Management of Septic Shock

An ultrasound-guided central vein catheter, an intra-arterial catheter, an invasive mechanical ventilation, a nasogastric tube, and a urinary catheter were placed in all patients under asepsis as soon as possible after Intensive Care Unit admission.

Fluids

Sepsis-induced tissue hypoperfusion defined as hypotension (mean arterial pressure [MAP] <65 mmHg) persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L (18 mg/dL) was managed with fluid resuscitation. The first 6-h goals of resuscitation included central venous pressure of 8–12 mmHg, MAP ≥65 mmHg, urine output ≥0.5 ml/kg/h, central or mixed venous oxygen saturation of 70% or 65%, respectively, and normalization of lactate. The initial fluid for resuscitation was crystalloids; albumin was used if substantial amount of crystalloid was required. Fluid challenge was guided by dynamic (e.g., pulse pressure or stroke volume variation) or static (e.g., arterial pressure, heart rate) variables.

Vasopressors and Inotropes

Noradrenaline was the vasopressor of choice to target MAP 65 mmHg. Vasopressin 0.04 units/min was added to improve the MAP, except in patients with acute coronary ischemia or preexisting coronary artery disease. Dobutamine infusion up to 15 μg/kg/min was tried in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output or ongoing signs of hypoperfusion

Steroids

Continuous infusion of hydrocortisone 200 mg/day was used in septic shock when adequate fluid resuscitation and vasopressor therapy were unable to restore hemodynamic stability. This was tapered over 5–7 days, depending on the response.

Blood and Blood Product Transfusions

Red blood cell transfusion was administered when hemoglobin (Hb) decreased to <7 g/dL to target Hb of 7–9 g/dL. Higher Hb was targeted in patients with myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease. Fresh frozen plasma and platelet transfusion were used only when a patient with deranged coagulation or low platelet count was bleeding or invasive procedures were planned. Platelets were prophylactically transfused with counts $<10 \times 10^9$/L

Antimicrobials and Source Control

Clinically appropriate cultures and imaging studies were performed before start of antimicrobial(s). At least two sets of blood cultures (both aerobic and anaerobic) were obtained before antimicrobial(s). Effective intravenous antimicrobials were aimed to be administered within the 1st h of recognition of septic shock and severe sepsis. Initial empiric therapy with ≥1 anti-infective agents was selected based on activity against all likely pathogens (bacterial and/or fungal) and pharmacology. Combination empirical therapy was used for neutropenic patients with severe sepsis and for difficult-to-treat, multidrug-resistant (MDR) bacterial pathogens. Antimicrobial regimen was reassessed daily for potential de-escalation, aided by procalcitonin trends and susceptibility profile. Duration of therapy was typically 5–7 days. However, patients with slow clinical response, undrainable septic foci, MDR bacteremia, and some fungal infections or immunodeficiency, including neutropenia, received a longer course of antimicrobial(s). Emergent source control with least physiologic insult (e.g., percutaneous rather than surgical drainage of an abscess) was sought and undertaken as early as possible. An intravascular access device as a possible source of sepsis was removed promptly.

Mechanical Ventilation

In patients on mechanical ventilation, target tidal volume of ≤6 mL/kg predicted body weight and plateau pressure of ≤30 cm H_2O was aimed at in sepsis-induced acute respiratory distress syndrome (ARDS). Positive end-expiratory pressure (PEEP) was applied to avoid alveolar collapse. Higher rather than lower level of PEEP, recruitment maneuver, and/or prone positioning was used for patients with severe refractory hypoxemia. Head of bed was elevated to 30°–45° to decrease the risk of aspiration and subsequent ventilator-associated pneumonia. Spontaneous breathing trial (SBT) with pressure support ventilation or T-piece was administered regularly to attempt weaning as and when the patient was conscious, hemodynamically stable, low ventilatory and PEEP requirement, and low FiO_2 requirement which could be safely delivered with a face mask. Successful SBT resulted in consideration for extubation. Conservative rather than liberal fluid strategy was the norm in patients with established sepsis-induced ARDS.

Renal Replacement

Continuous renal replacement therapy was used for fluid management in hemodynamically unstable septic acute kidney injury patients with oligoanuria and/or refractory metabolic acidosis or hyperkalemia. Sustained low-efficiency dialysis was the preferred modality except when it was hemodynamically intolerable or continuous anticoagulation not desirable. Sodium bicarbonate was avoided.

