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Year in review in intensive care medicine, 2005. III. Nutrition, pediatric and neonatal critical care, and experimental

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This review intends to summarize all articles published in Intensive Care Medicine in 2005, grouped by specific topics.

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Nutrition

The potential benefit of enteral immunonutrition remains uncertain and controversial despite numerous previous studies. Kieft and colleagues [1] completed another clinical trial in two ICUs. Strengths of their study are the randomized, double-blind design, inclusion of 597 adult ICU patients, and intention-to-treat analysis. The control feeds were isocaloric but the "immunonutrition" (Stresson Multi Fibre, Nutricia) had a higher total protein content. Immunonutrition had no effect on patient outcome regardless of whether assessed on a intention-to-treat or per-protocol basis. The authors also carried out post-hoc subgroup analyses in groups of interest: those with sepsis and Acute Physiology and Chronic Health Evaluation (APACHE) II scores of 10–20. Patients with sepsis are thought to be harmed by arginine-supplemented feeds, but no statistically significant difference was found in the small group ($n = 30$) of patients with sepsis. It is suggested midrange APACHE II score patients ($n = 336$) may benefit from immunonutrition, but no statistically significant difference was found in this study. However, a further post-hoc analysis in women ($n = 170$) showed a consistent trend to worse outcomes if given immunonutrition. As pointed out by the authors, this gender difference warrants further investigation.

An accompanying editorial by Heyland and Dahliwal [2] highlights the difficulty of separating the effects of the components of immunonutrition, especially in heterogeneous patient populations. A focus on single-nutrient supplements in homogeneous patient populations is advocated to determine the effects of glutamine, ω-3 fatty acids and antioxidants in patients having elective surgery and in the critically ill, with or without sepsis. To date, arginine supplementation appears to harm critically ill patients with sepsis and to have no benefit in other patient groups.

To determine the effect of parenteral glutamine on serum heat shock protein 70 (HSP-70) concentrations in critically ill patients Ziegler et al. [3] conducted an analysis of HSP-70 concentration in a subgroup of patients included in a clinical trial of glutamine-dipeptide supplemented parenteral nutrition at 0.5mg/kg per day in a surgical ICU. In previous experimental studies glutamine increased serum HSP-70 concentrations, and it is known that HSP-70 can protect against cellular injury and death in models of sepsis. The subgroup included in the study ($n = 29$) were patients who completed more than 7 days of parenteral nutrition. The patients supplemented with parenteral glutamine dipeptide ($n = 15$) had significantly greater HSP-70 concentrations at 7 days. The mean APACHE II at baseline was 13, and overall mortality is not stated; however, a relationship was found between glutamine induced increases in HSP-70 concentration and decreased ICU length of stay (or days of mechanical ventilation). While the association does not prove a cause-effect relationship, it provides an interesting hypothesis to explore for the mechanism of any effect of glutamine supplementation on clinical outcomes.

Another finding that warrants confirmation and further investigation is the potential benefit of olive oil based high-lipid parenteral nutrition. Huschak et al. [4] conducted a pilot study comparing olive oil based nutrition (ClinOleic 20%, Baxter, Germany) with a more conventional parenteral nutrition solution in which the lipid component was Lipofundin H 20% (Braun, Germany). The study group was 33 patients with multiple trauma, with the 18 "olive oil" solution patients receiving 75% of their nonprotein parenteral energy as lipid compared to 37% in the conventional group. Both groups were also introduced to enteral nutrition from day 1, but only to a maximum of 5 kcal/kg during the first 6 days. The feeds were isonitrogenous. Patients given the "olive oil" based nutrition had lower blood glucose concentrations and a shorter duration of mechanical ventilation (13 ± 9 vs. 20 ± 7 days) and ICU stay (18 ± 11 vs. 25 ± 7 days). The study was small and unblinded, and as the authors acknowledge, further studies are needed.

While nitrogen balance was virtually identical in the two study groups in the previous study, Bouletreau and colleagues [5] in a small ($n = 47$) but multicenter, randomized, blinded comparison of parenteral nutrition with energy ratio of 50:50 or 80:20 for glucose and lipid, found a small — 1.4g/day (95% CI 0.07–2.05) — nitrogen sparing effect in the glucose:lipid 80:20 group without any difference in clinical outcomes. The solutions used were Aminomixl, Aminomix2, and Lipoven (Fresenius) to give a daily total of 3 kcal/kg and 0.27 g/kg for both groups. Lipoven is a 20% soja oil emulsion. As expected, blood glucose trended higher in the 80:20 group, but it can be speculated that insulin rather than the glucose:lipid energy ratio per se caused the effect on nitrogen balance.

