Sepsis Abstract Collection

Early Antibiotics: *Kumar et. al.*
EGDT: *Rivers, PRISM*
Fluids: *SMART, ALBIOS*
Hemoglobin*: TRISS*
Vasopressors: *SOAP II, VASST*
Pressure Goals: *SEPSISPAM*
Steroids: *CORTICUS, APPROCHSS*
Glucose ICU: *NICE-SUGAR*

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

Objective: **To determine the prevalence and impact on mortality of delays in initiation of effective antimicrobial therapy from initial onset of recurrent/persistent hypotension of septic shock.**

Design: **A retrospective cohort study performed between July 1989 and June 2004.**

Setting: **Fourteen intensive care units (four medical, four surgical, six mixed medical/surgical) and ten hospitals (four academic, six community) in Canada and the United States.**

Patients: **Medical records of 2,731 adult patients with septic shock.**

Interventions: **None.**

Measurements and Main Results: **The main outcome measure was survival to hospital discharge. Among the 2,154 septic shock patients (78.9% total) who received effective antimicrobial therapy only after the onset of recurrent or persistent hypotension, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted (adjusted odds ratio 1.119 [per hour delay], 95% confidence interval 1.103–1.136, $p < .0001$). Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hrs was associated with an average decrease in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour (odds ratio 1.67; 95% confidence interval, 1.12–2.48). In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Median time to effective antimicrobial therapy was 6 hrs (25–75th percentile, 2.0–15.0 hrs).**

Conclusions: **Effective antimicrobial administration within the first hour of documented hypotension was associated with increased survival to hospital discharge in adult patients with septic shock. Despite a progressive increase in mortality rate with increasing delays, only 50% of septic shock patients received effective antimicrobial therapy within 6 hrs of documented hypotension. (Crit Care Med 2006; 34:1589–1596)**

Key Words: sepsis; antimicrobial; timing; delay; outcome

Despite the fact that current international guidelines suggest initiation of antimicrobial therapy within an hour of presentation with severe sepsis and septic shock, no clinical studies exist to support this recommendation (1). In reality, initiation of antimicrobial therapy for infections causing critical illness often awaits thorough clinical evaluation, resuscitative measures, initial stabilization, and investigative efforts (2–6).

Relatively few studies have rigorously examined the effect of delays of antimicrobial therapy in critically ill, infected patients (7–17). To the extent that these studies have been done, the delay has most often been timed to admission to the intensive care unit (ICU) or the emergency room. No studies have examined treatment delays in relation to defined physiologic variables such as hypotension. We have recently demonstrated that the onset of hypotension is a critical

*See also p. 1819.

From the Section of Critical Care Medicine, Health Sciences Centre/St. Boniface Hospital, University of Manitoba, Winnipeg, MB, Canada (AK, DR, BL, SS, RS); Section of Pulmonary and Critical Care Medicine, University of Wisconsin Hospital and Clinics, Madison, WI (KEW); Cooper Hospital/University Medical Center, Robert Wood Johnson Medical School, UMDNJ, Camden, NJ (JEP, SZ); St. Agnes Medical Center, Baltimore, MD (DF); Section of Pulmonary and Critical Care Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL (LT, DG); Laurentian University, Biomolecular Sciences Program and Department of Chemistry and Biochemistry, Sudbury, ON (AK); and Biostatistical Consulting Unit, Department of Community Health Sciences, University of Manitoba, Winnipeg, MB (MC).

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Address requests for reprints to: Anand Kumar, MD, E-mail: akumar61@yahoo.com

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EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANO FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

ABSTRACT

Background Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Methods We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

Results Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy ($P=0.009$). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean ($\pm$SD) central venous oxygen saturation (70.4$\pm$10.7 percent vs. 65.3$\pm$11.4 percent), a lower lactate concentration (3.0$\pm$4.4 vs. 3.9$\pm$4.4 mmol per liter), a lower base deficit (2.0$\pm$6.6 vs. 5.1$\pm$6.7 mmol per liter), and a higher pH (7.40$\pm$0.12 vs. 7.36$\pm$0.12) than the patients assigned to standard therapy ($P\leq0.02$ for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0$\pm$6.3 vs. 15.9$\pm$6.4, $P<0.001$).

Conclusions Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock. (N Engl J Med 2001;345:1368-77.)

