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Circular Normativa

Assunto: **Criação e Implementação da Via Verde de Sépsis (VVS)**

Nº: 01/DQS/DQCO
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Para: **Todas as Unidades do Serviço Nacional de Saúde**

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I. CONTEXTO

Dados portugueses indicam que 22% dos internamentos em unidades de cuidados intensivos são devidos a Sépsis adquirida na comunidade[1]. Estes casos originam uma mortalidade hospitalar global de 38%, ou seja quase três vezes superior à mortalidade dos casos de AVC internados no ano de 2007. A mortalidade das formas mais graves de Sépsis, nomeadamente do choque séptico, atinge 51%[1].

Dados recentes, vindos da Europa e dos Unidos da América (EUA), indicam que a Sépsis representa um grave problema de saúde pública, comparável ao acidente vascular cerebral (AVC) e ao enfarte agudo do miocárdio (EAM)[*].

Acresce que a incidência da doença cardiovascular está a diminuir, ao passo que a da Sépsis aumenta pelo menos 1,5% ao ano[3]. Este aumento de incidência radica no envelhecimento da população, na maior longevidade de doentes crónicos, na crescente existência de imunossupressão por doença ou por iatrogenia e no maior recurso a técnicas invasivas. A gravidade dos casos de Sépsis parece estar também a aumentar, sendo maior o número de doentes com falência orgânica associada à Sépsis (Sépsis grave). O aumento de incidência determinou aumento do número de mortos por Sépsis nos últimos anos, sendo também comparável à mortalidade por AVC e por EAM[3,4,5,6].

Como para o AVC e o EAM existe para a Sépsis um conjunto de atitudes que, se realizados numa fase precoce da doença, reduzem a morbi-mortalidade. Estas atitudes incluem a identificação e estratificação rápidas de doentes, a utilização de antibioterapia adequada e de estratégias de ressuscitação hemodinâmica guiada por objectivos. Sabemos hoje, por exemplo, que por cada hora que demoremos a administrar antibioterapia apropriada, há uma redução de 7.6% na sobrevivência[7].

A implementação de um protocolo terapêutico de Sépsis permite não só diminuir a mortalidade, mas, também, um redução substancial dos custos para as instituições. Uma implementação alargada destes protocolos terapêuticos representa um meio potencial para a melhoria da utilização dos recursos existentes, com contenção simultânea dos custos[8].

[*] Nos EUA, a incidência de AVC e de EAM estão estimadas em, respectivamente, 780 000 e 920 000 casos anuais[2]. A incidência de sepsis estima-se em 751 000 casos/ano, com custos anuais associados a ascenderem a 16.7 mil milhões de dólares[3]

O único estudo multicêntrico português[1] realizado revela também que é grande a margem de melhoria na resposta que os serviços de urgência nacionais dão aos casos de Sépsis grave e choque séptico, nomeadamente no que diz respeito à realização e ao timing de doseamento de lactato sérico e ao timing de administração de antibioterapia.

II. NORMA

Sendo, actualmente, aceite cientificamente que uma intervenção precoce e adequada, tanto em termos de antibioterapia[7] como de suporte hemodinâmico[9], pode melhorar significativamente o prognóstico dos doentes com Sépsis grave e choque séptico, é imperativa a implementação de mecanismos organizacionais que permitam a sua rápida identificação e instituição atempada de terapêutica optimizada. Neste sentido, a Direcção-Geral da Saúde, no uso das suas competências técnico-normativas, e através da tradução e adaptação das orientações existentes a nível nacional e internacional, validadas por um grupo de peritos, determina, por recomendação do Departamento da Qualidade na Saúde, a criação, a nível nacional, da Via Verde da Sépsis (VVS).

1. Centros Participantes

Fazem parte da VVS todos os Serviços de Urgência (SUs) nacionais: SU básicos (SUB), SU médico-cirúrgicos (SUMC) e SU polivalentes (SUP).

São definidos **dois níveis** de responsabilidade:

Nível 1: Serviços de Urgência **SEM** Cuidados Intensivos (SUBs e SUMCs de Hospitais que não possuam Unidades de Cuidados Intensivos)

Nível 2: Serviços de Urgência **COM** Cuidados Intensivos (SUMCs que possuam Unidades de Cuidados Intensivos e SUPs).

Como Unidade de Cuidados Intensivos (UCI) entende-se unidade de monitorização e tratamento intensivo com rácio enfermeiro/doente de, pelo menos, 1 para 2 e com médico dedicado em presença física 24 horas por dia.

A existência de uma UCI é determinante, não só para assegurar um local de tratamento e vigilância adequados, mas também porque o passo 4 do algoritmo é altamente dependente do *know-how* característico da medicina intensiva e do doente crítico, nomeadamente colocação de cateter venoso central, realização de *fluid challenge* com avaliação dinâmica da pressão venosa central (PVC), eventual uso de inotrópicos e vasopressores e avaliação de saturação venosa central de oxigénio ($SvcO_2$).

2. Orientação Clínica

Os SUs de nível 1 asseguram:

1. A identificação dos doentes, simultaneamente, com Sépsis, isto é suspeita de infecção (tabela 1) e pelo menos 2 critérios de Síndrome Resposta Inflamatória Sistémica (SIRS) (tabela 3) por um lado, e hipoperfusão, isto é hipotensão que persiste após administração de pelo menos 20 ml/Kg de SF [ou equivalente] e/ou hiperlactacidemia >4mmol/l, por outro lado. (Evidência Cientifica de nível 1C)
2. A realização de exames complementares iniciais (tabela 2),
    a. Colheita de hemoculturas (pelo menos dois e não mais do que três conjuntos de hemoculturas, colhidas por punção venosa, com técnica asséptica adequada e volume de sangue de acordo com o recomendado pelo fabricante ou, na ausência de recomendação, não inferior a 10ml por frasco), sem atrasar o início da antibioterapia (Evidência Cientifica de nível 1C)
    b. Outros exames microbiológicos adequados à situação, sem atrasar o início da antibioterapia (Evidência Cientifica de nível 1C),
    c. Gasimetria, hemograma, bioquímica
    d. Telerradiografia pulmonar (se suspeita de foco respiratório) (Evidência Cientifica de nível 1C)
3. A instituição de antibioterapia adequada (Evidência Cientifica de nível 1B),
4. O início de reposição de volémia (Evidência Cientifica de nível 1C) e
5. A referenciação e transporte para centro de nível 2.

As hemoculturas colhidas devem ser enviadas com o doente e a equipa de transporte para o hospital de nível 2.

Os SUs de nível 2 dispõem de, pelo menos, uma unidade intensiva e apoio laboratorial e de radiologia 24 horas por dia.

Deve estar sempre presente no SU um responsável pela VVS, explicitamente nomeado, baseado em critérios de cada hospital. Terá a seu cargo o cumprimento do algoritmo e a decisão de transferência.

3. Orientação Organizacional

a. Triagem de Doentes

A identificação e estratificação de doentes devem seguir um processo de **três passos**.

Passo 1: passo de identificação de caso-suspeito de sepsis.

O primeiro passo consiste na avaliação sistemática de todos doentes que recorram ao SU, no momento da triagem geral inicial, nomeadamente da Triagem de Prioridades (Manchester), como possíveis candidatos à VVS. Os critérios VVS não substituem a Triagem de Prioridades (Manchester), antes são aduzidos a esta. A presença de uma suspeita clínica de infecção (tabela 1) deve motivar a avaliação obrigatória da frequência cardíaca, frequência respiratória e temperatura corporal (critérios de síndrome de reposta inflamatória sistémica – SIRS – tabela 3). Doentes com uma queixa sugestiva de infecção e pelo menos dois critérios de SIRS (frequência cardíaca superior a 90 bpm, frequência respiratória superior a 20 cpm e temperatura corporal inferior a 36ºC ou superior a 38ºC) avançam para o passo 2.

Passo 2: confirmação médica de caso-suspeito de sepsis, de existência de hipoperfusão e de ausência de critérios de exclusão.

O segundo passo baseia-se na rápida reavaliação do doente por um médico do SU, com o objectivo de confirmar suspeita clínica de infecção, avaliar se existe hipoperfusão grave, traduzida por hipotensão (TAS<90mmHg) ou por hiperlactacidemia (>4mmol/l), e se não existem critérios de exclusão da VVS (tabela 4).

Os doentes com confirmação médica da suspeita clínica de infecção e hipoperfusão passam, não havendo critérios de exclusão, para o terceiro passo.

