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Great Ormond Street Hospital for Children
NHS Trust

Basic Immunology, Microbiology & Infectious Disease

Author: Joe Brierley 2005
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.

<table>
<thead>
<tr>
<th>Age</th>
<th>Heart Rate beats/min</th>
<th>Respiratory Rate</th>
<th>Leucocyte count x10^3/mm</th>
<th>Systolic Blood pressure mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/7-1/52</td>
<td>&gt;180</td>
<td>&gt;50</td>
<td>&gt;34</td>
<td>&lt;65</td>
</tr>
<tr>
<td>1/52-1/12</td>
<td>&gt;180</td>
<td>&gt;40</td>
<td>&gt;19.5 or &lt;5</td>
<td>&lt;75</td>
</tr>
<tr>
<td>1/12-1yr</td>
<td>&gt;180</td>
<td>&gt;34</td>
<td>&gt;17.5 or &lt;5</td>
<td>&lt;100</td>
</tr>
<tr>
<td>2-5yrs</td>
<td>&gt;140</td>
<td>&gt;20</td>
<td>&gt;15.5 or &lt;6</td>
<td>&lt;94</td>
</tr>
<tr>
<td>6-12yrs</td>
<td>&gt;130</td>
<td>&gt;18</td>
<td>&gt;13.5 or &lt;4.5</td>
<td>&lt;105</td>
</tr>
<tr>
<td>12-&lt;18yrs</td>
<td>&gt;110</td>
<td>&gt;14</td>
<td>&gt;11 or &lt;4.5</td>
<td>&lt;117</td>
</tr>
</tbody>
</table>

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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 criteria to define paediatric organ dysfunction have been reviewed (1). Several scoring systems were evaluated but few had been validated. It is therefore best to use organ dysfunction criteria rather than a MODS scoring system per se. (1).

**Organ Dysfunction Criteria. (1)**

<table>
<thead>
<tr>
<th><strong>Cardiovascular dysfunction</strong></th>
<th><strong>Respiratory</strong>(^b)</th>
<th><strong>Neurological</strong></th>
<th><strong>Hematological</strong></th>
<th><strong>Renal</strong></th>
<th><strong>Hepatic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>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:</td>
<td>PaO(_2)/FiO(_2) &lt;300 in absence of cyanotic heart disease or preexisting lung disease or PaCO(_2) &gt;65 torr or 20 mm Hg over baseline PaCO(_2) or proven need(^c) for &gt;50% FiO(_2) to maintain saturation 92% or need for non-elective invasive or non-invasive mechanical ventilation(^d)</td>
<td>Glasgow Coma Score ≤11 or acute change in mental status with a decrease in Glasgow Coma Score ≥3 points from abnormal baseline.</td>
<td>Platelet count &lt;80,000/mm(^3) or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic haematology/oncology patients) or international normalized ratio &gt;2</td>
<td>Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine</td>
<td>Total bilirubin ≥4 mg/dL (not applicable for newborn) or ALT 2 times upper limit of normal for age</td>
</tr>
<tr>
<td>Unexplained metabolic acidosis: base deficit &gt;5.0 mEq/L or increased arterial lactate &gt;2 times upper limit of normal or oliguria: urine output &lt;0.5 mL/kg/hr or prolonged capillary refill: &gt;5 secs or core to peripheral temperature gap &gt;3°C</td>
<td>PaCO(_2) &gt;65 torr or 20 mm Hg over baseline PaCO(_2)</td>
<td></td>
<td>Platelet count &lt;80,000/mm(^3) or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic haematology/oncology patients) or international normalized ratio &gt;2</td>
<td></td>
<td>Total bilirubin ≥4 mg/dL (not applicable for newborn) or ALT 2 times upper limit of normal for age</td>
</tr>
</tbody>
</table>

**BP**, blood pressure; **ALT**, alanine transaminase.

\(^a\)acute respiratory distress syndrome must include a PaO\(_2\)/FiO\(_2\) ratio ≤ 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO\(_2\)/FiO\(_2\) ratio must be ≤300 mm Hg; \(^b\)proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; \(^c\)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 Ill Children*. American Journal of Respiratory and Critical Care Medicine, Feb 15, 2005 (5)


**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 Ill Patients*: Am J Crit Care, Vol. 6, No. 3, pp. 204-209. (8)


van Saene HK, Petros AJ, 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 (11)

**Pediatric burns and sepsis**-*


PCCM review paper

**SCID**

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


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)


**Risk of infection in patients with indwelling medical devices**


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

**Antibiotics: appropriate choice**


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

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**

- **Opportunistic infections**
  Post-transplant/immunodeficiency/drug SE’s

### Other sources of information:

**Websites.**

### 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 fasciitis
- 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)

**Pathology associated with imbalance in pro- and anti-inflammatory response.**
Read excellent NEJM review-

**Immune dysfunction.**
- 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**

**Antibiotics: emergence of resistant strains, prophylaxis, SDD**
Requirements for microbiological surveillance and clinical sampling; Limitations of clinical investigations.


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**

- **Pyleonephritis**

- **Orbital cellulitis.**

- **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](http://www.emedicine.com/orthoped/topic438.htm), Updated Nov 2002 (38)

- **Opportunistic infections**
  Critical Care of Patients with HIV –Excellent web based review [http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-03-01](http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-03-01) Sept 2003 (42)
  [http://content.nejm.org/cgi/content/full/355/2/173](http://content.nejm.org/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.

References.

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


37. BMJ 2005; 330.7495.830


42. http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-03-01

43. http://content.nejm.org/cgi/content/full/355/2/173