THE systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock.[1] Along this continuum, circulatory abnormalities (intravascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock.[2] An indicator of serious illness, global tissue hypoxia is a key development preceding multiorgan failure and death.[2] The transition to serious illness occurs during the critical "golden hours," when definitive recognition and treatment provide maximal benefit in terms of outcome. These golden hours may elapse in the emergency department,[3] hospital ward,[4] or the intensive care unit.[5]

Early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure,[6] and urinary output[7] fails to detect persistent global tissue hypoxia. A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand.[2] End points used to confirm the achievement of such a balance (hereafter called resuscitation end points) include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH.[8] Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy.[9] In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation.[10]

Whereas the incidence of septic shock has steadily increased during the past several decades, the associated mortality rates have remained constant or have decreased only slightly.[11] Studies of interventions such as immunotherapy,[12] hemodynamic optimization,[9,13] or pulmonary-artery catheterization[14] enrolled patients up to 72 hours after admission to the intensive care unit. The negative results of studies of the use of hemodynamic variables as end points ("hemodynamic

From the Departments of Emergency Medicine (E.R., B.N., J.R., A.M., B.K., M.T.), Surgery (E.R.), Internal Medicine (B.N.), and Biostatistics and Epidemiology (S.H., E.P.), Henry Ford Health Systems, Case Western Reserve University, Detroit. Address reprint requests to Dr. Rivers at the Department of Emergency Medicine, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI 48202, or at erivers1@hfhs.org.

*The members of the Early Goal-Directed Therapy Collaborative Group are listed in the Appendix.

ORIGINAL ARTICLE

PROCESS

ARISE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*

ABSTRACT

BACKGROUND

After a single-center trial and observational studies suggesting that early, goal-directed therapy (EGDT) reduced mortality from septic shock, three multicenter trials (ProCESS, ARISE, and ProMISe) showed no benefit. This meta-analysis of individual patient data from the three recent trials was designed prospectively to improve statistical power and explore heterogeneity of treatment effect of EGDT.

METHODS

We harmonized entry criteria, intervention protocols, outcomes, resource-use measures, and data collection across the trials and specified all analyses before unblinding. After completion of the trials, we pooled data, excluding the protocol-based standard-therapy group from the ProCESS trial, and resolved residual differences. The primary outcome was 90-day mortality. Secondary outcomes included 1-year survival, organ support, and hospitalization costs. We tested for treatment-by-subgroup interactions for 16 patient characteristics and 6 care-delivery characteristics.

RESULTS

We studied 3723 patients at 138 hospitals in seven countries. Mortality at 90 days was similar for EGDT (462 of 1852 patients [24.9%]) and usual care (475 of 1871 patients [25.4%]); the adjusted odds ratio was 0.97 (95% confidence interval, 0.82 to 1.14; P=0.68). EGDT was associated with greater mean (±SD) use of intensive care (5.3±7.1 vs. 4.9±7.0 days, P=0.04) and cardiovascular support (1.9±3.7 vs. 1.6±2.9 days, P=0.01) than was usual care; other outcomes did not differ significantly, although average costs were higher with EGDT. Subgroup analyses showed no benefit from EGDT for patients with worse shock (higher serum lactate level, combined hypotension and hyperlactatemia, or higher predicted risk of death) or for hospitals with a lower propensity to use vasopressors or fluids during usual resuscitation.

CONCLUSIONS

In this meta-analysis of individual patient data, EGDT did not result in better outcomes than usual care and was associated with higher hospitalization costs across a broad range of patient and hospital characteristics. (Funded by the National Institute of General Medical Sciences and others; PRISM ClinicalTrials.gov number, NCT02030158.)

The members of the writing committee (Kathryn M. Rowan, Ph.D., Derek C. Angus, M.D., M.P.H., Michael Bailey, Ph.D., Amber E. Barnato, M.D., Rinaldo Bellomo, M.D., Ruth R. Canter, M.Sc., Timothy J. Coats, M.D., Anthony Delaney, M.D., Ph.D., Elizabeth Gimbel, R.N., B.S., Richard D. Grieve, Ph.D., David A. Harrison, Ph.D., Alisa M. Higgins, M.P.H., Belinda Howe, M.P.H., David T. Huang, M.D., M.P.H., John A. Kellum, M.D., Paul R. Mouncey, M.Sc., Edvin Music, M.S.I.S., Sandra L. Peake, M.D., Ph.D., Francis Pike, Ph.D., Michael C. Reade, M.B., B.S., D.Phil., M. Zia Sadique, Ph.D., Mervyn Singer, M.D., and Donald M. Yealy, M.D.) assume responsibility for the overall content and integrity of this article. The affiliations of the writing committee members are listed in the Appendix. Address reprint requests to Dr. Rowan at the Intensive Care National Audit and Research Centre, Napier House, 24 High Holborn, London WC1V 6AZ, United Kingdom, or at kathy.rowan@icnarc.org.

