52:975–981

41. Damas P, Layios N, Seidel L, Nys M, Melin P, Ledoux D (2011) Severity of ICU-acquired pneumonia according to infectious microorganisms. Intensive Care Med 37:1128–1135

42. Nguile-Makao M, Zahar JR, Francais A, Tabah A, Garrouste-Orgeas M, Allaouchiche B, Goldgran-Toledano D, Azoulay E, Adrie C, Jamali S, Clec'h C, Souweine B, Timsit JF (2010) Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensive Care Med 36:781–789

43. Bekaert M, Timsit JF, Vansteelandt S, Depuydt P, Vesin A, Garrouste-Orgeas M, Decruyenaere J, Clec'h C, Azoulay E, Benoit D (2011) Attributable mortality of ventilator-associated pneumonia: a reappraisal using causal analysis. Am J Respir Crit Care Med 184:1133–1139

44. Lee WL, Slutsky AS (2010) Sepsis and endothelial permeability. N Engl J Med 363:689–691

45. Schuetz P, Christ-Crain M, Zimmerli W, Mueller B (2011) Repeated measurements of endothelin-1 precursor peptides predict the outcome in community-acquired pneumonia. Intensive Care Med 37:970–980

46. Ewig S, Woodhead M, Torres A (2011) Towards a sensible comprehension of severe community-acquired pneumonia. Intensive Care Med 37:214–223

47. Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, Hill AT (2011) Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. Intensive Care Med 37:1409–1420

48. Suarez D, Ferrer R, Artigas A, Azkarate I, Garnacho-Montero J, Goma G, Levy MM, Ruiz JC (2011) Cost-effectiveness of the surviving sepsis campaign protocol for severe sepsis: a prospective nation-wide study in Spain. Intensive Care Med 37:444–452

49. Kalil AC, Sun J (2011) Low-dose steroids for septic shock and severe sepsis: the use of Bayesian statistics to resolve clinical trial controversies. Intensive Care Med 37:420–429

50. Moreno R, Sprung CL, Annane D, Chevret S, Briegel J, Keh D, Singer M, Weiss YG, Payen D, Cuthbertson BH, Vincent JL (2011) Time course of organ failure in patients with septic shock treated with hydrocortisone: results of the Corticus study. Intensive Care Med 37:1765–1772

51. Vouloumanou EK, Plessa E, Karageorgopoulos DE, Mantadakis E, Falagas ME (2011) Serum procalcitonin as a diagnostic marker for neonatal sepsis: a systematic review and meta-analysis. Intensive Care Med 37:747–762

52. Pletz MW, Wellinghausen N, Welte T (2011) Will polymerase chain reaction (PCR)-based diagnostics improve outcome in septic patients? A clinical view. Intensive Care Med 37:1069–1076

53. Martin EL, Ranieri VM (2011) Phosphorylation mechanisms in intensive care medicine. Intensive Care Med 37:7–18

54. Piton G, Manzon C, Cypriani B, Carbonnel F, Capellier G (2011) Acute intestinal failure in critically ill patients: is plasma citrulline the right marker? Intensive Care Med 37:911–917

55. Valentin A, Ferdinande P (2011) Recommendations on basic requirements for intensive care units: structural and organizational aspects. Intensive Care Med 37:1575–1587

56. Jaderling G, Calzavacca P, Bell M, Martling CR, Jones D, Bellomo R, Konrad D (2011) The deteriorating ward patient: a Swedish-Australian comparison. Intensive Care Med 37:1000–1005

57. Dehmel C, Braune SA, Kreymann G, Baehr M, Langebrake C, Hilgarth H, Nierhaus A, Dartsch DC, Kluge S (2011) Do centrally pre-prepared solutions achieve more reliable drug concentrations than solutions prepared on the ward? Intensive Care Med 37:1311–1316

58. Gayat E, Resche-Rigon M, Morel O, Rossignol M, Mantz J, Nicolas-Robin A, Nathan-Denizot N, Lefrant JY, Mercier FJ, Samain E, Fargeaudou Y, Barranger E, Laisne MJ, Brechat PH, Luton D, Ouanounou I, Plaza PA, Broche C, Payen D, Mebazaa A (2011) Predictive factors of advanced interventional procedures in a multicentre severe postpartum haemorrhage study. Intensive Care Med 37:1816–1825

59. Renton J, Pilcher DV, Santamaria JD, Stow P, Bailey M, Hart G, Duke G (2011) Factors associated with increased risk of readmission to intensive care in Australia. Intensive Care Med 37:1800–1808

60. Orwelius L, Backman C, Fredrikson M, Simonsson E, Nordlund P, Samuelsson A, Sjoberg F (2011) Social integration: an important factor for health-related quality of life after critical illness. Intensive Care Med 37:831–838

61. Minne L, Ludikhuize J, de Jonge E, de Rooij S, Abu-Hanna A (2011) Prognostic models for predicting mortality in elderly ICU patients: a systematic review. Intensive Care Med 37:1258–1268

62. CoBaTrICE collaboration (2011) International standards for programmes of training in intensive care medicine in Europe. Intensive Care Med 37:385–393

63. Hunziker S, Laschinger L, Portmann-Schwarz S, Semmer NK, Tschan F, Marsch S (2011) Perceived stress and team performance during a simulated resuscitation. Intensive Care Med 37:1473–1479

64. Lautrette A, Schwebel C, Gruson D, Talbot RW, Timsit JF, Souweine B (2011) Transfer of take-home messages in graduate ICU education. Intensive Care Med 37:1323–1330

65. Rubulotta F, Moreno R, Rhodes A (2011) Intensive care medicine: finding its way in the "European labyrinth". Intensive Care Med 37:1907–1912

66. Volpicelli G (2011) Sonographic diagnosis of pneumothorax. Intensive Care Med 37:224–232

67. Xirouchaki N, Magkanas E, Vaporidi K, Kondili E, Plataki M, Patrianakos A, Akoumianaki E, Georgopoulos D (2011) Lung ultrasound in critically ill patients: comparison with bedside chest radiography. Intensive Care Med 37:1488–1493

68. Dubourg J, Javouhey E, Geeraerts T, Messerer M, Kassai B (2011) Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis. Intensive Care Med 37:1059–1068

69. Koenig SJ, Lakticova V, Mayo PH (2011) Utility of ultrasonography for detection of gastric fluid during urgent endotracheal intubation. Intensive Care Med 37:627–631

70. Eslami S, Taherzadeh Z, Schultz MJ, Abu-Hanna A (2011) Glucose variability measures and their effect on mortality: a systematic review. Intensive Care Med 37:583–593

71. Albert SG, Ariyan S, Rather A (2011) The effect of etomidate on adrenal function in critical illness: a systematic review. Intensive Care Med 37:901–910

72. Lier H, Bottiger BW, Hinkelbein J, Krep H, Bernhard M (2011) Coagulation management in multiple trauma: a systematic review. Intensive Care Med 37:572–582

73. Shander A, Walsh CE, Cromwell C (2011) Acquired hemophilia: a rare but life-threatening potential cause of bleeding in the intensive care unit. Intensive Care Med 37:1240–1249