Pneumocystis Jirovecii and Cytomegalovirus pneumonia co-infections in the PICU - What’s new?

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Outline

- Current PcP issues?
  - Transmission dynamics
  - Diagnosis: role of PCT and 1-3 beta glucans?
  - Treatment issues? Alternatives & resistance to CTM
  - Prophylaxis- What’s new?
- Current CMV issues?
  - Transmission dynamics
  - Diagnosis: CMV isolation what does it mean?
  - Treatment Issues
    - What, for how long & response - ?resistance
    - Prophylaxis – is it necessary
- Co-infections – incidences
- Impact ART, CTM, ganciclovir, HFOV on outcomes
Transmission dynamics with PcP

- **Truly opportunistic infection in immunocompromised**
  - Symptomatic disease
    - SYSTEMATIC REVIEW OF OI in children with HIV- Punpanich W et al PIDJ 2011;30(10)e 192-202
      - PcP strongest association with HIV
      - Antemortem: OR 10.1 (17.7-62.1)

- But what about partially immunosuppressed?
  - Asymptomatic infection - in HIV exposed but uninfected
    - 70-80% of years have anti-PcP antibodies by 8 years
  - HIV exposed uninfected Ruffini D et al AIDS 2001
    - PcP Id in 51 of 105 children with severe pneumonia
    - n= 44 HIV infected vs. n = 7 HIV exposed uninfected
    - CD4% 18.3 vs. 53%
  - Jeena P et al Arch Dis Childhood 2005
    - PCP : n = 38/43 HIV infected vs n= 5/43 HIV exposed uninfected
    - Survival at hospital discharge, 2 year (55%, 29% vs. 100%)
Diagnosis of PcP

Clinical
- Age <6 months
- RDS- cyanosis with no adventitious sounds on chest auscultation
- Hypoxaemia on O2 Rx-ABG Acute hypoxaemic respiratory failure
- HIV infected:

Chest Radiological
- Initially: Diffuse interstitial with hyperinflation rarely patchy focal
- During illness: ARDS, rarely Pulmonary cyst, Pneumomedistinum/thorax
  - Sivit CJ et al Pediatr Radiol 1995

Supportive tests
- **PCT < 2.0**
- LDH: elevated but not at malignancy levels

Specimens
- Oro-pharyngeal secretions, Induced sputum, BAL, Blood, tissue biopsy

Laboratory testing: **Infection vs clinical disease**
- NPA/NBBAL/IS + COMPATIBLE SIGNS AND SYMPTOMS
  - Gomori/Giemsa/methamine silver, 5 or > oocysts on high power field
- PCR, 1-3 Beta glucans
- Histology with inflammatory cell
Diagnosis of PcP

- n -100 Adult cases

Samples
- BAL 86, ETT 8, NPA 1, Pleural fluid 3, Lung biopsy 2

Tests
- Giemsa stain, DFA, 1-3 Beta D Glucans (>80 pg/ml). PCR, FDG PET
- Combination of Giemsa and DFA specificity 100%
- Combination of PCR and 1-3 Beta D Glucan sensitivity 93%
- Latest: FDG PET with tracer for PCP = PCR or 1-3 BDG
PcP Treatment issues

- **Drug of choice & dose:**
  - Co-trimoxazole: 5 mg/kg/dose 6hrly of TMP x 21 d
  - IVI-dilute 1 ml drug to 25mls saline vs. oral ? When
  - Pentamidine, isethionate, micafungin, caspofungin

- **Role of corticosteroids in children:**
  - WHO HIV related pneumonia and diarrhea guideline 2011
  - Aim: Role of C/S in children with pneumonia and acute hypoxemic respiratory failure
  - Methods: Systemic review
  - Results: 2 low quality studies identified 1 showed minimal benefit other no benefit & Adverse effects of dissemination shown in case reports
  - Conclusion:
    - Small numbers and poorly designed studies
    - C/S not routinely recommended but use in PcP confirmed
Role of adjunctive corticosteroids for PCP in HIV infected adults

Briel M et al Cochrane Database 2006

Aim:
- Overall mortality and need for IPPV in PCP with pa O2 <70 mmHg and A-a gradient >35 mmHg in room air

Methods:
- Embase, Medline, cochrane library 1980-2004

Results:
- RR overall mortality with c/s = 0.68 (0.50-0.94) @ 3-4 months (n=6 studies)
- RR for need for IPPV with C/S = 0.38 (0.2-0.73) n= 3 studies

