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Sepsis

Along with extreme prematurity, congenital abnormalities, childhood malignancies, drowning, SIDS, and trauma, sepsis is one of the common causes of neonatal and paediatric mortality in Western countries.

International evidence-based guidelines for the management of neonatal, paediatric and adult sepsis have now been developed[1].

Early (< 1 - 6 hrs) aggressive management via goal-directed therapy is paramount to minimizing mortality[2].

Initial Resuscitation Goals

1. CVP 8-12 mm Hg, if ventilated or increased intra-abdominal pressure 10-15 mm Hg (CVP goal should probably be lower for preterm and small infants)[3]
2. MAP ≥ 65 mm Hg in adults

Minium acceptable systolic BP and MAP for children[4]

Age (years):	½	1	2-6	8-10	12	14	≥16
Systolic BP:	65	70	75	80	85	90	95
MAP	>40	>45	>50	>55	>60	>65	>65

IMPORTANT: Blood pressure alone should not be used as a reliable endpoint for resuscitation.

3. UO ≥ 0.5 - 1.0 ml/kg/hr
4. CV O_2 Saturation ≥ 70% - to achieve this consider transfusion to Hct ≥ 30%[5] and/or dobutamine infusion ≤20 µg/kg/min
5. Swan Ganz catheter directed therapy is of no benefit and may be harmful[6].
6. Early mechanical ventilation is probably important in children and infants due to poor respiratory reserve based on low FRC and the fact that positive pressure ventilation provides effective after load reduction.

Antibiotic Therapy

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[1] http://www.survivingsepsis.org/hcp_campaign_description.html
[2] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001 Nov 8;345(19):1368-77.
[3] A CVP of 3 - 5 may be adequate if CO is normal or supranormal, thus non-invasive CO measurement is desirable as soon as possible. The author's opinion is that non-invasive TTE is the best option.
[4] Based on 5th BP centile for age.
[5] Conflicts with Herbert's Hb in ICU study
[6] Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. JAMA. 2005 Oct 5;294(13):1664-70.

There is mounting evidence that early administration (< 2 hrs after presentation) of the 'right' antimicrobial agent strongly affects outcome[7].

If the source and type of sepsis in unclear, very broad spectrum coverage is appropriate for the first 48 hrs, until culture results are known.

Initial empiric therapy:

Neonate

Meningitis/encephalitis – penicillin + gentamicin + cefotaxime ± aciclovir (high dose[8])
Bacteraemia – penicillin + gentamicin[9]
Early onset Pneumonia – penicillin + gentamicin ± PO azithromycin[10] (OR PO clarithromycin[11]) NOTE: Erythromycin[12] can cause pyloric stenosis, azithromycin and clarithromycin lack safety data in neonates [13].
Nosocomial Pneumonia/bacteraemia – flucloxacillin + gentamicin
NEC - penicillin + gentamicin + metronidazole OR meropenem[14]
CVL/PIC – vancomycin + gentamicin
Suspected fungal sepsis – fluconazole OR ampothericin B

Child (> 1 month) and Adult

Meningitis/encephalitis – vancomycin + cefotaxime (OR ceftriaxone) ± dexamethasone (0.15 mg/kg q6h x 24-48 hrs[15]) ± aciclovir (add penicillin OR amoxycillin if < 4 months or > 15 yrs or immunosuppressed to cover Listeria)
Bacteraemia – flucloxacillin + cefotaxime (meningitis not excluded)
Endocarditis – flucloxacillin + gentamicin
Community Acquired Pneumonia – IV penicillin OR PO amoxycillin + PO roxithromycin (OR PO azithromycin if Pertussis[16])[17], if severe – flucloxacillin + cefotaxime + IV azithromycin[18], from tropical Australia – meropenem (to cover melioidosis) + azithromycin

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[7] Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest. 2000 Jul;118(1):146-55. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med. 2003 Dec;31(12):2742-51. Kumar A. Canadian Critical Care Conference, Whistler 2006.

[8] Kimberlin DW, Whitley RJ. Neonatal herpes: what have we learned. Semin Pediatr Infect Dis. 2005 Jan;16(1):7-16. Review.

[9] Routine use of cefotaxime in suspected infections in 1-3 day old neonates increases there all cause mortality. Clark RH, Bloom BT, Spitzer AR, Gerstmann DR. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics. 2006 Jan;117(1):67-74.

[10] 5 days effective for pertussis

[11] 7 days effective for pertussis – not available in Australia

[12] 7-14 days

[13] Altunaiji S, Kukuruzovic R, Curtis N, Massie J. Antibiotics for whooping cough (pertussis). Cochrane Database Syst Rev. 2005 Jan 25;(1):CD004404. Review.