Passo 3: Algoritmo terapêutico

O terceiro passo consiste no algoritmo terapêutico abaixo descrito.

b. Algoritmo terapêutico (terceiro passo)

Os dois objectivos fundamentais são a administração de antibioterapia adequada e a optimização da entrega tecidular de oxigénio.
O conceito de antibioterapia adequada radica na utilização de fármacos activos contra o microorganismo causal, em doses maximizadas, com boa penetração no foco de infecção e administrado na primeira hora após o reconhecimento do quadro (Evidência Cientifica de nível 1B).
É, portanto, necessária uma clara política de antibióticos no SU que permita que este objectivo seja cumprido.

A prescrição de antibióticos deve seguir as seguintes recomendações:

1. Antibioterapia endovenosa de largo espectro com um ou mais fármacos activos contra o agente bacteriano/ fúngico provável e com boa penetração no tecido/ órgão provavelmente afectado (Evidência Cientifica de nível 1B)
2. Rever a antibioterapia diariamente para optimizar eficácia, prevenir resistências e evitar toxicidade (Evidência Cientifica de nível 1C)

Deve existir um *stock* de antibióticos endovenosos no SU que assegure a sua rápida administração.

A terapêutica precoce orientada por objectivos assenta na obtenção, de forma sequencial, de três parâmetros hemodinâmicos claramente definidos (ver algoritmo – passo 4), com o intuito de optimizar o aporte de oxigénio aos tecidos periféricos. Estes objectivos são (Evidência Cientifica de nível 1C):

- Pressão venosa central (PVC) > 8 mmHg (ou 12 em doentes ventilados),
- Tensão arterial média (TAM) > 65 mmHg,
- Saturação venosa central de oxigénio ($SvcO_2$) > 70%.

Os objectivos preconizados devem ser atingidos nas primeiras 6 horas após a apresentação, o que implica que os doentes em centros de nível 1, após as medidas iniciais (ie – colheita de exames microbiológicos, primeira administração de antibiótico e início de fluidos - ver algoritmo - passo 3a), sejam rapidamente transferidos[#].

4. Formação

A implementação do processo implica a realização de formação específica.
O programa de formação inclui três tipos de curso:

- Curso de VVS para enfermeiros, focando o processo de triagem e de identificação de suspeita de sepsis e dando a conhecer a totalidade do algoritmo de tratamento;
- Curso de VVS para médicos de SU nível 1, focando os passos 1, 2, 3a e 3b e dando a conhecer o algoritmo global;
- Curso de VVS para médicos de SU nível 2, focando todos os passos do algoritmo terapêutica e a relação com as Unidades de Cuidados Intermédios e Intensivos.

5. Material

É necessário assegurar em TODOS os SU a existência do material, equipamento e fármacos necessários à concretização dos vários passos do respectivo "nível" de responsabilidade do SU na Rede da Via Verde da Sépsis.

6. Cronograma de Implementação

A implementação da VVS começará pelos Serviços de Urgência de Unidades de Saúde COM Cuidados Intensivos (Nível 2) e estar esta primeira fase concluída até final de 2010. A concretização da Rede deverá estar concluída até final de 2011.

Francisco George

Director-Geral da Saúde

[#] Tal como para as Vias Verdes do AVC e do EAM, poderá ser solicitada a colaboração do INEM para as transferências inter-hospitalares, no âmbito da Via Verde da Sépsis (despacho nº 5414/2008, DR nº42, 2ª Série, de 28 de Fevereiro; e "Documento Orientador sobre as Vias Verdes do EAM e do AVC", da Coordenação Nacional das Doenças Cardiovasculares – www.acs.min-saude.pt)

Referências Bibliográficas

1. Póvoa PR et al. Influence of vasopressor agent in septic shock mortality. Results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study). *Crit Care Med* 2009; 37: 410-6
2. Rosamond W et al. Heart Disease and Stroke Statistics - 2008 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;117: e25-e146
3. Angus DC et al. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303-10
4. Martin GS et al. The Epidemiology of Sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546-54
5. Annane D et al. Current Epidemiology of Septic Shock. The CUB-Réa Network. Am J Respir *Crit Care Med* 2003; 168: 165-72
6. Dombrovskiy V et al. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med* 2006; 35: 1244-50
7. Kumar A et al. Duration of Hypotension Before Initiation of Effective Antimicrobial Therapy is the Critical Determinant of Survival in Human Septic Shock. *Crit Care Med* 2006; 34: 1589-96
8. Shorr AF et al. Economic implications of an evidence-based sepsis protocol: Can we improve outcomes and lower costs? *Crit Care Med* 2007; 35(5): 1257-62
9. Rivers E et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *N Engl J Med* 2001; 345: 1368-77
10. Mandell LA et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clin Infect Dis* 2007; 44: S27-72
11. Solomkin JS et al. Guidelines for the Selection of Anti-infective Agents for Complicated Intra-abdominal Infections. *Clin Infect Dis* 2003; 37: 997-1005
12. Warren JW et al. Guidelines for Antimicrobial Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women. *Clin Infect Dis* 1999; 29: 745-58
13. Tunkel AR et al. Practice Guidelines for the Management of Bacterial Meningitis. *Clin Infect Dis* 2004; 39:1267-84
14. Garnacho-Montero et al. Impact of Adequate Antibiotic Therapy on the Outcome of Patients Admitted to the Intensive Care Unit with Sepsis. *Crit Care Med* 2003; 31: 2742-51
15. Garcia OJ, Doshi P, Otero RM, et al. Early Sepsis management. A meta-analysis of published studies. *Ann Emerg Med* 2008; 52 (Suppl) S59
16. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
17. Dellinger RP: Cardiovascular management of septic shock. *Crit Care Med* 2003; 31: 946–955
18. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
19. Linde-Zwirble WT, Angus DC: Severe sepsis epidemiology: Sampling, selection, and society. *Crit Care* 2004; 8:222–226
20. Dombrovskiy VY, Martin AA, Sunderram J, et al: Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: A trend analysis from 1993 to 2003. *Crit Care Med* 2007; 35:1414–1415
21. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004; 32:858–873
22. Dellinger RP, Carlet JM, Masur H, et al: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Intensive Care Med* 2004; 30: 536–555
23. Guyatt G, Schünemann H, Cook D, et al: Applying the grades of recommendations for antithrombotic and thrombolytic therapy: The seventh ACCP conference of antithrombotic and thrombolytic therapy. *Chest* 2004; 126:179S–187S
24. GRADE working group: Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328:1490–1498
25. Guyatt G, Gutterman D, Baumann MH, et al: Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an American College of Chest Physicians task force. *Chest* 2006; 129:174–181
26. Schünemann HJ, Jaeschke R, Cook DJ, et al, on behalf of the ATS Documents Development and Implementation Committee: An official ATS statement: Grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006; 174:605–614
27. Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31:1250–1256

28. Bone RC, Balk RA, Cerra FB, et al, and members of the ACCP/SCCM Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101:1644–1655 and *Crit Care Med* 1992; 20:864–874
29. Sprung CL, Bernard GR, Dellinger RP (Eds): Guidelines for the management of severe sepsis and septic shock. *Intensive Care Med* 2001; 27(Suppl 1):S1–S134
30. Sackett DL: Rules of evidence and clinical recommendations on the use of antithrombotic agents. *Chest* 1989; 95:2S–4S
31. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
32. Bendjelid K, Romand JA: Fluid responsiveness in mechanically ventilated patients: A review of indices used in intensive care. *Intensive Care Med* 2003; 29:352–360
33. Malbrain ML, Deeren D, De Potter TJ: Intraabdominal hypertension in the critically ill: It is time to pay attention. *Curr Opin Crit Care* 2005; 11:156–171
34. Varpula M, Tallgren M, Saukkonen K, et al: Hemodynamic variables related to outcome in septic shock. *Intensive Care Med* 2005; 31:1066–1071
35. Kortgen A, Niederprum P, Bauer M: Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. *Crit Care Med* 2006; 34:943–949
36. Sebat F, Johnson D, Musthafa AA, et al: A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients. *Chest* 2005; 127:1729–1743
37. Shapiro NI, Howell MD, Talmor D, et al: Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med* 2006; 34:1025–1032
38. Micek SST, Roubinian N, Heuring T, et al: Before-after study of a standardized hospital order set for the management of septic shock. *Crit Care Med* 2006; 34:2707–2713
39. Nguyen HB, Corbett SW, Steele R, et al: Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. *Crit Care Med* 2007; 35:1105–1112
40. Shorr AF, Micek ST, Jackson WL Jr, et al: Economic implications of an evidence based sepsis protocol: Can we improve outcomes and lower costs? *Crit Care Med* 2007; 35:1257–1262
41. Reinhart K, Kuhn HJ, Hartog C, et al: Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Med* 2004; 30: 1572–1578
42. Trzeciak S, Dellinger RP, Abate N, et al: Translating research to clinical practice: A 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest* 2006; 129: 225–232
43. Magder S: Central venous pressure: A useful but not so simple measurement. *Crit Care Med* 2006; 34:2224–2227
44. Bendjelid K: Right arterial pressure: Determinant or result of change in venous return? *Chest* 2005; 128:3639–3640
45. Vincent JL, Weil MH: Fluid challenge revisited. *Crit Care Med* 2006; 34:1333–1337
46. Trzeciak S, Dellinger RP, Parrillo JE, et al: Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: Relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med* 2007; 49:88–98
47. De Backer D, Creteur J, Dubois MJ, et al: The effects of dobutamine on microcirculatory alternations in patients with septic shock are independent of its systemic effects. *Crit Care Med* 2006; 34:403–408
48. Buwalda M, Ince C: Opening the microcirculation: Can vasodilators be useful in sepsis? *Intensive Care Med* 2002; 28:1208–1217
49. Boldt J: Clinical review: Hemodynamic monitoring in the intensive care unit. *Crit Care* 2002; 6:52–59
50. Pinsky MR, Payen D: Functional hemodynamic monitoring. *Crit Care* 2005; 9:566–572 Crit Care Med 2008 Reprint 23
51. Weinstein MP, Reller LP, Murphy JR, et al: The clinical significance of positive blood cultures: A comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. *Rev Infect Dis* 1983; 5:35–53
52. Blot F, Schmidt E, Nitenberg G, et al: Earlier positivity of central venous versus peripheral blood cultures is highly predictive of catheter-related sepsis. *J Clin Microbiol* 1998; 36:105–109
53. Mermel LA, Maki DG: Detection of bacteremia in adults: Consequences of culturing an inadequate volume of blood. *Ann Intern Med* 1993; 119:270–272
54. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416
55. Giamarellos-Bourboulis EJ, Giannopoulou P, Grecka P, et al: Should procalcitonin be introduced in the diagnostic criteria for the systemic inflammatory response syndrome and sepsis? *J Crit Care* 2004; 19:152–157
56. Tenover FC: Rapid detection and identification of bacterial pathogens using novel molecular technologies: Infection control and beyond. *Clin Infect Dis* 2007; 44:418–423
57. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension prior to initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596

