

INFECTIONS IN NEWBORNS SYNTHESIS (Infections, preterm and low birthweight outcomes)

Research Gaps from Cochrane Reviews (Cochrane Library Issue 3, 2007)

The faces indicate the direction of findings in each review:

- ☺ **Likely to be effective**
- ☹ **Both benefits and risks**
- ❓ **Uncertain or limited effect**
- ☹ **Likely to be ineffective or potentially harmful**

Important research implications are more likely to arise from reviews with uncertain findings or where the benefits and risks are mixed

CONTENTS

- ✚ During pregnancy
- ✚ Peri-partum
 - Admission procedures
 - Enemas
 - Group B Streptococcus
 - HIV
 - Immersion in water
 - Mode of birth
 - Induction of labour
 - Preterm PROM
 - Preventing infections during labour
 - Term PROM
- ✚ Intrapartum
- ✚ Third stage of labour
- ✚ Preventing infection in newborns
 - General
 - Specific
- ✚ Treating infection in newborns
 - General
 - Specific
- ✚ References

DURING PREGNANCY

- ☹ **Prophylactic antibiotics and infection in infants (Thinkhamrop 2002)**
Need further trials to address effects of prophylactic antibiotics on neonatal sepsis
- ☹ **Routine prescribing of antibiotics to women in preterm labour with intact membranes unlikely to reduced neonatal infections (King 2002)**
Does not give any research recommendations relating to newborns
- ❓ **Unclear effects on neonatal outcomes from treating bacterial vaginosis during pregnancy (McDonald 2005)**
Large trials are needed which can determine the effect of a screening programme for asymptomatic bacterial vaginosis on neonatal mortality and major measures of morbidity

- ? Unclear effects on neonatal outcomes from treating Chlamydia during pregnancy (Brocklehurst 1998)**
No trials reporting neonatal outcomes were located
- ? Third trimester antiviral therapy for preventing transmission of genital herpes to neonates (Hollier 2004)**
- Cochrane protocol
 - Cochrane review in progress
- ? Antibiotics during pregnancy for preventing transmission of Gonorrhoea to babies during birth (Brocklehurst 2002)**
- Need to test the assumption that early detection and treatment of gonorrhoea in pregnancy will alter subsequent perinatal outcome requires testing in randomized controlled trials
 - Need to investigate the association between genital gonococcal infection and adverse perinatal outcome in terms of prelabour rupture of the membranes and preterm birth
- ? Prophylactic drugs for helminthic infections (Haider 2005)**
- Cochrane protocol
 - Cochrane review in progress
- ☺ Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection (Brocklehurst 2002a)**
- Need to see if ongoing randomised trials of vitamin and nutritional supplementation show similar effectiveness to zidovudine or nevirapine
 - All children born to women receiving combination antiretroviral therapy in pregnancy should be followed up in order to monitor any evidence of long-term toxicity
- ? Interventions other than zidovudine, nevirapine and delivery by elective caesarean for reducing the risk of mother-to-child transmission of HIV infection (Brocklehurst 2002b)**
- If alternatives to antiretroviral therapy (such as vitamin and nutritional supplementation) are shown to be effective then there will be an urgent need for trials to compare these interventions with antiretroviral therapy
 - In order to reduce the burden of disease, need to identify those women who are HIV infected before an intervention can be given
- ? Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection (Wiysonge 2005)**
A large trial involving 4,495 HIV infected pregnant women in Harare (Zimbabwe Vitamin A for Mothers and Babies Project) will further clarify the effect of vitamin A supplementation on mother to child transmission of HIV infection when it is published
- ☺ Antibiotics for treating syphilis (Walker 2001)**
No RCTs were located – while it is clear that penicillin is effective, the optimum regimens are uncertain
- ? Antibiotics for treating trichomoniasis (Gülmezoglu 2002)**
Need to establish whether treating trichomonas in symptomatic or asymptomatic pregnant women reduces preterm birth
- ? Treating toxoplasmosis in pregnancy (Peyron 1999)**
- A large study could randomise health care clinics to no screening (existing practice in some countries) or screening, with follow up of seronegative women and treatment if they seroconvert
 - In countries where screening is already routine, all women would be offered routine screening, but treatment after seroconversion would be randomised
- ? Timing and type of prenatal treatment for congenital toxoplasmosis (Thiébaud 2003)**
- Cochrane protocol
 - Cochrane review in progress
- ? Antibiotics for treating ureaplasma (Raynes-Greenow 2004)**

