

Massimo Antonelli  
Elie Azoulay  
Marc Bonten  
Jean Chastre  
Giuseppe Citerio  
Giorgio Conti  
Daniel De Backer  
François Lemaire  
Herwig Gerlach  
Johan Groeneveld  
Goran Hedenstierna  
Duncan Macrae  
Jordi Mancebo  
Salvatore M. Maggiore  
Alexandre Mebazaa  
Philipp Metnitz  
Jerôme Pugin  
Jan Wernerman  
Haibo Zhang

## Year in review in Intensive Care Medicine, 2008: I. Brain injury and neurology, renal failure and endocrinology, metabolism and nutrition, sepsis, infections and pneumonia

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An increasing number of manuscript on neurological topics have been submitted and published during year 2008, ranging from head injury, subarachnoid hemorrhage, electrical disturbances and delirium.

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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

E. Azoulay  
Intensive Care Medicine Unit,  
Saint Louis Hospital, Paris, France

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

J. Chastre  
Reanimation Medicale, Hopital Pitié  
Salpêtrière, Paris, France

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

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

F. Lemaire  
Intensive Care Unit, Henri Mondor  
Hospital, Creteil, France

H. Gerlach  
Department of Anesthesiology,  
Vivantes-Klinikum Neukoelln,  
Berlin, Germany

J. Groeneveld  
Intensive Care Medicine Unit, VUMC,  
Amsterdam, The Netherlands

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

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

P. Metnitz  
Department of Anesthesia and General  
Intensive Care Medicine, University  
Hospital of Vienna, Vienna, Austria

J. Pugin  
Intensive Care Medicine Unit, University  
Hospital of Geneva, Geneva, Switzerland

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

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

## Traumatic brain injury

Recent experimental evidence suggests that matrix metalloproteinases (MMPs) are implicated in the pathophysiology of traumatic brain injury (TBI) by increasing blood–brain barrier permeability and exacerbating post-traumatic edema. MMPs are zinc-dependent and cell surface-associated endopeptidases that cleave all extracellular matrix (ECM) components, including collagen, laminin, and proteoglycans. The MMPs and their potential deleterious effects are tightly regulated at transcriptional and post-transcriptional levels through proform activation and by MMP tissue inhibitors (TIMPs). Two members of this family have a very specific and marked activity against gelatin and are termed gelatinases. *In vitro* studies have demonstrated that the secretion of gelatinases is significantly increased in cortical cultures when mechanical injury is simulated. In human TBI, data about the presence of gelatinases in the brain extracellular fluid (ECF) and their temporal profile, both in plasma and ECF, are still lacking. Sahuquillo's group [1] examined the acute profile of MMP-2 and MMP-9 in the plasma of patients with moderate or severe TBI and, more interestingly, in the brain extracellular fluid (ECF). High levels of gelatinases were found in plasma and brain ECF in the early phase of TBI, indicating that both local and systemic trauma-induced upregulation of gelatinases in the acute phase might play an important role in the pathophysiology of TBI and could be a future therapeutic target.

After admission in intensive care units (ICU), clinicians are often challenged with the contemporary management of intracranial priorities and extra-cranial complications. The incidence and severity of non-neurological organ dysfunction in acute neurological patients has been studied analyzing the database from the observational Sepsis Occurrence in Acutely Ill Patients (SOAP) study in 198 ICU [2]. The data comes from 373 cases, 12% of the 3,147 patients in the SOAP database, admitted with a neurological diagnosis, 41% with traumatic brain injury and 50% with cerebrovascular accident.

Neurological patients developed ICU-acquired sepsis and respiratory failure more frequently than the other patients, and length of stay, ICU and hospital mortality were higher compared with non-neurological patients. Multivariate logistic analysis showed that cardiovascular failure, hepatic failure, and ALI/ARDS were factors independently associated with a higher risk of death in the ICU.

One of the main intracranial therapy targets in the acute phase is high intracranial pressure (HICP). Mauritz [3] described ICP use in a sample of 1,856 severe TBI from a registry of patients admitted to Austrian ICUs between 1998 and 2004. Mauritz aimed to investigate reasons why patients did or did not receive ICP

monitoring and to describe factors influencing hospital mortality after severe TBI. The ad hoc created statistical model explains only 37% of the variance of the use of ICP monitoring, but clearly showed that severity and age are importantly associated with ICP monitoring. The more severe, as the less injured, cases were less likely to be submitted to ICP. That is likely to reflect a clinical judgment concerning who can benefit from invasive monitoring. An evaluation of potential salvageability is part of the decisional analysis. Interestingly, no clear, standardized definition of "salvageability" is available. Older patients are less often monitored. The second aim of the paper was to analyze the impact of several predictors, including ICP monitoring, on mortality at hospital discharge. The study confirms a clear association between the number of cases treated by center per year and better outcome. This supports the benefit of centralization, as shown in TBI and other neurological non-traumatic pathologies. Finally, an additional result was that the subgroup with the highest rate of ICP monitoring had the lowest mortality suggesting a utility of monitoring and treating high ICP.

Due to potential complication ICP related, even if minor in good hands, non-invasive methods of ICP measuring are appealing. Between others, the relationship between optic nerve sheath diameter (ONSD) and ICP in neurocritical care patients has been explored [4]. A significant relationship between ONSD and ICP was recorded. Changes in ICP were strongly correlated with changes in ONSD. Enlarged ONSD was a suitable predictor of elevated ICP. Even if the studied cohort was limited, non-invasive measurements were correlated with invasive ICP. This method, once validated in a wider number of patients, could be used as a screening test when raised ICP is suspected.

Stocchetti [5] quantified, in a prospective study of 407 consecutive TBI patients, the occurrence of HICP refractory to conventional medical therapy. In this TBI subset more aggressive therapies, as profound hyperventilation, barbiturates, decompressive craniectomy, are currently used. HICP is frequent; 153 patients had at least 1 day of ICP > 20 mmHg. Early surgery was necessary for 221 cases, and standard medical therapy [sedation, mannitol, cerebrospinal fluid (CSF) withdrawal, PaCO<sub>2</sub> 30–35 mmHg] was used in 135 patients. Reinforced treatment (PaCO<sub>2</sub> 25–29 mmHg, induced arterial hypertension, muscle relaxants) was used in 179 cases (44%), and second-tier therapies in 80 (20%). Surgical decompression and/or barbiturates were used in 28 of 407 cases (7%). Six-month outcome was favorable (good recovery or moderate disability) in 195 cases (53%). HICP was associated with worse outcome. Outcome for cases who had received second-tier therapies was significantly worse (43% favorable at 6 months,  $P = 0.03$ ). Therefore, HICP is frequent and is associated

with worse outcome. The indications for surgical decompression and/or barbiturates seem restricted to less than 10% of severe TBI.