Sedation and Paralysis

Continuous or intermittent sedation was titrated in mechanically ventilated sepsis patients, to a target Richmond Agitation–Sedation Score of 2 or higher. A short course of neuromuscular blocking agent (intermittent bolus or continuous infusion) not exceeding 48 h was used only for patients with early sepsis-induced ARDS and a PaO_2/FiO_2 <150 mmHg.

Venous Thromboembolism and Stress Ulcer Prophylaxis

Patients received daily subcutaneous low-molecular-weight heparin and/or intermittent pneumatic compression against venous thromboembolism. Dalteparin was used if creatinine clearance was <30 ml/min. Stress ulcer prophylaxis using proton pump inhibitor was given to all patients with risk factors for bleeding.

Nutrition and Glycemic Control

Enteral feeding was initiated in all patients as soon as the hemodynamics allowed. Low-dose feeding (e.g., up to 500 calories per day) was advanced as tolerated. Intravenous glucose and enteral nutrition was preferred to total parenteral nutrition (TPN) alone or in conjunction with enteral feeding. Prokinetics were initiated prophylactically. Continuous infusion feeds instead of bolus feeds were started if gastric residual volume was >50% of enteral intake. Feed intolerance with nasogastric feeds was managed with nasojejunal (NJ) feeds (NJ tube placed in radiology suite under fluoroscopy). A protocol for evaluation of safety, delivery, continuity, and success of enteral nutrition was in place for all patients. If this was also not tolerated, TPN was initiated. Euglycemia (target blood glucose 150–180 mg/dl) was maintained with continuous insulin infusion.

Supplementary Table: Summary of the double-blinded randomized placebo controlled trials of statins in sepsis						
First author (reference), year, center, country	Site of study	Statin: Placebo	Patients included in the study	Statin, dose, duration	Results: Primary and secondary outcomes	Strengths and limitations of the study as suggested by author
Novack V,[10] 2009, single center, Israel	Medicine ward and ICU	42:41	Age ≥18 years No prior statins in previous 3 months Suspicion/evidence of bacterial infection and on intravenous antibiotics Not in severe sepsis	Simvastatin, 40 mg/days, followed by 20 mg/days until hospital d/s or onset of severe sepsis	Primary Significant ↓ IL-6 and TNF-α in statin group after 72 h of therapy but no difference between groups Secondary No difference in biochemical and hematological profiles or any other major clinical outcomes upon enrollment and during hospitalization	Strengths Important preliminary evidence that statins may indeed affect the inflammatory response in acute bacterial infection Limitations Small sample size and underpowered study Selection bias cannot be excluded Cannot comment on the effects of statins over time and course of the inflammatory response
Kruger P,[11] 2011, single center, Australia	General ward and ICU	75:75	Suspicion/evidence of infection and on antibiotics ≥2 SIRS Prior statin therapy	Atorvastatin, 20 mg/days, for 28 days or hospital d/s	Primary No difference in severe sepsis or organ dysfunction over time between groups Secondary Hospital mortality and LOS not different between groups IL-6 ↓ over time with statin, but nonsignificant difference between groups Nonsignificant difference in HDL, TG between groups over time Adverse events No difference in CK, ALT between groups	Strengths First to examine use of continued statin on progression and regression of sepsis and inflammation in hospitalized patients of infection Confirms previous observations of the profound decrease in HDL seen in sepsis Limitations None commented