[14] Arrieta A. Use of meropenem in the treatment of serious infections in children: review of the current literature. Clin Infect Dis. 1997 Feb;24 Suppl 2:S207-12. Review.

[15] For Haemophilus or Pneumococcal disease

[16] If diagnosis is not Pertussis, use roxithromycin (tablet dissolves for children unable to take tablets and is much cheaper than azithromycin)

[17] Mycoplasma infections are common in children < 5 years of age, unlike what was previously reported: Othman N, Isaacs D, Kesson A. Mycoplasma pneumoniae infections in Australian children. J Paediatr Child Health. 2005 Dec;41(12):671-6. There is no evidence that therapy is effective : Gavranich

Aspiration pneumonia – penicillin + metronidazole OR clindamycin alone
Nosocomial Pneumonia[19] - ticarcillin/clavulanate OR piperacillin/tazobactam[20] + gentamicin[21] ± vancomycin[22]
Intra-abdominal sepsis/pancreatitis – amoxycillin + gentamicin + metronidazole OR piperacillin/tazobactam OR meropenem alone
CVL/PIC – vancomycin + gentamicin
Immunosuppressed – ticarcillin/clavulanate OR piperacillin/tazobactam + gentamicin ± vancomycin ± amphotericin B (consider voriconazole OR itraconazole OR casofungin[23]) ± trimethoprim/sulphamethoxazole/prednisolone[24] (if PCP) ± acyclovir ± ganciclovir

Narrower spectrum antibiotics to prevent superinfection can be used once the organism and its sensitivity is determined. Antibiotics should be stopped if a non-infectious cause of the clinical syndrome is identified, but beware that in many cases of sepsis or septic shock blood cultures will be negative.

Penicillin allergic patients:

1. Non- immediate allergy - use cephalosporin
2. Immediate hypersensitivity – use Vancomycin OR Clindamycin in children, use Moxifloxacin in adults

Source Control

Infective/inflammatory foci such as bowel perforation or intestinal ischemia should be addressed, abscesses should be drained, necrotic soft tissue debrided, and potentially infected devices removed, but only following adequate resuscitation.

Fluid Therapy

The recently reported Saline versus Albumin Evaluation study (SAFE)[25] has provided conclusive evidence that 4% albumin is as safe as normal saline for resuscitation, although no overall benefit of albumin use

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JB, Chang AB. Antibiotics for community acquired lower respiratory tract infections (LRTI) secondary to Mycoplasma pneumoniae in children. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004875. Review.

[18] Martinez JA, Horcajada JP, Almela M, Marco F, Soriano A, Garcia E, Marco MA, Torres A, Mensa J. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis. 2003 Feb 15;36(4):389-95. Epub 2003 Jan 31.

[19] The role of routine ETAs and BAL is controversial. Michel F, Franceschini B, Berger P, Arnal JM, Gainnier M, Sainty JM, Papazian L.Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: a role for routine endotracheal aspirate cultures. Chest. 2005 Feb;127(2):589-97. Luna CM, Vujacich P, Niederman MS, Vay C, Gherardi C, Matera J, Jolly EC. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. Chest. 1997 Mar;111(3):676-85.

[20] Zar HJ, Cotton MF. Nosocomial pneumonia in pediatric patients: practical problems and rational solutions. Paediatr Drugs. 2002;4(2):73-83. Review.

[21] Lynch JP 3rd. Hospital-acquired pneumonia: risk factors, microbiology, and treatment. Chest. 2001 Feb;119(2 Suppl):373S-384S. Review.

[22] Monotherapy is effective in less severe disease in several adult studies, but there is a mortality price to pay if initial selection is incorrect.

[23]

[24] Gagnon S, Boota AM, Fischl MA, Baier H, Kirksey OW, La Voie L. Corticosteroids as adjunctive therapy for severe Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med. 1990 Nov 22;323(21):1444-50. Bozzette SA, Sattler FR, Chiu J, Wu AW, Gluckstein D, Kemper C, Bartok A, Niosi J, Abramson I, Coffman J, et al. A controlled trial of early adjunctive treatment with corticosteroids for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. N Engl J Med. 1990 Nov 22;323(21):1451-7.

was seen. Subgroup analysis of the albumin-treated group revealed a trend towards decreased mortality in patients with septic shock, and a trend towards increased mortality in trauma patients, especially those with traumatic brain injury.

Use an initial volume challenge of 20 ml/kg (max 1L) over 5-30 min followed by boluses of 10ml/kg based on response. Large volumes of fluid may be required in patients with sepsis and capillary leak, up to 200 ml/kg over the first 24 hrs.

One study demonstrated that survival was improved in children with septic shock who received > 40 ml/kg within the first hour.[26]

There is evidence that albumin may be better than saline in severe malaria[27] and dengue.[28]

There is no evidence that albumin is better than saline in hypotensive term[29] or preterm[30] infants.