Conclusion:
- Number and size of trial low but benefit of C/S demonstrated

• NB. Fatal CMV associated adrenal insufficiency in AIDS patient on CORTICOSTERIODS. Int. Med 2007;46(a):617-20
PcP Treatment Resistance

**Identification**
- Cannot culture pathogen – difficulty in identifying resistance
- Sulfonamide resistance inferred from point mutation in dihydropteroate synthase gene

**Prevalence:**
- 80% USA, 20% Europe, 13% in South Africa
- Clinical relevance is uncertain
  - Spain 2000-7: n=7/207 cases - no effect on outcome or need for ICU

- No facilities for genetic testing
- Non responsive clinically - consider resistance change
- Significant relationship between use of sulfa drug (prophylaxis and treatment) and development of mutation
<table>
<thead>
<tr>
<th>AUTHOR /COUNTRY</th>
<th>SAMPLE SIZE</th>
<th>DHPS WITH Prophylaxis</th>
<th>DHPS WITHOUT Prophylaxis</th>
<th>STATISTICS</th>
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<tbody>
<tr>
<td>Kazanjian USA</td>
<td>n= 97</td>
<td>28/37 (76%)</td>
<td>14/60 (23%)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Helwig-larsen (Denmark)</td>
<td>n=152</td>
<td>18/29 (62%)</td>
<td>13/123 (11%)</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Ma Italy</td>
<td>n=107</td>
<td>6/31 (19%)</td>
<td>3/76 (4%)</td>
<td>P=0.017</td>
</tr>
</tbody>
</table>
Meta-analysis of salvage therapy for Pcp
Smego RA et al Arch Int Med 2001;161: 1529-33

- 27 published trials, case series & reports
- 497 patients failed initial treatment of mainly CTM

Efficacies of salvage treatment
- Clindamycin/primaquin = 92%
- Eflornithine hydrochloride = 53%
- Pentamidine = 39%

Conclusion:
- clindamycin and primaquine most effective
- Second option: TMP + dapsone
- ? Newer agents
PcP Prophylaxis

- **Limited evidence** - substantially reduces Pneumocystis pneumonia, early deaths in HIV infected infants
  - N=534 HIV infected, Lusaka Zambia
  - Cotrimoxazole vs placebo
  - Mortality Rate RR 0.67 (0.53-0.85) - decreases mortality by 33%
  - Hospitalization RR 0.77 (0.62-0.96)
  - Grimwade K, Swingler GH Cochrane 2006 Jan 25 (1)

- **Concerns with prophylaxis** (*Gill et al Bull WHO 2004*)
  - Cross resistance to ARI pathogens and malaria: Impede development of natural immunity to malaria
  - Is it necessary in HIV exposed uninfected children?
    - Unclear - Need further studies
  - Does cART roll-out alters need for prophylaxis?
Prolonged CTM in HIV Infected children in Africa- ARROW study Bwakura-Dangarembizi M et al NEJM 2014

Methods

- Uganda & Zimbabwe
- Children > 3 years on cART > 96 weeks, with no previous PcP but with insecticide treated bed nets
- n=758 - 2.1 years after commencing ART; mean age 7.9 years
- RCT -(382 stopped CTM vs. 376 continued CTM)

Results:

- Hospitalization 19% vs. 13% HR 1.64 -1.14- 2.37 p =0.007
  - due to malaria 47 vs. 21 cases &
  - other infections (pneumonia, sepsis, meningitis) 33 vs. 25 cases
- Deaths = 1% vs. 1%
- No difference in ADR but anaemia commoner in CTM stopped group

Recommendation

- continued use of CTM in HIV infected children on cART as reduces cost (at USD 12/PATIENT YEAR) from other related hospitalizations
CMV IN THE PICU

- CMV - ubiquitous, common in early childhood; immunocompetent = remains latent infection vs disease.

- Herpes: transmission via breast feeding proportional to HIV RNA shedding - CMV OR 1.8 (Gantt S AIDS 2008; 1453-60).

- By 3 months:
  - 90% of HIV eu (n=20) & 93% of HIV i (n=44) are CMV infected with demonstrable viral load of 3.2 & 2.7 copies/ml respectively.
  - CMV VL Highest first 3 months and then declines rapidly but persist for 7-9 months especially HIV i vs. HIV eu (72% vs. 47%).

- Strong correlation between CMV VL & HIV VL.