The evidence favoring earlier enteral nutrition creates a need to improve gastric emptying in many critically ill patients. A comparison by Ritz and colleagues [6] of erythromycin 70 or 200 mg or placebo in a randomized, blinded study in a randomly selected group of 35 mechanically ventilated patients (median admission APACHE II 19) found 70 and 200 mg doses were equally better than placebo in promoting gastric emptying. Gastric emptying was assessed using the [^{13}C] octanoic acid breath test as a 10-ml nutrient test meal on 2 consecutive days — on the first a baseline measurement of gastric emptying was made, and on the second the measurement was made after a dose of erythromycin or placebo. Both doses improved gastric emptying when it was delayed, but not when the baseline measurement was normal. Thus the lower dose of erythromycin, 70 mg, could be used instead of the commonly recommended 200 mg to improve gastric emptying, with a consequent reduction in side effects.

Cocaine body packers

The frequency of "body packing" — concealing cocaine in the body — is a sad reflection on international illicit drug trafficking. De Prost and others [7] describe no less than 581 subjects arrested over 4 years at the two Paris international airports who were referred under legal custody to a single emergency unit. The mean number of packets concealed was 70 ± 20, with a range of 18–150. When a packet ruptures, intoxication is massive and rapid. The presence of packets was confirmed by plain abdominal radiography; in 573 subjects the packets were excreted without complication. Only eight subjects needed ICU admission: six because of packet rupture and cocaine intoxication and two because of intestinal obstruction. Six subjects needed surgery: one had a cardiac arrest, one a myocardial infarction, one ventricular fibrillation and two status epilepticus. While the overall frequency of serious complications was low in this closely monitored group, it is a grim reminder of the adverse effects of drug trafficking.

Acute hepatic failure

The mortality rate in cases of acute hepatic failure remains high, with urgent liver transplantation providing the only hope for many patients. To examine the effect of a molecular adsorbent recirculating system (MARS) in acute hepatic failure Lai et al. [8] conducted a prospective observational study in ten consecutive patients referred to a regional liver transplant center. The system is an albumin-based dialysis system that removes both protein bound water insoluble and water soluble molecules. Eight patients had paracetamol hepatotoxicity, one a reaction to isoniazid, and one seronegative hepatitis. MARS was generally well tolerated. Treatment was associated with a significant increase in systemic vascular resistance, reduction in cardiac index, and clearance of urea and creatinine without any change in intracranial pressure, but the hemodynamic changes were not sustained. Based on their experience, the authors could not recommend the routine use of MARS in acute hepatic failure.

Glutathione

Glutathione is quantitatively the most important endogenous antioxidant defense, but it is depleted during critical illness. Flaring and colleagues [9] conducted a small prospective study in 11 patients with multiple organ failure and an ICU stay of at least 6 days to investigate the temporal changes in whole blood and plasma glutathione concentrations. Samples were taken every 3 days. Reference concentrations were determined in a group of 20 patients with chronic obstructive pulmonary disease and 10 healthy volunteers. Whole-blood glutathione concentrations in the ICU patients were below the interquartile range for patients with chronic obstructive pulmonary disease and normal volunteers throughout and did not significantly increase over the duration of the study. In contrast, plasma glutathione concentrations were generally greater than in the reference groups, again without any significant variation with time. The whole blood concentrations of glutathione more closely reflected patients' redox status. Just how long it takes for whole-blood glutathione concentration to return to normal, and its relationship to resolution of multiple organ failure, remains to be determined.

Pediatric and neonatal critical care

Intensive Care Medicine has had another productive year in presenting new knowledge to the pediatric and neonatal critical care community. There have been five major areas of clinical research featured in 2005: organization and practice, treatment, mechanical ventilation and respiratory support, assessment and monitoring, and clinical physiology.