58. Dellinger RP, Levy MM, Carlet, JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008 [published correction appears in *Crit Care Med* 2008; 36:1394 –1396]. *Crit Care Med* 2008; 36:296 –327.
59. Morrell M, Fraser VJ, Kollef MH: Delaying the empiric treatment of candida bloodstream infection until positive blood culture results are obtained: A potential risk factor for hospital mortality. *Antimicrob Agents Chemother* 2005; 49:3640–3645
60. Pappas PG, Rex JH, Sobel JD, et al: Guidelines for treatment of candidiasis. *Clin Infect Dis* 2004; 38:161–189
61. McCabe WR, Jackson GG: Gram negative bacteremia. *Arch Intern Med* 1962; 110: 92–100
62. Kreger BE, Craven DE, McCabe WR: Gram negative bacteremia: IV. Re-evaluation of clinical features and treatment in 612 patients. *Am J Med* 1980; 68:344–355
63. Leibovici L, Shraga I, Drucker M, et al: The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998; 244:379–386
64. Ibrahim EH, Sherman G, Ward S, et al: The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; 118:146–155
65. Hatala R, Dinh T, Cook DJ: Once-daily aminoglycoside dosing in immunocompetent adults: A meta-analysis. *Ann Intern Med* 1996; 124:717–725
66. Ali MZ, Goetz MB: A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis* 1997; 24: 796–809
67. Amsden GW, Ballow CH, Bertino JS: Pharmacokinetics and pharmacodynamics of anti-infective agents. *In:* Principles and Practice of Infectious Diseases. Fifth Edition
68. Mandell GL, Bennett JE, Dolin R (Eds). Philadelphia, Churchill Livingstone, 2000, pp 253–261
69. Hyatt JM, McKinnon PS, Zimmer GS, et al: The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcomes: Focus on antibacterial agents. *Clin Pharmacokinet* 1995; 28:143–160
70. Klastersky J: Management of fever in neutropenic patients with different risks of complications. *Clin Infect Dis* 2004; 39(Suppl 1):S32–S37
71. Safdar N, Handelsman J, Maki DG: Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis* 2004; 4:519–527
72. Paul M, Silbiger I, Grozinsky S, et al: Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev* 2006; (1):CD003344
73. Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al: Optimal management therapy for Pseudomonas aeruginosa ventilatorassociated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy. *Crit Care Med* 2007; 25:1888–1895
74. Jimenez MF, Marshall JC: Source control in the management of sepsis. *Intensive Care Med* 2001; 27:S49–S62
75. Moss RL, Musemeche CA, Kosloske AM: Necrotizing fascitis in children: Prompt recognition and aggressive therapy improve survival. *J Pediatr Surg* 1996; 31:1142–1146
76. Bufalari A, Giustozzi G, Moggi L: Postoperative intraabdominal abscesses: Percutaneous versus surgical treatment. *Acta Chir Belg* 1996; 96:197–200
77. Centers for Disease Control and Prevention: Guidelines for the prevention of intravascular catheter-related infections. *MMWR Morbid Mortal Wkly Rep* 2002; 51(RR-10):1–29
78. O'Grady NP, Alexander M, Dellinger EP, et al: Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis* 2002; 35:1281–1307
79. Mier J, Leon EL, Castillo A, et al: Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg* 1997; 173: 71–75
80. Evans A, Winslow BH: Oxygen saturation and hemodynamic response in critically ill mechanically ventilated adults during intrahospital transport. *Am J Crit Care* 1995; 4:106–111
81. Finfer S, Bellomo R, Boyce N, et al: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247–2256
82. Choi PTL, Yip G, Quinonez LG, et al: Crystalloids vs. colloids in fluid resuscitation: A systematic review. *Crit Care Med* 1999; 27: 200–210
83. Cook D, Guyatt G: Colloid use for fluid resuscitation: Evidence and spin. *Ann Intern Med* 2001; 135:205–208
84. Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: A systematic review of randomized trials. *BMJ* 1998; 316:961–964
85. Schortgen F, Lacherade JC, Bruneel F, et al: Effects of hydroxyethyl starch and gelatine on renal function in severe sepsis: A multicentre randomised study. *Lancet* 2001; 357: 911–916
86. Sakr Y, Payen D, Reinhart K, et al: Effects of hydroxyethyl starch administration on renal function in critically ill patients. *Br J Anaesth* 2007; 98:216–224
87. Hollenberg SM, Ahrens TS, Annane D, et al: Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. *Crit Care Med* 2004; 32:1928–1948
88. LeDoux D, Astiz ME, Carpati CM, et al: Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med* 2000; 28:2729–2732

