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Year in review in Intensive Care Medicine 2014: III. Severe infections, septic shock, healthcare-associated infections, highly resistant bacteria, invasive fungal infections, severe viral infections, Ebola virus disease and paediatrics

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Introduction

This third article for the 2014 Year in Review will report publications from intensive care on severe infections (including endocarditis and peritonitis), septic shock, healthcare and ventilator associated pneumonia, highly resistant bacteria, antimicrobial therapy (including antibiotic stewardship, therapeutic drug monitoring and de-escalation), invasive fungal infections, severe viral infections, Ebola virus disease and paediatrics.

Sepsis

Circulatory dysfunction is frequently present in patients admitted to the ICU. With the literature on diagnoses, treatment and monitoring of shock updating frequently, it is important to have up-to-date guidelines. An important process to facilitate the establishment of national/local guidelines is the production of a consensus statement of scientific societies. Therefore the European Society of Intensive Care Medicine formed a taskforce to review literature and expert opinions on the diagnosis, treatment and monitoring in circulatory shock. Their report was a long expected update on the publication of the International Consensus Conference on hemodynamic monitoring in shock in 2007 [1]. The Taskforce produced 44 statements using the GRADE system principles [2] and included studies published up to October 1st 2014 [3]. Therefore this consensus statement published in December 2014 issue of *Intensive Care Medicine* represents a very up-to-date view on current evidence. The Taskforce recommends NOT using currently recommended preload parameters as a sole target of fluid resuscitation or targeting any ventricular filling pressure or volume. The Taskforce recommends to fluid resuscitate patients using more than one single hemodynamic variable and to use dynamic instead of static variables to predict fluid responsiveness whenever possible. This is in sharp contrast with the recently published Guidelines on the treatment of sepsis and septic shock from the Surviving Sepsis Campaign (SSC) [4]. In addition, guiding fluid resuscitation by CVP might even prove to be harmful [5, 6]. Nevertheless the use of the SSC guidelines has been reported to improve survival from severe sepsis and septic shock [7]. Both the adherence to the resuscitation and the management bundles of the guideline were associated with improved survival. Participation of an individual site in the SSC resulted in a significant drop in hospital mortality every 3 months and increases in site compliance with the resuscitation bundle significantly improved ICU and hospital length of stay. In the context of the previous part the question arises whether these important clinical effects of the SSC-guideline result from the adequacy of the targets in the guideline or the effect of protocolized and standardized care. Most likely it's a combination of effects that warrants further optimization of the SSC-guideline rather than discarding them [8].

The adequacy of (fluid) resuscitation in every kind of circulatory failure depends on a good understanding of the physiology of the circulation. Three publications have contributed to this important aspect. Two publications focused on the understanding of venous return [9] and hypovolaemia [10]. These two topics are closely linked as the therapy for hypovolaemia is increasing venous return. The use of CVP in this context would be to assess whether the heart can efficiently handle the increase in venous return rather than using in increase in CVP as an indicator of adequately increased venous return [9]. In the most challenging circulatory failure (septic shock) where all aspects of the three pillars of the circulation (the vasculature, the volume and the heart) might be affected [9] the understanding the pathophysiology of cardiac failure is important as is likely to affect your treatment [11].

Important to realize is that the circulation volume is not equal to the total blood volume. This mistake is frequently made my junior doctors and nurses. In a compensated state of hypovolemia, the total blood volume (the sum of stressed and unstressed volume) is decreased while the stressed volume is maintained and therefore cardiac output may be maintained as well. This results from an increased activity of the sympathetic nervous system that translates in clinical practice into decreased peripheral perfusion. An important marker of decreased peripheral perfusion is a prolonged capillary

refill time [12]. Many studies have now shown that abnormal peripheral perfusion is an important warning sign in critically ill patients. Whether this is abnormal skin color [13], abnormal tissue hemoglobin saturation [14] or increased capillary refill time [15, 16]. As abnormal peripheral tissue perfusion can be corrected by specific therapy [17] the next logical step would be to incorporate the use of peripheral perfusion parameters and specific treatment into diagnostic and therapeutic protocols to define efficacy of the use of these parameters [18].

Although many techniques are available to assess the state of the circulation, echo (cardiography) has gained importance over the last years. The Taskforce of the ESICM recommends the use of echocardiography as the preferred modality in patients where clinical examination fails to determine the type of shock [3]. In addition, echocardiography is noninvasive technique to sequentially evaluate cardiac function in patients with circulatory failure and thus preferred over the routine use of a pulmonary artery catheter [3]. In mechanically ventilated critically ill patients the use of lung ultrasound significantly changes clinical decisions and therapeutic management. In a study of 189 patients, therapy was changed directly in 47 % of the patients [19]. In patients the combination of lung ultrasound and echocardiography has proven to be superior to using lung ultrasound only [20]. Therefore thoracic echocardiography should be an important competence of the current curriculum of a trainee in intensive care.

Sepsis and endocrinopathy

The role of the hypothalamic–pituitary–adrenal axis (HPA) in critically ill patients remains a subject of interest as the discussion on supporting this axis by use of hydrocortisone and vasopressin remains actual [21]. The HPA hormones seem to be related to severity of disease in early sepsis and progression to septic shock [22]. Although hydrocortisone has a vasopressor sparing effect, it doesn't seem to affect vasopressin levels nor mortality [21]. The role of both thus needs more clarification before recommendations for combined treatment can be made [23]. Also the discussion on the use of vasopressin as a hormone substitute or as a vasopressor needs clarification as the use as a vasopressor is associated with serious adverse events not related to vasopressin blood levels but more to the presence of a specific genotype [24].