Organization and practice

Pediatric clinical research is the mainstay of our practice since "much of the time pediatric intensivists are forced to extrapolate from studies that have been performed in adults" with the hope that the effects will be similar in children [10]. They clearly are not, and history has shown us that poorly researched treatments have risks and toxicities for children that could not have been anticipated beforehand. Central to any such research is parental consent, and Hulst et al. [11] studied why some 20% of parents refuse to have their child included in a research project. Interestingly, severity of illness did not appear to be an important factor; rather, the most common reason for parents refusing consent is the perception that the research protocol would be an additional burden to their child. Clearly, we need more insight and research into how best to conduct future studies. In this context, Diaz-Caneja et al. [12] gave us another side to this debate. They reported that admission to a pediatric intensive care unit (PICU) results in serious parental anxiety and stress with increased risk of later psychopathology. This work indicates that we need to look at ways in which to minimize parental separation or enhance their coping during admission, even when we approach them about a research proposal.

Another area of our organization and practice is the outcome of PICU admission and severity of illness scoring. Thorburn et al. [13] reported the higher mortality of invasive disease due to *Streptococcus pneumoniae* infection than that due to meningoccal disease. Odetola and Bratton [14] found that in a large cohort ($n = 559$) of chil-

dren admitted to the PICU with meningitis, severity of illness, particularly the presence of shock or coma, was associated with higher mortality. The instrument used by the former to measure severity of illness was the Paediatric Index of Mortality and that in the latter was the Pediatric Risk of Mortality. Van Keulen et al. [15] showed that the reliability of risk adjustment systems in both instruments is much lower than expected. The authors found that training and specific guidelines significantly increase interobserver agreement. Therefore according to the authors, these factors should be taken into account when using these systems to compare quality of care between different PICUs, and presumably between different conditions.

Treatment

Commonly used treatments have also been revisited in the *Journal* in the past year. Peters et al. [16] studied morphine pharmacokinetics (albeit in special circumstances) in neonates undergoing venoarterial extracorporeal membrane oxygenation (ECMO). The authors found that morphine clearance is reduced in infants requiring ECMO, possibly reflecting severity of illness, and that therapy should be guided by clinical monitoring when use is prolonged. Second, Burmester and Mok [17] compared the efficacy, infusion rate, and recovery profile of two neuromuscular blocking agents used in critically ill children: vecuronium and cisatracurium. Recovery of neuromuscular function was significantly faster with cisatracurium than vecuronium, and neuromuscular monitoring was not sufficient to eliminate prolonged recovery on vecuronium infusion. Third, Kneyber et al. [18] studied the use of antibiotics in respiratory syncytial virus (RSV) lower respiratory tract disease. Of 65 mechanically ventilated infants 95% were treated with antimicrobials, yet only a minority had evidence of bacterial infection. The authors concluded that in RSV "improvement in the diagnosis of a pulmonary concurrent bacterial infection is warranted" since antimicrobials are clearly being overused.

Other reports about treatment focused on less frequently used therapies. Lopez-Herce et al. [19] reported on elevated carboxyhemoglobin associated with sodium nitroprusside treatment, and Hasin et al. [20] reviewed treatment with activated protein C for meningococcal septic shock. Wahlstrom et al. [21] presented a retrospective analysis of 41 children with severe traumatic brain injury treated according to the "Lund concept," that is, using an intracranial pressure and normovolemia rather than cerebral perfusion pressure targeted therapy. There were no concurrent controls in the study and the numbers were small. However, the strength of the report is that, despite acceptance of cerebral perfusion pressure down to 40 mmHg in children, outcome remained favorable.

Mechanical ventilation and respiratory support

There have been a number of developments in respiratory support covering the whole range from noninvasive positive pressure ventilation to ECMO. First, in regard to noninvasive support Essouri et al. [22] showed in ten infants with upper airway obstruction that continuous positive airway pressure (CPAP) and bilevel positive airway pressure ventilation are both associated with significant and comparable decreases in respiratory effort. However, bilevel positive airway pressure ventilation was associated with patient-ventilator asynchrony. In older children Fauroux et al. [23] reported significant facial side effects when such therapy was used. These authors reported that when this form of support was used chronically, with commercial masks and strapping, facial skin injury occurred in 48% of patients (19/40), with skin necrosis in 8%. Of note, global facial flattening was present in 68% of patients.

Second, there have been three reports related to neonatal ventilation. Trevisanuto et al. [24] reported on a new device for the administration of CPAP. The authors studied 20 very low birth weight infants and compared the neonatal helmet CPAP with standard nasal CPAP and found, in the short-term, that helmet CPAP is as good as the standard therapy. Wald et al. [25] undertook two studies. In a bench study they examined whether a Y-piece adaptation of the ventilator circuit with closed suction, designed to reduce dead-space, would reduce ventilation requirements. The authors' conclusion was that their innovative dead-space, free-flow sensor might reduce volutrauma. In their second study [26] in 17 preterm infants switching from conventional ventilation to "split-flow ventilation" (i.e., where gas required for dead-space washout is split off from the ventilation circuit) resulted in significantly reduced ventilatory effort, as assessed by minute ventilation and ventilation index.