89. Martin C, Papazian L, Perrin G, et al: Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest* 1993; 103:1826–1831
90. Martin C, Viviand X, Leone M, et al: Effect of norepinephrine on the outcome of septic shock. *Crit Care Med* 2000; 28:2758–2765
91. De Backer D, Creteur J, Silva E, et al: Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? *Crit Care Med* 2003; 31:1659–1667
92. Day NP, Phu NH, Bethell DP, et al: The effects of dopamine and adrenaline infusions on acid-base balance and systemic haemodynamics in severe infection. *Lancet* 1996; 348:219–223
93. Le Tulzo Y, Seguin P, Gacouin A, et al: Effects of epinephrine on right ventricular function in patients with severe septic shock and right ventricular failure: A preliminary descriptive study. *Intensive Care Med* 1997; 23:664–670
94. Bollaert PE, Bauer P, Audibert G, et al: Effects of epinephrine on hemodynamics and oxygen metabolism in dopamineresistant septic shock. *Chest* 1990; 98: 949–953
95. Zhou SX, Qiu HB, Huang YZ, et al: Effects of norepinephrine, epinephrine, and norepinephrine-dobutamine on systemic and gastric mucosal oxygenation in septic shock. *Acta Pharm Sin* 2002; 23:654–658
96. Levy B, Bollaert PE, Charpentier C, et al: Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: A prospective, ran-domized study. *Intensive Care Med* 1997;23:282–287
97. Mackenzie SJ, Kapadia F, Nimmo GR, et al: Adrenaline in treatment of septic shock: Effects on haemodynamics and oxygen transport. *Intensive Care Med* 1991; 17: 36–39
98. Moran JL, O'Fathartaigh MS, Peisach AR, et al: Epinephrine as an inotropic agent in septic shock: A dose-profile analysis. *Crit Care Med* 1993; 21:70–77
99. Yamazaki T, Shimada Y, Taenaka N, et al: Circulatory responses to afterloading with phenylephrine in hyperdynamic sepsis. *Crit Care Med* 1982; 10:432–435
100. Gregory JS, Bonfiglio MF, Dasta JF, et al: Experience with phenylephrine as a component of the pharmacologic support of septic shock. *Crit Care Med* 1991; 19:1395–1400
101. Djillali A, Vigno P, Renault A, et al, for the CATS STUDY Group: Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: A randomized trial. *Lancet* 2007; 370:676–684
102. Regnier B, Rapin M, Gory G, et al: Haemodynamic effects of dopamine in septic shock. *Intensive Care Med* 1977; 3:47–53
103. Landry DW, Levin HR, Gallant EM, et al: Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; 95:1122–1125
104. Patel BM, Chittock DR, Russell JA, et al: Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology* 2002; 96:576–582
105. Dünser MW, Mayr AJ, Ulmer H, et al: Arginine vasopressin in advanced vasodilatory shock: A prospective, randomized, controlled study. *Circulation* 2003; 107: 2313–2319
106. Holmes CL, Patel BM, Russell JA, et al: Physiology of vasopressin relevant to management of septic shock. *Chest* 2001; 120: 989–1002
107. Malay MB, Ashton RC, Landry DW, et al: Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma* 1999; 47:699–705
108. Holmes CL, Walley KR, Chittock DR, et al: The effects of vasopressin on hemodynamics and renal function in severe septic shock: A case series. *Intensive Care Med* 2001; 27:1416–1421
109. Lauzier F, Levy B, Lamarre P, et al: Vasopressin or norepinephrine in early hyperdynamic septic shock: A randomized clinical trial. *Intensive Care Med* 2006; 32: 1782–1789
110. O'Brien A, Calpp L, Singer M: Terlipressin for norepinephrine-resistant septic shock *Lancet* 2002; 359:1209–1210
111. Sharshar T, Blanchard A, Paillard M, et al: Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; 31:1752–1758
112. Dünser MW, Mayr AJ, Tura A, et al: Ischemic skin lesions as a complication of continuous vasopressin infusion in catecholamine-resistant vasodilatory shock: Incidence and risk factors. *Crit Care Med* 2003; 31:1394–1398
113. Bellomo R, Chapman M, Finfer S, et al: Low-dose dopamine in patients with early renal dysfunction: A placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; 356: 2139–2143
114. Kellum J, Decker J: Use of dopamine in acute renal failure: A meta-analysis. *Crit Care Med* 2001; 29:1526–1531
115. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med* 1995; 333:1025–1032
116. Hayes MA, Timmins AC, Yau EHS, et al: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–1722
117. Annane D, Sebille V, Charpentier C, et al: Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002; 288:862–871
118. Briegel J, Forst H, Haller M, et al: Stress doses of hydrocortisone reverse hyperdynamic septic shock: A prospective, randomized, double-blind, single-center study. *Crit Care Med* 1999; 27:723–732

119. Bollaert PE, Charpentier C, Levy B, et al: Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med* 1998; 26:645–650
120. Sprung CL, Annane D, Briegel J, et al: Corticosteroid therapy of septic shock (CORTICUS). Abstr. *Am Rev Respir Crit Care Med* 2007; 175:A507
121. Briegel J, Vogeser M, Annane D, et al: Measurement of cortisol in septic shock: Interlaboratory harmonization. *Am Rev Respir Crit Care Med* 2007; 175:A436
122. Allolio B, Dorr H, Stuttmann R, et al: Effect of a single bolus of etomidate upon eight major corticosteroid hormone and plasma ACTH. *Clin Endocrinol (Oxf)* 1985; 22: 281–286
123. Reincke M, Allolio B, Würth G, et al: The hypothalamic-pituitary-adrenal axis in critical illness: Response to dexamethasone and corticotropin-releasing hormone. *J Clin Endocrinol Metab* 1993; 77:151–156
124. Oppert M, Schindler R, Husung C, et al: Low dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med* 2005; 33:2457–2464
125. Yildiz O, Doganay M, Aygen B, et al: Physiologic-dose steroid therapy in sepsis. *Crit Care* 2002; 6:251–259
126. Keh D, Boehnke T, Weber-Carstens S, et al: Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: A double-blind, randomized, placebocontrolled, crossover study. *Am J Respir Crit Care Med* 2003; 167:512–520
127. Bone RC, Fisher CJ, Clemmer TP: A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317:653–658
128. Cronin L, Cook DJ, Carlet J, et al: Corticosteroid treatment for sepsis: A critical appraisal and meta-analysis of the literature. *Crit Care Med* 1995; 23:1430–1439
129. The Veterans Administration Systemic Sepsis Cooperative Study Group: Effect on high-dose glucocorticoid therapy on mortality in patients with clinical signs of sepsis. *N Engl J Med* 1987; 317:659–665
130. Confalonieri M, Urbino R, Potena A, et al: Hydrocortisone infusion for severe community-acquired pneumonia: A preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171:242–248
131. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein c for severe sepsis. *N Engl J Med* 2001; 344:699–709
132. Abraham E, Laterre PF, Garg R, et al: Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005; 353:1332–1341
133. Vincent JL, Bernard GR, Beale R, et al: Drotrecogin alfa (activated) treatment in severe sepsis from the global open-label trial ENHANCE: Further evidence for survival and safety and implications for early treatment. *Crit Care Med* 2005; 33:2266–2277
134. Oxman AD, Guyatt GH: A consumer's guide to subgroup analyses. *Ann Intern Med* 1992; 116:78–84
135. Ely EW, Laterre PF, Angus DC, et al: Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med* 2003; 31:12–19
136. Kanji S, Perreault MM, Chant C, et al: Evaluating the use of drotrecogin alfa activated in adult severe sepsis: a Canadian multicenter observational study. *Intensive Care Med* 2007; 33:517–523
137. Bertolini G, Rossi C, Anghileri A, et al: Use of drotrecogin alfa (activated) in Italian intensive care units: The results of a nationwide survey. *Intensive care Med* 2007; 33: 426–434
138. European Medicines Agency *Evaluation of Medicines for Human Use.* http://www.emea.europa.eu/pdfs/human/press/pr/8509607en. pdf. Accessed October 22, 2007
139. 123. Hébert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion in critical care. *N Engl J Med* 1999; 340:409–417
140. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024–3029
141. Lorente JA, Landín L, dePablo R, et al: Effects of blood transfusion on oxygen transport variables in severe sepsis. *Crit Care Med* 1993; 21:1312–1318
142. Fernandes CJ, Akamine N, DeMarco FVC, et al: Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care* 2001; 5:362–567 Crit Care Med 2008 Reprint 25
143. Corwin HL, Gettinger A, Rodriguez RM, et al: Efficacy of recombinant human erythropoietin in the critically ill patient: A randomized double-blind, placebo-controlled trial. *Crit Care Med* 1999; 27:2346–2350
144. Corwin HL, Gettinger A, Pearl RG, et al: Efficacy of recombinant human erythropoietin in critically ill patients. *JAMA* 2002; 28:2827–2835
145. College of American Pathologists: Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA* 1994; 271:777–781
146. Canadian Medical Association Expert Working Group: Guidelines for red blood cell and plasma transfusion for adults and children. *Can Med Assoc J* 1997; 156:S1–S24
147. American Society of Anaesthesiologists Task Force on Blood Component Therapy: Practice guidelines for blood component therapy. *Anesthesiology* 1996; 84:732–747
148. Abdel-Wahab OI, Healy B, Dzik WH: Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. *Transfusion* 2006; 46:1279–1285