The interaction between immune system and infectious organism in not fully understood. In a recent What's new article, Douglas et al. [25] emphasized the role of innate response in sepsis. Indeed, Innate-like lymphocytes are a recently described subset of the immune response with known antibacterial properties. Human trial in critically ill patients provides the first evidence of the drop in MAIT cells during bacterial sepsis, which compounds the already known immune defects. The persistent depletion and potential for nosocomial infections is an interesting finding and likely to provide fertile grounds for future studies.

Infection and antimicrobial therapy

While it is now well recognized that early appropriate antimicrobial therapy reduces infection-related morbidity and mortality in the critically ill patients, the importance of pharmacodynamic (PD) dosing to optimize drug exposure continues to evolve. Since it is well recognized that beta-lactams efficacy is driven by the time the drug concentration exceeds the MIC (T > MIC) of the target pathogen, many of these strategies focused on altering infusion times. In the clinical setting, beta-lactam optimization strategies often include the use of a prolonged infusion (i.e., same dose administered over 3–4 h) for each dosing interval or as a continuous infusion where the total daily dose is given at a constant rate over 24 h. Each of these strategies has been reported to enhance the efficacy when compared to conventional regimens as reported by Bassetti et al. [26] in his editorial. In their interesting and intriguing study, De Waele et al. [27], using the DALI study (a prospective, multi-centre pharmacokinetic point-prevalence study) shown that in 343 critically ill patients receiving 8 different β-lactam antibiotics, antibiotic free drug concentrations remained below the MIC during 50 and 100 % of the dosing interval in 66 (19.2 %) and 142 (41.4 %) patients, respectively. The use of intermittent infusion was significantly associated with increased risk of non-attainment for both targets; creatinine clearance was independently associated with not reaching the 100 % free time above MIC (fT > MIC) target. The study demonstrated that when simulating an empirical setting where a broad range of pathogens at the susceptibility breakpoint is targeted, that target attainment using conventional β-lactam antibiotic dosing was generally inadequate. Although several factors play a role, use of intermittent infusion resulted in a three to four fold increase in the likelihood of not reaching the desired PK/PD targets. In another study, De Waele et al. [28] prospectively analyzed the effect of a dose adaption strategy using daily therapeutic drug monitoring (TDM) on the target attainment for meropenem and piperacillin/tazobactam when pneumonia was the primary infectious diagnosis. Forty-one patients

were included in the study. Eighty-five percent of patients in the TDM group needed dose adaptation, 5 required an additional increase. At 72 h, target attainment rates for 100 % $fT > 4MIC$ and 100 % $fT > MIC$ were higher in the TDM group: 58 vs. 16 % ($p = 0.007$) and 95 vs. 68 % ($p = 0.045$), respectively. The study supports a strategy of dose adaptation based on daily therapeutic drug monitoring that lead to an increase in PK/PD target attainment compared to conventional dosing in critically ill patients with normal kidney function.

Aminoglycosides continue to be essential antibiotic in ICU. When aminoglycosides are used in critically ill patients, it is crucial that their efficacy is maximized. Aminoglycosides are concentration dependent antibiotics, and the peak concentration over MIC is the relevant PK/PD parameter. Studies have shown that aminoglycosides have their maximal effect at a C_{max}/MIC ratio of 8–10. This means that TDM for efficacy may be helpful to guide therapy. Based on these considerations, as well as on the decreasing susceptibility of microorganisms, actual PK-guided dosing based on individual plasma concentrations is preferable in critically ill patients. Initial therapy (before any MIC is known) should use higher doses (amikacin 25–30 mg/kg, gentamycin 7–9 mg/kg and tobramycin 7–9 mg/kg) to compensate for the changes described, and the C_{max} of the previous dose should guide subsequent doses as reported by Dimopoulos [29] in his editorial. Under this context, recent studies shed more light on the aminoglycoside PK/PD properties in ICU patients. In a prospective study conducted by de Mont-mollin et al. [30] in a general ICU, 33 % of patients that receives a loading dose of amikacin of 25 mg/kg of total body weight (TBW), still had an amikacin C_{max} <60 mg/L. Positive 24-h fluid balance was identified as a predictive factor of C_{max} <60 mg/L. Low BMI tended to be associated with amikacin underdosing, when TBW was used, suggesting the need for higher doses in patients with a positive 24-h fluid balance. Whether these regimens are associated with improved outcomes is unknown, therefore other prospective randomized controlled studies are warranted to assess the effects of higher loading doses of amikacin on C_{max}, infection control and survival, and its impact on renal and hearing functions.

Other compound such as tigecyclin has been extensively studied because of potential activities on extensively drug-resistant bacterias. In 2010 and 2013, the US Food and Drug Administration (FDA) reported an increased risk of mortality associated with tigecycline use in comparison with other drugs in the treatment of serious infections. The analysis used a pooled group of randomized clinical trials including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), complicated skin and soft tissue infections (cSSTI),

complicated intra-abdominal infections (cIAI), and diabetic foot infections. On the basis of the pooled data analysis, the FDA recommended that alternatives to tigecycline should be considered in patients with severe infections. In their interesting article Montravers et al. [31] conclude that tigecyclin success rates in patients in ICU with severe infections appear comparable to those reported with other antibiotics; the overall success rate was 60 % at the end of treatment, and 53 % 7 days later. Furthermore, they report a survival rate of 85 % at day 28. Historically, clinical trials concerning management of critically ill and particularly ICU-admitted patients with tigecyclin are limited. Despite the obscure vision provided by an impressive number of meta-analyses, tigecyclin is expected to be used more often in approved indications and in off-label combination regimens for the treatment of MDR gram-negative infections in routine clinical practice. This is greatly supported by the Montravers study mentioned above. The increased medical need represented by the growing impact of multiresistant infections and the current lack of alternative or new antibiotics suggests that tigecycline benefit–risk continues to be positive.

