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The modules are provided for teaching purposes only and are not designed to be any form of standard reference or textbook. The views expressed in the modules do not necessarily represent the views of all the clinicians at Great Ormond Street Hospital and CATS. The authors have made considerable efforts to ensure the information contained in the modules is accurate and up to date. The modules are updated annually.

Users of these modules are strongly recommended to confirm that the information contained within them, especially drug doses, is correct by way of independent sources. The authors accept no responsibility for any inaccuracies, information perceived as misleading, or the success of any treatment regimen detailed in the modules.

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Basic Immunology, Microbiology & Infectious Disease

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Updated: Sara-Louise Hulme & Christine Pierce February 2007 Updated: Mette Jorgensen & Mehrengise Cooper August 2011

Associated clinical guidelines/protocols:

- GOSH Antimicrobial guidelines "orange book" BAL protocol
- Retroviral testing and treatment
- Infection Control guidelines
- Meningococcal Sepsis
- Bronchiolitis
- Pentoxifyline in neonatal sepsis

Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations.

They will not be repeated here.

Physiology:

- Innate and acquired immune system: Immune function of phagocytes, B cells, T cells, immunoglobulin and complement.
- Host defenses: epithelial/endothelial barriers
- Understand the immune response to infection

Microbiology:

- Organisms causing specific infections: Gram positive and Gram negative bacteria, fungi, protozoa, and viruses. Modes of transmission.
- Universal precautions and good working practice -hand washing, gloves etc
- Strategies to prevent cross infection:
- Sterilisation of equipment
- UK Immunisation schedule and contraindications to immunization

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum

Physiology & Pathophysiology:

- Basic pathology associated with an imbalance in pro- and anti-inflammatory response: Systemic Inflammatory Response Syndrome, septic shock and MODS - Multi-Organ Dysfunction Syndrome
- Basic Immune dysfunction: Innate & adaptive, cellular & humeral
- Risk of infection in patients with indwelling medical devices
- Antibiotics: appropriate choice
- Isolation precautions, infection control and reverse isolation procedure.

Specific Infections:

- Central Nervous System: meningitis, encephalitis, abscess
- Pulmonary parenchymal infections
- Peritonitis, abdominal sepsis
- Opportunistic infections

Curriculum Notes for Year 1:

Basic pathology associated with an imbalance in pro- and anti-inflammatory response: SIRS, septic shock and MODS

- sepsis and the systemic inflammatory response syndrome (SIRS) are common in critically ill children/neonates; it represents a major factor in ICU morbidity/mortality
- Pathogenesis increasingly understood but novel treatments to date failed to live up to expectations after promising *in vitro* + *in vivo* animal studies.

Basic (2), advanced (3) + (4)

DEFINITIONS

Sepsis was previously associated with many terms & nomenclature reflecting the complexity of the condition and similarity of inflammatory response to different aetiologies.

- aim of clarifying the diagnosis and treatment and to aid interpretation of research
- 2005 modified for children by consensus group (1)

Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis and septic shock. (1)

SIRS (1)

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- Core temperature of 38.5°C or 36°C.
- Tachycardia, defined as a mean heart rate 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5-hr time period.
- Mean respiratory rate 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or 10% immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g. white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)

Sepsis

SIRS in the presence of, or as a result of suspected or proven infection.

Severe sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Organ dysfunctions are defined in Organ dysfunction criteria table.

Septic shock

Sepsis and cardiovascular organ dysfunction as defined in Organ Dysfunction criteria table.

Age specific vital signs. (1)

	Heart Rate beats/min		Respiratory	Leucocyte	Systolic Blood
Age	Tachycardia	Bradycardia	Rate	count x10 ³ /mm	pressure mmHg
1/7-1/52	>180	<100	>50	>34	<65
1/52-1/12	>180	<100	>40	>19.5 or <5	<75
1/12-1yr	>180	<90	>34	>17.5 or <5	<100
2-5yrs	>140	NA	>20	>15.5 or <6	<94
6-12yrs	>130	NA	>18	>13.5 or <4.5	<105
12-<18yrs	>110	NA	>14	>11 or <4.5	<117

Multi Organ Dysfunction Syndrome (MODS) is the presence of altered organ function in the acutely ill patient such that homeostasis cannot be maintained without intervention. The cirteria to define paediatirc organ dysfunction have been reviewed (1). Several scoring systems were evealuated but few hade been validated. It is therefore best to use organ dysfunction criteria rather than a MODS scoring system per se. (1).