The use of hyperventilation and the adherence to international guidelines after TBI have been studied [6] analyzing data coming from 22 European centers, participating in the BrainIT initiative (<http://www.brainit.org>). One hundred and fifty-one patients and 7,703 ABGs, representing 2,269 ventilation episodes (VE), were included in the analysis. Patients without elevated intracranial pressure (ICP <20 mmHg) manifested a statistically significant higher PaCO<sub>2</sub> (36 ± 5.7 mmHg) in comparison to patients with elevated ICP (≥20 mmHg) (34 ± 5.4 mmHg). Intensified forced hyperventilation (PaCO<sub>2</sub> ≤ 25 mmHg) in the absence of elevated ICP was found in only 49 VE (2%). Early prophylactic hyperventilation was used in 1,224 VE (54%). During forced hyperventilation simultaneous monitoring of cerebral oxygenation was used in only 9%. Overall adherence to current guidelines seems common, but early prophylactic hyperventilation and the use of additional cerebral oxygenation monitoring during forced hyperventilation are not followed exposing the patient to potential iatrogenic complications.

After the acute phase, hormonal disturbances have been described both in TBI and in subarachnoid hemorrhage patients. Maiya [7] retrospectively studied acute anatomical changes in the pituitary gland in 41 TBI patients undergoing magnetic resonance imaging (MRI) during the acute phase. MRI scans from 43 normal healthy volunteers were used as controls. The pituitary glands were significantly enlarged in the TBI group. Twelve of the 41 cases (30%) demonstrated focal changes. In approximately 30% of patients acute TBI was associated with pituitary gland enlargement with specific lesions. MRI of the pituitary may provide useful information about the mechanisms involved in post-traumatic hypopituitarism.

The Neuro-Intensive Care and Emergency Medicine (NICEM) Section of the European Society of Intensive Care Medicine (ESICM) developed a document on neuromonitoring in neuro-intensive care [8]. The questions discussed and addressed in this manuscript were: (1) Who should have ICP monitoring and for how long? (2) What ICP technologies are available and what are their relative advantages/disadvantages? (3) Should CPP monitoring and autoregulation testing be used? (4) When should brain tissue oxygen tension [PbrO(2)] be monitored? (5) Should structurally normal or abnormal tissue be monitored with PbrO(2)? (6) Should microdialysis be considered in complex cases? This articulated paper provide useful information to clinicians working in NICU and also to those developing specialist NICU services within their hospital practice.

## Subarachnoid hemorrhage

The paper by Schlenk [9] in patients with subarachnoid hemorrhage suggests, as indicated by Strong [10] in the accompanying editorial, that great caution is needed in choice of a target range for plasma glucose if tight glycemic control with insulin is undertaken. The Authors in a prospective, nonrandomized, single-center study, explored whether hyperglycemia exerts deleterious effects via cerebral energy metabolism and the effects of cerebral high/low glucose in patients with aneurysmal subarachnoid hemorrhage. In all patients a microdialysis catheter was inserted. Cerebral low-glucose episodes and high-glucose episodes occurred independently of blood glucose levels. During high-glucose episodes cerebral microdialysate levels were normal, while cerebral low glucose, occurring more frequently in symptomatic patients, was associated with severe cellular distress, i.e., increase in lactate/pyruvate ratio, glutamate, glycerol and with unfavorable outcome. Cerebral low glucose was associated with severe metabolic distress and may present a target for therapy to improve clinical outcome. Tight glycemic control could be deleterious in this neurological population.

## Electrical activity in ICU/epilepsy

Legriel [11] studied 140 ICU patients with status epilepticus (SE). Median seizure time was 60 min and 58 patients had seizures longer than 30 min. The most common causes of SE were cerebral insult in 53% and anticonvulsant drug withdrawal in 20% of patients. No cause was identified in 35% of patients. Median time from SE to treatment was 5. The SE was refractory in 25% patients. Hospital mortality was 21%. By multivariate analysis, independent predictors of 30-day mortality were age, GCS at scene, continuous SE, symptomatic SE and refractory SE. Further studies are needed to evaluate the possible impact of early maximal anticonvulsant treatment on outcomes.

An increasing interest is rising re-evaluating the utility of monitoring cerebral electrical activity. This is done, usually, with continuous EEG system even if other, simpler, approaches are explored. Walsh [12] prospectively assessed whether the Entropy Module, a device to measure hypnosis in anesthesia, is a valid measure of sedation state in critically ill patients. Four hundred and seventy-five trained observer assessments were made and compared with concurrent entropy numbers. Entropy of the frontal EEG does not discriminate sedation state adequately for clinical use in ICU patients.

## Delirium and other neurological problems

Morandi [13] and coworkers undertook a multinational effort to identify conflicts in terminology and phenomenology of delirium to facilitate communication across medical disciplines and languages. The evaluation of the terminology used for acute brain dysfunction was determined conducting communications with 24 authors from academic communities throughout countries/regions that speak the 13 variants of the Romanic languages included into this manuscript. Interestingly only 54% use the term delirium to indicate the disorder as defined by the DSM-IV as an acute change in mental status, inattention, disorganized thinking and altered level of consciousness. Attempts towards standardization in terminology, or at least awareness of differences across languages and specialties, will help cross-talk among clinicians and researchers.

Cheung [14] surveyed the same topic in Canadian ICUs with a response rate of 58.3%. When an etiological cognitive dysfunction diagnosis was obvious, 83–85% responded with the medical diagnosis to explain the cognitive abnormalities; only 43–55% used the term “delirium”. In contrast, where an underlying medical problem was lacking, 74% of respondents diagnosed “delirium”. Non-pharmacological and pharmacological management varied considerably. Commonly selected pharmacological agents were antipsychotics and benzodiazepines, followed by narcotics, non-narcotic analgesics, and other sedatives. Canadian intensivists diagnose delirium based upon the presence or absence of an obvious medical etiology.

Looking for delirium scoring methods, Plaschke [15] assessed the agreement between the delirium ratings of two independent delirium assessment methods: the Confusion Assessment method for the ICU and the Intensive Care Delirium Screening Checklist (ICDSC). After excluding permanently unconscious patients with  $\leq 4$  on the Richmond Agitation Sedations scale (RASS), delirium was identified in 71 of the 174 patients (41%). The patients who were included were tested in 374 paired but researcher-independent ratings of delirium by both scoring methods. The kappa coefficient determined over 7 days of ICU stay was 0.80, indicating good agreement.