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Patel M,[12] 2012, single center, England	Ward	49:51	Age >18 years Suspicion/evidence of new infection ≥2 SIRS for <24 h No severe sepsis Statin naïve sepsis hospitalized patients	Atorvastatin, 40 mg/days, for hospital stay or up to a maximum of 28 days	Primary Significantly lower conversion to severe sepsis with statins Secondary No difference in rate of ICU admission or hospital readmission, LOS, and mortality at 28 days or 1 year Lipid profile Significant ↓ TC, LDL in statin group Adverse events None	Strengths First to examine the impact of the acute administration of statins on progression of sepsis in statin-naïve patients Supports previous observational studies that pre-existing statin therapy have better sepsis-related outcomes compared to matched controls 2nd largest RCT to date and the 1st to suggest benefit from acute statin therapy Limitations Trial did not achieve its recruitment target The screening process was neither specific nor sensitive for identifying patients with sepsis
Kruger P,[13] 2013, multicenter, Australia	21 ICUs	123:127	Critically ill adults Strong suspicion/ evidence of infection ≥3 SIRS within 48 h before randomization Organ dysfunction of <24 h	Atorvastatin, 20 mg/days, for 14 d or until death or d/s whichever is earlier Prior statin users (n=77)	Primary outcomes No difference in IL-6 between groups and over time Significant lower IL-6 levels at baseline in prior statin users Secondary outcomes Clinical No difference in ICU, hospital, 28 or 90 days mortality, or LOS Continued atorvastatin in prior statin users showed significant improvement at 28 days but not 90 days Biological No difference in CRP levels between groups or trends over time Lipid profile No difference in TC, HDL. or trends over time between groups Adverse events No difference in ALT, CK levels between groups	Strengths Multicenter study Preliminary evidence of safety of continuing statins in critically ill patients Studied the sickest cohort of patients Used a validated inflammatory marker as the primary end point, and stratified at baseline for prior statin use Demonstrated Pk-Pd effects by measuring plasma atorvastatin concentrations accompanied by ↓ plasma cholesterol Limitations This study was too small and the confidence intervals too large to exclude small but important differences in rates of hepatotoxicity and rhabdomyolysis Baseline difference in age despite randomization Higher and more variable IL-6 levels than previously reported in sepsis Underpowered study

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Papazian L,[14] 2013, multicenter, France	26 ICUs	146:138	Adults ≥2 days in ICU if VAP (modified CPIS ≥5 and and if quantitative BAL fluid, PTC, or an ETA)	Simvastatin, 60 mg/days, till ICU d/s, death, or 28 days, whichever is early Prior statin users (n=26)	Primary outcomes 28 days mortality not significantly decreased with statins Secondary outcomes No difference in 14 days, 90 days, and ICU mortality rates; days outside ICU between day 1 and 28; mortality rates in the subgroups with definite and probable VAP; number of ventilator free days (after successful weaning) between d1 and both 28 days and 90 days	Strengths Multicenter study VAP diagnosis based on bacteriological confirmation by quantitative cultures 1st to evaluate adjunctive statin therapy in a specific infection (VAP) Limitations Early trial termination so marginal benefits of statins cannot be commented Only specific for VAP Plasma levels of simvastatin not done
El Gendy,[15] 2014, single center, Egypt	ICU	54:54	Sepsis Age >18 years Suspicion/evidence of infection ≥2 SIRS, organ dysfunction, hypoperfusion or hypotension Appropriate antibiotic therapy commenced	Rosuvastatin, 20 mg/days for 14 days	Primary outcomes Significantly ↑ number of acceptable blood pressure and systemic perfusion days achieved in shorter time in statin group Secondary outcomes Significantly ↓ dose/ duration of vasopressor, arterial lactate, and ventilation days in statin group Significantly ↑ number of organ dysfunction/ failure free days in statin group Adverse events Safe from CK and transaminases elevation	Strengths None commented Limitations Comparison with other statins not done No measurement of plasma rosuvastatin levels
Truwit J, 2014,[16] multicenter, US	ICU	379:366	ARDS (<300 PaO$_2$/FiO$_2$ ratio) requiring mechanical ventilation <24 h of enrollment Suspicion/evidence of infection with any SIRS Prior statin users (54:55)	Rosuvastatin, 40 mg (load) followed by 20 mg/days, until day 3 after d/s from the ICU or study day 28 or hospital d/s, or death, whichever occurred earlier	Primary Mortality and ventilator free days did not differ significantly between groups Secondary No significant differences between groups in any of the other secondary outcomes Adverse events No significant differences between groups	Strengths Large, multicenter Plasma rosuvastatin levels measured Differs both in the choice of statin and in our requirement for a 48-h washout period for statins in order for patients to be eligible for enrollment Limitations None commented

ICUs: Intensive Care Units; IL: Interleukin; TNF-α: Tumor-necrosis-factor alpha; SIRS: Systemic inflammatory response syndrome; LOS: Length of hospital stay; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low density lipoprotein; ALT: Alanine aminotransferase; CK: Creatine kinase; TC: Total cholesterol; RCT: Randomized controlled trial; CRP: C-reactive protein; VAP: Ventilator-associated pneumonia; CPIS: Clinical Pulmonary Infection Score; BAL: Bronchoalveolar lavage; PTC: Plugged telescopic catheter; ETA: Endotracheal aspiration; ARDS: Acute respiratory distress syndrome; d/s: Discharge; ↑: Increase; ↓: Decrease