*The Protocolized Resuscitation in Sepsis Meta-Analysis (PRISM) study is a collaboration of the Protocolized Care for Early Septic Shock (ProCESS) Investigators, based in the United States; the Australasian Resuscitation in Sepsis Evaluation (ARISE) Investigators, based in Australia and New Zealand; the Protocolised Management in Sepsis (ProMISe) Investigators, based in the United Kingdom; and the International Forum for Acute Care Trialists. A complete list of the investigator groups is provided in the Supplementary Appendix, available at NEJM.org.

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ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H., Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H., Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D., Avinash B. Kumar, M.D., Christopher G. Hughes, M.D., Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H., Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D., Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D., and Todd W. Rice, M.D., for the SMART Investigators and the Pragmatic Critical Care Research Group*

ABSTRACT

BACKGROUND

Both balanced crystalloids and saline are used for intravenous fluid administration in critically ill adults, but it is not known which results in better clinical outcomes.

METHODS

In a pragmatic, cluster-randomized, multiple-crossover trial conducted in five intensive care units at an academic center, we assigned 15,802 adults to receive saline (0.9% sodium chloride) or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) according to the randomization of the unit to which they were admitted. The primary outcome was a major adverse kidney event within 30 days — a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction (defined as an elevation of the creatinine level to ≥200% of baseline) — all censored at hospital discharge or 30 days, whichever occurred first.

RESULTS

Among the 7942 patients in the balanced-crystalloids group, 1139 (14.3%) had a major adverse kidney event, as compared with 1211 of 7860 patients (15.4%) in the saline group (marginal odds ratio, 0.91; 95% confidence interval [CI], 0.84 to 0.99; conditional odds ratio, 0.90; 95% CI, 0.82 to 0.99; P=0.04). In-hospital mortality at 30 days was 10.3% in the balanced-crystalloids group and 11.1% in the saline group (P=0.06). The incidence of new renal-replacement therapy was 2.5% and 2.9%, respectively (P=0.08), and the incidence of persistent renal dysfunction was 6.4% and 6.6%, respectively (P=0.60).

CONCLUSIONS

Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline. (Funded by the Vanderbilt Institute for Clinical and Translational Research and others; SMART-MED and SMART-SURG ClinicalTrials.gov numbers, NCT02444988 and NCT02547779.)

From the Department of Medicine, Division of Allergy, Pulmonary, and Critical Care Medicine (M.W.S., J.D.C., G.R.B., T.W.R.), the Departments of Emergency Medicine (W.H.S.), Anesthesiology (J.P.W., J.M.E., A.B.K., C.G.H., A.H., L. Weavind, A.D.S.), Biomedical Informatics (J.P.W., J.M.E.), Surgery (J.M.E., O.D.G., A.K.M.), Health Policy (J.M.E.), Biostatistics (L. Wang, D.W.B.), and Pharmaceutical Services (J.L.S.), and the Division of Nephrology and Hypertension, Vanderbilt Center for Kidney Disease and Integrated Program for Acute Kidney Disease (E.D.S.) — all at Vanderbilt University Medical Center, Nashville. Address reprint requests to Dr. Rice at the Department of Medicine, Vanderbilt University Medical Center, T-1218 MCN, 1161 21st Ave. S., Nashville, TN 37232, or at todd.rice@vanderbilt.edu.

*A complete list of the SMART Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

ABSTRACT

BACKGROUND

Although previous studies have suggested the potential advantages of albumin administration in patients with severe sepsis, its efficacy has not been fully established.

METHODS

In this multicenter, open-label trial, we randomly assigned 1818 patients with severe sepsis, in 100 intensive care units (ICUs), to receive either 20% albumin and crystalloid solution or crystalloid solution alone. In the albumin group, the target serum albumin concentration was 30 g per liter or more until discharge from the ICU or 28 days after randomization. The primary outcome was death from any cause at 28 days. Secondary outcomes were death from any cause at 90 days, the number of patients with organ dysfunction and the degree of dysfunction, and length of stay in the ICU and the hospital.