Soja [16] implemented delirium monitoring, test reliability, and monitor compliance of performing the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) in trauma patients. Following a web-based teaching module, bedside nurses evaluated patients daily for depth of sedation with the RASS and for the presence of delirium with the CAM-ICU. On randomly assigned days, evaluations by nursing staff were followed by evaluations by an expert evaluator to assess compliance and reliability of the CAM-ICU in trauma patients. Overall agreement (kappa) between nurses and expert

evaluator was 0.77. The survey revealed that nurses were confident in performing the CAM-ICU, realized the importance of delirium, and were satisfied with the training that they received. Defining the etiology of hyponatremia in acute neurological patients is a sometime an intriguing challenge. Brimiouille [17] assessed whether hyponatremia is associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or with cerebral salt-wasting syndrome (CSWS). Measurement of blood, plasma, and red blood cell volumes to discriminate SIADH and CSWS. Renal, adrenal and thyroid functions were normal in all patients. Average blood, plasma, and red blood cell volumes were 54, 37 and 17 ml/kg in control patients and 54, 37 and 18 ml/kg in hyponatremic patients, respectively. The adequate blood volumes in hyponatremic patients confirmed the diagnosis of SIADH and did not support the concept of CSWS.

Hausfater [18] studied the effect of non-exertional heatstroke on serum procalcitonin (PCT) levels in 53 patients with defined heatstroke during the August 2003 heat wave in France were analyzed; 30-day mortality was recorded. Among the 53 patients included, 14 (26%) were admitted to an intensive care unit (ICU). At 30 days, 24 patients (45%) had died. Median PCT value was 0.58  $\mu\text{g/l}$  and 31 (58%) patients had PCT above 0.2  $\mu\text{g/l}$  (PCT+). Temperature above or equal to 40°C was the only variable significantly associated with fatal outcome. Median PCT values were similar between survivors and non-survivors ( $P = 0.22$ ). High serum PCT levels was observed in heatstroke without concomitant bacterial infection. The PCT was not a valid mortality predictor in heatstroke, but could be an indicator of the severity of illness.

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## Endocrinology and renal failure

The use of a single dose of etomidate to facilitate laryngeal intubation is still widespread in spite of the demonstration of the potential of the drug to inhibit the last step in cortisol synthesis in the adrenal cortex. The recent CORTICUS study also shows the in vivo capability of the drug to suppress ACTH-cortisol responses, at least in septic patients. The clinical consequences, however, remain unclear, in spite of awareness of the problem for decades. The paper by Vinclair et al. [19] somewhat adds to the evidence in describing the in vivo effects of etomidate in non-septic patients in the course of time, in terms of ratios of circulating  $11\beta$ -deoxycortisol to cortisol, reflecting in vivo activity of the last enzymatic step in cortisol synthesis potentially inhibited by etomidate. The results suggest, in the absence of a control group, that the ratio increases after etomidate administration and is associated with a diminished rise in circulating cortisol upon ACTH. The etomidate effect has waned in 91% of

patients after 48 h. Again, the clinical consequences remain unclear.

Adrenal insufficiency has been recently observed in critically ill patients with liver cirrhosis and severe sepsis. du Cheyron et al. [20] thus postulated that hyperreninemic hypoaldosteronism may be common and may have an impact on outcome in patients with acute on chronic liver failure. The authors thus investigated the relation between the adrenal production of gluco- and mineralo-corticoids, inflammatory status and outcome in critically ill patients with liver cirrhosis. They included 50 consecutive patients with liver cirrhosis and applied a corticotropin stimulation test within 12 h following ICU admission. Hyperreninemic hypoaldosteronism syndrome was defined as basal renin over aldosterone ratio (RRA) higher than 2. They found impaired adrenal function in 41 (82%) patients. 26 patients (52%) presented with an RRA >2. Patients with RRA >2 exhibited greater disease severity and organ dysfunction scores at baseline, but risk-adjusted mortality rates were not different between the two groups. Renin and IL-6 plasma concentrations were positively correlated. A Cox regression analysis revealed hyperreninemic hypoaldosteronism syndrome, IL-6 higher than 400 pg/ml and severe renal failure to be independent predictors of 30-day mortality. The authors concluded that adrenal dysfunction was common in critically ill cirrhotic patients. Hyperreninemic hypoaldosteronism syndrome was related to a greater pro-inflammatory status and degree of acute organ failure, and was independently associated with a worse prognosis.

In attempts to prevent harmful acute kidney injury (AKI) and acute renal failure (ARF) in the critically ill, control of intraabdominal hypertension may contribute. To this end, accurate measurements of intraabdominal pressure are warranted. Malbrain and colleagues [21] compared 315 (15 observers) manual Foley catheter, and automated Spiegelberg catheter and CiMON<sup>®</sup>-balloon catheter measurements with the applied hydrostatic pressure in a 3-l container. The measurements (between 0–30 cm H<sub>2</sub>O) were very close to each other. It is therefore suggested that manual are as good as automated measurements (and vice versa).

Other preventive measures may include drug treatments and in this context Heemskerk et al. [22] report on the interesting potential of inhibiting NO-induced soluble guanylate cyclase by methylene blue (MB) administration. In a small ( $n=9$ , uncontrolled) series of (refractory) septic shock patients, they suggested on the basis of a decrease in NO metabolites and excretion of renal tubular injury markers in the urine that MB (4 mg/kg over 4 h) was able to decrease renal tubular damage and increase renal function parameters. However, the outcome benefits of such treatment warrant further study. The results obtained may thus increase our mechanistic rather than therapeutic insight.

When AKI/ARF has nonetheless developed, renal replacement therapy must be initiated, the type, timing and dosing of which continues to be subject of debate. In a randomized study on septic patients ( $n=10/9$ ) with need for renal replacement, high volume (65 ml/kg per h) was compared with low volume (35 ml/kg per h) hemofiltration [23]. The former treatment resulted in less norepinephrine requirements to maintain mean arterial blood pressure and urine output tended to increase. There was no effect on renal recovery/survival in this small, but unique (randomized!) study, while the effect on hemodynamics confirms observational data.

Extracorporeal therapy with polymyxin-B to scavenge endotoxin in severely septic patients has been tried before. In the study by Cantaluppi et al. [24] however, the technique was used to evaluate its effect on circulating proapoptotic factors in gram-negative sepsis ( $n=8$  PMX-B,  $n=8$  standard care) that could play a role, among others, in the development of organ damage such as AKI/ARF. There were some indications that this therapy indeed worked in this preliminary mechanistic study. Circulating proapoptotic factors on cultured renal cells diminished, as well as SOFA/RIFLE scores, proteinuria and tubular enzymes. The data suggest a role of apoptosis in the development of sepsis-related AKI/ARF.

When clinicians have decided on the basis of likelihood of resuming endogenous renal function, to discontinue renal replacement therapy, some patients later again need such treatment. This issue has been addressed retrospectively by Wu et al. [25] from Taiwan, who, not unexpectedly, found that, among others, oliguria, high age and SOFA, and a long period of prior need for renal replacement predicted its recurrent need (in 30%, within 30 days). Indeed, some patients may have only partial recovery of renal function or remain on renal replacement therapy even months after the initial insult. Moreover, AKI/ARF is a risk factor for chronic renal failure over decades. The paper thus again nicely illustrates that AKI/ARF with need for renal replacement therapy is not a benign disorder and the future challenge, of course, is to find ways to promote full recovery and limit (recurrent) need for renal replacement therapy.