Last, there were three reports covering the boundaries of respiratory support. Vento et al. [27] examined the effect of high-frequency oscillatory ventilation (HFOV) on lung mechanics and epithelial lining fluid cytokines in 40 premature babies randomly assigned to HFOV or synchronized intermittent mandatory ventilation. Early and exclusive use of HFOV combined with optimum volume strategy resulted in significantly higher dynamic respiratory compliance, lower expiratory airway resistance and oxygenation index, and lower transforming growth factor-β_1 concentrations in the bronchoalveolar lavage fluid. Lindwall et al. [28] examined in a pilot study the effect of adding 10 ppm inhaled nitric oxide (iNO) or placebo gas (nitrogen) to nasal CPAP. In 15 infants with respiratory distress syndrome a 30-min exposure to iNO resulted in a moderate improvement in oxygenation, with no effect on systemic circulatory parameters. Macintosh et al. [29] reported their successful and prolonged use of ECMO for 20 days in

a 10-year old girl with acute hypoxic respiratory failure (AHRF). In an accompanying editorial Des Bohn [30] commented that the case report by Macintosh et al. [29] took ECMO into "uncharted waters where many would have not considered it an option." His conclusion was that "we should await the results of the current randomized trial in the United Kingdom to see whether the use of ECMO in adults with AHRF takes on a new lease of life."

Assessment and monitoring

In the field of assessment and monitoring there have been developments in pediatric neurological, respiratory, and cardiac critical care. For example, in 102 severely brain injured children Carter and Butt [31] showed that somatosensory evoked potentials taken during the first 9 days of illness were the best overall predictor of outcome 5 years after injury. In contrast to this successful form of noninvasive assessment, Nagdyman et al. [32] using near-infrared spectroscopy to derive a cerebral tissue oxygenation index found that in 60 children with congenital heart disease it was questionable whether noninvasively measured the index could be used to detect reliably a low jugular bulb venous saturation.

In respiratory critical care there were two reports in the *Journal*. Willis et al. [33] found that in 17 endotracheally intubated, mechanically ventilated children assessment of effort of breathing during even minimal mechanical ventilation may underestimate postextubation effort. Postextubation pressure-rate product was best approximated by T-piece ventilation. Heulitt et al. [34] in an experimental setting showed that tidal volume can be measured accurately at the expiratory valve of a conventional ventilator. In cardiac intensive care assessment and monitoring Egan et al. [35] showed that in 16 infants and children undergoing biventricular repair of congenital heart lesions routine clinical assessments of parameters of cardiac performance agreed poorly with invasive determinations of these indices. Since management decisions based on inaccurate clinical assessments may be detrimental, the authors concluded that further evaluation of invasive hemodynamic monitoring should be undertaken. On a similar theme Rossi et al. [36] found that over a period of 8 years (comparing 710 patients with 1,656 historical controls) outcome after congenital heart surgery was improved by point-of-care testing and monitoring of blood lactate, particularly in neonates.

Last, two other reports covered organ-specific forms of monitoring. Davis et al. [37] compared two indirect methods of measuring intra-abdominal pressure and found that transurethral bladder pressure via a urinary catheter with 1 ml/kg body weight of sterile saline instilled into the bladder was accurate and outperformed intragastric manometry. Naulaers et al. [38] used near-infrared spectroscopy over the liver and found that determining the tissue oxygenation index of the liver may provide be a noninvasive means for measuring distal ileal blood flow.

Clinical physiology

A number of studies have extended our understanding of clinical pathophysiology. In sepsis den Brinker et al. [39] reported that all 44 PICU survivors of meningococcal septic shock showed signs of sick euthyroid syndrome on admission, and that thyroid hormone level changes in the first 24 h were indicative of likely PICU stay. Also in meningococcal disease, Carrol et al. [40] found that in 63 children with varying severity of disease an anti-inflammatory cytokine profile (i.e., interleukin (IL) 1 receptor antagonist, IL-10, and soluble tumor necrosis factor receptors) were associated with the development of severe disease and septic shock. Also, van Woensel [41] observed that in 61 such patients — 19 with meningitis, 17 with meningitis and shock, and 25 with fulminant septicemia — human neutrophil elastase and granzyme B were related to disease severity during the initial phase of illness. Furthermore, prolonged neutrophil activation was associated with the extent of organ dysfunction during the subsequent period of critical care. Last, Briassoulis et al. [42] found that in 38 patients randomized to receive either immune-enhancing or non-immune-enhancing enteral nutrition during the early phase of septic shock, early immune-enhancing nutrition appeared to modulate cytokine levels.