- SYSTEMATIC REVIEW OF OI in children with HIV:
  - CMV associated with fatality OR 14.4 (6.7-30.8) (Punpanich W etal PIDJ 2011;30(10)e 192-202.)
Presentation

Definition of Symptomatic neonatal disease

- Positive CMV culture or PCR any secretions within first three weeks +
  - Life threatening: Pneumonitis, oesophagitis, colitis, severe TCP
  - Microcephaly: OFC <2 SD below the mean for age or <2nd centile
  - Symmetric IUGR: birth weight and OFC <2 SD below mean for age.
  - Thrombocytopenia: <100/dL
  - Conjugated hyperbilirubinaemia: >66 micromol/L

Acute disease outside the neonatal period

Presentation

- direct effect: viral syndrome, lung, liver, gut, CNS
- Indirect: secondary infection, delayed recovery

Diagnosis:

- No clear guidelines = includes immunocompromised patient with features of CMV disease (chorioretinitis, sensori-neural deafness) + CMV on PCR or histology from samples at the site (e.g. BAL, CSF, histology esophagitis or colitis, vitreous/aqueous humor samples)

Pathogenesis

- pro-inflammatory + coagulopathy & anti-inflammatory
Diagnosis: infection vs disease

Screening & radiological

- **Abnormal ophthalmology screen**: chorioretinitis, retinal detachment, optic atrophy, cataract, retinal scarring
- **Abnormal hearing assessment**: unequivocally failed or >30 dB hearing loss on two or more age-appropriate audiolologic tests
- **Abnormal cranial US**: ventriculomegaly & intracerebral calcifications
- **Abnormal cranial CT**: cortical atrophy/dysgenesis/dysplasia, ventriculomegaly, cerebellar hypoplasia/asymmetry, migration abnormalities and intracranial calcifications

Laboratory

- **Specific IgM neonates only** = congenital infection – IgG = infection
- **Pp65** = sensitive & LESS specific
- **CMV Blood DNA PCR** rapid detection, more sensitive for early disease. Confirms infection A negative test does not exclude CMV infection.
  - CMV DNA PCR + 66% - missed in 15% of CMV/BPN - Martinson NA, AIDS 2007
- **CMV Culture & histology**: Shell vial assay – delay, low sensitivity
- **CMV Viral load**: > 100 000 copies/ml – high risk of CMV disease
  - allows monitoring – clearance of viraemia
CMV viraemia for diagnosing CMV Pneumonitis
Hsiao et al 2013

- At a CMV viral load cut off of log 4.1, there was a 70% prediction rate for CMV pneumonia with a sensitivity of 78% and specificity of 69%, at this cut-off level.

- CMV viral load and being HIV-infected had OR of 12.12 (95%CI 5.3-27.5) and OR of 4.7 (95%CI 1.5-14.5) respectively for predicting CMV pneumonia.
Usefulness of **CMV viral loads in defining CMV disease and the value of ganciclovir therapy in HIV-infected children with pneumonia admitted to intensive care**


**Method**

- Ventilated children with pneumonia suspected of being CMV infected were enrolled.
- Cases were classified as having CMV disease, infection or being CMV uninfected based on clinical features and a CMV DNA PCR result.
- Non-bronchoscopic bronchoaveolar lavage and blood samples were taken for CMV viral loads among CMV DNA PCR positive cases.
- Ganciclovir was commenced on children diagnosed with CMV disease & cART was administered according to a HIV DNA PCR result.
- CMV viral loads were repeated on blood 14 days after ganciclovir therapy. Outcomes were stratified by HIV and CMV status.
Results

- Ninety seven children were enrolled; 38 were classified as CMV disease, 27 CMV infection and 32 were CMV uninfected.
- Survival rates of 73.0%, 92.6% and 87.5% respectively.
- Prevalence of HIV infection in these three groups was 60.5%, 29.6% and 28.1% respectively.
- An elevated CMV viral loads above log 4.1 on NBBAL or plasma correlated with a diagnoses of CMV disease (AUC = 0.825; CI 0.71- 0.94; sensitivity 86.2%, specificity 77.8%; AUC = 0.74; 95% CI 0.61-0.81 sensitivity 75.9% and specificity 74.1% respectively).
- HIV-infected children with CMV disease on ganciclovir and antiretroviral therapy had higher CMV viral loads and worst outcomes with a mortality rate of 36.4%.