RESULTS

During the first 7 days, patients in the albumin group, as compared with those in the crystalloid group, had a higher mean arterial pressure ($P=0.03$) and lower net fluid balance ($P<0.001$). The total daily amount of administered fluid did not differ significantly between the two groups ($P=0.10$). At 28 days, 285 of 895 patients (31.8%) in the albumin group and 288 of 900 (32.0%) in the crystalloid group had died (relative risk in the albumin group, 1.00; 95% confidence interval [CI], 0.87 to 1.14; $P=0.94$). At 90 days, 365 of 888 patients (41.1%) in the albumin group and 389 of 893 (43.6%) in the crystalloid group had died (relative risk, 0.94; 95% CI, 0.85 to 1.05; $P=0.29$). No significant differences in other secondary outcomes were observed between the two groups.

CONCLUSIONS

In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days. (Funded by the Italian Medicines Agency; ALBIOS ClinicalTrials.gov number, NCT00707122.)

From Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Ca' Granda–Ospedale Maggiore Policlinico, Università degli Studi di Milano (P.C., G.I., L.G.), Dipartimento di Anestesia, Rianimazione e Terapia del Dolore, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico (P.C., L.C., L.G.), IRCCS–Istituto di Ricerche Farmacologiche Mario Negri (S.M., R.L.), Dipartimento di Scienze della Salute, Università degli Studi di Milano Bicocca (R.F., A.P.), and Dipartimento di Emergenza–Urgenza, Azienda Ospedaliera S. Paolo–Polo Universitario (G.I.), Milan, Consorzio Mario Negri Sud, Santa Maria Imbaro (G.T., M.R., C.F.), Anestesiologia e Rianimazione, Dipartimento Emergenza–Urgenza, Chirurgia Generale e dei Trapianti, Policlinico Universitario S. Orsola Malpighi, Bologna (S.F.), Dipartimento di Emergenza–Urgenza, Azienda Ospedaliera S. Gerardo, Monza (G.G.), Policlinico Universitario A. Gemelli, Università Cattolica, Rome (M.A.), Ospedale del Mugello–Azienda Sanitaria di Firenze, Florence (V.P.), and Ospedale S. Croce, Moncalieri (G.F.) — all in Italy. Address reprint requests to Dr. Gattinoni at the Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Università degli Studi di Milano, Via F. Sforza 35, 20122 Milan, Italy, or at gattinon@policlinico.mi.it.

*Investigators of the Albumin Italian Outcome Sepsis (ALBIOS) study are listed in the Supplementary Appendix, available at NEJM.org.

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Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

Lars B. Holst, M.D., Nicolai Haase, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Jan Wernerman, M.D., Ph.D., Anne B. Guttormsen, M.D., Ph.D., Sari Karlsson, M.D., Ph.D., Pär I. Johansson, M.D., Ph.D., Anders Åneman, M.D., Ph.D., Marianne L. Vang, M.D., Robert Winding, M.D., Lars Nebrich, M.D., Helle L. Nibro, M.D., Ph.D., Bodil S. Rasmussen, M.D., Ph.D., Johnny R.M. Lauridsen, M.D., Jane S. Nielsen, M.D., Anders Oldner, M.D., Ph.D., Ville Pettilä, M.D., Ph.D., Maria B. Cronhjort, M.D., Lasse H. Andersen, M.D., Ulf G. Pedersen M.D., Nanna Reiter, M.D., Jørgen Wiis, M.D., Jonathan O. White, M.D., Lene Russell, M.D., Klaus J. Thornberg, M.D., Peter B. Hjortrup, M.D., Rasmus G. Müller, M.D., Morten H. Møller, M.D., Ph.D., Morten Steensen, M.D., Inga Tjäder, M.D., Ph.D., Kristina Kilsand, R.N., Suzanne Odeberg-Wernerman, M.D., Ph.D., Brit Sjøbø, R.N., Helle Bundgaard, M.D., Ph.D., Maria A. Thyø, M.D., David Lodahl, M.D., Rikke Mærkedahl, M.D., Carsten Albeck, M.D., Dorte Illum, M.D., Mary Kruse, M.D., Per Winkel, M.D., D.M.Sci., and Anders Perner, M.D., Ph.D., for the TRISS Trial Group* and the Scandinavian Critical Care Trials Group

ABSTRACT

BACKGROUND

Blood transfusions are frequently given to patients with septic shock. However, the benefits and harms of different hemoglobin thresholds for transfusion have not been established.