Organ Dysfunction Criteria. (1)

Cardiovascular dysfunction

Despite administration of isotonic intravenous fluid bolus 40 mL/kg in 1 hr

- Decrease in BP (hypotension) 5th percentile for age or systolic BP 2 SD below normal for age OR
- Need for vasoactive drug to maintain BP in normal range (dopamine 5g/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
 OR
- Two of the following

Unexplained metabolic acidosis: base deficit >5.0 mEq/L Increased arterial lactate >2 times upper limit of normal

Oliguria: urine output <0.5 mL/kg/hr Prolonged capillary refill: >5 secs

Core to peripheral temperature gap >3°C

Respiratory^b

- PaO₂/FiO₂ <300 in absence of cyanotic heart disease or preexisting lung disease
- PaCO₂ >65 torr or 20 mm Hg over baseline PaCO₂

OR

• Proven need^c for >50% FiO₂ to maintain saturation 92%

OR

Need for non-elective invasive or non-invasive mechanical ventilation^d

Neurological

Glasgow Coma Score ≤11

OR

• Acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline.

Hematological

- Platelet count <80,000/mm³ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic haematology/oncology patients)
- International normalized ratio >2

Renal

• Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatic

- Total bilirubin ≥4 mg/dL (not applicable for newborn)
- OR
- ALT 2 times upper limit of normal for age

BP, blood pressure; ALT, alanine transaminase.

bacute respiratory distress syndrome must include a PaO₂/FiO₂ ratio≤ 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO₂/FiO₂ ratio must be ≤300 mm Hg; cproven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.

Paediatric MODS used in the following: Leclerc F et al. *Cumulative Influence of Organ Dysfunctions and Septic State on Mortality of Critically III Children*. American Journal of Respiratory and Critical Care Medicine, Feb 15, 2005 **(5)**

Outcome of children with MODS on Day 1 of PICU admission. Typpo et al. Day One MODS is associated with Poor Functional Outcome and Mortality in the Pediatric Intensive Care Unit. *Pediatr Crit Care Med.* 2009 September; 10(5): 562–570 **(6)**

Read Pinsky's review *Dysregulation of the Immune Response in Severe Sepsis*Am J Med Sci 2004;328(4):220–229. **(7)** Re imbalance in pro- and anti-inflammatory response in sepsis

Basic understanding of Immune dysfunction: T cell & B cell dysfunction, barrier dysfunction (gut translocation, burns), dysfunctional phagocytosis (CGD), complement deficiencies and SCID.

A basic immunology textbook should suffice e.g. Roitt: Essential Immunology. 11th Edition 2006.

Gut translocation:

Stechmiller et al. *Gut Dysfunction in Critically III Patients*: Am J Crit Care, Vol. 6, No. 3, pp. 204-209. **(8)**

Bonten MJ et al. Selective digestive decontamination in patients in intensive care. The Dutch Working Group on Antibiotic Policy. J Antimicrob Chemother.2000 Sep; 46(3): 351-62. **(9)** Kollef M. Opinion: *The clinical use of selective digestive decontamination*. CritCare. 2000; 4(6): 327–

332. doi: 10.1186/cc716. Published online 2000 **(10)** van Saene HK, Petros AJ, Ramsay G, Baxby D *All great truths areiconoclastic: selective*

decontamination of the digestive tract moves from heresy to level 1 truth. Intensive Care Med. 2003 May; 29 (5): 677-90 (11)

Pediatric burns and sepsis-

Sheridan R. *Sepsis in pediatric burn patients*. Pediatr Crit Care Med 2005 Vol. 6, No. 3 (Suppl.) **(12)** PCCM review paper

SCID

See- http://www.emedicine.com/med/topic2214.htm

For others see list in this molecular review-somewhat cutting edge.

Lim M and Elenitoba-Johnson K. *The Molecular Pathology of Primary Immunodeficiencies*. Journal of Molecular Diagnostics, Vol. 6, No. 2, May 2004 **(13)**

Identify pts at risk inflammatory response, nosocomial infections.

Obviously the answer is ALL OF THEM, but especially see: -

Angus DC, Wax RS. Epidemiology of sepsis: an update. Crit Care Med.