Finally, in regard to cardiac support, there were three key observations. Plumpton and Haas [43] reported that in 36 infants undergoing postcardiopulmonary bypass (CPB) there was risk of marked suppression of thyroid hormone levels especially in those under 3 months of age who required CPB longer than 120 min. Hak et al. [44] observed in 12 neonates under 7 days old with severe lung disease undergoing ECMO that regulation of the vitamin D endocrine system appeared to be aberrant. Malagon et al. [45] found that dexamethasone (1 mg/kg) before CPB was associated with a brief but significant reduction in postoperative cardiac troponin T production.

Experimental studies

As in previous years experimental studies contributed to a large extent to the original studies published in the *Journal*, most dealing with acute lung injury and mechanical ventilation, on the one hand, and treatment strategies targeting endotoxemia and sepsis, on the other hand. The other addressed problems related to brain trauma, hemorrhage, or other topics.

Acute lung injury and mechanical ventilation

The papers by Vecellio et al. [46] and Räsänen and Gavriely [47] addressed technical aspects related to the use of mechanical ventilation. In a bench experiment Vecellio et al. [46] investigated the effect of various respirator settings on the amount of terbutaline delivered using a jet nebulizer synchronized with the inspiratory phase. While the inspiratory air flow was inversely correlated with both the total amount of drug delivered and the median particle size, positive end-expiratory pressure (PEEP) increments up to 8 cmH_2O had no effect. The authors also demonstrated that their mathematical model well predicted the experimental data, thus allowing testing other devices in the future. Räsänen and Gavriely [47] addressed the question of whether applying PEEP affects the acoustic transmission of broad-band noise through the respiratory system in oleic acid induced porcine acute lung injury. Recruitment of gas exchange areas in the lung by incremental PEEP until 15 cmH_2O normalized the otherwise increased sound transmission in the dependent lung regions concomitant with improved compliance and gas exchange, thus indicating efficient recruitment.

A number of papers studied problems associated with lung recruitment maneuvers. Reissman et al. [48] addressed the question of whether the usual collapse resulting from suctioning through an endotracheal tube can be avoided. In both an artificial lung model and in lung-lavaged pigs the authors showed that extending the patient tubing limbs into the trachea via a double-lumen endotracheal tube and suctioning from the expiratory lumen leads to markedly improved lung gas volume as assessed by computed tomography and consequently to arterial oxygenation. Henzler et al. [49] highlighted the potential pitfalls of generating pressure-volume curves. In a porcine lung lavage model repetitive measurements of the thoracopulmonary pressure-volume curve using an inbuilt algorithm of a standard ventilator caused a significantly impaired arterial oxygenation resulting from a fall in aerated lung volume. Odenstedt el al. [50] focused on the hemodynamic side effects of lung recruitment techniques. In lavage- and endotoxin-induced porcine lung injury they first showed that both a vital capacity approach with sustained lung inflation at 40 cmH_2O and using pressure-controlled ventilation with a peak airway pressure of 40 cmH_2O and a PEEP of 20 cmH_2O efficiently improves gas exchange but at the expense of a marked fall in aortic flow by more than 50% in either model. This hemodynamic effect was only partially prevented by prior volume expansion. Using electric impedance tomography the same authors subsequently showed that slowing the recruitment maneuver leads to marked attenuation of this undesired side effect. Finally, Markhorst et al. [51] investigated the abdominal and rib cage motion during high-frequency oscillation in surfactant-depleted piglets that underwent a recruitment maneuver by increasing airway pressure to 40 cmH_2O. The authors demonstrated that "optimal airway pressure" as defined by adequate gas exchange achieved with the lowest distending pressure possible is associated with minimal abdominal and maximal chest tidal displacements.