149. Warren BL, Eid A, Singer P, et al: High-dose antithrombin III in severe sepsis: A randomized controlled trial. *JAMA* 2001; 286: 1869–1878
150. Wiedermann CJ, Hoffmann JN, Juers M, et al: High-dose antithrombin III in the treatment of severe sepsis in patients with a high risk of death: Efficacy and safety. *Crit Care Med* 2006; 34:285–292
151. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
152. Amato MBP, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347–354
153. Brochard L, Roudot-Thoraval F, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1998; 158:1831–1838
154. Brower RG, Fessler HE, Shade DM, et al: Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med* 1999; 27:1492–1498
155. Stewart TE, Meade MO, Cook DJ, et al: Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998; 338:355–361
156. Eichacker PQ, Gerstenberger EP, Banks SM, et al: Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. *Am J Respir Crit Care Med* 2002; 166:1510–1514
157. Tobin MJ: Culmination of an era in research on the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1360–1361
158. Marini JJ, Gattinoni L: Ventilatory management of acute respiratory distress syndrome: A consensus of two. *Crit Care Med* 2004; 32:250–255
159. Hager DN, Krishnan JA, Hayden DL, et al: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172:1241–1245
160. Ferguson ND, Frutos-Vivar F, Esteban A et al: Airway pressures, tidal volumes, and mortality in patients with acute respiratory distress syndrome *Crit Care Med* 2005; 33: 21–30
161. Hickling KG, Henderson S, Jackson R: Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: A prospective study. *Crit Care Med* 1994; 22:1568–1578
162. Bidani A, Tzouanakis AE, Cardenas VJ, et al: Permissive hypercapnia in acute respiratory failure. *JAMA* 1994; 272:957–962
163. Kallet RH, Jasmer RM, Luce JM, et al: The treatment of acidosis in acute lung injury with THAM. *Am J Respir Crit Care Med* 2000; 161:1149–1153
164. Weber T, Tschernich H, Sitzwohl C, et al: Tromethamine buffer modifies the depressant effect of permissive hypercapnia on myocardial contractility in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2000; 162:1361–1365
165. Marini JJ, Ravenscraft SA: Mean airway pressure: Physiologic determinants and clinical importance—Part I: Physiologic determinants and measurements. *Crit Care Med* 1992; 20:1461–1472
166. Gattinoni L, M.R., Caspani ML, et al: Constant mean airway pressure with different patterns of positive pressure breathing during the adult respiratory distress syndrome. *Bull Eur Physiopathol Respir* 1985; 21: 275–279
167. Pesenti A, Marcolin R, Prato P, et al: Mean airway pressure vs. positive end-expiratory pressure during mechanical ventilation. *Crit Care Med* 1985; 13:34–37
168. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351: 327–336
169. Villar J, Kacmarek RM, Pérez-Méndez L, et al, for the ARIES Network: A high PEEP-low tidal volume ventilatory strategy improves outcome in persistent ARDS: A randomized controlled trial. *Crit Care Med* 2006; 34: 1311–1318
170. Amato MB, Barbas CS, Medeiros DM, et al: Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med* 1995; 152:1835–1846
171. Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775–1786
172. Stocker R, Neff T, Stein S, et al: Prone positioning and low-volume pressure-limited ventilation improve survival in patients with severe ARDS. *Chest* 1997; 111: 1008–1017
173. Lamm WJ, Graham MM, Albert RK: Mechanism by which prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 1994; 150:184–193
174. Jolliet P, Bulpa P, Chevrolet JC: Effects of the prone position on gas exchange and hemodynamics in severe acute respiratory distress syndrome. *Crit Care Med* 1998; 26: 1977–1985
175. Gattinoni L, Tognoni G, Pesenti A, et al: Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med* 2001; 345:568–573

176. Guerin C, Gaillard S, Lemasson S, et al: Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. *JAMA* 2004; 292: 2379–2387
177. Mancebo J, Fernandez R, Blanch L, et al: A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2006; 173:1233–1239
178. Antonelli M, Conti G, Rocco M, et al: A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998; 339: 429–435
179. Drakulovic MB, Torres A, Bauer TT, et al: Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. *Lancet* 1999; 354:1851–1858
180. van Nieuwenhoven CA, Vandenbroucke-Grauls C, van Tiel FH, et al: Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A randomized study. *Crit Care Med* 2006; 34: 396–402
181. Ferrer M, Esquinas A, Leon M, et al: Noninvasive ventilation in severe hypoxemic respiratory failure: A randomized clinical trial *Am J Respir Crit Care Med* 2003; 168: 1438–1444
182. Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med* 1996; 335:1864–1869
183. Esteban A, Alia I, Tobin MJ, et al: Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med* 1999; 159:512–518
184. Esteban A, Alia I, Gordo F, et al: Extubation outcome after spontaneous breathing trials 26 Crit Care Med 2008 Reprint with T-tube or pressure support ventilation. *Am J Respir Crit Care Med* 1997; 156: 459–465
185. Brochard L, Rauss A, Benito S, et al: Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med* 1994; 150:896–903
186. Connors AF Jr, McCaffree DR, Gray BA: Evaluation of right-heart catheterization in the critically ill patient without acute myocardial infarction. *N Engl J Med* 1983; 308: 263–267
187. Iberti TJ, Fischer EP, Leibowitz AB, et al: A multicenter study of physicians' knowledge of the pulmonary artery catheter: Pulmonary artery catheter study group. *JAMA* 1990; 264:2928–2932
188. Al-Kharrat T, Zarich S, Amoateng-Adjepong Y, et al: Analysis of observer variability in measurement of pulmonary artery occlusion pressures. *Am J Respir Crit Care Med* 1999; 160:415–420
189. Osman D, Ridel C, Ray P, et al: Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med* 2007; 35:64–68
190. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of goal-oriented hemodynamic therapy in critically ill patients: SvO2 collaborative group. *N Engl J Med* 1995; 333:1025–1032
191. Richard C, Warszawski J, Anguel N, et al: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 2003; 290: 2713–2720
192. Wheeler AP, Bernard GR, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213–2224
193. Sandham JD, Hull RD, Brant RF, et al: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003; 348:5–14
194. Shah MR, Hasselblad V, Stevenson LW, et al: Impact of the pulmonary artery catheter in critically ill patients: Meta-analysis of randomized clinical trials. *JAMA* 2005; 294: 1664–1670
195. Harvey S, Harrison DA, Singer M, et al: Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-man): A randomised controlled trial. *Lancet* 2005; 366:472–477
196. Ware LB, Matthay MA: The acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1334–1349
197. Sibbald WJ, Short AK, Warshawski FJ, et al: Thermal dye measurements of extravascular lung water in critically ill patients: Intravascular starling forces and extravascular lung water in the adult respiratory distress syndrome. *Chest* 1985; 87:585–592
198. Martin GS, Mangialardi RJ, Wheeler AP, et al: Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2002; 30:2175–2182
199. Schuller D, Mitchell JP, Calandrino FS, et al: Fluid balance during pulmonary edema: Is fluid again a marker or a cause of poor outcome? *Chest* 1991; 100:1068–1075
200. Mitchell JP, Schuller D, Calandrino FS, et al: Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 1992; 145:990–998
201. Wiedemann HP, Wheeler AP, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
202. Brook AD, Ahrens TS, Schaiff R, et al: Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27:2609–2615
203. Marx WH, DeMaintenon NL, Mooney KF, et al: Cost reduction and outcome improvement in the intensive care unit. *J Trauma* 1999; 46:625–629
204. MacLaren R, Plamondon JM, Ramay KB, et al: A prospective evaluation of empiric versus protocol-based sedation and analgesia. *Pharmacotherapy* 2000; 20:662–672

205. De Jonghe B, Cook D, Appere-De-Vecchi C, et al: Using and understanding sedation scoring systems: A systematic review. *Intensive Care Med* 2000; 20:662–672
206. Devlin JW, Boleski G, Mlynarek M, et al: Motor activity assessment scale: A valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. *Crit Care Med* 1999; 27:1271–1275
207. Kollef MH, Levy NT, Ahrens TS, et al: The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest* 1998; 114:541–548
208. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med* 2000; 342: 1471–1477
209. Kress JP, Vinayak AG, Levitt J, et al: Daily sedative interruption in mechanically ventilated patients at risk for coronory disease. *Crit Care Med* 2007; 35:365–371
210. Klessing HT, Geiger HJ, Murray MJ, et al: A national survey on the practice patterns of anesthesiologist intensivists in the use of muscle relaxants. *Crit Care Med* 1992; 20: 1341–1345
211. Murray MJ, Cowen J, Deblock H, et al: Clinical practice guidelines for sustained neuromuscular blockade in the critically ill adult. *Crit Care Med* 2002; 30:142–156
212. Hansen-Flaschen JH, Brazinsky S, Basile C, et al: The use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. *JAMA* 1991; 266:2870–2875
213. Freebairn RC, Derrick J, Gomersall CD, et al: Oxygen delivery, oxygen consumption, and gastric intramucosal pH are not improved by a computer-controlled, closedloop, vecuronium infusion in severe sepsis and septic shock. *Crit Care Medicine* 1997; 25:72–77
214. Shapiro BA, Warren J, Egol AB, et al: Practice parameters for sustained neuromuscular blockade in the adult critically ill patient: An executive summary. *Crit Care Med* 1995; 23:1601–1605
215. Meyer KC, Prielipp RC, Grossman JE, et al: Prolonged weakness after infusion of atracurium in tow intensive care unit patients. *Anesth Analg* 1994; 78:772–774
216. Lacomis D, Petrella JT, Giuliani MJ: Causes of neuromuscular weakness in the intensive care unit: A study of ninety-two patients. *Muscle Nerve* 1998; 21:610–617
217. Gooch JL, Suchyta MR, Balbierz JM, et al: Prolonged paralysis after treatment with neuromuscular blocking agents. *Crit Care Med* 1991; 19:1125–1131
218. Rudis MI, Sikora CA, Angus E, et al: A prospective randomized controlled evaluation of peripheral nerve stimulation versus standard clinical dosing of neuromuscular blocking agents in critically ill patients. *Crit Care Med* 1997; 25:575–583
219. Frankel H, Jeng J, Tilly E, et al: The impact of implementation of neuromuscular blockade monitoring standards in a surgical intensive care unit. *Am Surg* 1996; 62: 503–506
220. Strange C, Vaughan L, Franklin C, et al: comparison of train-of-four and best clinical assessment during continuous paralysis. *Am J Respir Crit Care Med* 1997; 156:1556–1561
221. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345: 1359–1367
222. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461
223. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; 79:992–1000
224. Finney SJ, Zekveld C, Elia A, et al: Glucose control and mortality in critically ill patients. *JAMA* 2003; 290:2041–2047
225. Krinsley JS: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003; 78:1471–1478
226. Egi M, Bellomo R, Stachowski E, et al: Variability in blood glucose concentrations and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105:233–234
227. Pittas AG, Siegel RD, Lau J: Insulin therapy for critically ill hospitalized patients. *Arch Int Med* 2004; 164:2005–2011
228. Brunkhorst FM, Kuhnt E, Engel C, et al: Intensive insulin therapy in patient with Crit Care Med 2008 Reprint 27 severe sepsis and septic shock is associated with an increased rate of hypoglycemia—Results from a randomized multicenter study (VISEP). Abstr. *Infection* 2005; 33: 19–20
229. Preiser JC: Intensive glycemic control in medsurg patients (European Glucontrol trial). Program and abstracts of the Society of Critical Care Medicine 36th Critical Care Congress, February 17–21, 2007, Orlando, FL
230. Current Controlled Trials: A multi-centre, open label, randomised controlled trial of two target ranges for glycaemic control in intensive care unit (ICU) patients. http://controlled-trials.com/isrctn/trial/ISRCTN04968275/0/04968275.html. Accessed June 10, 2007
231. Nichols JH: Bedside testing, glucose monitoring, and diabetes management. *In:* Principles of Point of Care Testing. Kost GJ (Ed). Philadelphia, Lippincott Williams & Wilkins, 2002
232. Kanji S, Buffie J, Hutton B, et al: Reliability of point-of-care testing for glucose measurement in critically ill adults. *Crit Care Med* 2005; 33:2778–2785123