Albumin can cause anaphylaxis.[31]

Vasopressors and Inotropes

Vasopressor therapy may need to be started before volume resuscitation is complete as a life saving measure. IV adrenalin boluses titrated to the BP can be used until large bore IV access is attained in cases of overwhelming sepsis or hypovolvaemia.

Add vasopressors to fulfil the resuscitation goals if fluid therapy has not succeeded. Use CVC as soon as available, but vasopressors can be temporarily used via a peripheral vein (adrenalin and dobutamine are less vasoconstrictive than dopamine and noradrenalin in this context).

Initial treatment[32]

1. Dopamine 5 - 20 µg/kg/min (if mean BP low): ↑ HR, contractility and SVR,
   OR
   Dobutamine 5 - 15 µg/kg/min (if mean BP OK): ↑ HR, contractility but ↓ SVR, hence can lead to ↓ BP particularly in neonates[33].

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[25] Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R; SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004 May 27;350(22):2247-56.
[26] Carcillo JA, Davis AL, Zaritsky A. Role of early fluid resuscitation in pediatric septic shock. JAMA. 1991 Sep 4;266(9):1242-5.
[27] Maitland K, Pamba A, English M, Peshu N, Marsh K, Newton C, Levin M. Randomized trial of volume expansion with albumin or saline in children with severe malaria: preliminary evidence of albumin benefit. Clin Infect Dis. 2005 Feb 15;40(4):538-45. Epub 2005 Jan 25. Note that the control group (maintenance fluids only) had the lowest mortality, but they comprised of less sick children.
[28] Ngo NT, Cao XT, Kneen R, Wills B, Nguyen VM, Nguyen TQ, Chu VT, Nguyen TT, Simpson JA, Solomon T, White NJ, Farrar J. Acute management of dengue shock syndrome: a randomized double-blind comparison of 4 intravenous fluid regimens in the first hour. Clin Infect Dis. 2001 Jan 15;32(2):204-13. Epub 2001 Jan 15.
[29] Oca MJ, Nelson M, Donn SM. Randomized trial of normal saline versus 5% albumin for the treatment of neonatal hypotension. J Perinatol. 2003 Sep;23(6):473-6.
[30] Osborn DA, Evans N. Early volume expansion for prevention of morbidity and mortality in very preterm infants. Cochrane Database Syst Rev. 2004;(2):CD002055. Review.
[31] Eriksson M, Nilsson B, Modig J, Acosta R, Johansson B, Larsson A. [A case report. Hypotensive reaction caused by albumin infusion] Lakartidningen. 2001 Jan 31;98(5):439-42. Swedish.
[32] Butt W. Septic shock. Pediatr Clin North Am. 2001 Jun;48(3):601-25, viii. Review.
[33] Subhedar NV, Shaw NJ. Dopamine versus dobutamine for hypotensive preterm infants. Cochrane Database Syst Rev. 2003;(3):CD001242. Review.

Adult intensivists are concerned about the neuroendocrine effects of dopamine and the myocardial apoptosis effects of dobutamine, thus tend to use noradrenalin initially, but there is vast experience with these drugs in small children indicating they are effective and reasonably safe.

2. Noradrenalin 0.05 – 1.0 µg/kg/min (if above is not effective): more effective that 1, ↑SVR predominantly, less pro-arrhythmic and less ↑ HR[34]

Lose dose dopamine in of no value in preventing renal failure[35].

Then consider

1. Hydrocortisone 1 mg/kg q8h – based on adult data[36], role of free cortisol measurement or ACTH stimulation test is debatable. In preterm neonates there is good evidence low dose hydrocortisone alleviates hypotension and allows inotrope weaning[37], but recent unpublished data suggests an association between indomethacin plus hydrocortisone use and small bowel perforation. The CORTICUS trial and another trial of hydrocortisone with and without fludrocortisone are awaited.

2. Vasopressin – 'relative or absolute vasopressin deficiency' is a new concept is septic shock. VP is effective in refractory hypotension but can cause ↓ CO and splanchic ischaemia, thus should be used with caution. Does of > 0.04 Units/min in adults are associated with myocardial ischaemia and cardiac arrest. Data for children is even more limited. One recommended regime for children is 0.001 µg/kg/min (as per brain death protocol), but this is a relatively high dose. VP should not normally be used if myocardial contractility is depressed. Terlipressin is currently under investigation also[38], but has a long half life. Australian VASST trial results are awaited.

3. If contractility is reduced and filling is adequate agents such as dobutamine, milrinone, adrenalin, calcium (1 mmol/kg/day infused constantly), and methylene blue[39] (a related drug NG-methyl-L-arginine hydrochloride is under investigation, but may increase mortality[40]) are useful.