HFOV in gaining interest among ICU physicians as a potential novel protective ventilatory strategy in patients with severe acute lung injury. For it to function properly small tidal volumes are applied with a high frequency on lungs that are maintained open by a continuous distending pressure (CDP). The optimal tidal volume and CDP are difficult to assess during high-frequency oscillation. The need for a simple method to monitor and optimize tidal volume and CDP during HFOV is obvious. In a surfactant-depletion models in piglets, Markhorst et al. [51] investigated noninvasive respiratory inductive plethysmography based on the breath-to-breath analysis of the rib cage and abdomen displacement as a method to measure tidal volumes and CDP during HFOV. These investigators showed that maximal tidal volume and minimal abdominal displacement coincide with the best respiratory compliance, oxygenation, and ventilation. This method should now be validated in patients receiving HFOV.

Three papers dealt with the inflammatory response associated with acute lung injury. Ankermann et al. [52] showed in surfactant-lavaged newborn piglets that application of topical anti-IL-8 antibodies increases IL-8 production and polymorphonuclear neutrophil migration, ultimately worsening lung function, and the authors consequently discouraged the use of this therapeutic approach. Jaber et al. [53] highlighted the deleterious properties of prolonged mechanical ventilation. Piglets ventilated for 3 days rather than 3 h only presented with markedly reduced diaphragmatic dysfunction affiliated with increased tissue oxidative stress and diminished enzymatic antioxidant capacity. Dahlem et al. [54] finally underscored the injurious effect of high-amplitude pressure changes during mechanical ventilation, i.e., shear stress. In a rat model of intratracheal fibrinogen and thrombin instillation the highest pressure amplitude (35/5 cmH_2O) was affiliated with suppression of alveolar fibrinolytic activity due to local production of the plasminogen activator inhibitor and increased lung edema.

Hemorrhagic, brain trauma and miscellanous

The impact of different fluids for volume resuscitation was studied by Persson and Grände [55]. Rats were hemorrhaged by 20 ml/kg of their blood volume and then received either gelatin, hydroxyethyl starch, albumin, or shed blood. Controls were treated with approximately four times the volume saline. Albumin was more effective in increasing plasma volume as measured using radioactive iodine labeled albumin than the artificial colloids; saline and one-third of this volume red blood cells were similarly

efficient as these compounds. In porcine hemorrhaged by 20–30% of their circulating volume Laesser et al. [56] showed that the angiotensin II receptor 2 blocker candersatan markedly improves survival after retransfusion, which was associated with both higher jejunal intraluminal free nitric oxide and transmucosal potential, a marker of cell viability of the intestinal epithelium as well as its ability to transport ions. Interestingly, adding the angiotension receptor 1 blocker PD123319 blunted this beneficial effect.

Moinard et al. [57] addressed the often overlooked nutritional status in brain injury. In rat model of brain trauma induced by fluid percussion the authors showed that brain injury is associated with renal failure, long-lasting anorexia, increased myofibrillar proteolysis as assessed by an increased 3-methylhistidine excretion, and intestinal atrophy, ultimately leading to muscle atrophy and a pronounced catabolic state. Whether the frequently administered antioxidant *N*-acetylcysteine has neuroprotective effects in brain injury was investigated by Thomale et al. [58]. In rats subjected to "controlled cortical impact" the authors measured the perfusion of the pericontusional cortex using laser Doppler flowmetry, cerebral edema formation and contusion volume. In contrast to previous reports, *N*-acetylcysteine had no beneficial effect in this model of focal brain trauma, thus cautioning the use of this antioxidant under these conditions.

Experimental studies in endotoxemia and sepsis

A diagnostic problem during sepsis was addressed by Venkatesh et al. [59]. The authors nicely demonstrated in a rat model of rapidly developing, early endotoxic shock that subcutaneous PO_2 and PCO_2 closely follow the gut luminal PCO_2 and plasma lactate concentrations, albeit tissue energy charge remained unaffected.