233. Wilson M, Weinreb J, Soo Hoo GW: Intensive insulin therapy in critical care: A review of a dozen protocols. *Diabetes Care* 2007; 30:1005–1011
234. Mauritz W, Sporn P, Schindler I, et al: Acute renal failure in abdominal infection: Comparison of hemodialysis and continuous arteriovenous and continuous hemofiltration. *Anasth Intensivther Nortfallmed* 1986; 21:212–217
235. Bartlett RH, Mault JR, Dechert RE, et al: Continuous arteriovenous hemofiltration: Improved survival in surgical acute renal failure. *Surgery* 1986; 100:400–408
236. Kierdorf H: Continuous versus intermittent treatment: Clinical results in acute renal failure. *Contrib Nephrol* 1991; 93:1–12
237. Bellomo R, Mansfield D, Rumble S, et al: Acute renal failure in critical illness: Conventional dialysis versus continuous hemodiafiltration. *Am Soc Artif Intern Organs J* 1992; 38:M654–M657
238. Bellomo R, Farmer M, Parkin G, et al: Severe acute renal failure: A comparison of acute continuous hemodiafiltration and conventional dialytic therapy. *Nephron* 1995; 71:59–64
239. Kruczinski K, Irvine-Bird K, Toffelmire EB, et al: A comparison of continuous arteriovenous hemofiltration and intermittent hemodialysis in acute renal failure patients in intensive care unit. *Am Soc Artif Intern Organs J* 1993; 38:M778–M781
240. Van Bommel EH, Bouvy ND, Sob KL, et al: Acute dialytic support for the critically ill: Intermittent hemodialysis versus continuous arteriovenous hemodiafiltration. *Am J Nephrol* 1995; 15:192–200
241. Guerin C, Girard R, Selli JM, et al: Intermittent versus continuous renal replacement therapy for acute renal failure in intensive care units: Results from a multicenter prospective epidemiological survey. *Intensive Care Med* 2002; 28:1411–1418
242. Kellum JA, Angus DC, Johnson JP, et al: Continuous versus intermittent renal replacement therapy: A meta-analysis. *Intensive Care Med* 2002; 28:29–37
243. Tonelli M, Manns B, Feller-Kopman D: Acute renal failure in the intensive care unit: A systematic review of the impact of dialytic modality on mortality and renal recovery. *Am J Kidney Dis* 2002; 40:875–885
244. Mehta RL, McDonald B, Gabbai FB, et al: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163
245. Gasparovic V, Filipovic-Greie I, Merkler M, et al: Continuous renal replacement therapy (CRRT) or intermittent hemodialysis (IHD)—What is the procedure of choice in critically ill patients? *Ren Fail* 2003; 25:855–862
246. Augustine JJ, Sandy D, Seifert TH, et al: A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. *Am J Kidney Dis* 2004;44:1000–1007
247. Uehlinger DE, Jakob SM, Ferrari P, et al: Comparison of continuous and intermittent renal replacement therapy for acute renal failure. *Nephrol Dial Transplant* 2005; 20:1630–1637
248. Vinsonneau C, Camus C, Combes A, et al: Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multipleorgan dysfunction syndrome: A multicentre randomised trial. *Lancet* 2006; 368:379–85
249. John S, Griesbach D, Baumgärtel M, et al: Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: A prospective, randomized clinical trial. *Nephrol Dial Transplant* 2001; 16:320–327
250. Misset B, Timsit JF, Chevret S, et al: A randomized cross-over comparison of the hemodynamic response to intermittent hemodialysis and continuous hemofiltration in ICU patients with acute renal failure. *Intensive Care Med* 1996; 22:742–746
251. Ronco C, Bellomo R, Homel P, et al: Effects of different doses in continuous venovenous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 2000; 356:26–30
252. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, et al: Effects of early highvolume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: A prospective, randomized trial. *Crit Care Med* 2002; 30:2205–2211
253. Schiffl H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 2002; 346:305–310
254. Saudan P, Niederberger M, De Seigneux S, et al: Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int* 2006;70:1312–1317
255. Cooper DJ, Walley KR, Wiggs BR, et al: Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis: A prospective, controlled clinical study. *Ann Intern Med* 1990; 112:492–498
256. Mathieu D, Neviere R, Billard V, et al: Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: A prospective, controlled clinical study. *Crit Care Med* 1991;19:1352–1356
257. Cade JF: High risk of the critically ill for venous thromboembolism. *Crit Care Med* 1982; 10:448–450
258. Halkin H, Goldberg J, Modal M, et al: Reduction in mortality in general medical inpatients by low-dose heparin prophylaxis. *Ann Intern Med* 1982; 96:561–565
259. Pingleton SK, Bone RC, Pingleton WW, et al: Prevention of pulmonary emboli in a respiratory intensive care unit. *Chest* 1981; 79:647–650
260. Belch JJ, Lowe DO, Ward AG, et al: Prevention of deep vein thrombosis in medical patients by low-dose heparin. *Scott Med J* 1981; 26:115–117