Antimicrobial de-escalation

Another way to save antimicrobials is to deescalate as often as possible. Many important papers have been published in the journal on this field.

Antimicrobial de-escalation is a clinical approach to empirical antibiotic treatment of serious infections that attempts to balance the need for appropriate initial therapy with the need to limit unnecessary antimicrobial exposure in order to curtail the emergence of resistance. Although the concept of antimicrobial de-escalation seems to make intuitive sense, clinicians should ask themselves what the realistic expectations of such a strategy are. Intensivists should expect that a de-escalation approach to antimicrobial therapy in critically ill patients will optimize patient's outcomes as said by Dr Kollef [32] in his editorial. In his interesting and complete study, Garnacho-Montero et al. [33] evaluated 628 patients with severe sepsis or septic shock at ICU admission who were treated empirically with broad-spectrum antibiotics. Antibiotic therapy was guided by written protocols advocating for de-escalation therapy once the microbiological results became available (day of culture results), although this decision was ultimately the responsibility of the physician in charge of the patient. By multivariate analysis, factors independently associated with in-hospital mortality were septic shock, SOFA score

on the day of culture results, and inappropriate empirical antimicrobial therapy, whereas de-escalation of antimicrobial therapy was found to be a protective factor for hospital survival. Additionally, among patients receiving appropriate therapy the only factor independently associated with mortality was SOFA score on the day of culture results, whereas de-escalation therapy was again found to be a protective factor.

In the setting of neutropenic patient with severe sepsis or septic shock, use of broad-spectrum antibiotics is recommended. To date, the first study on the safety of de-escalation in neutropenic patients has been published in this journal by Mokart et al. [34]. De-escalation of antimicrobial therapy consisted either to delete one of the empirical antibiotic of a combined treatment, or, whenever possible, to use a betalactam antibiotic with a narrower spectrum of activity. Cumulative incidence of de-escalation of the empirical antimicrobial treatment among the 101 patients of the cohort, was 44 %, (95 % confidence interval, CI 38–53 %), including 30 (68 %) patients with ongoing neutropenia, while a microbiological documentation was available in 63 (63 %) patients. De-escalation did not significantly modify the hazard of death within the first 30-day [HR = 0.51 (95 % CI 0.20–1.33)], nor within the 1 year after ICU-discharge [HR = 1.06 (95 % CI 0.54–2.08)]. The results of the study are encouraging and impressive: for the first time the authors has shown that, in ICU, de-escalation is frequently performed in neutropenic cancer patients with severe sepsis and this approach appears not to affect the outcomes.

Surprising and apparently not expected results for de-escalation therapy were shown by Leone et al. [35] in their multicenter, non-blinded, randomized noninferiority trial included patients with severe sepsis that were randomly assigned to de-escalation or continuation of empirical antimicrobial treatment. The results shown the median duration of ICU stay was 9 [interquartile range (IQR) 5–22] days in the de-escalation group and 8 (IQR 4–15) days in the continuation group, respectively (p = 0.71). The mean difference was 3.4 (95 % CI −1.7 to 8.5). A superinfection occurred in 16 (27 %) patients in the de-escalation group and six (11 %) patients in the continuation group (p = 0.03). The numbers of antibiotic days were 9 (28–30, 36–41) and 7.5 (27–30, 36–39) in the de-escalation group and continuation group, respectively (p = 0.03). Mortality was similar in both groups. The current study casts significant doubt whether the reduction of the spectrum of the antibiotic can be considered safe as a routine measure. The authors demonstrated that de-escalation, defined as narrowing the spectrum of the antibiotic, was inferior to continuation of the initial antibiotic therapy with length of stay as the primary

outcome parameter. Furthermore, antibiotic use was higher in the de-escalation group presumably driven by the number of superinfections in the de-escalation group. A key element in the study of the potential role of de-escalation is a uniform definition of de-escalation. De-escalation—defined as narrowing the spectrum of an antibiotic treatment—should be cautiously applied, based on each particular patient's clinical status and considering the ICU environment as a whole.

Healthcare-associated pneumonia

Vallés et al. [42] prospectively compared the epidemiology, antibiotic therapy and clinical outcomes between 449 patients with community acquired pneumonia (CAP), 133 health care acquired pneumonia (HCAP) and 144 immunocompromised patients (ICP) with pneumonia admitted in 34 Spanish ICUs over a 1 year period. They found that HCAP patients had more comorbidities and had a worse clinical status as compared to the two other subgroups and that both HCAP and ICP more often needed mechanical ventilation and more often underwent tracheostomy. The incidence of gram-negative pathogens, MRSA and *Pseudomonas aeruginosa* was low overall, but higher in HCAP and ICP. Inappropriate empirical antibiotic therapy was 6.5 % in CAP, 14.4 % in HCAP and 38.6 % in ICP while mortality was the highest in ICP (38.6 %) and did not differ between CAP (18.4 %) and HCAP (21.2 %). The authors concluded that empirical antibiotic regimens recommended for CAP would be appropriate for 90 % of the patients with HCAP and that consequently systematically covering multidrug-resistant pathogens in HCAP is not necessary.