Conclusions

- A CMV viral load on NBBAL or plasma is a useful diagnostic tool to define CMV disease.
- Novel therapies are required to improve outcomes.
Recommended treatment

Asymptomatic disease: Treatment is not recommended

Symptomatic disease

• **Initial treatment:** Intravenous ganciclovir 5 mg/kg over one hour twice a day for 14-21 days and then once daily for 6 weeks

Retinitis

• Intravitreal injections of ganciclovir (2 mg/injection) for 1-4 doses over a period of 7-10 days +

• Valganciclovir 15mg/kg mg PO (BD for 14-21 days, then o.d) OR Ganciclovir 5 mg/kg IV q12h for 14-21 days, then valganciclovir

Pneumonitis/Colitis:

• Ganciclovir 5 mg/kg IV 12hrly, switch to valganciclovir 15mg/kg mg PO 12h once child tolerates PO Rx or after 2 weeks for CNS disease

• Total Duration: 42 days or until signs/symptoms have resolved

Resistant Cases: Foscarnet & cidofovir
Empiric ganciclovir in HIV infected children admitted to SBAH

- Infants with very severe pneumonia (CMV & PcP prototype) n = 96; 23 deaths (24%)
- HIV infected = 83 (VL 2.3 m) & HIV exposed = 13
- CMV disease (VL > 10000) n = 40; PcP = 9; deaths = 17 (42%)
- CMV infection (VL 1-10000) n = 21; PcP = 5; deaths = 2 (10%)
- CMV negative n = 35; PcP = 7; deaths = 4 (11%)
- Cd4 count inversely related CMV viral load
- HIV viral load related to CMV viral load
- Odds of dying:
  - CMV disease 5.73 +/- 1.7 - 19.3
  - PcP = 2.55
- Empiric ganciclovir no difference no impact on outcome
Valganciclovir

- Is a valyl-ester prodrug of oral ganciclovir
- Has a **bioavailability of nearly 70 percent** (compared with 7 percent for oral ganciclovir); and, at doses of 16mg/kg, produces serum ganciclovir levels that are similar to that measured with intravenous administration of ganciclovir for children
Oral Valganciclovir Is Noninferior to Intravenous Ganciclovir for the Treatment of Cytomegalovirus Disease in Solid Organ Transplant Recipients


Oral valganciclovir shows comparable safety and is not inferior to i.v. ganciclovir for treatment of cytomegalovirus disease in organ transplant recipients and provides a simpler treatment strategy, but care should be taken in extrapolating to organ transplant recipients not properly represented in the present study.

Key words: Cytomegalovirus disease, ganciclovir, posttransplant, valganciclovir, viral kinetics

Received 27 April 2007, revised 22 May 2007 and accepted for publication 04 June 2007
Figure 1: Kaplan-Meier curves showing cumulative probability of persistence of clinical symptoms and viral eradication in patients treated with either oral valganciclovir or i.v. ganciclovir (intention-to-treat population). There were no differences between treatment groups. Black lines denote the valganciclovir treatment arm and gray lines represent the i.v. ganciclovir treatment arm. (A) Cumulative probability of persistent viremia (cutoff level of 600 copies/mL plasma). (B) Cumulative probability of persistent active CMV disease (as assessed by the investigator).
Pharmacological: Equivalence Ganciclovir & Valganciclovir

- Trang and colleagues 1993
  - Pharmacokinetics of IV ganciclovir in 27 neonates
  - Max serum concentration was $5.5 \pm 1.6 \text{ mcg/ml}$ after dose of $4 \text{ mg/kg}$ and $7 \pm 1.6 \text{ mcg/ml}$ after $6 \text{ mg/kg}$
  - Volume of distribution increased with increasing weight
  - Mean elimination half life was 2.4 hours

- Zhang and colleagues 2003
  - 11 children
  - Dose of $5 \text{ mg/kg}$ 12hly IVI for 15 days ganciclovir
  - Oral ganciclovir administration $50 \text{ mg/kg}$ 12hly - 3 mths
  - Adequate serum ganciclovir concentrations for treatment
Vanganciclovir for symptomatic congenital cytomegalovirus disease

- Multi-centered study (USA) comparing IV ganciclovir for 6 weeks vs. oral valganciclovir for 6 months in symptomatic children with CMV disease given treatment at 1 month of age.

- @ 6 months, no difference in hearing loss was noted (AOR 1.7 (0.77-3.79)) but at 12 & 24 months significant differences in hearing loss AOR 3.34 (1.31-8.53) & AOR 2.66 (1.02-6.90) were noted respectively.

- Developmental differences were only seen for language reception.