2001 Jul; 29(7 Suppl): S109-16. (14)

Fidler KJ, Wilson P, Davies JC, Turner MW, Peters MJ, Klein NJ: *Increased incidence and severity of the systemic inflammatory response syndrome in patients deficient in mannose-binding lectin.* Intensive Care Med. 2004 Jul; 30(7): 1438-45. Epub 2004 May 04. **(15)** Work done at GOS on genetic susceptibility to infection

Meredith L. Allen, MB.BS, FRACP; Mark J. Peters, MRCP, PhD; Allan Goldman, MB BChB, MRCP; Martin Elliott, MD, FRCS; Ian James, MB ChB, FRCA; Robin Callard, BSc, PhD; Nigel J. Klein. *Early postoperative monocyte deactivation predicts systemic inflammation and prolonged stay in pediatric cardiac intensive care.* Crit Care Med 2002 Vol. 30, No. 5 **(16)**

Mark Peters, Andy Petros, Garth Dixon, David Inwald and Nigel Klein: *Acquired immunoparalysis in paediatric intensive care: prospective observational study.* 1999; 319; 609-610 BMJ **(17)**

Risk of infection in patients with indwelling medical devices

McGee and Gould. *Preventing Complications of Central Venous Catheterization*. NEJM. Number 12Volume 348:1123-1133 **(18)**

Folafoluwa et al. *Nosocomial catheter-related bloodstream infections in a pediatric intensive care unit: Risk and rates associated with various intravascular technologies.* Pediatr Crit Care Med 2003 Vol. 4, No. 4 **(19)**

Pierce CM, Wade A, Mok Q. Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. Intensive Care Med. 2000 Jul; 26(7): 967-72. (20)

Provonost et al. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU. NEJM 2006; 355:2725-2732 (21)

Antibiotics: appropriate choice

Shlaes DM, et al. Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Infect Control Hosp Epidemiol. 1997 Apr; 18(4): 275-91. (22)

Fridkin, Scott K. *Increasing prevalence of antimicrobial resistance in intensive care units*. Crit Care Med. Volume 29(4) Supplement April 2001 pp N64-N68 **(23)**

Isolation precautions, infection control and reverse isolation procedure (24) Useful review

Specific Infections:

Details on how to manage infections involving organ systems are available and it will be useful to read this in conjunction with specific management related to organ support.

Included reference for each, though you're **not** expected to read them all

• Central Nervous System: meningitis, encephalitis, abscess

Hunstad, David A. MD: Bacterial Meningitis in Children. Pediatric Case Reviews. 2(4): 195-208, October 2002. **(25)**

Barford G et al. *Viral Infection and Antiviral Therapy in NICU*. Journal of Perinatal & Neonatal Nursing. 18(3): 259-274, July 2004. **(26)**

Encephalitis case/review www.hawaii.edu/medicine/pediatrics/pedtext/s06c15.html

Pathan et al. *Pathophysiology of meningococcal meningitis*+septicaemia. Arch. Dis. Child 2003; 88: 601-7. (22)–You'd better read this it's Naz's **(27)**

Kielian T. *Immunopathogenesis of brain abscess*. Journal of Neuroinflammation 2004, 1:16 doi: 10.1186/1742-2094-1-16 **(28)**

Bacterial meningitis and meningococcal septicaemia. NICU Guidelines 2010.

http://www.nice.org.uk/nicemedia/live/13027/49339/49339.pdf (29)

However much of this will be management of IC mass/ICP-see neuro module

Pulmonary parenchymal infections

Covered throughout syllabus and really encompasses most of ICU. Major points -ventilation, ventilator acquired pneumonias, BAL, use of lung protective strategies, non-invasive ventilation in severely immuno-suppressed/those with poor prognosis if invasively ventilated etc

• Peritonitis, abdominal sepsis

Microbiology and management of intra-abdominal infections in children. Brook I. Pediatrics International. Mostly supportive organ care + surgical liaison.

Opportunistic infections

Post-transplant/immunodeficiency/drug SE's

Bojko et al. Acute hypoxemic respiratory failure in children following bone marrow transplantation: An outcome and pathologic study. Critical Care Medicine. 23(4): 755-759, April 1995. **(30)**

Other sources of information:

Websites.

http://www.rcsed.ac.uk/journal/vol45_3/4530010.htm - Educational review of sepsis and the systemic inflammatory response syndrome from Aberdeen.

Information for Year 2 ITU Training (advanced):

Year 2 ITU curriculum

Physiology & Pathophysiology:

- Initiation of inflammation: Roles of LPS, teichoic acid, cytokine release, endothelial activation, endothelial immune cell interaction, role of platelets and coagulation system.
- More advanced Immune dysfunction. T cell & B cell dysfunction, barrier dysfunction (gut translocation, burns), dysfunctional phagocytosis (CGD), complement deficiencies and SCID.
- Autogenous infection: routes and methods of prevention
- Antibiotics: emergence of resistant strains, prophylaxis, SDD
- Requirements for microbiological surveillance and clinical sampling; Limitations of clinical investigations.