Need RCTs to determine if antibiotic treatment for women with ureaplasma in the vagina will reduce the likelihood of preterm birth

- ☺ **Antibiotics for symptomatic urinary tract infections during pregnancy (Vazquez 2003)**
Need to evaluate antibiotics such as nitrofurantoin, trimethoprim-sulfamethoxazole, cephalosporins and penicillins by comparing duration and acceptability, and by measuring neonatal outcomes

PERI-PARTUM

Admission Procedures

- ? **Routine perineal shaving on admission in labour (Basevi 2000)**
No trials reported neonatal outcomes

Enemas

- ? **Enemas versus no enemas (Cuervo 1999)**
No research recommendations given

Group B Streptococcus

- ☺ **Intrapartum antibiotics given to women colonized with group B streptococcus reduce neonatal infections (Smail 1996)**
 - Need effective strategies to detect maternal colonisation with group B streptococcus
 - Optimal time and method to detect maternal colonisation with group B streptococcus is unknown
 - Unclear whether prophylaxis should only be given to women with identified risk factors or to all women colonized with GBS
 - Need more data on maternal risk factors for neonatal GBS in different populations
- ? **Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection (Stade 2004)**
Need a large multi-centred double-blinded randomised trial measuring relevant outcomes including colonisation of infants with GBS, early-onset GBS infection, early-onset GBS pneumonia and meningitis, and mortality rates, which overcomes the methodological limitations of past trials

HIV

- ☺ **Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection (Brocklehurst 2002a)**
 - The effectiveness of elective Caesarean section in women receiving optimal antiretroviral therapy needs further evaluation.
 - Need to determine the potential value of nevirapine used for longer durations in breastfeeding populations in further reducing the risk of mother-to-child transmission
 - Need to see if ongoing randomised trials of vaginal cleansing and breast versus artificial feeding show similar effectiveness to zidovudine or nevirapine
- ? **Interventions other than zidovudine, nevirapine and delivery by elective caesarean for reducing the risk of mother-to-child transmission of HIV infection (Brocklehurst 2002b)**
If alternatives to antiretroviral therapy (such as vaginal cleansing and breast versus artificial feeding) are shown to be effective then there will be an urgent need for trials to compare these interventions with antiretroviral therapy
- ☺ **Caesarean delivery for prevention of mother-to-child transmission of HIV-1 (Read 2005)**
Need to assess the effectiveness of caesarean section for preventing mother-to-child transmission of HIV-1 among HIV-1-infected women with undetectable viral loads (with or without antivirals)

Immersion in water

- ? **Effect of immersion during pregnancy, labour and birth (Cluett 2002)**
Need large collaborative randomised trials addressing safety with regard to infection and other neonatal outcomes

Mode of birth

- ? **Elective caesarean delivery versus vaginal delivery to reduce perinatal transmission of the hepatitis C virus (McIntyre 2005)**
- Cochrane protocol
 - Cochrane review in progress

Induction of labour

- ☺ **Intravenous oxytocin versus expectant management for neonatal infection (Kelly 2001)**
Need to look at different intervals of commencing oxytocin or different doses of oxytocin
- ? **Intravenous oxytocin versus vaginal or intracervical PGE2 for neonatal infection (Kelly 2001)**
Need to look at different intervals of commencing oxytocin or different doses of oxytocin