Two physiological reviews and notes have dealt with renal failure, as part of a cardio-renal syndrome and as a basis for renal replacement therapy [26, 27]. The authors extend the link between heart and kidney beyond congestive heart failure and also indicate a more aggressive approach in the use of different renal therapies.

Hemofilter circuits used for extracorporeal renal replacement therapy have an expected lifespan of 48–72 h. However, they often clot prematurely which impairs azotemic control and has also effects on costs and nursing workload. Antithrombin (AT) deficiency has been associated with hemofilter thrombosis (HT) in patients with sepsis. Lanquetot et al. [28] investigated whether there was

an association between AT level activity and HT occurrence during early continuous hemofiltration. They included 48 consecutive patients following cardiopulmonary bypass. Subjects were grouped according to the appearance of one or more episodes of hemofilter thrombosis. Morbidity and mortality did not differ significantly between the two groups. The authors found initial AT activity to be low in both groups. On the following days AT activity was lower in the HT group but was not found to be a predictor of HT in multivariate analysis. The authors concluded that the potential interest of monitoring AT levels to adapt anticoagulant strategy needs to be analyzed in larger series of patients.

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## Metabolism and nutrition

During 2008 there has been a number of studies over tight glucose control. Honiden et al. [29] reported in a prospective observational study that early tight glucose control, within 48 h from ICU admission, was associated with a better outcome in terms of mortality, ventilator free days, and length of stay. Also after the use of stepwise regression analysis, the differences between the two groups remained associated with the timing of the tight glucose control. The result calls for a prospective randomized trial to address the timing of tight glucose control. Two studies report of the advantages of a computerized algorithm to facilitate and to increase success rate of tight glucose control. Pachler et al. [30] evaluated their algorithm in a small randomized study. They found a mean blood glucose value within the target range and a lower hyperglycemic index in the group using a computerized algorithm, but also a shorter sampling interval. Safety was evaluated by hypoglycemia, which was inconclusive, with overall only one hypoglycemic event in the 25 + 25 patients. In a questionnaire, nurses were in favor of the computerized algorithm. Vogelzang et al. [31] report from a large observational study that the hypoglycemia rate was low (0.85%) and that target level was reached faster and with fewer samples when the computerized algorithm was used. Lapichino et al. [32] investigated if tight glucose control affected NO-metabolism as reflected by the circulating levels of asymmetric-dimethylarginine. In a prospective study of 72 patients in septic shock they found no difference attributable to tight glucose control in clinical outcome parameters or in asymmetric-dimethylarginine. Mean blood glucose were 110 versus 163 mg/dl, respectively, in the two groups.

Ornithine transcarbamylase deficiency is a rare disorder usually diagnosed in childhood, which may also have an adult onset and which gives encephalopathy and obscure unconsciousness. Panlaqui et al. [33] report of a case and point out the possible treatment with hemodia-

filtration, protein elimination, and ammonia scavenging medications. The possibility of recovery with correct diagnosis and treatment makes awareness of such a rare condition important.

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## Nutrition

Nguyen et al. [34] used manometry to study gastric motility. In a small case-control study they showed that critically ill patients have an impaired motility both in the antrum and pyloric region. Furthermore, the synchronization between the two regions was also impaired in the critically ill patients. Using gastric scintigraphic data Nguyen et al. [35] also report from a small observational study that the mode of sedation may influence gastric emptying. Patients kept on midazolam and morphine had a significantly slower gastric emptying as compared to patients kept on propofol. The result clearly calls for a larger prospective randomized study. The cumulated energy deficit in ICU patients primarily on enteral nutrition, which has been reported in several studies, is mainly related to underfeeding during the initial week of ICU stay. Desachy et al. [36] report of a prospective randomized study in 100 consecutive patients given enteral nutrition introduced stepwise or all at once. Success rate in terms of calories delivered was significantly better in the groups given the full dose of enteral nutrition from start. That group had a larger fraction of gastric residues >300 ml, but the rate of adverse events necessitating complementary parenteral nutrition was similar in the two groups. Adverse effects related to the use of prokinetic therapy was reported by Nguyen et al. [37] in an observational study of 180 consecutive patients receiving erythromycin, metoclopramide or the combination of the two. Patients given the combination had a higher rate of diarrhea, but no single patient had a positive toxin test for *Clostridium difficile*.

The role of immuno-modulating diets (IMDs) in critically ill patients is controversial. Marik and colleagues [38] in the November issue published a meta-analysis to determine the impact of IMDs on hospital mortality, nosocomial infections and length of stay (LOS) in critically ill patients.

By using the MEDLINE, Embase, Cochrane Register of Controlled Trials as data source, were selected randomized control trials (RCTs) that compared the outcome of critically ill patients receiving an IMD or a control diet. Twenty-four studies (with a total of 3,013 patients) were included in the meta-analysis; 12 studies included ICU patients, 5 burn patients and 7 trauma patients. Four of the studies used formulas supplemented with arginine, two with arginine and glutamine, nine with arginine and fish oil (FO), two with arginine, glutamine and FO, six with

glutamine alone and three studies used a formula supplemented with FO alone. Overall IMDs had no effect on mortality or LOS, but reduced the number of infections. Mortality, infections and LOS were significantly lower only in the ICU patients receiving the FO IMD. The authors concluded that an IMD supplemented with FO improved the outcome of medical ICU patients (with SIRS/sepsis/ARDS). IMDs supplemented with arginine with/without additional glutamine or FO do not appear to offer an advantage over standard enteral formulas in ICU, trauma and burn patients.

The ratio of omega-3 to omega-6 polyunsaturated fatty acids in the diet is suggested to have implications on the severity of the inflammatory response. Friesecke et al. [39] randomized 177 consecutive patients on parenteral nutrition, also stratified for SIRS or not, to receive a standard fat emulsion or a fish-oil enriched emulsion rich in omega-3 polyunsaturated fatty acids. Endpoints were interleukin 6 and monocyte HLA-DR as well as a number of morbidity/mortality parameters. No differences in any of the parameters studied were seen, which illustrates the difficulty to reproduce the promising results from animal studies in a relevant clinical material.

Regulation of the activity of transcription factor NF-kappaB is an important therapeutic effect of the major omega-3 fatty acids in FO, eicosapentaenoic and docosahexaenoic acid (EPA and DHA). Using the articles obtained by a Pubmed research, Singer and colleagues [40] reviewed three aspects of NF-kappaB/inflammatory inhibition by fish oil: (1) the inhibition of the NF-kappaB pathway at different levels, (2) the production of Resolvin D1 and Protectin D1 that are potent, endogenous, DHA-derived lipid mediators that attenuate neutrophil migration and tissue injury in peritonitis and ischemia-reperfusion injury, (3) the modulation of vagal tone with potential anti-inflammatory effects. The authors concluded that whether the pleiotropic actions of EPA/DHA contribute to FO's therapeutic effect in sepsis remained to be shown.