- CMV viral load reduction was greater with 6 months of valganciclovir than 6 weeks of IV ganciclovir therapy and with greater reductions at 12 and 24 months.

- Significant neutropenia (grade 3 or 4) of 37.5% and 63% were seen at 2 weeks and 6 months with IV ganciclovir while oral valganciclovir had a safety profile similar to placebo at 2 weeks of treatment (19% vs. 20%).

- CMV disease itself is associated with blood dyscrasias.

- Increased in ALT/AST with IV ganciclovir use.
Adverse effects of therapy

- Difficult to distinguish between that disease & treatment

- 50% in IV GCV phase & 32% in Valgancyclovir phases

  - n = 120 immunocompromised children with CMV,
    - commonest ADR were granulocytopenia (17%) & thrombocytopenia (10%)
      - Pescovitz et al

  - n = 16 children:
    - hypokalemia (25%),
    - decreased renal function, sepsis, or thrombocytopenia (19%),
    - leukopenia, coagulopathies, hypertension, pneumonia, or immune system disorders (13%)
Cost considerations

- Cymevene Vials (5X 500mg) (tender) @ R 1,976.26 + Vat
- Valcyte Powder 50mg/ml 100ml @ R 1,762.88 incl Vat
- Valcyte Tablets 450 mg (on tender) @ R9,607.75 incl Vat
  - Cost mg/kg similar but wastage great with ivi and tablet

Estimation of cost for administering ivi ganciclovir for 6/52 with hospital stay vs. 6/52 of oral suspension valganciclovir

- For a patient weighing 5kg : ivi ganciclovir 5mg/kg 12hourly = 50mg daily ivi that equates to two vials per day = R790.50 +R3000(hospital cost)/per day x 42 days=R159201,16
- Oral valganciclovir syrup 16mg/kg 12hourly=80mg daily=6720mg for 42 days which equate to just less than two bottles = R3525.76 with limited in-hospital cost

Uncertain issues

- Non registered or licensed in children in RSA
- Efficacy not established with upfront use in HIV infected group
Prevention of CMV Disease

- Previously, treatment was only administered once CMV disease occurred. This resulted in an overall incidence of CMV disease of approximately 20 to 60 percent.
- Subsequently, preventive strategies have been developed that have significantly lowered the incidence of CMV disease, which is approximately 5 percent with modern approaches.
- **Prevention of CMV disease following transplantation:** 900 mg once daily beginning within 10 days of transplantation; continue therapy until 100 days (heart or kidney-pancreas transplant) or 200 days (kidney transplant) post-transplantation.
- **DO WE NEED CMV PROPHYLAXIS LONG TERM HIV INFECTED CHILDREN?** No data.
### Relationship between CMV, PcP & HIV status – SBAH experience

<table>
<thead>
<tr>
<th>Opportunistic infections</th>
<th>HIV infected n=83</th>
<th>HIV exposed uninfected n=13</th>
<th>TOTAL n=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV disease</td>
<td>36 (43.4)</td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>CMV disease without PcP</td>
<td>27 (32.5)</td>
<td>4</td>
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<tr>
<td>CMV infection</td>
<td>18 (21.7)</td>
<td>3</td>
<td>21</td>
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<tr>
<td>CMV infection without PcP</td>
<td>13 (15.7)</td>
<td>3</td>
<td></td>
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<tr>
<td>No CMV</td>
<td>29 (34.9)</td>
<td>6</td>
<td>35</td>
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<tr>
<td>CMV disease + PcP</td>
<td>9 (10.8)</td>
<td>0</td>
<td>9</td>
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<tr>
<td>CMV infection + PcP</td>
<td>5 (6.0)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>PcP without CMV</td>
<td>7 (8.4)</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>
PcP & CMV in radionuclide-contaminated area in children - Russia

Parazitologiiia 1996; 30: 223-8

- Antemortem: n = 563 children 0-12 months
  - PCP incidence 33%, CMV 33.7%
  - Co-infection rate 8.2% (1-2 months 8.5% vs. 6-12 months 14.5%)

- Serology testing n = 103
  - PcP 88%, CMV 24.6%
  - Co-infection 53.4% vs. 16.7% in Moscow (clean area) n = 30

- Postmortem: n = 1809 children
  - PCP 4%, CMV 11.1%
  - Co-infection 1.3%

- Conclusion
  - peculiar symbiotic relationship that increases infectiousness
Impact of HAART on CMV without anti-CMV specific therapy  Mihailescu R et al Rom J Int med 2008; 46:305-11