Preterm PROM

- ☺ **Routine use of antibiotics (erythromycin) for preterm prelabour PROM (Kenyon 2003)**
Future trials of antibiotic prophylaxis for preterm prelabour rupture of membranes need to measure long term outcomes – ORACLE study data for seven year olds is due in 2008
- ? **Planned management for prelabour rupture of membranes at 34 to 37 weeks' gestation (Buchanan 2004)**
- Cochrane protocol
 - Cochrane review in progress

Preventing infections during labour

- ? **Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding Group B Streptococcal and HIV) (Lumbiganon 2004)**
Since chlorhexidine solution is quite safe, not expensive and vaginal irrigation is not difficult to perform, there is a need for a well-designed randomized controlled trial with adequate sample size to evaluate this simple intervention, as well as determining the optimal volume of the solution used for irrigation

Term PROM

- ? **Prelabour prophylactic antibiotics for term PROM (Flenady 2002)**
Future trials of prelabour prophylactic antibiotics for term PROM should be blinded, adequately sized to address clinically important maternal and neonatal outcomes and include a cost analysis
- ☺ **Planned management for prelabour rupture of membranes at term (37 weeks or more) (Dare 2006)**
- Future trial design should attempt to blind outcomes such as maternal and neonatal infection and to report these outcomes in a standardised way
 - Outcomes such as maternal satisfaction, maternal and neonatal infectious morbidity, other neonatal morbidities, and longer term child development/disability need to be included in future trials

INTRAPARTUM

- ? **Antibiotics for treating intra-amniotic infections (Hopkins 2002)**
Need to look at comparisons of different regimens and to measure long term outcomes such as consequences of neonatal cerebral damage
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THIRD STAGE OF LABOUR

- ? **Prophylactic antibiotics for manual removal of retained placenta in vaginal birth (Chongsomchai 2006)**
Multicentre randomised controlled trials comparing antibiotic prophylaxis and placebo or no antibiotic use after manual removal of placenta in vaginal birth are urgently needed

PREVENTING INFECTION IN NEWBORNS

General infections

? **G-CSF and GM-CSF for preventing neonatal infections (Carr 2003)**

The UK PROGRAMS RCT assessing whether prophylactic GM-CSF can reduce systemic infection or mortality in infants at high risk of postnatal neutropenia has recently completed accrual

? **Gowning by attendants and visitors in newborn nurseries for preventing neonatal infection (Webster 2003)**

- Assessing the effect of over gowns in well-baby nurseries is not warranted due to changes in hospital practices
- Gowning in neonatal intensive care nurseries needs to be assessed in a properly randomized study (which take account of clustering if applicable) using outcomes such as death and systemic infection
- Other infection control interventions might be investigated first, due to the expense of gowning

? **Intravenous immunoglobulin for preventing infection in preterm and/or low-birth-weight infants (Ohlsson 2004a)**

- Need to pursue other avenues other than prophylactic immunoglobulins to enhance the immune system of preterm and/or LBW infants, and to prevent nosocomial infections
- The prophylactic use of IVIG should be based on a full economic evaluation and a clinical decision analysis that incorporates baseline risk for serious nosocomial infections, both clinical and economic outcomes following prophylactic IVIG, and values attached to infections prevented - such analyses have not been performed

? **Intravenous in-line filters for preventing neonatal infections (Foster 2006)**

Need further RCTs of IV in-line filters (0.22 micron positively charged 96 hour IV versus 1.2 micron) used for lipid administration in term and preterm neonates; measuring mortality, septicemia, periventricular leukomalacia, necrotising enterocolitis, systemic and local thrombus, local phlebitis and costs

☺ **Kangaroo mother care to reduce infection in low birthweight infants (Conde-Agudelo 2003)**

Promising results need to be confirmed or refuted in well-designed RCTs that control for selection bias at entry, drop outs, completeness of follow-up, and bias in assessing outcomes

? **Methods of securing peripheral vascular catheters for reducing neonatal infection (Sivasangari 2005)**