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[34] Holmes CL. Vasoactive drugs in the intensive care unit. Curr Opin Crit Care. 2005 Oct;11(5):413-7. Review. There is currently a noradrenalin vs. adrenalin adult multi-centre trial underway in Europe.

[35] Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. 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 Dec 23-30;356(9248):2139-43.

[36] Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA. 2002 Aug 21;288(7):862-71.

[37] Ng PC, Lee CH, Bnur FL, Chan IH, Lee AW, Wong E, Chan HB, Lam CW, Lee BS, Fok TF. A double-blind, randomized, controlled study of a "stress dose" of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. Pediatrics. 2006 Feb;117(2):367-75.

[38] Matok I, Vard A, Efrati O, Rubinshtein M, Vishne T, Leibovitch L, Adam M, Barzilay Z, Paret G. Terlipressin as rescue therapy for intractable hypotension due to septic shock in children. Shock. 2005 Apr;23(4):305-10.

[39] Kirov MY, Evgenov OV, Evgenov NV, Egorina EM, Sovershaev MA, Sveinbjornsson B, Nedashkovsky EV, Bjertnaes LJ. Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. Crit Care Med. 2001 Oct;29(10):1860-7.

[40] Bakker J, Grover R, McLuckie A, Holzapfel L, Andersson J, Lodato R, Watson D, Grossman S, Donaldson J, Takala J; Glaxo Wellcome International Septic Shock Study Group. Administration of the nitric oxide synthase inhibitor NG-methyl-L-arginine hydrochloride (546C88) by intravenous infusion for up to 72 hours can promote the resolution of shock in patients with severe sepsis: results of a randomized, double-blind, placebo-controlled multicenter study (study no. 144-002). Crit Care Med. 2004 Jan;32(1):1-12.

Triiodothyronine (T3) is suggested to be of use but studies in animals do not suggest benefit in septic shock[41], but perhaps in haemorrhagic shock[42].

High dose milrinone (75 µg/kg bolus plus 0.75 µg/kg/min infusion for 36 hrs) has been shown to be particularly effective in preventing low cardiac output state post CV surgery – PRIMACORP study[43].

However there is no benefit and possible harm if CO is driven to supranormal levels[44].

Red Blood Cell (RBC) Transfusion

Optimum haemoglobin for critically ill children or adults has not been ascertained.

There is evidence that RBC transfusion is immunosuppressive[45] and contributes to the development of ARDS[46].

Lower haemoglobins (transfused if < 7.0 and maintained between 7–9 g/L vs. transfused < 10 and maintained 10-12 g/L and) are safe and confer mortality advantage in sicker adults[47], except in acute myocardial infarction and unstable angina[48].

Ideal transfusion thresholds for preterm neonates may be higher. A more restrictive policy (lowest transfusion threshold was Hct < 22% if not requiring respiratory support in 500-1300 gram infants) does

[41] Glembot TM, Hill MA, Britt LD. The effect of thyroid hormone supplementation on hemodynamic stability and survival in an endotoxin-induced model of physiologic stress. J Surg Res. 1996 Feb 15;61(1):77-83.
[42] Dulchavsky SA, Lucas CE, Ledgerwood AM, Grabow D, Brown TR, Bagchi N. Triiodothyronine (T3) improves cardiovascular function during hemorrhagic shock. Circ Shock. 1993 Jan;39(1):68-73.
[43] Hoffman TM, Wernovsky G, Atz AM, Bailey JM, Akbary A, Kocsis JF, Nelson DP, Chang AC, Kulik TJ, Spray TL, Wessel DL. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics. Am Heart J. 2002 Jan;143(1):15-21. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, Bailey JM, Akbary A, Kocsis JF, Kaczmarek R, Spray TL, Wessel DL. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003 Feb 25;107(7):996-1002.
[44] Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. N Engl J Med. 1995 Oct 19;333(16):1025-32.
[45] Shorr AF, Jackson WL, Kelly KM, Fu M, Kollef MH. Transfusion practice and blood stream infections in critically ill patients. Chest. 2005 May;127(5):1722-8.
[46] Silverboard H, Aisiku I, Martin GS, Adams M, Rozycki G, Moss M.The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma. 2005 Sep;59(3):717-23.
[47] Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999 Feb 11;340(6):409-17. Erratum in: N Engl J Med 1999 Apr 1;340(13):1056.
[48] Hebert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I; Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? Crit Care Med. 2001 Feb;29(2):227-34.

not reduce the need for transfusions and does not reduce the donor exposure rate and may increase the risk of IVH, PVL and apnoea[49]. Further large RCTs are awaited from Australia.