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## Sepsis and infections

In the January issue, in conjunction with Critical Care Medicine was published the controversial guidelines for management of severe sepsis and septic shock with the intent of providing an update to the original Surviving Sepsis Campaign clinical management guidelines, "Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock," published in 2004 [41]. The authors used the GRADE system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations. Key recommendations, listed by category, include: early goal-

directed resuscitation of the septic patient during the first 6 h after recognition (1C); blood cultures prior to antibiotic therapy (1C); imaging studies performed promptly to confirm potential source of infection (1C); administration of broad-spectrum antibiotic therapy within 1 h of diagnosis of septic shock (1B) and severe sepsis without septic shock (1D); reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate (1C); a usual 7–10 days of antibiotic therapy guided by clinical response (1D); source control with attention to the balance of risks and benefits of the chosen method (1C); administration of either crystalloid or colloid fluid resuscitation (1B); fluid challenge to restore mean circulating filling pressure (1C); reduction in rate of fluid administration with rising filling pressures and no improvement in tissue perfusion (1D); vasopressor preference for norepinephrine or dopamine to maintain an initial target of mean arterial pressure  $\geq$  65 mm Hg (1C); dobutamine inotropic therapy when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy (1C); stress-dose steroid therapy given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy (2C); recombinant activated protein C in patients with severe sepsis and clinical assessment of high risk for death (2B except 2C for post-operative patients). In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, target a hemoglobin of 7–9 g/dl (1B); a low tidal volume (1B) and limitation of inspiratory plateau pressure strategy (1C) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure in acute lung injury (1C); head of bed elevation in mechanically ventilated patients unless contraindicated (1B); avoiding routine use of pulmonary artery catheters in ALI/ARDS (1A); to decrease days of mechanical ventilation and ICU length of stay, a conservative fluid strategy for patients with established ALI/ARDS who are not in shock (1C); protocols for weaning and sedation/analgesia (1B); using either intermittent bolus sedation or continuous infusion sedation with daily interruptions or lightening (1B); avoidance of neuromuscular blockers, if at all possible (1B); institution of glycemic control (1B) targeting a blood glucose  $<$ 150 mg/dl after initial stabilization (2C); equivalency of continuous veno-veno hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1A); use of stress ulcer prophylaxis to prevent upper GI bleeding using H2 blockers (1A) or proton pump inhibitors (1B); and consideration of limitation of support where appropriate (1D). Recommendations specific to pediatric severe sepsis include: greater use of physical examination therapeutic end points (2C); dopamine as the first drug of choice for hypotension (2C); steroids only in children with suspected or proven adrenal insufficiency

(2C); a recommendation against the use of recombinant activated protein C in children (1B). The authors concluded that evidenced-based recommendations regarding the acute management of sepsis and septic shock are the first step toward improved outcomes for this important group of critically ill patients.

The field of biomarkers for systemic inflammatory response syndrome (SIRS) and sepsis is continuously evolving. The role of osteopontin, a protein with cell signaling functions in the interstitium upon inflammation, has been studied as a sepsis marker, by Vaschetto et al. [42] in 56 SIRS/sepsis patients (vs. 56 controls). The investigators demonstrated that circulating osteopontin could be used as a marker of IL-6 release and of sepsis (vs. SIRS), even though the levels were elevated in SIRS (vs. control) as well. Osteopontin appeared capable of increasing IL-6 secretion by macrophages *in vitro*. It is unclear how specific the findings were for microbial infection, however. Dulhunty et al. [43] reported on a multi-center study ( $n = 3,543$  patients) done in Australia and New Zealand to answer the question whether severe non-infectious SIRS differs from severe sepsis in the ICU, regarding epidemiological issues. Even though mortality rates were similar, severe non-septic SIRS was more common and more often associated with neurological abnormalities and causes of death, than severe sepsis. This study adds to the idea that infection *per se* is not a major determinant of patient outcome, in contrast to the response of the body to either non-infectious or infectious threats.

Interactions of inflammatory mediators (or biomarkers) in sepsis remain immensely complex. de Kruif et al. [44] demonstrated that some of these biomarkers are dose-dependently inhibited by corticosteroid treatment, and variations in the gene expression of interleukins 23 and 27 appeared to be different between septic ICU patients, non-septic bacteremic patients and healthy controls [45]. And patients undergoing elective cardiac surgery, preoperative levels of apolipoprotein CI were associated with increased perioperative levels of TNF- $\alpha$  in patients experiencing endotoxemia [46].

Payen and colleagues [47] assessed blood leucocytes gene profiling in the course of the septic shock recovery period and tested the relation between encoding gene expression and protein level in 17 septic shock patients. Gene expression levels were studied on a dedicated microarray of 340 genes involved in inflammatory processes. The time-related gene expression study showed significant changes in ten genes. Among them, S100A8 and S100A12 had a reduced expression over time compared with D0, whereas CD74's expression increased. By RT-qPCR, the S100A8 plasma levels decrease in parallel with the gene expression decrease. The CD74 gene expression evolution significantly correlated with HLA-DR monocyte expression.

Moreno and coworkers [48] wished to evaluate the value of the PIRO concept in septic patients. PIRO stands for predisposition, infection, response and outcome. The predictive value for outcome of pre-morbid factors, together with infectious features in the ICU and the subsequent changes in sequential organ failure assessment (SOFA) were evaluated. The SAPS 3 database was used for this purpose, on 2,628 patients with signs of infection in the ICU >48 h. Sepsis, severe sepsis and septic shock were defined according to standard criteria. Hospital mortality was 41%. Predictive factors were scored as the SAPS 3 PIRO score which appeared to have excellent (even somewhat better than the SAPS 3 model) predictive value for mortality. The conclusion of the authors is that PIRO components independently contribute to outcome prediction. Thereby, the study is one of the first to argue in favor of the clinical validity as well as the practicability or usefulness of the PIRO concept.

Early identification of septic patients at high risk of death may provide an opportunity to change the treatment strategy to improve the outcome. Because plasma midregional pro-atrial natriuretic peptide (MR-proANP) concentrations have recently emerged as a valuable tool for individual risk assessment in such a setting, Seligman et al. investigated the prognostic role of this marker in 71 consecutive patients who developed VAP [49]. The study demonstrated that MR-proANP levels were significantly higher in VAP patients dying within 28 days when compared to survivors. In multivariate logistic regression models of predictors of death including age, sex, APACHE II, and blood creatinine, MR-proANP levels on the day of diagnosis of VAP and on day 4 turned out to be the only parameters that remained as independent predictors.