- Cochrane protocol
- Cochrane review in progress

? **Multiple versus single lumen umbilical venous catheters for reducing neonatal infection (Kabra 2005)**

Need well-designed and adequately powered RCTs to compare safety in multiple versus single lumen catheters (including consideration of the type of catheter material)

? **Probiotics for prevention of infection in preterm infants (AlFaleh 2005)**

- Cochrane protocol
- Cochrane review in progress

? **Prophylactic antibiotics to reduce infection in neonates with umbilical artery catheters (Inglis 2004) or umbilical venous catheters (Inglis 2005) ventilated newborn infants (Inglis 2004)**

Further RCTs may not be practicable or ethical as most neonates are on antibiotics or commence antibiotics at the time of catheter insertion or infants who are mechanically ventilated. However the question of whether or not to continue antibiotics once blood cultures have returned negative remains unanswered

☺ **Prophylactic intravenous antifungal agents to prevent infection in very low birth weight infants (McGuire 2004)**

- Need to assess longer term outcomes such as neurodevelopmental outcomes
- Could compare intravenous fluconazole versus oral nystatin prophylaxis in a large RCT
- It is not clear which population subgroups are likely to benefit most from prophylactic antifungal therapy
- Need to establish optimal dose regimens and duration of prophylaxis
- Need to consider the clinical consequences of the emergence of antifungal resistance
- A cluster randomized trial, where the neonatal nursery/unit/centre is the unit of randomization, might be appropriate

? Prophylactic oral antifungal agents to prevent systemic Candida infection in preterm infants (Austin 2003)

- Need more RCTs, comparing oral antifungal agents with placebo and with each other, including an assessment of side effects
- Need to ensure the agents used are appropriate for Candida subspecies types, current sensitivity patterns and background colonisation rates

? Prophylactic versus selective antibiotics for term newborn infants of mothers with risk factors for neonatal infection (Ungerer 2004)

- Need RCTs in infants who may benefit most from antibiotic therapy
- It may be appropriate to separately evaluate interventions in neonates exposed to individual specific risk factors or combinations of these risk factors
- Trials should address long term outcomes such as neurodevelopmental outcomes and clinically important outcomes such as mortality and proven infection/sepsis
- Need to consider clinical consequences of antibiotic resistance

☹ Repeated lumbar or ventricular punctures in newborns with intraventricular haemorrhage (Whitelaw 2001)

Since this intervention may result in CSF infection, other interventions are suggested to address protection of the infant's brain from raised pressure

? Selenium supplementation to prevent short-term morbidity in preterm neonates (Darlow 2003)

Need a trial to assess the effect of maternal selenium supplementation from 20 weeks gestation on outcomes for very preterm infants – this trial would have to be very large

☹ Topical ointment for preventing infection in preterm infants (Conner 2003)

Analyses of the impact of a short duration of topical ointment on the risk of infection and the relationship to fluid balance are still required

? Topical umbilical cord care at birth (Zupan 2004)

- Need studies comparing inexpensive interventions (such as alcohol, antiseptics or antibiotics; powders, solutions or ointments) with no specific topical cord care
- A package of care promoting good hygiene at birth and until the cord separation could compare water and soap with an antiseptic (such as chlorhexidine, iodine or powders)
- Harmful effects of antimicrobials such as effect of iodine on thyroid gland function and possible interference with neonatal screening for congenital hypothyroidism, should be taken into account
- The bacteriostatic properties of colostrum applied to the cord stump could be evaluated in a RCT

☹ Vancomycin for prophylaxis against sepsis in preterm neonates (Craft 2000)

- Further RCT of prophylactic vancomycin (or other agent, such as teicoplanin) for preventing sepsis would be useful, particularly in infants less than 1000 grams, with indwelling catheters, and evaluating potential ototoxicities and nephrotoxicities.
- However an RCT to determine the risk of development of resistant organisms with low dose vancomycin prophylaxis would require a very large sample size and may never achieve adequate power.
- Need to evaluate antibiotic lock technique at the time of tubing changes to the stopcock and catheter as this technique avoids exposing the infant to any significant antibiotic concentrations
- Need studies of catheters impregnated with antibiotics and/or antibacterials which may reduce nosocomial catheter related infections in the neonatal population