Ventilatory-acquired pneumonia

Diagnosis of ventilator-associated pneumonia (VAP) is a problem that is not yet fully solved. In fact, there have been no major advances since the last meta-analysis published by the Cochrane Collaboration [43]. Real major advances will come from rapid PCR point-of-care techniques, but these results are not yet available. In 2014, Bos et al. [44] published an article in the What's New in Intensive Care section on potential innovations that could improve early recognition of VAP. Those authors suggested that new techniques are promising in detecting airway colonization and pulmonary infection at the early phase. The first technique would use colorimetric assays inside the endotracheal tubes to detect the type of bacteria and the pattern

of resistance. The second technique is based on the detection of volatile compounds (hydrocarbons, alcohols, aldehydes, ketones and, sulfide-containing molecules) released by bacteria that cause VAP. These techniques are still in a very early clinical phase and need to be validated.

Postoperative nosocomial pneumonia is a threatening complication of major surgery (cardiovascular, thoracic and abdominal), with very high morbidity and mortality. All improvements that can help prevent postoperative pneumonia are welcome. Preoperative oral care is a non-standard prophylactic measure. Bergan et al. [45] performed a prospective study implementing several oral-hygiene measures, including a dentist visit, brushing teeth and tongue and, oral rinse with chlorhexidine (0.12 %) twice a day until surgery. With these measures, they were able to reduce pneumonia from an incidence rate of 32 cases to 1000 ventilator days in the 6 months period before the study to 10 cases per 1000 days of mechanical ventilation during the 6 months following the study. Oral chlorhexidine rinsing in the preoperative period (OR, 17) and on the day of surgery significantly were significantly protective for post-operative pneumonia. Oral chlorhexidine rinses and dental hygiene are cheap, easy and effective measures for preventing pneumonia after cardiac surgery.

Colonization with resistant bacteria

Colonization is a better indicator for bacterial dynamics than infection, since colonization only leads to infection in a small group but contributes significantly to the epidemiology of these bacteria. Knowledge about the time until clearance of resistant bacteria is of great importance for understanding nosocomial dynamics and for predicting effects of interventions. In his study Haverkate et al. [46] studied all patients screened on admission and twice weekly for resistant bacteria in 13 ICUs in 8 European countries (MOSAR-ICU trial, 2008–2011). 125 unique patients had 141 episodes of colonization and at least one readmission. Thirty-two patients were colonized with two or more resistant bacteria. Median times until clearance were 4.8 months for all resistant strains, 1.4 months for highly resistant enterobacteriaceae, less than 1 month for MRSA, and 1.5 months for vancomycin resistant enterococci. For all antimicrobial-resistant bacterial species, 50 % of the patients had lost colonization when readmitted two or more months after the previous ICU admission. Although this study was performed on a selection of hospital patients (i.e., patients admitted to ICUs), the results are of critical importance since these patients are especially prone to colonization and (subsequent) infection.

Bacteremia and MRSA

Bacteremia is one of the major causes of nosocomial infection in the intensive care unit (ICU), ICU-acquired bloodstream infection (ICU-BSI) is associated with increased morbidity and length of stay, resulting in excess costs and high mortality of critically ill patients. Although there are variations due to heterogeneous information sources and variety of local clinical practices, coagulase-negative staphylococci, Staphylococcus aureus, and Enterobacteriaceae species are the pathogens most frequently responsible for nosocomial bacteremia. Energy deficit in ICU patients is mainly caused by reduced intake due to under-prescribed calories and frequent feeding interruptions. Cumulated energy deficit build-up during the first days of ICU stay appears an independent factor contributing to nosocomial infections. In their interesting study, Ekpe et al. [47] investigated the impact of energy deficit on the microbiological results of the blood cultures of prolonged acute mechanically ventilated patients who experienced a first ICU-BSI episode. Daily energy balance was compared according to the microbiological results of the blood cultures of 92 consecutive prolonged (>96 h) acute mechanically ventilated patients who developed a first episode of ICU-BSI. Among the 92 ICU-BSI, 9 were due to methicillin-resistant Staphylococcus aureus (MRSA). The cumulated energy deficit of patients with MRSA ICU-BSI was greater than those with ICUBSI caused by other pathogens. ICU admission, risk factors for nosocomial infections, nutritional status, and conditions potentially limiting feeding did not differ significantly between the two groups. Patients with MRSA ICU-BSI had lower delivered energy and similar energy expenditure, causing higher energy deficits. More severe energy deficit and higher rate of MRSA blood cultures ($p = 0.01$ comparing quartiles) were observed. The conclusions of the study were that early in-ICU energy deficit was associated with MRSA ICU-BSI in prolonged acute mechanically ventilated patients. Results suggest that limiting the early energy deficit could be a way to optimize MRSA ICU-BSI prevention.

Bacteremia is an important cause of mortality, prolonged stay and excess healthcare costs even in paediatric intensive care units (PICU). An estimated 70 % of BSIs occurring in PICU are thought to be related to the use of central venous catheters (CVCs). Adherence to full sterile procedures may be compromised when CVCs are inserted as part of emergency resuscitation and stabilisation, particularly outside the intensive care unit. Half of emergency admissions to PICU in the UK occur after stabilisation at other hospitals. In their study Harron et al. [48] made in UK determined whether bloodstream infection (BSI) occurred more frequently in children admitted to PICU after inter-hospital transfer compared to within hospital admissions. Multivariable regression

showed no significant difference in rates of PICU-acquired BSI by source of admission (incidence-rate ratio for inter-hospital transfer versus within-hospital admission = 0.97, 95 % CI 0.87–1.07) after adjusting for other risk-factors. Rates of inter-hospital transfers decreased more rapidly between 2003 and 2012: 17.0 % (95 % CI 14.9–19.0 % per year) compared with 12.4 % (95 % CI 9.9–14.9 % per year) for within hospital admissions. The median time to first PICU-acquired BSI did not differ significantly between inter-hospital transfers (7 days, IQR 4–13) and within-hospital admissions (8 days, IQR 4–15). The authors concluded that inter-hospital transfer was no longer a significant risk factor form PICU-acquired BSI. Given the large proportion of infection occurring in the second week of admission, initiatives to further reduce PICU-acquired BSI should focus on maintaining sterile procedures after admission.