Recombinant Human Activated Protein C (rhAPC, drotrecogin alfa, Xigris)

Since the PROWESS Study[50], despite its lack of effect on long-term outcome[51], drotrecogin alfa has become widely, but not universally used for adult sepsis. The benefit in terms of 28 day mortality increases with increasing probability of death of ≥ 20% independent of illness severity[52]. Drotrecogin alfa doubles the risk of serious bleeding complications and should not be used in sepsis with a low risk of death, e.g. single organ failure or APACHE II score < 25[53]. Early treatment may be more effective[54].

There are case reports of dramatic clinical improvement with drotrecogin alfa use in neonates[55] and children[56] with severe sepsis.

The ENHANCE trial results suggest a significant risk of serious bleeding in children, with 5.7% (n=5) experiencing intracerebral bleeding, causing 2 deaths[57]. A large RCT in children has been halted due to an excess of serious ICH and futility.

PICUs in Australia do not use drotrecogin alfa, except for carefully selected exceptional cases.

Immunoglobulin

Suspected or subsequently proven sepsis in neonates – no evidence of benefit of routine use, further trials awaited (INIS Study)[58].

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[49] Bell EF, Strauss RG, Widness JA, Mahoney LT, Mock DM, Seward VJ, Cress GA, Johnson KJ, Kromer IJ, Zimmerman MB. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics. 2005 Jun;115(6):1685-91.

[50] Dhainaut JF, Laterre PF, Janes JM, Bernard GR, Artigas A, Bakker J, Riess H, Basson BR, Charpentier J, Utterback BG, Vincent JL; Recombinant Human Activated Protein C Worldwide Evaluation in Sepsis (PROWESS) Study Group. Drotrecogin alfa (activated) in the treatment of severe sepsis patients with multiple-organ dysfunction: data from the PROWESS trial. Intensive Care Med. 2003 Jun;29(6):894-903. Epub 2003 Apr 24.

[51] Angus DC, Laterre PF, Helterbrand J, Ely EW, Ball DE, Garg R, Weissfeld LA, Bernard GR; PROWESS Investigators. The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis. Crit Care Med. 2004 Nov;32(11):2199-206.

[52] Ely EW, Laterre PF, Angus DC, Helterbrand JD, Levy H, Dhainaut JF, Vincent JL, Macias WL, Bernard GR; PROWESS Investigators. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. Crit Care Med. 2003 Jan;31(1):12-9.

[53] Abraham E, Laterre PF, Garg R, Levy H, Talwar D, Trzaskoma BL, Francois B, Guy JS, Bruckmann M, Rea-Neto A, Rossaint R, Perrotin D, Sablotzki A, Arkins N, Utterback BG, Macias WL; Administration of Drotrecogin Alfa (Activated) in Early Stage Severe Sepsis (ADDRESS) Study Group. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med. 2005 Sep 29;353(13):1332-41.

[54] Vincent JL, Bernard GR, Beale R, Doig C, Putensen C, Dhainaut JF, Artigas A, Fumagalli R, Macias W, Wright T, Wong K, Sundin DP, Turlo MA, Janes J. 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 Oct;33(10):2266-77.

[55] Albuali WH, Singh RN, Fraser DD, Scott LA, Kornecki A. Drotrecogin alfa activated treatment in a neonate with sepsis and multi organ failure. Saudi Med J. 2005 Aug;26(8):1289-92.

[56] Sajan I, Da-Silva SS, Dellinger RP. Drotrecogin alfa (activated) in an infant with gram-negative septic shock. J Intensive Care Med. 2004 Jan-Feb;19(1):51-5.

[57] Goldstein B, Nadel S, Peters M, Barton R, Machado F, Levy H, Haney DJ, Utterback B, Williams MD, Giroir BP. ENHANCE: Results of a global open-label trial of drotrecogin alfa (activated) in children with severe sepsis. Pediatr Crit Care Med. 2006 Mar 28; [Epub ahead of print]

Prophylaxis against sepsis in preterm infants – one study showed a 3-4% reduction in incidence of sepsis and severe sepsis but no reduction in morbidity and mortality[59]. Immunoglobulin is not being used for prophylaxis in Australian neonatal units.

Use of polyclonal IgG may be useful in older children and adults with severe sepsis, but remains experimental[60].

Heparin

Heparin has anti-inflammatory properties and low-dose (10 Units/kg/HR) has been reported to be of benefit in sepsis[61]. Low-dose unfractionated heparin (UFH) was independently associated with lower mortality than controls in the PROWESS, KyberSept and OPTIMIST trials.

Antithrombin III (AT3)

High dose antithrombin III has been subject to a RCT in adults (KyberSept) demonstrating overall no benefit and an increased risk of haemorrhage, especially in patients also receiving heparin[62]. Subsequent analysis of the same data revealed a 14% reduction in mortality in patients not receiving heparin and who had DIC[63]. Also the same investigators demonstrated a reduced mortality out to 90 days if high dose AT3 was used in patients not receiving heparin but had a high risk of death[64].