METHODS

In this multicenter, parallel-group trial, we randomly assigned patients in the intensive care unit (ICU) who had septic shock and a hemoglobin concentration of 9 g per deciliter or less to receive 1 unit of leukoreduced red cells when the hemoglobin level was 7 g per deciliter or less (lower threshold) or when the level was 9 g per deciliter or less (higher threshold) during the ICU stay. The primary outcome measure was death by 90 days after randomization.

RESULTS

We analyzed data from 998 of 1005 patients (99.3%) who underwent randomization. The two intervention groups had similar baseline characteristics. In the ICU, the lower-threshold group received a median of 1 unit of blood (interquartile range, 0 to 3) and the higher-threshold group received a median of 4 units (interquartile range, 2 to 7). At 90 days after randomization, 216 of 502 patients (43.0%) assigned to the lower-threshold group, as compared with 223 of 496 (45.0%) assigned to the higher-threshold group, had died (relative risk, 0.94; 95% confidence interval, 0.78 to 1.09; P=0.44). The results were similar in analyses adjusted for risk factors at baseline and in analyses of the per-protocol populations. The numbers of patients who had ischemic events, who had severe adverse reactions, and who required life support were similar in the two intervention groups.

CONCLUSIONS

Among patients with septic shock, mortality at 90 days and rates of ischemic events and use of life support were similar among those assigned to blood transfusion at a higher hemoglobin threshold and those assigned to blood transfusion at a lower threshold; the latter group received fewer transfusions. (Funded by the Danish Strategic Research Council and others; TRISS ClinicalTrials.gov number, NCT01485315.)

From the Department of Intensive Care (L.B.H., N.H., L.H.A., U.G.P., N.R., J. Wiis, J.O.W., L.F [illegible] G.M., M.H.M., M.S., A.P.[illegible]ial Unit, Center for Clinical [illegible]arch (J. Wetterslev, P.W. [illegible]or Transfusion Medicine [illegible]italet and University o [illegible] Copenhagen, Randers Hospital, Randers (M.L.V., H.B., M.A.T.), Herning Hospital, Herning (R.W., D.L., R.M.), Hvidovre Hospital, Hvidovre (L.N., C.A.), Aarhus University Hospital, Aarhus (H.L.N., D.I.), Aalborg University Hospital, Aalborg (B.S.R.), Holbæk Hospital, Holbæk (J.R.M.L.), Kolding Hospital, Kolding (J.S.N.), and Hjørring Hospital, Hjørring (M.K.) — all in Denmark; Karolinska University Hospital, Huddinge, Stockholm (J. Wernerman, I.T., K.K., S.O.-W.), Karolinska University Hospital, Solna (A.O.), and Södersjukhuset, Stockholm (M.B.C.) — all in Sweden; Haukeland University Hospital and University of Bergen, Bergen, Norway (A.B.G., B.S.); Tampere University Hospital, Tampere (S.K.), and Helsinki University Hospital and University of Helsinki, Helsinki (V.P.) — all in Finland; and Liverpool Hospital, Sydney (A.Å.). Address reprint requests to Dr. Perner at the Department of Intensive Care, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark, or at anders.perner@regionh.dk.

*Members of the Transfusion Requirements in Septic Shock (TRISS) Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

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Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

ABSTRACT

BACKGROUND

Both dopamine and norepinephrine are recommended as first-line vasopressor agents in the treatment of shock. There is a continuing controversy about whether one agent is superior to the other.

METHODS

In this multicenter, randomized trial, we assigned patients with shock to receive either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure. When blood pressure could not be maintained with a dose of 20 μg per kilogram of body weight per minute for dopamine or a dose of 0.19 μg per kilogram per minute for norepinephrine, open-label norepinephrine, epinephrine, or vasopressin could be added. The primary outcome was the rate of death at 28 days after randomization; secondary end points included the number of days without need for organ support and the occurrence of adverse events.

RESULTS

The trial included 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine. The baseline characteristics of the groups were similar. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group; odds ratio with dopamine, 1.17; 95% confidence interval, 0.97 to 1.42; P=0.10). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (207 events [24.1%] vs. 102 events [12.4%], P<0.001). A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1044 patients with septic shock or the 263 with hypovolemic shock (P=0.03 for cardiogenic shock, P=0.19 for septic shock, and P=0.84 for hypovolemic shock, in Kaplan–Meier analyses).