Peritonitis

Faecal peritonitis (FP) is a common cause of secondary peritonitis caused by spillage of faecal material from the large bowel into the peritoneum. The Genetics of Sepsis and Septic Shock in Europe (GenOSept) project is investigating the influence of genetic variation on the host response and outcomes in a large cohort of patients with sepsis admitted to ICUs across Europe. Tridente et al. [49] reported in their study data for 977 FP patients admitted to 102 centers across 16 countries. The most common causes of FP were perforated diverticular disease (32.1 %) and surgical anastomotic breakdown (31.1 %). The ICU mortality rate at 28 days was 19.1 %, increasing to 31.6 % at 6 months. The cause of FP, pre-existing co-morbidities and time from estimated onset of symptoms to surgery did not impact on survival. The strongest independent risk factors associated with an increased rate of death at 6 months, included age, higher APACHE II score, acute renal and cardiovascular dysfunction within one week of admission to ICU, hypothermia, lower haematocrit and bradycardia on day 1 of ICU stay.

Infective endocarditis

Although recent literature is plenty of studies concerning all aspects of infective endocarditis (IE), very few focus on severe IE requiring admission to the ICU. In their "My paper 10 years later" Wolff et al. [50] affirmed that since the publication of the paper in 2004 a lot of information has been accumulated on management of IE. While 3 sets of blood cultures allow the identification of about 90 % of cases, culture negative IE still remains a

diagnostic challenge. Blood-polymerase chain reaction in valve tissue may yield a microbiologic diagnosis. New imaging techniques such as PET-CT scans have shown additive value in patient with intra-cardiac device or valvular prosthesis. Systematic cerebral magnetic resonance imaging can lead to modification of therapeutic plans. The decision to operate and the timing of cardiac surgery should take into account the presence of congestive heart failure, neurological complications, renal failure, and multiorgan dysfunction syndrome. The strongest independent predictor of post-operative mortality was the pre-operative multiorgan failure score. Neurological failure also represented a major determinant of mortality, regardless of the mechanism of neurological complication.

Fungal infections and colonization

Fungal infections and in particular *Candida* species are responsible for between 9–12 % of all bloodstream infections and are the fourth most common cause of nosocomial bloodstream infections in most US population surveys and the sixth or seventh most common cause in European surveys. *Candida* bloodstream infections occur at highest rates in the ICU population, with this setting accounting for 33–55 % of all candidemias. In their complete and useful review Leon et al. [36] described that a high proportion of ICU patients become colonized with *Candida* species, but only 5–30 % develop invasive candidiasis. Invasive candidiasis and candidaemia are difficult to predict and early diagnosis remains a major challenge. In addition, microbiological documentation occurs often late in the course of infection. Delays in initiating appropriate treatment have been associated with increased mortality. In an attempt to decrease *Candida*-related mortality, an increasing number of critically ill patients without documented *candida* infections receive empirical systemic antifungal therapy, leading to concern for antifungal overuse. Scores/predictive rules permit the stratification and selection of high risk patients who may benefit from early antifungal therapy. However, they have a far better negative predictive value than positive predictive value. New biomarkers [mannan, antimannan, (1,3)-β-D-glucan and polymerase chain reaction] are being increasingly used to enable earlier diagnosis and, ideally, to provide prognostic information and/or therapeutic monitoring. Although reasonably sensitive and specific, these techniques remain largely investigational, and their clinical usefulness has yet to be established.

In their elegant study, Lortholary et al. [37] reported the active hospital-based surveillance program of incident episodes of candidemia in twenty-four tertiary care

hospitals in Paris area. Among 2507 adult cases included, 2571 *Candida* isolates were collected and species were *C. albicans* (56 %), *C. glabrata* (18.6 %), *C. parapsilosis* (11.5 %), *C. tropicalis* (9.3 %), *C. krusei* (2.9 %) and *C. kefyr* (1.8 %). Candidemia occurred in ICU in 1206 patients (48.1 %). When comparing ICU vs. non-ICU patients, the former had significantly more frequent surgery during the past 30 days, were more often pre-exposed to fluconazole and treated with echinocandin, and were less frequently infected with *C. parapsilosis*. A significant increased incidence in the overall population and ICU was found. Echinocandins initial therapy increased over time in ICU (4.6 % first year of study, to 48.5 % last year of study, $p < 0.0001$). ICU patients had a higher day 30 death rate than non-ICU patients [odds ratio (OR) 2.12, 95 % CI 1.66–2.72, $p < 0.0001$]. The day 30 and early (<day 8) death rates increased over time in ICU (from 41.5 % the first to 56.9 % the last year of study ($p = 0.001$) and 28.7–38.8 % ($p = 0.0292$), respectively). The authors concluded that the availability of new antifungals and the publication of numerous guidelines did not prevent an increase of candidaemia and death in ICU patients in Paris area. Apparently in contrast with the Paris study, Colombo et al. [38] retrospectively analyzed 1392 episodes of candidaemia in adult patients (647 in ICU) from 22 Brazilian hospitals. Comparing the characteristics of candidaemia in ICU patients in 2 periods (2003–2007, period 1 and 2008–2012, period 2), and assessed predictors of 30-day mortality. They reported that 30-day mortality rate decreased from 76.4 % in period 1–60.8 % in period 2 ($p < 0.001$). Predictors of 30-day mortality by multivariate analysis were older age, period 1, receipt of corticosteroids and higher APACHE II score, while treatment with an echinocandin were associated with a higher probability of survival. The authors concluded that the incorporation of echinocandins as primary therapy of candidemia seems to be associated with better outcome. As in bacterial infections however, adequate treatment remains of paramount importance in treating infections in critically ill patients. Also in patients with *candida* blood stream infections, inadequate source control and antifungal treatment have been associated with increased mortality [51]. Another important phenomenon in the management of *Candida* infections is represented by the emergence of resistance in *Candida* spp. Antifungal drug resistance was considered less problematic in *Candida* spp. than in other pathogens, but recent increases in resistance to both echinocandins and azoles have led to clinical failures. In their extensive review Maubon et al. [39] reported that acquired fluconazole resistance is frequent in *C. glabrata* (from 4 to 16 %), which increasingly displays cross-resistance to voriconazole. So far, multi-drug resistant phenotype against azole and echinocandins, has only been described for *C. glabrata* and is a matter of serious concern.