Current international guidelines do not recommend the use of AT3.

Management of DIC

Actively bleeding patients with coagulopathy should be managed aggressively.

Thresholds for use of FFP, platelets, cryoprecipitate in non-bleeding DIC patients are not established.

At least one adult study indicates that the risk-benefit ratio of FFP transfusion in critically ill medical patients with coagulopathy (INR > 1.5) but no active bleeding may not be favourable, with no reduction in

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[58] Ohlsson A, Lacy JB. Intravenous immunoglobulin for suspected or subsequently proven infection in neonates. Cochrane Database Syst Rev. 2004;(1):CD001239. Review.
[59] Ohlsson A, Lacy JB. Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants. Cochrane Database Syst Rev. 2004;(1):CD000361. Review.
[60] Alejandria MM, Lansang MA, Dans LF, Mantaring JB. Intravenous immunoglobulin for treating sepsis and septic shock. Cochrane Database Syst Rev. 2002;(1):CD001090. Review. Pildal J, Gotzsche PC. Polyclonal immunoglobulin for treatment of bacterial sepsis: a systematic review. Clin Infect Dis. 2004 Jul 1;39(1):38-46. Epub 2004 Jun 1. Review.
[61] Davidson BL, Geerts WH, Lensing AW. Low-dose heparin for severe sepsis. N Engl J Med. 2002 Sep 26;347(13):1036-7.
[62] Warren BL, Eid A, Singer P, Pillay SS, Carl P, Novak I, Chalupa P, Atherstone A, Penzes I, Kubler A, Knaub S, Keinecke HO, Heinrichs H, Schindel F, Juers M, Bone RC, Opal SM; KyberSept Trial Study Group. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. JAMA. 2001 Oct 17;286(15):1869-78. Erratum in: JAMA 2002 Jan 9;287(2):192.
[63] Kienast J, Juers M, Wiedermann CJ, Hoffmann JN, Ostermann H, Strauss R, Keinecke HO, Warren BL, Opal SM; KyberSept investigators. Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. J Thromb Haemost. 2006 Jan;4(1):90-7.
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new bleeding episodes and more acute lung injury (ALI) in the transfused group[65]. Thus current recommendations indicate that FFP should not be used unless bleeding is active.

Transfusion thresholds for platelets are also controversial, with evidence that transfusion thresholds of < 10 vs. < 20 x 10^9/L are equally effective in uncomplicated myelo-suppression in preventing bleeding complications[66].

If thrombocytopaenia is secondary to sepsis, current practice is more conservative[67]. The recent Surviving Sepsis Guidelines recommend, based on 3 consensus statements, recommends the following thresholds:

- < 5 x 10^9/L as an absolute indication for transfusion in the absence of bleeding
- 5-30 x 10^9/L if bleeding risk is increased for other reasons (e.g. INR > 1.5)
- > 50 x 10^9/L if surgical or invasive procedures are contemplated

Neonatal and preterm infant platelet transfusion thresholds are traditionally higher (< 20-50 x 10^9/L), but there is no evidence to support this rationale[68].

Fibrinogen < 1 g/L is associated with an increased risk of bleeding and is the threshold to consider replacement as Cryoprecipitate[69].

Granulocyte transfusion (GTX)

No good evidence to support or refute its use in neonatal sepsis[70].

Good adult studies in sepsis are also lacking[71], although a recent case control analysis in Candidiasis suggests that high dose GTX results in a better than expected survival[72].

G-CSF and GM-CSF

Granulocyte stimulating factors have been studied in neonates and may reduce mortality in severe sepsis with neutropenia but larger trials are awaited[73].

Filgrastim (r-metHuG-CSF) has been subject to a RCT in adult pneumonia and multiple organ dysfunction syndrome (MODS) without neutropenia with no effect on mortality or complications[74].

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Granulocyte stimulating factors (often PEG Filgrastim) is widely used in immuno-suppressed patients with resultant neutropenia, but its role once sepsis in established remains unproven.

Glucose Control

Intensive insulin therapy to maintain glucose between 80 mg/dl (4.4 mmol/L) and 110 mg/dl (6.1 mmol/L) has recently been demonstrated to reduce mortality in adult surgical intensive care,[75] but not in medical intensive care, although morbidity was improved[76]. Maintaining glucose very tightly is associated with frequent hypoglycaemic events and most Australian ICUs have not adopted such an aggressive approach[77]. Further studies are awaited, particularly the NICE-SUGAR trial which examines two ranges of glucose control.

Mechanical Ventilation

Sepsis is the commonest cause of acute lung injury (ALI). Optimal management of ALI improves survival, in terms of death from MODS.