- Clinical, virological and immunological monitoring
- 2 types of tests: Roboscreen & Qaigen = Both tests equivalent
- n=105 HIV infected CMV IgG positive cases – 86 placed on HAART
- 26 cases CMV viraemia (n=14; CD4 <50) all received HAART and within 16.5 weeks viral load undetected
- Conclusions: HAART reduced CMV viral loads and prevented undetected asymptomatic infection from becoming disease
Effect of CMV on normalization of selected T cell subsets in children with Perinatal HIV Rx with cART

Kapetanoic et al PLOS One 2015n10(3) 0120477

- n=107, CMV naïve 37%, CMV + viraemia 14%, CMV + avireamia 49%
- CMV naïve patients - faster recovery of CD8+ T-cells independent of HIV VL response to ART, CD4% or cART
- CMV co-infection has detrimental effect on T cell subsets in response to cART
  - Greater effect in those with viraemia as compared to those avireamic
- Therefore need to adjust response rate to cART in patient with CMV
Impact of ganciclovir, cART & advanced organ support on outcome of HIV infected children with CMV associated pneumonia: A retrospective review

Jeena PM*, Githinji L*Adhikari M* submitted 2015

- Electronic data set of all admissions at PICU at IALCH, during 2010

- 405 children admitted, 261 (64.4%) were HIV unexposed uninfected, 77 (19.0%) were HIV-1 infected, 48 (11.9%) HIV exposed uninfected & 19 (4.7%) were HIV unknown.

- Mortality rates HIC uninfected vs infected similar at 15.3% and 22.1% respectively (p=0.27).

- CMV was isolated from 39 (50.7%) of the 77 HIV infected

- Survival rate of HIV-infected children with CMV associated pneumonia who received cART and ganciclovir therapy without HFOV was 92.3%.

- 18.3% of CMV pneumonia needed HFOV – SR= 90%
CONCLUSIONS

- Data supports strong association of PcP and CMV with HIV infection but also seen in HIV exposed uninfected.
- Diagnosis is challenging—both diseases have a stage of infection and disease.
  - Need combination of clinical, radiological & microbiology—PCT, 1-3 beta glucans, CMV viral load.
- Both significant mortality - untreated.
- Treatment concerns include CTM with corticosteroids for confirmed PCP disease only and Ganciclovir and valganciclovir (cost effective) for CMV disease.
- Diagnosis and management of resistance important.
- Cotrimoxazole Prophylaxis is a useful and cost effective in HIV infected infants and older children even on cART.
- Preemptive or prophylaxis for CMV needs investigation.
- cART is one of the main stay of treatment for these cases.
<table>
<thead>
<tr>
<th>Country/city</th>
<th>Time of study</th>
<th>Number</th>
<th>PICU/hospital discharge</th>
<th>30 month survival</th>
<th>Long term survival</th>
</tr>
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<tbody>
<tr>
<td>United Kingdom Cooper S (ICM)</td>
<td>1992-02</td>
<td>42</td>
<td>62%</td>
<td>50%</td>
<td>50%</td>
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<tr>
<td>USA Curtis R (AJRCCM)</td>
<td>1995-97</td>
<td>155</td>
<td>50%</td>
<td>-</td>
<td>30%</td>
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<tr>
<td>Johannesburg Mathiva R (SAJCC)</td>
<td>1998</td>
<td>62</td>
<td>12%</td>
<td>-</td>
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<tr>
<td>France Bedos J (CCM)</td>
<td>1999</td>
<td>34</td>
<td>65%</td>
<td>36%</td>
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<tr>
<td>Durban Thirst E + Jeena P(SAMJ/ ADC)</td>
<td>2003</td>
<td>49</td>
<td>42%</td>
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<td>Stellenbosch Rabie H (J Trop Ped)</td>
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<td>47</td>
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<td>Cape Town Cowburn ADC</td>
<td>2003-04</td>
<td>68</td>
<td>75% (PICU)</td>
<td>25%</td>
<td>19%</td>
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<tr>
<td>Pretoria Kitchen OP (press)</td>
<td>2008-9</td>
<td>53</td>
<td>68%</td>
<td>-</td>
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<tr>
<td>Durban Jeena (press)</td>
<td>2010</td>
<td>77</td>
<td>78% (PICU)</td>
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</table>
Aim: role of CMV in HIV infected cases on IPPV with PCP
Methods: prospective study treated with TMP/SMX. Non responders – open lung biopsy
Results: n=25 mean age 3.3 months
Antenatal lung biopsy n=17, post mortem n=8