Fluconazole resistance remains uncommon in *C. albicans* (<5 %), but is more prevalent in *C. parapsilosis* (4–10 %) and *C. tropicalis* (4–9 %), however recent data shows that may reflect geographical differences. Acquired resistance to echinocandins is increasingly reported for most of the clinically important *Candida* spp. It remains uncommon in *C. albicans* (<1 %), *C. tropicalis* (<5 %) and *C. krusei* (<7 %), but is now becoming frequent in *C. glabrata* (8–15 %).

Candida spp. colonization of the airway is frequently reported in mechanically ventilated critically ill patients, and its clinical significance is difficult to evaluate. *Candida* has a low affinity for alveolar pneumocytes and histologically documented pneumonia has been rarely reported. Hematogenous dissemination in the context of candidemia may be responsible for multiple pulmonary abscesses and should be viewed as a distinct entity. Hence the existence of true candidal pneumonia is doubtful and recovery of *Candida* spp. from the respiratory tract should generally be considered as colonization and does not justify antifungal therapy. In their double-blind, placebo-controlled, multicenter pilot randomized trial, Martin et al. [40] tried to demonstrate a benefit of antifungal therapy in critically ill patients with positive airway secretion specimens for *Candida* spp. They recruited 60 patients into the randomized trial: 29 patients specifically treated with antifungals. Markers of inflammation and all clinical outcomes were comparable between placebo and antifungal treatment group at baseline and over time. At baseline, plasma TNF-alpha levels were higher in the patients colonized with *Candida* compared to the observational group (mean ± SD) (21.8 ± 23.1 vs. 12.4 ± 9.3 pg/ml $p = 0.02$) and that these patients had lower innate immune function as evidenced by reduced whole blood ex vivo LPS-induced TNF-alpha production capacity (854.8 ± 855.2 vs. 1559.4 ± 1290.6 pg/ml $p = 0.01$). This study does not provide evidence to support a larger trial examining the efficacy of empiric antifungal treatment in patients with *Candida* in the endotracheal secretions. Similar negative impact in duration of mechanical ventilation has been obtained with inhaled amphotericin-B patients with airway colonization with *Candida* sp. Ampho-B inhalation therapy was not associated with increased decolonization and might even prolong duration of mechanical ventilation possibly due to the toxicity of the drug on the lungs [52].

In addition, in a small randomized study on the efficacy of empiric treatment of suspected ventilator associated pneumonia in patients with *candida* colonization of the respiratory tract did not prove to be effective [40]. In this study persistent inflammation and immunosuppression were associated with *Candida* colonization of the lung. What to do with respiratory tract colonization in critically ill patients therefore remains an important problem [53].

For the prevention of fungal infections, oral prophylaxis with nystatin has been recently evaluated and shown to result in a reduction of *Candida* colonization [41].

The development of the *Candida* colonization index (CI) has been viewed as a major conceptual advance in the characterization of supporting the progression from colonization to infection in surgical patients [54]. In their "My paper twenty year later" Eggimann et al. [55] affirmed that since the publication of the paper in 1994, many centers have used the CI or a methodology derived from its original description to assess the dynamics of *Candida* colonization in different sub-groups of critically ill patients at risk of invasive candidiasis. Unfortunately, these data have not been validated in large multicenter trials. Several studies have indirectly suggested the validity and potential usefulness of the CI, but almost exclusively in surgical patients. Among the pitfalls, it should be emphasized that it is work-intensive with a limited bedside practicability. Furthermore, only limited data are available for nonsurgical patients, and its cost effectiveness and usefulness for the management of critically ill patients remain to be proven in large prospective clinical trials.

Koulenti et al. [56] analyzed data on epidemiology, clinical aspects and diagnostic novelties in invasive pulmonary aspergillosis (IPA) in ICU patients. They concluded that the identification of high-risk profiles for IPA of ICU patients without apparent immunosuppression might help in achieving earlier IPA diagnosis as it would lead to a higher level of suspicion and a lower threshold to perform thorough diagnostic work-out for patients at high-risk. Epidemiological research with the aim to identify the high-risk patient for IPA is going on (http://www.aspicu2.org).

In recent years, antineoplastic treatment regimens in hematological patients have intensified. This has led to a significant increase in ICU admissions due to severe infectious complications. Among these patients, pulmonary infiltrates with a fungal etiology are among the most common findings associated with febrile episodes. The increasing availability of high resolution and multislice CT has rendered the conventional chest radiograph more or less obsolete for diagnosing lung infiltrates in febrile neutropenic patients [57].