? **Vitamin A supplementation for preventing infection in very low birth weight infants (Darlow 2002)**

Need a trial of vitamin A in an intravenous lipid emulsion versus intramuscular injections in very low birth weight infants

☺ **Vitamin E supplementation for prevention of morbidity and mortality in preterm infants (Brion 2003)**

Need a multicentre RCT of vitamin E (excluding high-dose intravenous administration) begun within 48 hours of birth and given for more than one week in extremely low birth weight infants in order to determine the optimal dose of vitamin E (dose at which benefits such as retinopathy of prematurity could be seen without the presence of adverse effects such as an increased risk of sepsis)

Specific infections

Candida

? **Patient isolation measures for infants with candida colonization or infection on the transmission of candida (Mohan 2006)**

- Cochrane protocol
- Cochrane review in progress

Group B Streptococcus

? **Intramuscular penicillin for preventing early onset group B streptococcal infection in newborn infants (Woodgate 2004)**

- Need large RCT which allows analyses of outcomes in subgroups (e.g. according to maternal risk factors, use of intrapartum antibiotics, gestational age)
- Need to measure late-onset GBS disease and neurodevelopmental status
- Could investigate a selective intervention delivered in the immediate postpartum period as an adjunct to maternal antibiotic prophylaxis
- Attention needs to be given to the risk profile of the participants
- Need to assess effect of widespread use of penicillin on the emergence of resistant organisms in neonatal nurseries

NEC

? **Arginine supplementation for preventing necrotising enterocolitis in preterm infants (Shah 2004)**

Need large multicentre RCT of arginine supplementation in preterm neonates (focusing on the incidence of NEC stage 2 or 3) – 750 infants in each arm would be needed

? **Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth-weight neonates (Foster 2004)**

- Need further trials to assess oral IgA in extremely low birth-weight neonates (<1000 grams).
- Need to measure outcomes such as length of hospital stay, hospital readmissions, need for total parenteral nutrition administration, growth and development in childhood and parenteral emotional and financial costs.
- Would require 1000 infants to show a 50% reduction in NEC

? **Prophylactic antibiotics for preventing necrotising enterocolitis in preterm infants (Bury 2001)**

- Need a large trial with sample size sufficient to examine all important benefits and harms (including bacterial resistance) associated with prophylactic antibiotic administration
- Extended surveillance is necessary to determine whether antibiotic resistance has emerged

☺ **Restricted versus liberal water intake for preventing necrotising enterocolitis in preterm infants (Bell 2001)**

- Need to determine the critical period during which water intake must be controlled
- Need to develop models for predicting optimal water intakes that take into account the most important determinants of water requirement such as birth weight, gestational age, postnatal age, and ambient humidity.
- Future studies should target extremely premature infants as they are most vulnerable to the consequences of under- and over-hydration.

☺ **Umbilical artery catheters in the newborn: effects of catheter design (end vs. side hole) (Barrington 1999)**
Need more studies of catheters with non-standard designs, in particular addressing the safety of the oxygen electrode tipped catheter

? **Umbilical artery catheters in the newborn: effects of catheter materials (Barrington 1999)**
Newer catheter materials and silastic catheters need to be compared with PVC in RCTs

☺ **Umbilical artery catheters in the newborn: effects of position of the catheter tip (Barrington 1999)**
No further research relating to the risk of infection and catheter tip positioning was proposed

PERTUSSIS

? **Antibiotics for preventing whooping cough (pertussis) (Altunaiji 2005)**

- Urgent need for larger randomized controlled trials for prophylaxis against whooping cough, with clearly measured clinical outcomes (e.g. clinical cure, duration of symptoms, severity and improvement), microbial eradications, microbial relapse, adverse effects, compliance and attack rate
- Need to compare antibiotics with placebo for prophylaxis against whooping cough in vaccinated and unvaccinated patients
- Short-duration trials with newer macrolides such as azithromycin, clarithromycin and roxithromycin are desirable