Specific Infections:

- Pyleonephritis
- Orbital cellulitis.
- · Necrotising fascitis
- · Septic arthritis, osteomyelitis.
- HIV
- TB

Curriculum Notes for Year 2:

Initiation of inflammation:

Roles of LPS, teichoic acid, cytokine release, endothelial activation, endothelial – immune cell interaction, role of platelets and coagulation system.

Glauser, Michel P. Pathophysiologic basis of sepsis: Considerations for future strategies of intervention. CCM. 28(9) Supplement: S4-S8, September 2000. (3)

Hack and Zeerleder. The endothelium in sepsis: Source of and a target

for Inflammation. Crit Care Med 2001 Vol. 29, No. 7 (Suppl.) (31)

Faust SN, Heyderman RS, Levin M. Coagulation in severe sepsis: a

central role for thrombomodulin and activated protein C. Crit Care Med.

2001 Jul; 29(7 Suppl): S62-7; discussion S67-8. (32)

Pathology associated with imbalance in pro- and anti-inflammatory response.

Read excellent NEJM review-

Hotchkiss R AND Karl I. *The Pathophysiology and Treatment of Sepsis.* N Engl J Med 348; 2 www.nejm.org January 9, 2003 **(2)**

Immune dysfunction.

Mark Peters, Andy Petros, Garth Dixon, David Inwald and Nigel Klein: *Acquired immunoparalysis in paediatric intensive care observational study. prospective* 1999;319;609-610 BMJ **(17)**

Meredith L. Allen, MB.BS, FRACP; Mark J. Peters, MRCP, PhD; Allan Goldman, MB BChB, MRCP; Martin Elliott, MD, FRCS; Ian James, MB ChB, FRCA; Robin Callard, BSc, PhD; Nigel J. Klein. *Early postoperative monocyte deactivation predicts systemic inflammation and prolonged stay in pediatric cardiac intensive care*. Crit Care Med 2002 Vol. 30, No. 5 **(16)**

Autogenous infection: routes and methods of prevention

Bonten MJ et al. Selective digestive decontamination in patients in intensive care. The Dutch Working Group on Antibiotic Policy. J Antimicrob Chemother.

2000 Sep; 46(3): 351-62. Review. (9)

Kollef M. Opinion: The clinical use of selective digestive decontamination. Crit

Care. 2000; 4(6): 327-332. doi: 10.1186/cc716. Published online 2000

October 2. (10)

van Saene HK, <u>Petros AJ</u>, Ramsay G, Baxby D All great truths are iconoclastic: selective decontamination of the digestive tract moves from heresy to level 1 truth. Intensive Care Med. 2003 May; 29(5): 677-90. Epub 2003 Apr 10. **(11)**

Antibiotics: emergence of resistant strains, prophylaxis, SDD

Fridkin, Scott K. *Increasing prevalence of antimicrobial resistance in intensive care units*. Crit Care Med. Volume 29(4) Supplement April 2001 pp N64-N68 **(22)**

Requirements for microbiological surveillance and clinical sampling; Limitations of clinical investigations.

Scheckler W et al. Requirements for infrastructure and essential activities of infection control and epidemiology in hospitals: consensus panel report. Society for Healthcare Epidemiology of America. Infect Control Hosp Epidemiol.1998 Feb; 19(2): 114-24. **(33)**

Although American rather than UK has many simple facts, and is best review of appropriate structure for infection control.

Specific Infections:

Pulmonary parenchymal infections including TB

Heyns L et al. *Management of children with tuberculosis admitted to a PICU.* Pediatric Infectious Disease Journal. 17(5): 403-407, May 1998 **(34)**

Pyleonephritis

Craig and Hodson. Treatment of acute pyelonephritis in children. BMJ 328 (7433): 179 (35)

Orbital cellulitis.