Viral pneumonia

In recent years, viral community-acquired pneumonia (CAP) has been reported as a frequent microbial etiology in severe CAP. This is due in part to the new diagnostic techniques that allow to detect old and new viruses. Middle East respiratory syndrome (MERS) is one of these new viral diseases, which is caused by an RNA beta-coronoravirus. Leung and Gomersall [58] described in *Intensive Care Medicine* the epidemiology, pathogenesis, clinical features, diagnosis, treatment, and implications for intensive care management. The clinical features of this disease are indistinguishable from other viral diseases, including viral pneumonitis. Diagnosis is made by means of epidemiological background (Middle-East travel) plus the examination of blood, urine, stool, conjunctival swabs and cerebrospinal fluid samples, in which the virus can be found using real-time reverse-transcription PCR. Most patients admitted to the ICU require mechanical ventilation. Shock and renal failure are also frequent. Unfortunately, there is no specific antiviral treatment.

Ebola infection

Ebola virus is one of the most virulent human pathogens. Since 1976, Ebola virus disease (EVD) has caused more than 20 outbreaks in Africa, with case fatality rates of 30–90 %, in the absence of any approved treatment or vaccination. It is transmitted by direct contact through broken skin or mucous membranes with blood, urine, saliva, feces, vomit, and other body fluids of symptomatic infected patients or convalescent persons, or through contaminated needle sticks. The 2014 EVD outbreak in West Africa is a public health emergency of international concern. Tattevin et al. [59] affirmed that every physician active in emergency departments or ICU worldwide may turn out to be involved in the care of patients suspected of EVD. Their take-home messages from this paper were (1) suspect EVD in any patient who presents with fever within three weeks after a stay in Guinea, Sierra Leone, Liberia, or Nigeria; (2) while implementing infection control procedures to prevent any secondary cases (in case EVD is confirmed), ensure that all plausible differential diagnoses are appropriately considered and managed.

Even Parkes-Ratanshi et al. [60] in their article urgently recommend that health facilities consult national guidelines on EVD and develop local action plans. During this epidemic this internet and social media such as Twitter are being effectively used to disseminate information by the WHO, governments and the medical press. As the WHO are predicting that that the end of the epidemic is far away and it may infect up to 100,000 people before it is controlled; it is essential that the global medical community remains informed and vigilant. The critical care teams working with patients who have been evacuated to resource rich settings during the current epidemic must share their best practices as soon as possible.

Regarding the organ dysfunction, Beeching et al. [61] in their article explained that the pathogenesis of EVD shows both similarities with and differences from other causes of viral haemorrhagic fever or bacterial sepsis. Systematic prospective observational studies are essential to clarify the pathogenesis and pathophysiology of disease in humans and to inform the development of evidence based clinical scoring systems and management algorithms, as well as the evaluation of novel therapeutic agents. Improving access to basic supportive care is essential. The role and possible benefit of more aggressive critical care interventions continue to be debated.

Paediatrics

Deep trouble: unwanted effects of sedation and support

We have had a year of notable submissions including novel reviews of large datasets, randomized controlled trials, and state-of-the-art "What's new" articles. However, arguably the most compelling piece of paediatric intensive care literature from 2014 in ICM was the simple but profound recollection of a month spent on a paediatric intensive care unit: 'Coma alarm dreams' [62]. Written by a remarkable young man describing his recovery from a gunshot wound to the head, this 500-word piece provides an uncomfortable insight into our patient's experiences. We may hardly notice monitor alarms; they form the soundtrack of our working lives. But for our patients the experience may be the complete opposite: dreams, nightmares and hallucinations.

Dr Emeriaud and colleagues [63] from Montreal, highlighted another problem during paediatric critical illness that is easily overlooked. They performed repeated estimations of maximal inspiratory diaphragmatic electrical activity (EAdimax) in 55 ventilated children. This first systematic description of the natural history of this parameter provides in number of insights; there were frequent periods of little or no detectable diaphragmatic activity during mechanical ventilation; those values that were seen during during full ventilation were much lower than pre-extubation or spontaneous breathing; and patients intubated mainly because of a lung pathology exhibited higher EAdi ($p < 0.01$) than did patients supported for other reasons. The authors add to the emerging view that we may be oversedating and oversupporting many of our patients. The possibility of using EAdi as a proxy endpoint for clinical trials or as a biomarker for guiding mechanical ventilation is intriguing.

Ventilation/ARDS

"How to manage ventilation in pediatric acute respiratory distress syndrome" by Kneyber, Jouvert and Rimensburger [64] returned to this theme of the limitations of our current practice and the need to recognize the potential harm we might be causing. They present a candid view of the many gaps in our knowledge: is our (new) Berlin definition sufficient for selection of patients for randomized trials? Is it appropriate to infer guidance from adult studies? Does ∼6 mls/kg tidal volume really represent our best guess safe and effective ventilation during both acute and recovery phase of lung injury? Can we generate clinically meaningful guidance from the bedside tools such as transpulmonary pressure (TPP) measurements and electrical impedance tomography (EIT)? Perhaps most pressingly, many paediatric intensivists treasure the use of high frequency oscillation in paediatric ARDS on very limited evidence. Surely we need clinical trial data in the face of the results from the Oscillate and Oscar trials. We are again challenged to provide data to systematise our sedation and weaning policies.

ECMO

Drs MacLaren, Brown and Thiagarajan [65] gave us a view of "What's new in pediatric ECMO" from four continents. Overall survival after ECMO is improving and therefore other indications are starting to be considered (bridge to lung transplantation anyone?). They highlighted specific area of concerns including the need for more information about advantages of specific pumps or anticoagulant regimens. But above all there is a clear need for long-term follow up. Recent reports of very high rates of late death for cardiac ECMO make this point starkly: only 10 % of hypoplastic left heart syndrome cases who received ECMO were alive 5 years later. The impact on the family with high rates of post-traumatic stress, the importance of neurological complications, and the value of neurodevelopment follow-up, as highlighted in the journal in 2013, were noted [66–68].