Lipoproteins, and in particular high-density lipoproteins (HDL), have been demonstrated to play an important role in modulating inflammation and the response to infection. Because apolipoprotein CI (apoCI) protects against the development of murine bacterial sepsis and is virtually completely depleted in human sepsis, its time-course in patients with severe sepsis may predict survival. This hypothesis was confirmed in a small pilot study performed by Berbee et al. [50]. Upon hospitalization, apoCI levels were approximately 5 times lower than normal values in 16 septic patients. Remarkably, apoCI levels remained low in non-survivors, whereas apoCI levels gradually increased to normal levels in survivors.

During the host response to infection and the development of sepsis and shock, vasopressor-insensitive hypotension (shock) may supervene for which the clinician may consider adjunctive therapy with hydrocortisone. Kaufmann et al. [51] again demonstrated in 30 patients with septic shock that hydrocortisone treatment decreases vasopressor requirements and circulating IL-6. Moreover, this therapy preserved opsonization (zymosan)-dependent



neutrophil functions, while suppressing spontaneous hydrogen peroxide release (flow cytometry). The (small) study was placebo-controlled. These data may help our understanding of the mechanism of action of steroid therapy in septic shock and suggest that hydrocortisone has no major immunosuppressive effects on neutrophils limiting host defences.

Severe sepsis and septic shock are serious complications of hematological malignancies. Vandijck and colleagues [52] compared characteristics and outcomes in ICU patients with hematological malignancies and severe sepsis/septic shock who had or had not received recent intravenous chemotherapy. Among the 186 patients, there were 77 patients with severe sepsis and 109 with septic shock; 91 (49%) had received recent intravenous chemotherapy. In-hospital, and 6-month mortality rates were 45.1 versus 58.9%, and 50.5 versus 63.2% in patients with and without recent chemotherapy, respectively. By multivariate analysis, previous chemotherapy was protective. After adjustment with a propensity score for recent chemotherapy, chemotherapy was not associated with outcome.

Activated protein C for severe sepsis patients is a controversial therapy. In the study of Kalil and Sun [53], the authors aimed to respond to two questions. The first was, what is the current probability that activated protein C is not better than the control? and, if the current probability is not small, then the second question was, how many patients will be needed for the activated protein C confirmatory trial? To give an adequate response to these questions, the authors used a Bayesian statistical approach. The *P* value commonly used in frequentist statistical methods only tell us how likely we will observe the reported data when the null hypothesis is true, but does not tell us the actual probability of treatment effect. Bayesian methodology, however, can provide this actual (or current) probability. To do this, all available data is selected for the prior probability. The prior distributions were defined as severe skeptic, moderate skeptic, mild skeptic and enthusiastic. The authors found that, except for the enthusiastic analysis, the current probabilities that activated protein C is not better than the control are not small (range, 0.14-0.48). The number of patients needed for a confirmatory trial ranged between 0 and 8,350. The authors concluded that a confirmatory trial with about 600 patients with severe sepsis and high risk of death can provide a convincing answer for moderate and mild skeptic physicians regarding the efficacy of the drug.

In a special article published in the November issue Finfer et al. [54] report on the ongoing new trial of activated protein C for persistent septic shock. The authors, members of the steering committee of the trial, fully discuss the potential benefits and harm of this drug and provide in-depth explanations about organizational issues and the sponsor's role, the design and the goals of this ongoing study, the safety monitoring and the analysis and

report of the data. A full disclosure of the conflicts of interest is provided in the ESM file accompanying this article, together with the complete study protocol. Because its particular characteristics, this article is accompanied by editors' comments [55], and two editorials: one providing an European view on this issue [56], the other providing a North-American view [57].

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## Infections and pneumonia

Intravascular-device related infections remain among the most frequent infectious complications of intensive care treatment. Yet, the absolute risk on infection per catheter per day is low, hampering the analysis of intervention studies aimed to reduce this incidence. In a large study by Gowardman et al. [58], the incidence density of tip colonization (15.1/1,000 catheter days) was almost ten times as high as that of catheter-related infection (1.8/1,000 catheter days). In another observational study, the incidence density of arterial catheter colonization was 19.9 per 1000 catheter days, and the relative risk of colonization increased in time [59], as did the risk for central venous catheter-related infection in a Spanish multi-center study [60].

Indeed, bacterial growth on the tip of catheters has been used as a proxy for catheter-related infections. In a prospective study, Souweine and coworkers [61] determined that in patients without a clinical suspicion of catheter-related infection, the chance of bacterial growth on the tip was 4.7% (8.0 per 1,000 catheter days) and that administration of antibiotics at the time of removal was associated with a lower risk of tip colonization. Therefore, proportions of patients on antibiotics at the time of line removal should be taken into account when using this proxy as an endpoint.

All predictions are difficult, especially when they involve the outcome of infections and sepsis. Yet, several studies aimed to identify accurate prognostic factors. An increment of C-reactive protein of 10 mg/l increased the odds of death after ICU-discharge with 1.09 (95% CI 1.03–1.16) after adjustment for age, APACHE II score predicted mortality and Delta SOFA with an area under the receiver operating characteristic curve of 0.85 (95% CI 0.73–0.96) [62]. In ICU patients, high loads of herpes simplex type I virus in bronchoalveolar lavage fluid were associated with mortality. Boer and coworkers [63] developed a prognostic model for the presence of post-traumatic stress syndrome after abdominal sepsis, that included age, length of ICU stay and having traumatic memories of the ICU or hospital stay [64].

The numbers of studies evaluating genetic associations with outcome is now rapidly increasing. Angiotensin-converting enzyme insertion/deletion polymorphism was

not associated with outcome in sepsis and ARDS (Villar et al. [65]).

Selective Decontamination of the Digestive Tract (SDD) is a frequently used infection prevention measure in some countries. In SDD, non-absorbable antibiotics are applied topically and it has been assumed that detectable systemic levels of these agents, such as tobramycin, will not be reached. However, detectable serum levels of tobramycin were measured in 63% of patients receiving both SDD and CVVH. One patient had a toxic level of 3 mg/l [66]. In a randomized cross-over study, Langgartner and coworkers [67] demonstrated that appropriate bacterial concentrations of meropenem in patients on continuous renal replacement therapy could be achieved with continuous infusion, with similar areas under the curve but longer times above the MIC as with intermittent bolus injection.

Water sinks are considered as relevant sources for many bacterial species, including *Pseudomonas aeruginosa*. In a non-outbreak setting, these bacteria were isolated from 86% of samples taken from U-bends and in 5% of those from tap water. Yet, based upon genotyping, only 1 of 14 patients was colonized by a *P. aeruginosa* clone also isolated from water samples [68].