Jain, Arun M.D.; Rubin, Peter A. D. M.D., F.A.C.S. *Orbital Cellulitis in Children*. International Ophthalmology Clinics. 41(4): 71-86, 2001 **(36**)

Necrotising fascitis –

BMJ editorial. Bad news, need early surgical consultation and really any unusual feature with a cellulitus should prompt concern. *BMJ* 2005; 330.7495.830 (37)

Septic arthritis, osteomyelitis

This is hard to diagnose in ICU child:

Septic Arthritis. http://www.emedicine.com/orthoped/topic438.htm. Updated Nov 2002 (38) Osteomylitis. http://www.emedicine.com/ped/topic1677.htm. Updated May 2006 (39) VanderHave, Kelly L; Raab, Gregory E. Pediatric hip disorders. Curr Op in Orthop. 15(6): 411-416, Dec 2004. (40)

Darvile and Jacobs. *Management of acute hematogenous osteomyelitis in children*. Pediatr Infect Dis J, 2004;23:255–258. **(41)**

Opportunistic infections

Critical Care of Patients with HIV –Excellent web based review http://hivinsite.ucsf.edu/lnSite.jsp?page=kb-03-03-01 Sept 2003 (42) http://content.nejm.rog/cgi/content/full/355/2/173 May 2006 (43)

PVL Staphylococcal infection – Panton Valentine Leucocidin Toxin

Infection with PVL Staph can cause dilemmas with both diagnosis and management. This paper describes the experience at St. Mary's Hospital.

Cunnington et al. Severe invasive Panton-Valentine Leucocidin positive Staphylococcus aureus infections in children in London, UK. Journal of Infection, Volume 59, Issue 1, July 2009, Pages 28-36 (44)

References.

- 1. Goldstein B, Giroir B, Randolph A; and the members of the International Consensus Conference on Pediatric Sepsis. *International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics*. Pediatr Crit Care med 2005 (6) 1
- Hotchkiss R AND Karl I. The Pathophysiology and Treatment of Sepsis. N Engl J Med 348; 2 www.nejm.org January 9, 2003
- 3. Glauser, Michel P. Pathophysiologic basis of sepsis: Considerations for future strategies of intervention. CCM. 28(9) Supplement: S4-S8, September 2000.
- 4. Bochud P-J, Calandra T. *Pathogenesis of sepsis: new concepts and implications for future treatment.* BMJ Feb 2003 (vol 326).
- 5. Leclerc F et al. Cumulative Influence of Organ Dysfunctions and Septic State on Mortality of Critically III Children. American Journal of Respiratory and Critical Care Medicine, Feb 15, 2005
- 6. Typpo et al. Day One MODS is associated with Poor Functional Outcome and Mortality in the Pediatric Intensive Care Unit. Pediatr Crit Care Med 2009; 10(5): 562-570.
- 7. Pinsky M. Dysregulation of the Immune Response in Severe Sepsis. Am J Med Sci 2004; 328(4): 220–229
- 8. Stechmiller et al. Gut Dysfunction in Critically III Patients: Am J Crit Care, Vol. 6, No. 3, pp. 204-209