Non-invasive ventilation

At the other end of the spectrum of severity of respiratory failure, we published an important study from Kremlin-Bicetre Hospital in Paris, documenting the associations of a change in practice from predominantly invasive ventilation to predominantly nasopharyngeal CPAP support in

infants with bronchiolitis [69]. The authors readily acknowledge that they cannot account for potential confounders that might arise from other changes in practice or case mix. That said, the numbers of cases observed ($n = 525$) and the size of the effect: 81 % invasive ventilation falling to 12 % over 10 years with associated significant reductions in length of stay and costs mean that we should not ignore these data.

The increasing options and environments in which non-invasive ventilation may be useful was highlighted by Dr Schlapbach and colleagues [70] from Brisbane Australia. High-Flow Nasal Cannula was increasingly used in predominantly aeromedical transports over a median distance of 205 km. The availability of HFNC was associated with a reduced need for intubation when adjusted for PIM2 score, age, and the presence respiratory disease. Changes in the case mix received in Brisbane do limit the interpretation of these data but they form part of a steady trend towards increasing use of non-invasive support in our speciality. This was reviewed by Argent and Biban [71] who asked: "What's new on NIV in the PICU: does everyone in respiratory failure require endotracheal intubation"? In this piece they highlighted the very few published randomised studies (5) and prospective cohort studies (10) which represent the best data on NIV in paediatric critical illness currently available. One of the problems around generating evidence is the variety of techniques, triggering mechanisms, patient interfaces as well as options for patient selection and timing. These combine to make good research in this area difficult. However this is no excuse for not attempting it. Argent and Biban put it clearly: Non-invasive techniques have potential to "substantially improve the safety of ventilator support for children, and improve access to ventilatory support for both acute and chronic conditions. Given that respiratory problems are among the most important cause of childhood deaths across the world, it behoves us to explore the potential and collect the data."

Paediatric airway

Research on the paediatric airway was a strong theme in this year's ICM. Dr Wakeham and colleagues [72] used the Virtual Paediatric Intensive Care database to document the very wide variability in practice around tracheostomy use on 82 North American paediatric intensive care units. Only 6.6 % of 13,323 admissions underwent tracheostomy at a median length of stay of 14 days. Interquartile range was 7.4–25.7 days. Tracheostomy rate amongst the larger contributors to the study varied from 0 to 13.4 %. The authors right suggest that these differences are unlikely to be attributable to case mix differences alone. This sets paediatric

intensivists a serious challenge to remove unhelpful variability on practice.

Dr Baranwal and colleagues [73] made a valuable contribution to another unknown in paediatric airway management. They asked if 24-h dexamethasone pretreatment was superior to 6-h pretreatment for prevention of postextubation airway obstruction in children? They recruited 124 children between the ages of 3 months and 12 years in an elegant randomized double-blind trial. The two groups were similar at baseline. The longer (24 h) pre-treatment significantly reduced both the incidence (24 h pre-treatment 65 %, 43/66 vs. 6 h 83 %, 48/58; $p = 0.02$, relative risk 0.79, 95 % CI 0.63–0.97) [74] and duration of post-extubation airway obstruction as assessed by a modified croup score. The longer pre-treatment halved the re-intubation rate (0.53, 95 % CI 0.19–1.49): but the study was not powered to detect a difference in these relatively rare events (only 14 re-intubations took place in the study). The implications of these data are not clear since pre-treating for 24 h might mean delaying extubation in some scenarios.

Outcome prediction

Prince et al. [75] from London examined the association of 'weight-for-age' and case mix adjusted outcomes in 14,307 critically ill children. In addition to the size of this dataset, a strength was the comparison to a healthy reference population in the United Kingdom. Not surprisingly, critically ill children have lower weight-for-age than do their healthly peers. This study confirmed the findings amongst adults and in smaller paediatric studies that children with weight-for-age above the population mean have significantly better case-mix adjusted survival. The similar 'obesity paradox' has been observed in adults with sepsis. Indeed the association of weight-for-age and standardised mortality ratio follows a U-shaped distribution (as do many things in intensive care). The accompanying editorial from Nadel and Argent points out how much more information we need to understand the nutritional needs of our patient [76].

Zinter et al. [77] described outcomes for 10,365 paediatric cancer emergency admissions out of 246,346 admissions to the US virtual PICU systems database. A diagnosis of leukaemia of lymphoma 'outside of first induction,' still carries a 'high-risk' tariff in the Paediatric Index of Mortality scoring system at ICU admission [78]. But things may be changing. Overall survival for paediatric cancer continues to improve with 83 % 5 year survival but 38 % of paediatric cancer patients make at least one visit to the ICU. This large series observed only a 6.8 % ICU mortality to cancer admissions to PICU. This figure lower than many series quote for previously healthy

children with community-acquired sepsis or acute respiratory distress syndrome (ARDS) on PICU The observed relative risk of PICU death with cancer is still highly significant at 2.9 (95 % CI 2.7–3.1), but the truth is that this reflects the overall improvement in PICU outcomes more than cancer lagging behind. Acute myeloid leukaemia cases had much worse outcome in multiple variant analysis. Strikingly a 50 % survival of ECMO in both solid and haematological cancer patients was seen—

though the post hematopoietic stem cell transplant group did uniformly badly.

In summary, 2014 was characterized by two main themes: mining of large datasets to reveal patterns in our care of which we were previously unaware, and observations highlighting the many and varied gaps in our knowledge.

Conflicts of interest None.

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