ROTAVIRUS

? **Oral immunoglobulin for preventing rotavirus infection in low birth weight infants (Mohan 2002)**

- Newer preparations of anti-rotaviral immunoglobulins (colostrums from cows immunized against rotavirus and egg yolk immunoglobulins from hens immunized against rotavirus) have not been assessed for preventing rotavirus infections in neonates
- Premature and low birth weight infants have higher mortality and morbidity associated with rotavirus infection and therefore studies should include this population of infants
- Need to measure effects on morbidity, mortality and health resource utilisation, as well as prevention of rotavirus infection, and reduction in duration of viral excretion which would determine the duration of expensive infection control measures, and cost-effectiveness

? **Oral immunoglobulin for preventing rotavirus diarrhoea in low birth weight infants (Mohan 2002)**

- Need to assess high titre anti-rotaviral immunoglobulin preparations in rotavirus infected infants, especially in LBW or premature infants
- RCTs should use rapid diagnosis to ascertain rotavirus infection as an eligibility criterion in order to avoid confusion with other gastro-intestinal infections in LBW infants
- Need to measure effects on morbidity, mortality and health resource utilisation, as well as prevention of rotavirus infection, and reduction in duration of viral excretion which would determine the duration of expensive infection control measures, and cost-effectiveness

UREAPLASMA

? **Erythromycin for preventing chronic lung disease in intubated preterm infants at risk for ureaplasma (Mabanta 2003)**

- Need larger studies to test prophylactic treatment of high risk infants.
- Methods of detection of any colonisation and timing of treatment are important factors to consider in trial design
- Need to investigate adverse effects associated with erythromycin
- Trials should comment on other common neonatal morbidities including NEC and IVH.

TREATING INFECTION IN NEWBORNS

? **G-CSF and GM-CSF for treating neonatal infections (Carr 2003)**

- Need to assess G-CSF or GM-CSF in infants with microbiologically proven systemic infection associated with severe neutropaenia with an adequately powered, well designed RCT
- Future trials should focus on infants with systemic infection and a neutrophil count less than $1.7 \times 10^9/L$

- Trials should recruit sufficient infants infected with organisms associated with a significant mortality risk
- Available data does not support further RCTs of infants who are not neutropaenic
- Future studies should include long term neurological and neurodevelopmental follow-up

? Intravenous immunoglobulin for suspected or subsequently proven infection in neonates (Ohlsson 2004b)

- Need well-designed trials of targeted IVIG preparations (IVIG preparations with high concentrations of antibodies to specific organisms commonly causing infection in a local setting) – such a trial is ongoing in the UK, Australia, NZ and Europe (INIS)).
- Other potentially more effective interventions to prevent or treat neonatal infections should also be explored

? Systemic antifungal drugs for invasive fungal infection in preterm infants (Clerihew 2004)

- Need a large RCT to determine whether any of the newer antifungal preparations reduce mortality and adverse neurodevelopmental outcomes compared with conventional amphotericin B.
- Such a trial may require use of cluster-randomised trial design with neonatal centre as the unit of randomisation
- Need to research relative convenience and cost effectiveness of available drugs. (e.g. drugs absorbed well orally may be more convenient and cost-effective in practice)
- Need to consider the effect of increased use of particular agents on emergence of organisms resistant to antifungal drugs

CYTOMEGALOVIRUS

? Antiviral agents for symptomatic congenital cytomegalovirus infection (Jones 2003)

- Cochrane protocol
- Cochrane review in progress

HERPES SIMPLEX

? Antiviral agents for treating herpes simplex (Walker 2003)

- Cochrane protocol
- Cochrane review in progress

MENINGITIS

⊖ Intraventricular antibiotics for bacterial meningitis (Shah 2004)