Two papers dealt with new novel therapeutic strategies aimed at macrophage function during endotoxemia and sepsis. Chang et al. [60] showed that the perfluorochemical FC-77 has a pronounced anti-inflammatory effect on endotoxin-stimulated macrophages in vitro as documented by a fall in cytokine and prostaglandin E_2 release as a result of cyclooxygenase 2 suppression and inhibition of nuclear factor κB activation, while Babayigit et al. [61] demonstrated that the macrophage activator β-glucan protects against secondary lung injury, as assessed by the inflammatory response in cells obtained from bronchoalveolar lavage fluid, in a rat model of abdominal sepsis induced by cecal ligation and puncture. Yang et al. [62] examined the impact of bile on the intestinal epithelial barrier function. Common bile duct ligation in mice increases gut barrier dysfunction with enhanced permeability and bacterial translocation, which in turn may be ameliorated with bile gavage, and this effect was apparently due to the decreased formation of the tight junction proteins ZO-1 and occludin: in rat enterocyte monolayers adding bile increased the expression of these molecules. Siegemund et al. [63] nicely demonstrated in endoxotemic pigs that the selective inducible isoform of nitric oxide synthase inhibitor *N*-[3-(aminomethyl)benzyl]acetamidine hydrochloride (mol. wt. 1,400) improves intestinal wall acidosis, thus confirming previous work from other groups, primarily by correcting pathological flow distribution within the gut wall. Finally, Öter et al. [64] studied the effects of repetitive hyperbaric oxygen on liver function and morphology in rats undergoing intraperitoneal inoculation of live *Escherichia coli*. In contrast to repetitive hyperbaric oxygen or antibiotics alone, the combination of these two strategies normalized tissue antioxidant capacity and prevented the histopathological effects associated with sepsis. These authors suggest that maximizing the oxygenation of tissues using hyperbaric oxygen could be an interesting adjuvant therapy in bacterial sepsis.

Several other studies more closely investigated therapeutic approaches that are part of the standard clinical day-to-day practice, but that rely upon the mechanisms that are often poorly understood. Iba et al. [65] investigated the effects of combining 125 IU/kg antithrombin III) with either danaproid or unfractioned heparin on organ injury in rat endotoxic shock. Antithrombin III in combination with danaproid attenuated both liver and kidney dysfunction, which was associated with a less pronounced inflammatory response, increased prostacyclin production, and reduced white blood cell adhesion. Two further papers examined the question of the catecholamine of choice for treating septic shock. Di Giantomasso et al. [66] studied the effects of epinephrine in sheep that had received intravenous *E. coli*. Although stabilizing blood pressure and increasing in cardiac output epinephrine not only impaired renal, mesenteric, and coronary conductance but also simultaneously caused hyperglycemia and lactic acidosis, most likely due to its inherent metabolic properties. These findings indicate that despite the apparent "deshocking" effects epinephrine induces abdominal organ dysfunction and has profound detrimental metabolic effects. This provides another word of caution regarding the use of epinephrine in patients with septic shock, in part due to its β-stimulatory effects on metabolism. In contrast, Peng et al. [67] characterized the renal effects of incremental (0.1–0.5 μg/kg per minute) noradrenaline in *E. coli* challenged dogs. Catecholamine infusion partly restored the bacteremia-induced marked fall in renal blood flow, which was directly related to the increased perfusion pressure.

The mediators responsible for the reversible myocardial depression observed during sepsis remains to be fully identified. Several groups have proposed that proinflammatory mediators such as tumor necrosis factor α play a role. Jacobs et al. [68] had previously observed that lyzozyme originating from neutrophils mediates myocardial depression in an E. *coli* model of septic shock in dogs. Using a right ventricular trabecular preparation, these

authors showed that lyzozyme binds cardiomyocytes, specifically to a membrane glycoprotein containing a particular *N*-glycan moiety. Interestingly, a lectin binding the same sugars also depressed cardiomyocyte contractility in their preparation. These results may open a novel therapeutic approach for septic cardiac depression, i.e., by modulating lyzozyme-sugar interactions.

Correctly assessing plasma volume in critically ill patients remains a challenge. Plasma volume can be approached using radiolabeled proteins, colloids, or dyes. It can also be calculated by deducing the plasma volume from the blood volume, measured with labeled erythrocytes and hematocrit. Determining plasma volume with radioisotopes is particularly difficult in critically ill patients because of concern over irradiation effects. Another complication, particularly in patients with sepsis, is the increased endothelial permeability to macromolecules. Two different techniques for plasma volume measurement in septic patients were compared by Margarson and Soni [69]. The "standard" ^{125}I-labeled albumin technique was compared to a method based on the rapid infusion of a 40-g bolus of unlabeled albumin via a central venous catheter. The concentration of albumin was measured shortly after the bolus injection in this latter group. The volume of distribution of radiolabeled albumin was assessed using standard techniques. The technique based on the rapid infusion of unlabeled albumin gave a precise estimate of the plasma volume, within 10–15% of the values given by the standard ^{125}I-labeled albumin technique. This work validates the use of a simple, safe, and rapid method to measure the plasma volume in critically ill patients.