*Candida* infections remain a crucial issue in the ICU. In a 1-year National perspective observational study conducted in 24 adult French ICUs Bougnoux and colleagues [69] determined the concomitant incidence, molecular diversity, management and outcome. The study enrolled 262 with nosocomial candidemia and/or candiduria. The mean incidences of candidemia and candiduria were 6.7 and 27.4/1,000 admissions, respectively. Eight percent of candiduric patients developed candidemia with the same species. The mean interval between ICU admission and candidemia was  $19.0 \pm 2.9$  days, and  $17.2 \pm 1.1$  days for candiduria. *C. albicans* and *C. glabrata* were isolated in 54.2 and 17% of blood and 66.5 and 21.6% of urine *Candida*-positive cultures, respectively. Fluconazole was the most frequently prescribed agent. Crude ICU mortality was 61.8% for candidemic and 31.3% for candiduric patients. Seventy-five percent of the patients were infected with a unique *C. albicans* strain; cross-transmission between seven patients was suggested in one hospital. No difference in susceptibility and genetic background were found between blood and urine strains of *Candida* species.

It is difficult to judge the quality of care in different ICUs. Objective and reproducible criteria are badly needed, but hampered by the absence of a gold standard. Najjar-Pellet and coworkers [70] proposed a scoring system based upon 95 variables that might serve as a tool for quality assessment in future studies. One quality variable, not included in the previously mentioned scoring system, is the recognition of rare diseases, such as, for instance acute disseminated encephalomyelitis (ADEM). In a retrospective multi-center study of 6 years Sonnevile and

coworkers [71] describe the characteristics of 20 ADEM patients needing ICU admission. ADEM is not a benign disease, as 25% of the patients died and 35% had persistent functional sequelae.

P Damas and colleagues [72] in an observational single-center study assessed the temporal relationship between ICU-acquired infection (IAI) and the prevalence and severity of organ dysfunction or failure (OD/F). Almost 2,200 patients hospitalized for more than 2 days during a 2-year observation period were studied: 845 did not acquire IAI, 306 of whom had infection on admission (IOA); 346 did acquire IAI, 125 of whom had IOA. The SAPS II and SOFA score of the first 24 h were significantly higher in patients with than in those without IAI. SOFApreinf of IAI patients was also higher than the SOFAMax of patients without IAI both in patients with ( $12.1 \pm 4.6$  vs.  $8.9 \pm 4.7$ ) and those without IOA ( $9.2 \pm 4.0$  vs.  $6.7 \pm 3.5$ ). SOFApreinf represented 85.7% of the value of SOFAMax in patients with IAI. SOFApreinf increased significantly with the occurrence of sepsis, severe sepsis, or septic shock during ICU stay. The authors concluded that ICU-acquired infections are significantly associated with hospital mortality; but their contribution to OD/F seems minor.

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## Advances in treatment

Aminoglycosides are broad-spectrum antibiotics active against most pathogens responsible for ventilator-associated pneumonia (VAP), even those with multidrug-resistance patterns. However, the systemic use of this antibiotic class is limited by its toxicity and poor penetration into the lung. Aerosol administration offers the theoretical advantage of achieving high antibiotic concentrations at the infection site and low systemic absorption, thereby avoiding renal toxicity. However, some uncertainties persist regarding the real usefulness of such a mode of administration, since during mechanical ventilation (MV), high amounts of the particles dispersed by conventional nebulizers remain in the ventilatory circuits and the tracheobronchial tree before reaching the distal lung. In a study carried out in subjects with healthy lungs, Ehrmann et al. [73] showed that, using an optimized nebulization technique with a vertical spacer placed underneath a vibrating mesh nebulizer, doses of 60 mg/kg amikacin were associated with serum concentrations equal to or less than those obtained after intravenous infusion of 15 mg/kg amikacin. Because amikacin systemic pharmacokinetics reflect deposition of the nebulized drug in the distal pulmonary parenchyma, these data strongly support the hypothesis that optimized nebulization of antimicrobial agents may permit to obtain very high lung parenchyma concentrations during a

sufficiently long period of time for achieving bactericidal activity.

Despite advances in prophylactic perioperative antibiotic therapy, post-operative pneumonia is a feared complication following major surgery and is associated with an ICU mortality of 10–20%. One of the major predisposing factors is insufficient target-site concentration of antibiotics used for prophylaxis. Because ventilation/perfusion mismatch due to atelectasis may also influence antibiotic distribution to lung tissue, hence increasing the risk of post-operative pneumonia, Hutschala et al. compared the penetration of levofloxacin into the lung of two groups of patients, using microdialysis probes to sequentially determine in vivo lung tissue levels. The first group consisted of five patients who underwent coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) (atelectasis model), and the second one, of five patients operated with the off-pump coronary artery bypass grafting (OPCAB)-technique [74]. In the OPCAB-group, the median of the maximum concentration of levofloxacin in lung tissue was significantly higher compared with the CPB-group, establishing that atelectasis formations lead to critically lower lung tissue concentrations of levofloxacin in non-dependent parts of lung tissue. Such data emphasizes the necessity of direct interstitial antibiotic measurement to re-evaluate commonly accepted prophylactic and therapeutic antibiotic dosages in various clinical settings and pulmonary diseases associated with the formation of atelectasis.

To favorably impact the outcome of patients with severe nosocomial sepsis, antibiotic therapy covering the offending pathogen has to be initiated without delay, which implies administration within 24 h of clinical deterioration. In patients at risk for infection with multi-drug resistant (MDR) pathogens, the clinician has to resort to broad-spectrum antimicrobials, which are themselves linked with the emergence of multi-drug resistance. The potential value of systematic endotracheal tracheal surveillance cultures as a tool to predict involvement of MDR microorganisms in VAP was studied by two independent groups of investigators [75, 76]. In the first study, Depuydt et al. were able to document that a 3-weekly tracheal aspirate protocol in intubated patients had a sensitivity to predict MDR pathogens of 69% with a specificity of 96%. Appropriate antibiotic coverage within 24 and 48 h following MDR VAP was 77 and 89%, respectively. A carbapenem-based empirical scheme would have been equally appropriate (83 vs. 77% at 24 h; 83 vs. 89% at 48 h), but a beta-lactam-fluoroquinolone empirical therapy would have been less (59 vs. 77% at 24 h; 59 vs. 89% at 48 h) as would have been beta-lactam-aminoglycoside therapy (68 vs. 77% at 24 h; 68 vs. 89% at 48 h). Very similar results were obtained by Papadomichelakis et al. in a retrospective cohort study of patients who had developed VAP or bloodstream

infection (BSI) caused by a MDR pathogen, and in whom tracheal aspirates were obtained twice weekly and rectal swabs once weekly. Knowledge of previous colonization improved the rate of adequate empiric antimicrobial treatment (91 vs. 40% in VAP and 86 vs. 50% in BSI cases,  $P < 0.05$ ), confirming that colonization surveillance for resistant gram-negative microorganisms is predictive of subsequent infection etiology and can improve empiric antimicrobial treatment adequacy in a critical care setting.