<table>
<thead>
<tr>
<th>PNEUMONIA</th>
<th>HISTOPATHOLOGY</th>
<th>CULTURES</th>
<th>FINAL DIAGNOSIS</th>
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</thead>
<tbody>
<tr>
<td>CMV</td>
<td>7 (28%)</td>
<td>5</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>CMV+PJP</td>
<td>8 (32)</td>
<td>3</td>
<td>9 (36)</td>
</tr>
<tr>
<td>PJP</td>
<td>7 (28)</td>
<td>1</td>
<td>6 (24)</td>
</tr>
<tr>
<td>LUNG FIBROSIS</td>
<td>3 (12)</td>
<td>3</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

pp65 false negative in 24%
CMV+ PJP, CD4 = 110 (52- 162),CMV CD4 = 306 (202-346)
Outcome – 72 % Mortality, Hospital 88% MR
Empiric treatment with ganciclovir should be considered
CMV in infancy- impact on survival and progression of HIV infection


No relationship to faster progression

<table>
<thead>
<tr>
<th>AGE</th>
<th>HIV - No CMV</th>
<th>HIV with CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 YEARS</td>
<td>n= 65</td>
<td>n= 16</td>
</tr>
<tr>
<td>@ 2 YEARS Mortality rate</td>
<td>23.6%</td>
<td>20%</td>
</tr>
<tr>
<td>@5 YEARS Mortality Rate</td>
<td>39.6%</td>
<td>40%</td>
</tr>
</tbody>
</table>

VS.
Prevalence & outcome of CMV-associated pneumonia in HIV infection
Zampoli M et al PIDJ 2011

- n= 202 severe pneumonia of which 124 HIV infected - median age 3.2 months
- Prevalence CMV 28% (HIV + vs. – =36% vs. 15%) vs. PcP (27%) vs. other viruses (19%)
- Overall Hospital MR 25% (HIV+ vs. - = 35% vs.11%, OR 4.5 CI 1.9-11.8)
- HIV & CMV + OR 2.5 for mortality but ns when adjusted for CD4 <15% OR 1.78 CI 0.6-4.6
- Conclusion: CMV associated pneumonia poor outcome - need increased access to anti-virals

Pena A REV Chilena infecto 2007; 24: 477-84

- CMV in 12.6% of HIV infected Chilean children
- 92% category C - 61% immune category 3
Does CMV predict poor prognosis in PCP treated with CORTICOSTEROIDS?


DENMARK:
- n= 148 with PCP on bal
- Co-identification of CMV and PCP in patients treated with C/S was associated with a 2 x higher mortality at 3 months
- Conclusion: Active CMV may be an important cause of failing treatment of severe PCP in those treated with C/S

Spain:
- C/S use no impact on risk of developing or relapsing TB

PROGNOSTIC MARKERS-SHORT TERM MORTALITY IN PJP

Benfield et al. Chest 2001
- n = 47 adults
- Prognostic markers on Multivariate analysis
  - AGE (RR4.1; 95% CI 1.8-9.3)
  - PRIOR EPISODE OF PJP
  - CULTURE OF CMV (RR 2.7 95%CI 1.3-5.6)
    - Increased association in both IPPV and non IPPV BUT Much more common and carries poor outcome in HIV associated PJP on IPPV
  - USE OF PROPHYLAXIS AT DIAGNOSIS
    - (RR 5.6 95% CI 2.2 – 14.4)
  - THERAPY OTHER THAN CTM
    - (RR 3.1 CI 1.2-8.5)
- Not related
  - Po2
  - Serum LDH
Co-infection post medical immunosuppression
Pliquett RU et al Wur J Clin Micro 2012; 32(9): 2429-37
- Outbreak of 30 PcP cases in 2005-7
- Rx Ganciclovir & CTM
- In hospital mortality 10% overall 3 year MR 30% but CMV did not increase mortality
- 2002-4 no PcP no CMV
Tygerberg PICU HIV experience

- Retrospective study in 2003 – 47 cases (10%), No HAART
- Median age 4 months, Length of stay 6 days > non infection (p=0.0001)
- Cases had ARF due to PCP in 38%, 51% had CMV
- 17 died in PICU and 4 shortly post ICU
- Survival rate = 26/47 (60%)
- SR associated with lower lymphocyte count and higher gamma globulin
Outcome: children receiving IPPV