Scorpion envenomation is associated with significant morbidity and mortality in relation with cardiogenic shock and pulmonary edema following massive endogenous catecholamine release. Debate continues over the direct effects of scorpion venom toxins on the cardiovascular system. To differentiate between effects on endogenous catecholamines and direct toxic effects by venom toxins Ouanes-Besbes et al. [70] injected scorpion venom to dogs either once or twice 30 min apart. Although these authors found similar plasma toxin levels after the first and the second injection, the second injection did not induce similar catecholamine levels, nor did it markedly affect hemodynamic parameters. These results suggest that the first injection exhausted the stores of catecholamines. These authors also demonstrated that the venom toxins per se have limited direct effects on the cardiovascular system.

Agonists of peroxisome proliferator activated receptors (PPARs) modulate inflammation by interfering directly with the transcription of proinflammatory genes. In a nonlethal rabbit model of endotoxemia Wiel et al. [71] tested the hypothesis that the PPAR-α agonist fenofibrate protects endothelial function and influences coagulation. These authors showed that fenofibrate added to the food for 15 days before the experiments significantly attenuates the effect of endotoxin administered as an intravenous bolus. Fenofibrate-treated animals had a better endothelial-dependent relaxation of vessels, and the deendothelialization induced by lipopolysaccharide (LPS) was less pronounced. Interestingly, the monocyte expression of tissue factor was also decreased in rabbits fed with fenofibrate.

Marzocco et al. [72] described a murine model of multiple organ dysfunction after shock induced by zymosan injected into the peritoneum. Using this "nonseptic" model, they showed that pretreatment of mice with the PPAR-γ ligand $\Delta^{12,14}$-prostaglandin J_2 decreases the local and systemic inflammatory response to zymosan and reduces renal, hepatic, and pancreatic dysfunction, assessed by both histology and biomarkers of organ injury. Volman et al. [73] tested the effects of pentoxifilline, a phosphodiesterase inhibitor on multiple-organ dysfunction syndrome (MODS) induced by the sequential injection of LPS and zymosan in mice. At the doses tested, pentoxifilline did not significantly modify the survival rate, fever, or body weight, nor did it prevent gross organ damage. In an editorial accompanying these contribution [72, 73] Marshall emphasized the difficulty to model the complex clinical situation known as MODS [74]. MODS is the leading cause of death in critically ill patients. This condition arises after a few days of intensive care support, typically in patients with septic shock, pancreatitis, multiple trauma, and burns. MODS is a new syndrome that has appeared with the recent improvement in supporting failing organs. Prolonging the life of such critically ill patients has allowed one to observe new consequences of sustained systemic inflammation. MODS may also develop as a consequence, or a secondary effect, of therapies such as mechanical ventilation, hemodynamic support, and multiple transfusions. It is likely that these two aspects are intimately interdependent. This in itself explains why it is so difficult to model MODS, and why the clinical relevance of results obtained in animal models are often questionable. Animal models are, however, valuable for addressing discrete biological questions to open avenues for potential therapeutic approaches.

The transcriptional activation of proinflammatory genes is a key event in the pathogenesis of endotoxemia. It has been established that NF-κB plays a central role in triggering the transcription of many genes induced by LPS. Mitaka et al. [75] reported that NF-κB blockade using a pyrrolidinone derivative (N2733) prevented the development of hypotension as well as metabolic and gastric mucosal acidosis in a hypodynamic canine model of endotoxic shock. Similar data were reported by other investigators in a murine endotoxemia model. These results support the concept that NF-κB blockade is beneficial in endotoxemia. However, NF-κB blockade should also be tested in infectious models, i.e., with live bacteria, since

the inflammatory reaction is at least in part also beneficial for an efficient clearance of micro-organisms. Song et al. [76] investigated the role of other transcription factors: signal transducer and activator of transduction (STAT) -4 and -6 in a murine peritonitis model (cecal ligature and puncture, CLP). STATs are also key modulators of the transduction of genes encoding for proteins of the innate and adaptive immunity and proteins of the inflammatory response. CLP induced a skewing towards T helper (Th) 2 responses with increased IL-10 and decreased IL-2 and interferon-γ production. STAT-4 knockout mice showed an even greater Th2 response after CLP than littermates and had increased mortality. In contrast, CLP induced a predominant Th1 response in STAT-6 deficient mice and a survival benefit compared with STAT-4 knockout animals. However, both STAT-4 and STAT-6 knockout mice had a greater mortality than littermates, suggesting that both transcription factors are important in a balanced fashion to maximize the animals' ability to survive bacterial sepsis.

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