Adult recommendations in ALI/ARDS based on several large RCTs[78] are:

1. $V_T \sim 6$ ml/kg based on *predicted (lean) body weight*
2. $PIP_{plat} \leq 30$ cm H_2O
3. Permissive hypercarbia to achieve 1. and 2. (unless ICP is increased)

PEEP should be titrated to optimize lung recruitment (maximum compliance), minimized FiO_2 whilst providing acceptable oxygenation.

Prone positioning can improve oxygenation, but a RCTS trial in children with ALI of prone positioning for 20 hrs per day conferred no benefit[79]. In adults there is no clear cut benefit either from prone positioning ≥ 6 hrs per day[80].

The semirecumbent position (bed head raised to 45°) has been demonstrated to decrease the incidence of ventilator associated pneumonia in adults, probably due to a reduction is gastric contents micro-aspiration[81], but this target position is difficult to achieve.[82]

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Daily trials of spontaneous breathing (e.g. CPAP, T-piece or PS ≤7) reduce the duration of mechanical ventilation.[83]

Volume targeted ventilation in neonates reduces the duration of mechanical ventilation, incidence of pneumothorax and high grade ICH.[84]

High Frequency Oscillation

HFO provides rescue therapy for severe hypoxia and hypercarbia. Its effect on morbidity and mortality has not been clearly defined.

There is no consensus on when it should be applied, but one approach is to use HFO once:

a. $FiO_2 \geq 60\%$ on optimal PEEP to maintain oxygen saturation ≥ 80%
OR
b. PIP > 30 cm H_2O despite low V_T ventilation and optimum PEEP
OR
c. Permissive hypercarbia creates difficulties maintaining pH > 7.2

Adults – MOAT trial suggests HFO is safe and effective and may reduce mortality.[85]

Children – excellent rescue therapy, may reduce pneumothoraces and longer term oxygen requirement, and may improve survival.[86]

Term neonates – only one RCT of HFO as rescue therapy without any benefit in terms of CLD, survival or ECMO useage.[87]

Preterm – recent Cochrane review of 11 studies concluded no clear benefit. Increased rate of IVH only occurred in 2 studies when HFO was used with poor lung recruitment strategy. [88]

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Non-invasive ventilation (NIV)

Non-invasive ventilation reduces the need for ETI in hypoxaemic and hypercapnic respiratory failure, but overall affect on mortality is unclear due to heterogeneity of trials[89] [90] [91]. The benefit of CPAP alone vs. BiLevel ventilation in hypoxic disease is unclear, but CPAP may be at least as effective.

Used as an adjunct therapy for failed weaning NIV results in shorter time of ETI, lower tracheostomy rate, and lower mortality[92].

Studies in infants and children suggest similar benefits in acute respiratory failuer[93]. Many studies indicate NIV is effective in children with infective complications and long term support of neuromuscular diseases, cystic fibrosis, Ondine's curse and asthma.

Nitric Oxide

Nitric oxide in paediatric and adult ARDS transiently improves oxygenation but there is no evidence of an effect on survival [94] [95]. The effect on oxygenation may be enhanced by HFO[96].

Term neonates with PPHN nitric oxide at 20 ppm reduces the need for ECLS, but not mortality[97].

Surfactant

This guideline will not discuss the use of surfactant in preterm and term neonates.

In adult and paediatric ARDS surfactant administration is known to at least temporarily improve gas exchange. A recent RCT in children using calfactant demonstrated a reduced mortality in ALI[98].

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Bicarbonate Therapy

Bicarbonate therapy for improving haemodynamics is not recommended for hypoperfusion-induced lactic acidaemia with pH ≤ 7.15. Two studies in adults indicate no benefit in terms of cardiac output when bicarbonate therapy is compared to an equi-molar concentration of sodium as normal saline.[99]

One neonatal study suggests a temporary benefit in terms of cardiac output of bicarbonate administration to acidotic term and preterm infants.[100]

Haemofiltration

There is no evidence to support the use of continuous venovenous haemofiltration for the treatment of sepsis independent of renal replacement needs. Research is being conducted on high volume haemofiltration (HVHF) with and without renal failure to improve haemodynamics and outcome in severe sepsis.[101]

Plasmaphoresis

There is increasing evidence that plasmapheresis can improve survival in septic shock, but further studies are awaited.[102]

DVT prophylaxis

DVT prophylaxis using unfractionated heparin or low-molecular weight heparin is of proven benefit in acutely ill adult medical patients without contraindications to anticoagulation.[103]

In trauma patients initial application of pulsatile leg pumps followed by enoxaparin 24-48 hrs later is better than deferred enoxaparin alone.[104]

Leg pumps alone should be used in adults when anticoagulation in contraindicated.

Studies in children are lacking, but patients older than 15-18 years should probably be considered for at mechanical prophylaxis or LMWH. Younger children with multiple risk factors should also be considered for DVT prophylaxis.