CONCLUSIONS

Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events. (ClinicalTrials.gov number, NCT00314704.)

From the Department of Intensive Care, Erasme University Hospital (D.D.B., A.B., J.-L.V.); the Department of Intensive Care, Brugmann Hospital, Université Libre de Bruxelles (P.G.); and the Department of Intensive Care, Centre Hospitalier (D.C.) — all in Brussels; the Department of Intensive Care, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium (P.B., P.D.); the Department of Medicine III, Intensive Care Unit 13H1, Medical University of Vienna, Vienna (C.M.); and the Department of Anesthesia and Critical Care, Rio Hortega University Hospital, Valladolid, Spain (C.A.). Address reprint requests to Dr. De Backer at the Department of Intensive Care, Erasme University Hospital, Rte. de Lennik 808, B-1070 Brussels, Belgium, or at ddebacke@ulb.ac.be.

*Members of the Sepsis Occurrence in Acutely Ill Patients II (SOAP II) trial group are listed in the Appendix.

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Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

James A. Russell, M.D., Keith R. Walley, M.D., Joel Singer, Ph.D., Anthony C. Gordon, M.B., B.S., M.D., Paul C. Hébert, M.D., D. James Cooper, B.M., B.S., M.D., Cheryl L. Holmes, M.D., Sangeeta Mehta, M.D., John T. Granton, M.D., Michelle M. Storms, B.Sc.N., Deborah J. Cook, M.D., Jeffrey J. Presneill, M.B., B.S., Ph.D., and Dieter Ayers, M.Sc., for the VASST Investigators*

ABSTRACT

BACKGROUND

Vasopressin is commonly used as an adjunct to catecholamines to support blood pressure in refractory septic shock, but its effect on mortality is unknown. We hypothesized that low-dose vasopressin as compared with norepinephrine would decrease mortality among patients with septic shock who were being treated with conventional (catecholamine) vasopressors.

METHODS

In this multicenter, randomized, double-blind trial, we assigned patients who had septic shock and were receiving a minimum of 5 μg of norepinephrine per minute to receive either low-dose vasopressin (0.01 to 0.03 U per minute) or norepinephrine (5 to 15 μg per minute) in addition to open-label vasopressors. All vasopressor infusions were titrated and tapered according to protocols to maintain a target blood pressure. The primary end point was the mortality rate 28 days after the start of infusions.

RESULTS

A total of 778 patients underwent randomization, were infused with the study drug (396 patients received vasopressin, and 382 norepinephrine), and were included in the analysis. There was no significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate (35.4% and 39.3%, respectively; P=0.26) or in 90-day mortality (43.9% and 49.6%, respectively; P=0.11). There were no significant differences in the overall rates of serious adverse events (10.3% and 10.5%, respectively; P=1.00). In the prospectively defined stratum of less severe septic shock, the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% vs. 35.7%, P=0.05); in the stratum of more severe septic shock, there was no significant difference in 28-day mortality (44.0% and 42.5%, respectively; P=0.76). A test for heterogeneity between these two study strata was not significant (P=0.10).

CONCLUSIONS

Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors. (Current Controlled Trials number, ISRCTN94845869.)

From the iCAPTURE Centre, Vancouver, BC (J.A.R., K.R.W., A.C.G., M.M.S.); St. Paul's Hospital, V A.R., K.R.W., J.S., A.C.G. ttawa Hospital, Univers awa (P.C.H.); Kelowna G elowna, BC, and Unive lumbia, Vancouver (C.L Hospital, Toronto (S.M.); Toronto General Hospital, Toronto Western Hospital, and University of Toronto, Toronto (J.T.G.); and St. Joseph's Hospital and McMaster University, Hamilton, ON (D.J. Cook) — all in Canada; and Alfred Hospital and Monash University, Melbourne (D.J. Cooper); and Royal Melbourne Hospital and University of Melbourne (J.J.P.) — all in Melbourne, Australia. Address reprint requests to Dr. Russell at Critical Care Medicine, St. Paul's Hospital, 1081 Burrard St., Vancouver, BC V6Z 1Y6, Canada, or at jrussell@mrl.ubc.ca.

*Investigators who participated in the Vasopressin and Septic Shock Trial (VASST) are listed in the Appendix.