► Developed countries
  ► Survival rates respiratory vs. non respiratory (47% vs. 74%)
  ► PICU survival 50-81%
  ► 3 month median survival 68-90%
  ► Medium term survival 0-60%
  ► 2 year survival 12.5% (Great Ormond street)

► NPPV better than IPPV,
  ► survival 100% vs. 38%
  ► < Adverse effects n = 24
    ► Confalonieri M Int Care Med 2002:28: 1233-38
Short/long term outcome in PJP with ARF
Forrest DM et al Arch Intern med 1999;159:741-6

- Retrospective 5 year Chart Review
- n = 39 patients with 41 admission for IPPV
- Short term Mortality 56.4%
- Long term survival PJP with ARF (30%) = PJP without ARF (32%)
- Predictors of in hospital mortality
  - Poor Score on scoring system
  - Duration of previous maximal therapy > 5 days
Outcome of PJP in the PICU

- Developing countries:
  - **PICU Mortality:**
    - 1996: Durban 60%...... Jeena P et al Crit care med
    - 1998: Johannesburg: 88%..Mathivha R et al SAMJ
    - 2001: Cape Town 28.5%..Zar H et al Ped Crit care
    - 2003 Durban 58% ........Thirst E et al SAMJ
  - **MEDIUM TERM PJP SURVIVAL**
    - Durban 2005: approximately 30 % survival @ 2 YEARS of those leaving the PICU ... Jeena PM et al Arch Dis Childh
PcP in ICU: SURVIVAL & PROGNOSTIC FEATURES: ‘THE FRENCH EXPERIENCE’


- **Subjects:** ARF due to AIDS related PJP
- **Cases Series**
  - n=110, CPAP 66 (60%), IPPV 34 (31%), nil 10 (9%)
  - 34 IPPV (12 ab-initio + 22 failed CPAP) PICU MR 76% (n =25)
  - 3 month mortality = 34.6% (25%-44%)
  - 12 month survival = 47% (36%-58%)
  - 24 month survival = 36%

- **Multiple logistic regression**
  - DELAYED IPPV > 3 days = OR 6.7 (1.9-23.9)
  - Duration of IPPV >6 days = OR 2.8 (1.1-6.9)
  - Pneumothorax = OR 5 (1.7-14.7)
  - Nosocomial infection
    - 100% prediction of death by 3 months
Prognostic Factors: withholding & withdrawal

- French study: Multiple logistic regression
  - Delayed in IPPV > 3 days = OR 6.7 (1.9-23.9)
  - Duration of IPPV >6 days = OR 2.8 (1.1-6.9)
  - Pneumothorax in PcP = OR 5 (1.7-14.7)
  - PaO2 / AaO2 levels - persistently low
    100% prediction of death by 3 months

- Bedos J-P etal crit care med 1999; 27(6):1109-5

- USA Study: Multivariate analysis
  - Age (RR4.1; 95% CI 1.8-9.3)
  - Culture of CMV (RR 2.7 95%CI 1.3-5.6)
    - carries poor outcome in HIV associated PJP on IPPV
  - Therapy other than CTM (RR 3.1 CI 1.2-8.5)
  - Lack of PcP Prophylaxis prior to diagnosis (RR 5.6 CI 2.2-14.4)

- Benfield et al Chest 2001

- Risk factors in cART era
  - Co-morbidities, weight loss, decreased albumin
Clinical monitoring vs. laboratory monitoring:
ARROW trial
Revill PA et al AIDS 2105; 29(@): 201-10

- **Methods**
  - N=1206 on cART + CTM

- **Results:**
  - Use of clinical monitoring = laboratory monitoring in terms of efficacy and safety
  - Reduce CD4 monitoring to annually decreases ICER by USD 6084/QALY and > 12 years by USD769/QALY
  - Cost of CTM S12/patient year

- **Recommendation**
  - provide CTM and ART and reduce monitoring

Proportion alive

Years from randomisation

HR = 0.57
[0.43-0.77]
p = 0.0002

Cotrimoxazole Placebo

Cotox 265
Placebo 269

265 232 177 106 47
211 143 72 29
Cotrimoxazole prophylaxis for OI in children with HIV

- WHO/UNICEF: Cotrimoxazole
  - Dose 5-10 mg/kg/day of the trimethoprim component
- Duration
  - From 6 weeks -12 months or
  - until child proven to HIV negative and 3 months after breast feeding has ceased or
  - CD4 >15% or asymptomatic and >12 months
- Surrogate markers for continued prophylaxis
  - CD4% <15% or TLC <1200