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Central line placement in children is associated with a high rate of subclinical intravascular thrombosis (50%) but routine prophylaxis is currently not recommended[105], except for long term lines (current RCH recommendations).

Role of early vs late trachesotomy

Early (≤ 7 days) tracheostomy in adult intensive care reduces ventilator days, length of care and may decrease mortality.[106] [107]

Most adult ICUs use bronchoscopic guided percutaneous tracheostomies in this context[108]. Percutaneous tracheotomies are not widely used in PICUs due to technical difficulties relating to patient size. But early surgical tracheostomy can be considered for paediatric patients who are likely to be difficult to wean from mechanical ventilation.[109]

A recent RCT study in adult multi-trauma patients did not show a clear-cut benefit on morbidity or mortality[110]. A recent meta-analysis of trauma studies also showed no benefit from early tracheostomy, except in head injured patients.[111]

Patient selection probably is important, to select those that will benefit from early tracheostomy. Patients discharged 'early' from ICU with a tracheotomy must receive adequate non-ICU care to avoid life-threatening complications.

Stress Ulcer Prophylaxis

Routine prophylaxis is widely practiced in the adult world, despite no real placebo controlled trials – early studies compared H_2 antagonists or sucralfate to antacids. Also the incidence of stress ulceration in intensive care is declining and is now very low. Although mortality is higher in critically ill patients with GI bleeding, GIT haemorrhage is not the cause of death. Helicobacter infection may play a role in those that bleed.[112]

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More recent trials suggest no benefit from prophylaxis.[113]

Studies in adults indicate that ranitidine is more effective than sucralfate and does not incur an increased risk of nosocomial pneumonia despite earlier concerns.[114]

Omeprazole may be more effective than H_2 antagonists.[115]

Stress ulcer prophylaxis in critically ill children has not been studied, but can be administered to children with risk factors – prolonged mechanical ventilation, coagulopathy, head trauma.

Enteral feeding is presumed to be protective, and once established may mean H_2 antagonists could be stopped.

Nutrition

Enteral feeding of critically ill patients is cheaper that parental nutrition and reduces infectious complications.[116] [117] There is still some concern that enteral feeding increases the risk of nosocomial pneumonia.[118]

Enteral feeding can be administered even to the sickest children, those on ECLS.[119]

In head injured patients early enteral feeding may improve neurological outcome.[120]

Acute pancreatitis managed with enteral feeding tends to have less morbidity.[121]

Introduction of intensive enteral feeding program in a PICU in Brazil was associated with mortality reduction.[122]

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Immune modulating enteral and parental nutrition is the subject of much research with a meta-analysis indicating at least a reduction in infective complications if enteral feeding method is used.[123]

In children there has been one RCT of immune modulating enteral nutrition with no hard end-point benefit[124].

Enteral feeding, at least in older patients, is more likely to be successful if the transpyloric route is used[125].

Sedation and Muscle Relaxation

Sedation can be maintained by continuous infusions and/or boluses of midazolam and morphine. Boluses rather than infusions, daily interruption or reductions in the level of sedation may decrease the duration of mechanical ventilation.[126]

In adults the use of propofol rather than boluses of lorazepam may reduce ventilator days[127], but propofol should not be used in children routinely in this context, and probably not adults.[128]

Muscle relaxation should be used sparingly, if at all. Intermittent boluses of shorter acting agents reduce the chance of prolonged muscle weakness.

Removal of spontaneous respiratory drive by muscle relaxation does not consistently improve gas exchange, and can dramatically worsen hypoxemia is patients with severe lung disease (personal experience).

In neonates pancuronium may confer some benefit in selected cases if ventilation in asynchronous.[129]

Morphine is preferred in neonates.[130] Midzolam in neonates should be used with caution.[131]

BIS (bispectral index) monitoring and sedation scales shows promise in achieving adequate sedation levels in muscle relaxed children.[132]

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Malaria

Albumin may reduce mortality in hypovolaemic children with severe malaria when compared to normal saline[133].

If transfusion is not immediately available for severely anaemic children (Hb < 5 g/dL) with falciparum malaria, volume expansion with saline or albumin is safe and reduces the need for emergency intervention. Aggravating cardiac failure should not be seen as a contraindication to volume resuscitation.

Exchange transfusion can be considered in those with high parasite loads and cerebral involvement[134].

Metabolic acidosis may not be due to circulatory failure[135].

ECLS

Australian data will be presented and reviewed at ANZICS this October with an approach formulated.

VV-ECMO may be used successfully in ARDS related to severe sepsis, but the role of VA-ECMO to support circulatory failure is debatable with variable success rates[136] [137].

Sepsis Prevention in Intensive Care

Gut Decontamination

CVL Management

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