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High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D., for the SEPSISPAM Investigators*

ABSTRACT

BACKGROUND

The Surviving Sepsis Campaign recommends targeting a mean arterial pressure of at least 65 mm Hg during initial resuscitation of patients with septic shock. However, whether this blood-pressure target is more or less effective than a higher target is unknown.

METHODS

In a multicenter, open-label trial, we randomly assigned 776 patients with septic shock to undergo resuscitation with a mean arterial pressure target of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group). The primary end point was mortality at day 28.

RESULTS

At 28 days, there was no significant between-group difference in mortality, with deaths reported in 142 of 388 patients in the high-target group (36.6%) and 132 of 388 patients in the low-target group (34.0%) (hazard ratio in the high-target group, 1.07; 95% confidence interval [CI], 0.84 to 1.38; P=0.57). There was also no significant difference in mortality at 90 days, with 170 deaths (43.8%) and 164 deaths (42.3%), respectively (hazard ratio, 1.04; 95% CI, 0.83 to 1.30; P=0.74). The occurrence of serious adverse events did not differ significantly between the two groups (74 events [19.1%] and 69 events [17.8%], respectively; P=0.64). However, the incidence of newly diagnosed atrial fibrillation was higher in the high-target group than in the low-target group. Among patients with chronic hypertension, those in the high-target group required less renal-replacement therapy than did those in the low-target group, but such therapy was not associated with a difference in mortality.

CONCLUSIONS

Targeting a mean arterial pressure of 80 to 85 mm Hg, as compared with 65 to 70 mm Hg, in patients with septic shock undergoing resuscitation did not result in significant differences in mortality at either 28 or 90 days. (Funded by the French Ministry of Health; SEPSISPAM ClinicalTrials.gov number, NCT01149278.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Asfar at the Department of Medical Intensive Care and Hyperbaric Medicine, University Hospital of Angers, 4 rue Larrey, F-49933 Angers CEDEX 9, France, or at piasfar@chu-angers.fr.

*Additional investigators in the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

ABSTRACT

BACKGROUND

Hydrocortisone is widely used in patients with septic shock even though a survival benefit has been reported only in patients who remained hypotensive after fluid and vasopressor resuscitation and whose plasma cortisol levels did not rise appropriately after the administration of corticotropin.

METHODS

In this multicenter, randomized, double-blind, placebo-controlled trial, we assigned 251 patients to receive 50 mg of intravenous hydrocortisone and 248 patients to receive placebo every 6 hours for 5 days; the dose was then tapered during a 6-day period. At 28 days, the primary outcome was death among patients who did not have a response to a corticotropin test.

RESULTS

Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotropin (125 in the hydrocortisone group and 108 in the placebo group). At 28 days, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotropin (39.2% in the hydrocortisone group and 36.1% in the placebo group, $P=0.69$) or between those who had a response to corticotropin (28.8% in the hydrocortisone group and 28.7% in the placebo group, $P=1.00$). At 28 days, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died ($P=0.51$). In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock.

CONCLUSIONS

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. (ClinicalTrials.gov number, NCT00147004.)

From Hadassah Hebrew University Medical Center, Jerusalem (C.L.S., Y.G.W., J. Benbenishty, incaré Hospital, Universi UniverSud Paris, Garche .); Charité Universitätsm ampus Virchow-Klinikum Hospital de St. António dos Capuchos, Centro Hospitalar de Lisboa Central, Lisbon, Portugal (R.M.); Bloomsbury Institute of Intensive Care Medicine, University College London, London (M.S.); Analytica International, Loerrach, Germany (K.F.); Klinikum Mannheim, Mannheim, Germany (A.K.); Zentralklinikum Augsburg, Augsburg, Germany (H.F.); St. Luc University Hospital, Université Catholique de Louvain, Brussels (P.-F.L.); Friedrich Schiller Universität, Jena, Germany (K.R.); Health Services Research Unit, University of Aberdeen, Aberdeen, United Kingdom (B.H.C.); Hôpital Lariboisière, Denis Diderot University of Paris, Paris (D.P.); and Klinikum der Universität, Ludwig Maximilians Universität, Munich, Germany (J. Briegel). Address reprint requests to Dr. Sprung at the General Intensive Care Unit, Department of Anesthesiology and Critical Care Medicine, Hadassah Hebrew University Medical Center, P.O. Box 12000, Jerusalem, Israel 91120, or at sprung@cc.huji.ac.il.