International guidelines recommend screening patients for methicillin-resistant *Staphylococcus aureus* (MRSA) on admission, although consensus on sites required for optimum detection has not been reached. To determine whether throat and rectal swabs identified a significant number of additional MRSA-colonized patients not captured by swabbing at keratinized skin carriage sites (anterior nares, perineum and axillae), Batra et al. [77] evaluated 1,470 consecutive ICU patients. One hundred and five (7%) patients were admitted with MRSA, of which only 63 (60%) were detected by a pooled keratinized skin swab. A further 36 (34%) patients were detected only by throat or rectal swabs. Indeed, throat and rectal swabs combined had a higher sensitivity than pooled keratinised skin swabs (76 vs. 60%  $P = 0.03$ ). Thus, a complete identification of patients colonized by MRSA may need sampling of the throat and rectum, and not only the anterior nares, axillae, and peritoneum.

Bacterial colonization of the respiratory tract frequently persists, even when a patient receives antimicrobial treatment, and even though the colonizing bacteria are, in vitro, susceptible to the antibiotics. To test the hypothesis that antibiotics with presumed efficacy, based on in vitro susceptibility testing, reduce the likelihood of persistence of respiratory tract colonization, compared to antibiotics presumed to be ineffective or when no antibiotics were administered at all, Visscher et al. [78] analyzed endotracheal aspirate cultures performed during ICU stay in a large cohort of 715 mechanically ventilated ICU patients. Systemic antibiotics were administered on 7,102 (61%) of patient days. Antibiotic use was associated with non-persistence for all pathogens, except *Acinetobacter* species and *P. aeruginosa*. Relative risks for non-persistence (as compared to ineffective or no antibiotics) ranged from 3.1 (95% CI 1.4–6.6) for *H. influenzae* to 0.5 (0.3–1.0) for *Acinetobacter* species. Pathogen-specific characteristics, such as the ability of biofilm formation of *P. aeruginosa*, or patient-specific characteristics, such as the severity of underlying disease or immune paralysis, could both be involved, but further studies are needed to elucidate this matter.

Unlike *Mycobacterium tuberculosis*, nontuberculous mycobacteria (NTM) exist in the environment and can be isolated from clinical specimens in the absence of true

infection. In patients with complicated and critical conditions, such as those admitted to ICU, the clinical significance of NTM in respiratory specimens and the prognostic impact of NTM pulmonary infection are even more difficult to understand than in stable patients. Therefore, Shu et al. conducted a retrospective study including all medical ICU patients with NTM being isolated from respiratory specimens within a period of 8.5 years to evaluate the clinical significance of the presence of NTM and compare the demographic characteristics, clinical manifestations, and outcome in patients with NTM pulmonary infection with those with NTM colonization and control subjects whose respiratory samples were culture-negative for mycobacteria [79]. Among the 5,378 patients admitted to medical ICUs, NTM were isolated from 169 (5.8%) patients. Of them, 47 (28%) were considered NTM pulmonary infection. Within 100 days after ICU admission, significantly more patients with NTM infection died than those with NTM colonization and control subjects (47 vs. 8 vs. 14%,  $P < 0.001$ ). Therefore, keeping a high suspicion when NTM is isolated and using careful consideration when starting anti-NTM treatment should be emphasized.

### Diagnosis

In the absence of a clinically available gold standard, VAP is usually diagnosed according to a combination of criteria, such as systemic signs of infection, abnormalities on chest radiograph, and microbiological identification of pathogens; however, each of these criterions combines high sensitivity with low specificity. In an attempt to raise diagnostic accuracy, Luyt et al. [80] assesses the predictive capacity for the diagnosis of VAP of serum procalcitonin levels before and on the day it is suspected. Among the 73 suspected episodes VAP was confirmed by quantitative bronchoalveolar lavage cultures in 32 and refuted in 41. On day 1 a 0.5 ng/ml procalcitonin threshold had 72% sensitivity but only 24% specificity for diagnosing VAP. Between “before” and day 1, procalcitonin increased in 41 and 15% of patients with and without VAP, respectively. Thus, crude values and procalcitonin rise had poor diagnostic value for VAP in this particular setting and should not be used to initiate antibiotics when VAP is clinically suspected.

Mixed results were also observed by El Solh et al. [81] when they examined the potential role of serum and alveolar soluble triggering receptor expressed on myeloid cells (sTREM-1) as a biological marker of pulmonary aspiration syndromes. While circulating levels of sTREM-1 were comparable between those with aspiration syndromes and controls, the alveolar levels of sTREM-1

were higher in patients with culture-positive pulmonary aspiration compared with those culture-negative pulmonary aspiration ( $P < 0.001$ ). A cut-off value of 250 pg/ml for alveolar sTREM-1 achieved a sensitivity of 66% and a specificity of 92% with an area under the curve of 0.87.

Because cells and secretions recovered by bronchoalveolar lavage (BAL) can be microscopically examined immediately after the procedure to detect the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, this technique is particularly well suited to provide rapid identification of patients with pneumonia. However, it is commonly assumed that prior antimicrobial therapy can dramatically decrease its sensitivity. In order to re-assess the influence of antibiotics on the value of various BAL cytological parameters in diagnosing VAP, Linssen et al. [82] studied 335 episodes of clinically suspected VAP in 282 patients. There was no difference in areas under the curve (AUCs) of receiver operating characteristic curves between patients with and without antibiotic therapy for any parameter studied. The most prominent AUCs were: total cell count, 0.65; percentage polymorphonuclear neutrophils, 0.71; and percentage infected cells, 0.90. Based on these data, it appears that the percentage of infected cells in BALF can be reliably used for diagnosing VAP in patients receiving antibiotic therapy, provided that the introduction of the new antibiotics was recent (less than 72 h).

### Prevention

VAP remains a major problem in intensive care units and effective preventive measures are eagerly searched for. The presence of an endotracheal tube (ETT) not only compromises the natural barrier between the oropharynx and trachea, but also provides a protected environment for pathogens since a biofilm develops on its inner and outer surfaces. In an attempt to prevent bacterial colonization of the lower respiratory tract in patients requiring mechanical ventilation, Berra et al. [83] developed a polyurethane ETT coated with silver sulfadiazine. In a second study, the same group of investigators randomized 46 adult patients to be intubated with a standard non-coated ETT, or with a silver sulfadiazine-coated ETT [84]. Coating with silver sulfadiazine prevented bacterial colonization of the ETT and was associated with a thinner mucus layer. Although preliminary, these data support the hypothesis that an endotracheal tube coated externally and internally with a potent antiseptic product such as silver could exert a sustained antimicrobial effect within the proximal airways and block biofilm formation at its surface.

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