261. Gardlund B: Randomized, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases: The Heparin Prophylaxis Study Group. *Lancet* 1996; 347:1357–1361
262. Samama MM, Cohen AT, Darmon JY, et al: A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patient. *N Engl J Med* 1999; 341:793–800
263. Dahan R, Houlbert D, Caulin C, et al: Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: A randomized double-blind trial. *Haemostasis* 1986; 16:159–164
264. Hirsch DR, Ingenito EP, Goldhaber SZ: Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA* 1995; 274:335–337
265. Fraisse F, Holzapfel L, Couland JM, et al: Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD: The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med* 2000; 161:1109–1114
266. Kupfer Y, Anwar J, Seneviratne C, et al: Prophylaxis with subcutaneous heparin significantly reduces the incidence of deep venous thrombophlebitis in the critically ill. Abstr. *Am J Crit Care Med* 1999; 159(Suppl): A519
267. Geerts W, Cook D, Shelby R, et al: Venous thromboembolism and its prevention in critical care. *J Crit Care* 2002; 17:95–104
268. Attia J, Ray JG, Cook DJ, et al: Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med* 2001; 161: 1268–1279
269. King CS, Holley AB, Jackson JF, et al: Twice 28 Crit Care Med 2008 Reprint vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A metaanalysis. *Chest* 2007; 131:507–516
270. Vanek VW: Meta-analysis of effectiveness of intermittent pneumatic compression devices with a comparison of thigh-high to knee-high sleeves. *Am Surg* 1998; 64: 1050–1058
271. Turpie AG, Hirsh J, Gent M, et al: Prevention of deep vein thrombosis in potential neurosurgical patients: A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med* 1989; 149:679–681
272. Agu O, Hamilton G, Baker D: Graduated compression stocking in the prevention of venous thromboembolism. *Br J Surg* 1999; 86:992–1004
273. German Hip Arthroplasty Trial Group (GHAT): Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement: A randomized trial. *Arch Orthop Trauma Surg* 1992; 111:110–120
274. Colwell CW, Spiro TE, Trowbridge AA, et al: Use of enoxaparin, a low-molecular-weightheparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement: A clinical trial comparing efficacy and safety. *J Bone Joint Surg Am* 1994; 76:3–14
275. Geerts WH, Jay RM, Code KI, et al: A comparison of low-dose heparin with lowmolecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996; 335:701–707
276. Basso N, Bagarani M, Materia A, et al: Cimetidine and antacid prophylaxis of acute upper gastrointestinal bleeding in high risk patients. *Am J Surg* 1981; 141:339–342
277. Bresalier RS, Grendell JH, Cello JP, et al: Sucralfate versus titrated antacid for the prevention of acute stress-related gastrointestinal hemorrhage in critically ill patients. *Am J Med* 1987; 83:110–116
278. Poleski MH, Spanier AH: Cimetidine versus antacids in the prevention of stress erosions in critically ill patients. *Am J Gastroenterol* 1986; 81:107–111
279. Stothert JC, Simonowitz DA, Dellinger EP, et al: Randomized prospective evaluation of cimetidine and antacid control of gastric pH in the critically ill. *Ann Surg* 1980; 192: 169–174
280. Cook DJ, Fuller HD, Guyatt GH, et al: Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994; 330: 377–381
281. Schuster DP, Rowley H, Feinstein S, et al: Prospective evaluation of the risk of upper gastrointestinal bleeding after admission to a medical intensive care unit. *Am J Med* 1984; 76:623–629
282. Misra UK, Kalita J, Pandey S, et al: A randomized placebo controlled trial of ranitidine versus sucralfate in patients with spontaneous intracerebral hemorrhage for prevention of gastric hemorrhage. *J Neurol Sci* 2005; 239:5–10
283. Friedman CJ, Oblinger MJ, Suratt PM, et al: Prophylaxis of upper gastrointestinal hemorrhage in patients requiring mechanical ventilation. *Crit Care Med* 1982; 10: 316–319
284. Hastings PR, Skillman JJ, Bushnell LS, et al: Antacid titration in the prevention of acute gastrointestinal bleeding: A controlled, randomized trial in 100 critically ill patients. *N Engl J Med* 1978; 298:1041–1045
285. Cook DJ, Witt LG, Cook RJ, et al: Stress ulcer prophylaxis in the critically ill: A meta-analysis. *Am J Med* 1991; 91:519–257
286. Kahn JM, Doctor JN, Rubenfeld GD: Stress ulcer prophylaxis in mechanically ventilated patients: Integrating evidence and judgment using a decision analysis. *Intensive Care Med* 2006; 32:1151–1158
287. Cook D, Guyatt G, Marshall J, et al: A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998; 338:791–797
288. Cook DJ, Reeve BK, Guyatt GH, et al: Stress ulcer prophylaxis in critically ill patients: Resolving discordant meta-analyses. *JAMA* 1996; 275:308–314
289. Levy MJ, Seelig CB, Robinson NJ, et al: Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997; 42:1255–1299

290. Conrad SA, Gabrielli A, Margolis B, et al: Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med* 2005; 33:760–765
291. Vandenbroucke-Grauls CMJ, Vandenbroucke JP: Effect of selective decontamination of the digestive tract on respiratory tract infections and mortality in the intensive care unit. *Lancet* 1991; 338:859–862
292. Selective Decontamination of the Digestive Tract Trialists' Collaborative Group: Metaanalysis of randomised controlled trials of selective decontamination of the digestive tract. *BMJ* 1993; 307:525–532
293. Kollef M: The role of selective digestive tract decontamination on mortality and respiratory tract infections: A meta-analysis. *Chest* 1994; 105:1101–1108
294. Heyland DK, Cook DJ, Jaeschke R, et al: Selective decontamination of the digestive tract: An overview. *Chest* 1994; 105: 1221–1229
295. Hurley JC: Prophylaxis with enteral antibiotics in ventilated patients: Selective decontamination or selective cross-infection? *Antimicrob Agents Chemother* 1995; 39: 941–947
296. D'Amico R, Pifferi S, Leonetti C, et al: Effectiveness of antibiotic prophylaxis in critically ill adult patients: Systematic review of randomised controlled trials. *BMJ* 1998; 316:1275–1285
297. Nathens AB, Marshall JC: Selective decontamination of the digestive tract in surgical patients: A systematic review of the evidence. *Arch Surg* 1999; 134:170–176
298. Redman R, Ludington E, Crocker M, et al: Analysis of respiratory and non-respiratory infections in published trials of selective digestive decontamination. Abstr. *Intensive Care Med* 2001; 27(Suppl 1):S128
299. Safdar N, Said A, Lucey MR: The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: A systematic review and meta-analysis. *Liver Transpl* 2004; 10: 817–827
300. Liberati A, D'Amico R, Pifferi S, et al: Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care (Cochrane Review).*In:* The Cochrane Library. Issue 1. Chichester, UK: Wiley, 2004
301. Silvestri L, van Saene HKF, Milanese M, et al: Impact of selective decontamination of the digestive tract on fungal carriage and infection: Systematic review of randomised controlled trials. *Intensive Care Med* 2005; 31:898–910
302. Silvestri L, Milanese M, Durì D, et al: Impact of SDD on bloodstream infections: A systematic review of randomized trials. Abstr. *Intensive Care Med* 2005; 31(Suppl 1): S87
303. Hammond JMJ, Potgieter PD: Is there a role for selective decontamination of the digestive tract in primarily infected patients in the ICU? *Anaesth Intensive Care* 1995; 23: 168–174
304. De Jonge E, Schultz M, Spanjaard L, et al: Selective decontamination of digestive tract in intensive care. *Lancet* 2003; 362: 2119–2120
305. De Jonge E, Schultz MJ, Spanjaard L, et al: Effects of selective decontamination of the digestive tract on mortality and acquisition of resistance bacteria on intensive care: A randomised controlled trial. *Lancet* 2003; 362:1011–1016
306. Hammond JM, Potgieter PD, Saunders GL, et al: Double blind study of selective decontamination of the digestive tract in intensive care. *Lancet* 1992; 340:5–9
307. de la Cal MA, Cerda E, van Saene HKF, et al: Effectiveness and safety of enteral vancomycin to control endemicity of methicillinresistant Staphylococcus aureus in a medical/surgical intensive care unit. *J Hosp Infect* 2004; 56:175–183
308. Silvestri L, van Saene HKF, Milanese M, et al: Prevention of MRSA pneumonia by oral vancomycin decontamination: A randomised trial. *Eur Respir J* 2004; 23:921–926
309. Cerda E, Abella A, de la Cal MA, et al: Enteral vancomycin controls methicillinresistant Staphylococcus aureus endemicity in an intensive care burn unit: A 9-year prospective study. *Ann Surg* 2007; 245: 397–407
310. Curtis JR: Interventions to improve care during withdrawal of life-sustaining treatments. *J Palliat Med* 2005; 8(Suppl 1): S116–S131
311. Thompson BT, Cox PN, Antonelli M, et al: Challenges in end-of-life care in the ICU: Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003: Executive summary. *Crit Care Med* 2004; 32:1781–1784
312. Heyland DK, Tranmer J, O'Callaghan CJ, et al: The seriously ill patient: Preferred role in end of life decision making. *J Crit Care* 2003; 18:3–10
313. Curtis JR, Engelberg RA, Wenrich MD, et al: Missed opportunities during family conferences about end-of-life care in the intensive care unit. *Am J Respir Crit Care Med* 2005; 171:844–849
314. Watson RS, Carcillo JA, Linde-Zwirble WT, et al: The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* 2003; 167:695–701
315. Goldstein B, Giroir B, Randolph A: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6:2–8
316. Pollard AJ, Britto J, Nadel S, et al: Emergency management of meningococcal disease. *Arch Dis Child* 1999; 80:290–296
317. den Brinker M, Joosten KFM, Lime O, et al: Adrenal insufficiency in meningococcal sepsis: Bioavailable cortisol levels and impact of interleukin-6 levels and intubation with etomidate on adrenal function and mortality. *Clin Endocrinol Metab* 2005; 90: 5110–5117