- 9. Bonten MJ et al. Selective digestive decontamination in patients in intensive care. The Dutch Working Group on Antibiotic Policy. J Antimicrob Chemother.2000 Sep; 46(3): 351-62.
- 10. Kollef M. Opinion: The clinical use of selective digestive decontamination. CritCare. 2000; 4(6): 327–332. doi: 10.1186/cc716. Published online 2000
- 11. Van Saene HK, Petros AJ, Ramsay G, Baxby D *All great truths areiconoclastic: selective decontamination of the digestive tract moves from heresy to level 1 truth.* Intensive Care Med. 2003 May; 29(5): 677-90
- 12. Sheridan R. Sepsis in pediatric burn patients. Pediatr Crit care Med 2005 Vol 6, No 3 (suppl). Lim M and Elenitoba-Johnson K.
- 13. *The Molecular Pathology of Primary Immunodeficiencies*. Journal of Molecular Diagnostics, Vol. 6, No. 2, May 2004.
- 14. Angus DC, Wax RS. Epidemiology of sepsis: an update. Crit Care Med.2001 Jul; 29(7 Suppl): S109-16.
- 15. Fidler KJ, Wilson P, Davies JC, Turner MW, Peters MJ, Klein NJ: Increased incidence and severity of the systemic inflammatory response syndrome in patients deficient in mannose-binding lectin. Intensive Care Med. 2004 Jul; 30(7): 1438-45. Epub 2004 May 04
- 16. Meredith L. Allen, MB.BS, FRACP; Mark J. Peters, MRCP, PhD; Allan Goldman, MB BChB, MRCP; Martin Elliott, MD, FRCS; Ian James, MB ChB, FRCA; Robin Callard, BSc, PhD; Nigel J. Klein. Early postoperative monocyte deactivation predicts systemic inflammation and prolonged stay in pediatric cardiac intensive care. Crit Care Med 2002 Vol. 30, No. 5
- 17. Mark Peters, Andy Petros, Garth Dixon, David Inwald and Nigel Klein: *Acquired immunoparalysis in paediatric intensive care: prospective observational study.* 1999; 319; 609-610 BMJ.
- 18. McGee and Gould. Preventing Complications of Central Venous Catheterization. NEJM. Number 12Volume 348:1123-1133
- 19. Folafoluwa et al. Nosocomial catheter-related bloodstream infections in a pediatric intensive care unit: Risk and rates associated with various intravascular technologies. Pediatr Crit Care Med 2003 Vol. 4. No. 4
- 20. Pierce CM, Wade A, Mok Q. Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. Intensive Care Med. 2000 Jul; 26(7): 967-72
- 21. Provonost et al. An Intervention to Decrease Catheter-Related Bloodstream Infections in the ICU. NEJM 2006; 355: 2725-32.
- 22. Shlaes DM, et al. Society for Healthcare Epidemiology of Americia and infectious Diseases Society of America Joint Committee on the prevention of Antimicrobial Resistance: guidelines for the prevention of antimicrobial resistance in hospitals. Infect Control Hops Epidemiol 1997 Apr: 18(4) 275-91
- 23. Fridkin, Scott K. *Increasing prevalence of antimicrobial resistance in intensive care units.* Crit care Med. Volume 29(4) Supplement April 2001 pp N64-N68.
- 24. Eggimann P. Pittet D. Infection control in ICU. Chest. 2001 Dec: 120(6): 2059-93.
- 25. Hunstad, David A. MD: Bacterial Meningitis in Children. Pediatric Case Reviews. 2(4): 195-208, October 2002.
- 26. Barford G et al. Viral Infection and Antiviral Therapy in NICU. Journal of Perinatal & Neonatal Nursing. 18(3): 259-274, July 2004.
- 27. Pathan et al. *Pathophysiology of meningococcal meningitis+septicaemia*. Arch. Dis. Child 2003; 88: 601-7. (22)
- 28. Kielian T. Immunopathogenesis of brain abscess. Journal of Neuroinflammation 2004, 1:16 doi: 10.1186/1742-2094-1-16.
- 29. Bacterial meningitis and meningococcal septicaemia. NICE Guidelines 2010. www.nice.org.uk/nicemedia/live/13027/49339.pdf
- 30. Bojko et al. *Acute hypoxemic respiratory failure in children following bone marrow transplantation: An outcome and pathologic study.* Critical Care Medicine. 23(4): 755-759, April 1995.
- 31. Hack and Zeerleder. The endothelium in sepsis: Source of and a target for Inflammation. Crit Care Med 2001 Vol. 29, No. 7 (Suppl.)
- 32. Faust SN, Heyderman RS, Levin M. Coagulation in severe sepsis: central role for thrombomodulin and activated protein C. Crit Care Med.2001 Jul; 29(7 Suppl): S62-7; discussion S67-8.
- 33. Scheckler W et al. Requirements for infrastructure and essential activities of infection control and epidemiology in Hospitals: consensus panel report. Society for Healthcare Epidemiology of America. Infect Control Hosp Epidemiol.1998 Feb; 19(2): 114-24.
- 34. Heyns L et al. Management of children with tuberculosis admitted to a PICU. Pediatric Infectious Disease Journal. 17(5): 403-407, May 1998

- 35. Treatment of acute pyelonephritis in children. Craig and Hodson. Treatment of acute pyelonephritis in children. BMJ 328 (7433): 179
- 36. Jain, Arun M.D.; Rubin, Peter A. D. M.D., F.A.C.S. Orbital Cellulitis in Children. International Ophthalmology Clinics. 41(4): 71-86, 2001
- 37. BMJ 2005; 330.7495.830
- 38. http://www.emedicine.com/orthoped/topic438.htm
- 39. http://www.emedicine.com/ped/topic1677.htm.
- 40. VanderHave, Kelly L; Raab, Gregory E. *Pediatric hip disorders*. Curr Op in Orthop. 15(6): 411-416, Dec 2004.
- 41. Darvile and Jacobs. *Management of acute hematogenous osteomyelitis in children*. Pediatr Infect Dis J, 2004; 23:255–258.
- 42. http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-03-01
- 43. http://content.nejm.org/cgi/content/full/355/2/173
- 44. Cunnington A et al. Severe invasive Panton-Valentine Leucocidin positive Staphylococcus aureus infections in children in London, UK. Journal of Infection 2009; 59: 28-36