*Members of the Corticosteroid Therapy of Septic Shock (CORTICUS) study group are listed in the Appendix.

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ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

ABSTRACT

BACKGROUND

Septic shock is characterized by dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities. We hypothesized that therapy with hydrocortisone plus fludrocortisone or with drotrecogin alfa (activated), which can modulate the host response, would improve the clinical outcomes of patients with septic shock.

METHODS

In this multicenter, double-blind, randomized trial with a 2-by-2 factorial design, we evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. After drotrecogin alfa (activated) was withdrawn from the market, the trial continued with a two-group parallel design. The analysis compared patients who received hydrocortisone plus fludrocortisone with those who did not (placebo group).

RESULTS

Among the 1241 patients included in the trial, the 90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group and 49.1% (308 of 627 patients) in the placebo group (P=0.03). The relative risk of death in the hydrocortisone-plus-fludrocortisone group was 0.88 (95% confidence interval, 0.78 to 0.99). Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the placebo group at ICU discharge (35.4% vs. 41.0%, P=0.04), hospital discharge (39.0% vs. 45.3%, P=0.02), and day 180 (46.6% vs. 52.5%, P=0.04) but not at day 28 (33.7% and 38.9%, respectively; P=0.06). The number of vasopressor-free days to day 28 was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group (17 vs. 15 days, P<0.001), as was the number of organ-failure–free days (14 vs. 12 days, P=0.003). The number of ventilator-free days was similar in the two groups (11 days in the hydrocortisone-plus-fludrocortisone group and 10 in the placebo group, P=0.07). The rate of serious adverse events did not differ significantly between the two groups, but hyperglycemia was more common in hydrocortisone-plus-fludrocortisone group.

CONCLUSIONS

In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo. (Funded by Programme Hospitalier de Recherche Clinique 2007 of the French Ministry of Social Affairs and Health; APROCCHSS ClinicalTrials.gov number, NCT00625209.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Annane at Service de Médecine Intensive et Réanimation, Hôpital Raymond Poincaré, 104 Blvd. Raymond Poincaré, 92380 Garches, France, or at djillali.annane@aphp.fr.

*A complete list of investigators in the APROCCHSS trial is provided in the Supplementary Appendix, available at NEJM.org.

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Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators*

ABSTRACT

BACKGROUND

The optimal target range for blood glucose in critically ill patients remains unclear.

METHODS

Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). We defined the primary end point as death from any cause within 90 days after randomization.

RESULTS

Of the 6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 3010 and 3012 patients, respectively. The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratio for death in the intensive-control group, 1.31 and 1.07, respectively; P=0.10). Severe hypoglycemia (blood glucose level, ≤40 mg per deciliter [2.2 mmol per liter]) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001). There was no significant difference between the two treatment groups in the median number of days in the ICU (P=0.84) or hospital (P=0.86) or the median number of days of mechanical ventilation (P=0.56) or renal-replacement therapy (P=0.39).

CONCLUSIONS

In this large, international, randomized trial, we found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter. (ClinicalTrials.gov number, NCT00220987.)

The NICE-SUGAR study is a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, for International H Sydney), the Canadia Group, and the Van th Research Institute Columbia). The NIC ng committee (Sir F.J.F.I.C.M., Dean R. Chittock, F.R.C.P.C., Steve Yu-Shuo Su, Ph.D., Deborah Blair, R.N., Denise Foster, R.N., Vinay Dhingra, F.R.C.P.C., Rinaldo Bellomo, F.J.F.I.C.M., Deborah Cook, M.D., Peter Dodek, M.D., William R. Henderson, F.R.C.P.C., Paul C. Hébert, M.D., Stephane Heritier, Ph.D., Daren K. Heyland, M.D., Colin McArthur, F.J.F.I.C.M., Ellen McDonald, R.N., Imogen Mitchell, F.R.C.P., F.J.F.I.C.M., John A. Myburgh, Ph.D., F.J.F.I.C.M., Robyn Norton, Ph.D., M.P.H., Julie Potter, R.N., M.H.Sc.(Ed.), Bruce G. Robinson, F.R.A.C.P., and Juan J. Ronco, F.R.C.P.C.) assumes full responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Finfer at the George Institute for International Health, P.O. Box M201, Missenden Rd., Sydney NSW 2050, Australia, or at sfinfer@george.org.au.

*The Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study committees and investigators are listed in the Appendix.

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