318. Kanter RK, Zimmerman JJ, Strauss RH, et al: Pediatric emergency intravenous access: Evaluation of a protocol. *Am J Dis Child* 1986; 140:132–134
319. Ngo NT, Cao XT, Kneen R, et al: Acute management of dengue shock syndrome: A randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. *Clin Infect Dis* 2001; 32:204–213
320. Carcillo JA, Davis AL, Zaritsky A: Role of early fluid resuscitation in pediatric septic shock. *JAMA* 1991; 266:1242–1245
321. Han YY, Carcillo JA, Dragotta MA, et al: Early reversal of pediatric-neonatal septic shock by community physicians is associated with improved outcome. *Pediatrics* 2003; 112:793–799
322. Ranjit S, Kissoon N, Jayakumar I: Aggressive management of dengue shock syndrome may decrease mortality rate: A suggested protocol. *Pediatr Crit Care Med* 2005; 6:412–419
323. Willis BA, Dung NM, Loan HT, et al: Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med* 2005; 353:877–889
324. Dung NM, Day NP, Tam DT, et al: Fluid replacement in dengue shock syndrome: A randomized, double-blind comparison of four intravenous-fluid regimens. *Clin Infect Dis* 1999; 29:787–794
325. Ceneviva G, Paschall JA, Maffei F, et al: Hemodynamic support in fluid-refractory pediatric septic shock. *Pediatrics* 1998; 102: e19
326. Keeley SR, Bohn DJ: The use of inotropic and afterload-reducing agents in neonates. *Clin Perinatol* 1988; 15:467–489
327. Barton P, Garcia J, Kouatli A, et al: Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock: A prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996; 109:1302–1312
328. Lindsay CA, Barton P, Lawless S, et al: Pharmacokinetics and pharmacodynamics of milrinone lactate in pediatric patients with septic shock. *J Pediatr* 1998; 132:329–334
329. Irazuzta JE, Pretzlaff RK, Rowin ME: Amrinone in pediatric refractory septic shock: An open-label pharmacodynamic study. *Pediatr Crit Care Med* 2001; 2:24–28
330. Powell KR, Sugarman LI, Eskenazi AE, et al: Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. *J Pediatr* 1991; 117:515–522
331. Masutani S, Senzaki H, Ishido H, et al: Vasopressin in the treatment of vasodilatory shock in children. *Pediatr Int* 2005; 47: 132–136
332. Booy R, Habibi P, Nadel S, et al: Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 2001; 85:386–390
333. Carcillo JA, Fields AI, American College of Critical Care Medicine Task Force Committee Members: Clinical practice parameters for hemodynamic support of pediatric and neonatal patients in septic shock. *Crit Care Med* 2002; 30:1365–1378
334. Pizarro CF, Troster EJ, Damiani D, et al: Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med* 2005; 33:855–859
335. Riordan FA, Thomson AP, Ratcliffe JM, et al: Admission cortisol and adrenocorticotrophic hormone levels in children with meningococcal disease: Evidence of adrenal insufficiency? *Crit Care Med* 1999; 27: 2257–2261
336. De Kleijn ED, Joosten KF, Van Rijn B, et al: Low serum cortisol in combination with high adrenocorticotrophic hormone concentrations is associated with poor outcome in children with severe meningococcal disease. *Pediatr Infect Dis J* 2002; 21:330–336
337. Markovitz BP, Goodman DM, Watson S, et al: A retrospective cohort study of prognostic factors associated with outcome in pediatric severe sepsis: What is the role of steroids? *Pediatr Crit Care Med* 2005; 6:270–274
338. Hazelzet JA, de Kleijn ED, de Groot R: Endothelial protein C activation in meningococcal sepsis. *N Engl J Med* 2001; 345: 1776–1777
339. de Kleijn ED, de Groot R, Hack CE, et al: Activation of protein C following infusion of protein C concentrate in children with severe meningococcal sepsis and purpura fulminans: A randomized, double-blinded, placebo-controlled, dose-finding study. *Crit Care Med* 2003; 31:1839–1847
340. Nadel S, Goldstein B, Williams MD, et al: Drotrecogin alfa (activated) in children with severe sepsis: A multicentre phase III randomized controlled trial. *Lancet* 2007; 369: 836–843
341. Krafte-Jacobs B, Sivit CJ, Mejia R, et al: Catheter-related thrombosis in critically ill children: Comparison of catheters with and without heparin bonding. *J Pediatr* 1995; 126:50–54
342. Pierce CM, Wade A, Mok Q: Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. *Intensive Care Med* 2000; 26:967–972
343. Chaïbou M, Tucci M, Dugas MA, et al: Clinically significant upper gastrointestinal bleeding acquired in a pediatric intensive care unit: A prospective study. *Pediatrics* 1998; 102:933–938
344. Gauvin F, Dugas M, Chaïbou M, et al: The impact of clinically significant upper gastrointestinal bleeding in a pediatric intensive care unit. *Pediatr Crit Care Med* 2001; 2:294–298
345. Foland JA, Fortenberry JD, Warshaw BL, et al: Fluid overload before continuous hemofiltration and survival in critically ill children: A retrospective analysis. *Crit Care Med* 2004; 32:1771–1776

346. Branco RG, Garcia PC, Piva JP, et al: Glucose level and risk of mortality in pediatric septic shock. *Pediatr Crit Care Med* 2005; 6:470–472
347. Faustino EV, Apkon M: Persistent hyperglycemia in critically ill children. *J Pediatr* 2005; 146:30–34
348. Cam PC, Cardone D: Propofol infusion syndrome. *Anaesthesia* 2007; 62:690–701
349. Parke TJ, Stevens JE, Rice AS, et al: Metabolic acidosis and fatal myocardial failure after propofol infusion in children: Five case reports. *BMJ* 1992; 305:613–616
350. Lacroix J, Hebert PC, Hutchison JS, et al: Transfusion strategies for patients in pediatric intensive care units. *N Engl J Med* 2007; 256:1609–1619
351. El-Nawawy A, El-Kinany H, Hamdy El-Sayed M, et al: Intravenous polyclonal immunoglobulin administration to sepsis syndrome patients: A prospective study in a pediatric intensive care unit. *J Trop Pediatr* 2005; 51:271–278
352. Meyer DM, Jessen ME: Results of extracorporeal membrane oxygenation in children with sepsis: The Extracorporeal Life Support Organization. *Ann Thorac Surg* 1997; 63:756–761
353. Goldman AP, Kerr SJ, Butt W, et al: Extracorporeal support for intractable cardiorespiratory failure due to meningococcal disease. *Lancet* 1997; 349:466–469
354. Cinel I, Dellinger RP: Guidelines for severe infections: Are they useful. *Curr Opin Crit Care* 1006; 12:483–488
355. Levy MM, Pronovost PJ, Dellinger RP, et al: Sepsis change bundles: Converting guidelines into meaningful change in behaviour and clinical outcome. *Crit Care Med* 2004; 32(Suppl):S595–S597
356. Meduri GU, Golden E, Freire AX, et al: Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. *Chest* 2007; 131:1954–1963
357. The National Heart, Lung, and Book Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–1684

ANEXO 1- Tabelas

	Tabela 1: Critérios de Presunção de Infecção
a)	Tosse + (dispneia ou dor pleurítica)
b)	Dor lombar + (disúria ou polaquiúria)
c)	Dor abdominal ou icterícia
d)	Diminuição aguda do nível de consciência
e)	Cefaleias + vómitos
f)	Sinais inflamatórios cutâneos extensos
g)	Critério clínico do responsável

	Tabela 2: Exames complementares iniciais
a)	Hemoculturas
b)	Outros exs microbiológicos de acordo com o foco provável de infecção
c)	Gasimetria de sangue arterial
d)	Hemograma com plaquetas (se possível com % de neutrófilos imaturos)
e)	Ionograma, ureia, creatinina, glicose e PCR
f)	RX pulmonar na suspeita de foco respiratório
g)	Estudo da coagulação (se disponível)

	Tabela 3: Critérios de SIRS
a)	Frequência Cardíaca > 90 bpm
b)	Frequência respiratória > 20 cpm
c)	Temperatura corporal < 36ºC ou > 38ºC

	Tabela 4: Critérios de Exclusão da VVS
a)	Gravidez
b)	ICC descompensada / Sindrome coronário agudo
c)	Doença cerebrovascular aguda
d)	Hemorragia digestiva activa
e)	Estado de mal asmático
f)	Politrauma / grandes queimados
g)	Doente não candidato a técnicas de suporte orgânico

Anexo 2- Algoritmo

	Critérios de Presunção de Infecção
a)	Tosse + (dispneia ou dor pleurítica)
b)	Dor lombar + (disúria ou polaquiúria)
c)	Dor abdominal ou icterícia
d)	Diminuição aguda do nível de consciência
e)	Cefaleias + vómitos
f)	Sinais inflamatórios cutâneos extensos
g)	Critério clínico do responsável

	Critérios Exclusão da VVS (1
a)	Gravidez
b)	ICC descompensada / Sd coronário agudo
c)	Dça cerebrovascular aguda
d)	Hemorragia digestiva activa
e)	Estado de mal asmático
f)	Politrauma / gds queimados
g)	Dte não candidato a técnicas de suporte orgânico (situação para limitação de cuidados)