Further trials comparing intraventricular and intravenous antibiotics with intravenous antibiotics alone are not justified

ORAL CANDIDIASIS

? Antifungal agents for treating oral candidiasis (Gray 2004)

- Cochrane protocol
- Cochrane review in progress

PERTUSSIS

⊕ Antibiotics for treating whooping cough (pertussis) (Altunaiji 2005)

- Urgent need for larger randomized controlled trials for treating whooping cough, with clearly measured clinical outcomes (e.g. clinical cure, duration of symptoms, severity and improvement), microbial eradications, microbial relapse, adverse effects, and compliance
- Need to compare antibiotics with placebo for treating whooping cough in vaccinated and unvaccinated patients
- Short-duration trials with newer macrolides such as azithromycin, clarithromycin and roxithromycin are desirable

SEPSIS

? Antibiotic regimens for suspected early neonatal sepsis (Mtitimila 2004)

Need more studies to compare between and within monotherapies and combination therapies and to assess address short and long-term adverse effects.

- ? Antibiotic regimens for suspected late onset sepsis in newborn infants (Gordon 2005)**
- Need more studies to compare different antibiotic regimens which assess short and long-term adverse effects
 - Need to compare narrow versus broad spectrum antibiotic regimens
 - Ongoing surveillance of types of organisms and increasing antibiotic resistance is important to direct further research
 - Need to assess cost effectiveness and the impact of antibiotics in different settings and lower gestational age groups
- ? Doses of gentamicin for treating suspected or proven neonatal sepsis (Rao 2006)**
Need more studies comparing ‘multiple doses per day’, ‘one dose per day’ and a ‘more extended dosing regimen of once in 36-48 hours’ of gentamicin in infants less than 32 weeks gestation
- ? Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropaenia (Mohan 2003)**
Need adequately powered multi-centre trials of granulocyte transfusions which measure mortality and length of hospital stay as well as long term neurological and immunological outcomes and cost-effectiveness
- ? Pentoxifylline in addition to antibiotics for neonatal sepsis (Haque 2002)**
- Need RCTs of pentoxifylline in neonates with suspected early and late onset sepsis
 - Need to measure clinically important co-morbidities of sepsis (e.g. chronic lung disease, periventricular leukomalacia, duration of assisted ventilation, necrotizing enterocolitis etc) and long term neurological outcome
 - Comparisons of pentoxifylline with other adjunctive modalities such as colony stimulating factors or intravenous immunoglobulins should be considered.
- ? Recombinant human activated protein C (rhAPC) for severe neonatal sepsis (Kylat 2006)**
- Initially should undertake RCTs of rhAPC in full term infants with confirmed or suspected sepsis. If minimal adverse effects and significant clinical benefit are found, then trials including infants with less severe sepsis and preterm and LBW infants (highest risk of serious bleeding and intracranial haemorrhage) should be performed
 - Then adequately powered trials of rhAPC therapy for severe neonatal sepsis can be undertaken
 - Need to measure clinically important consequences of sepsis (e.g. chronic lung disease, periventricular leukomalacia, duration of assisted ventilation, necrotizing enterocolitis) and neurological outcomes
 - rhAPC could also be compared with other adjuncts to antimicrobials, such as early goal directed fluid resuscitation, tight glycaemic control, modulators of inflammation, immunomodulators, haematopoietic colony stimulating factors, anticoagulants or fibrinolytics

TETANUS

- ☺ Diazepam for treating tetanus (Okoromah 2004)**
Future research effort should be directed towards preventive interventions and ultimate eradication of tetanus

UREAPLASMA

- ? Erythromycin for preventing chronic lung disease in intubated preterm infants with ureaplasma (Mabanta 2003)**
- Need larger studies to test treatment of infants with proven colonisation
 - Methods of detection of colonisation and timing of treatment are important factors to consider in trial design
 - Need to investigate adverse effects associated with erythromycin
 - Trials should comment on other common neonatal morbidities including NEC and IVH
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