

**CEYLON COLLEGE OF  
PHYSICIANS**

**MEDICINE UPDATE**

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#### **4.1 Antibiotics during pregnancy and birth defects.**

Exposure to antibiotics during the month before the estimated date of conception through the end of the first trimester was studied in 13,155 mothers of infants with at least one major birth defect and compared to randomly selected mothers with infants without birth defects in the same geographical region. Their findings were,

1. Sulphonamides were associated with 6 major birth defects including anencephaly and hypoplastic left heart syndrome.
2. Nitrofurantoin was associated with 4 birth defects.
3. Penicillins, Erythromycins and cephalosporins appear to be safe.
4. Quinolones is not recommended during pregnancy.

**Ref:** Crider K.S. et al Arch. Pediatr. Adolesc. Med 2009 Nov; 163:978.

#### **4.2 Nephrogenic Systemic Fibrosis (NSF) – some aspects.**

NSF is a disorder characterized by skin tightening, joint contractures and sometimes fibrosis of internal organs. It occurs mainly in patients who have received Gadolinium based contrast agents. The extent of skin and joint involvement correlated with amount of gadolinium exposure and developed within 3 months in 2/3rds of patients thus exposed. Skin biopsies reveal the presence of Gadolinium. About 1% of haemodialysis patients who received Gadolinium contrast develop NSF. The GFR of < 30ml /mt is a risk factor for Gadolinium related NSF.

**Ref:** Abujudeh H.H. et al Radiology 2009 Oct; 253: 81.  
Lee C.U. et al Arc.Dermatol. 2009 Oct; 145:1095.

#### **4.3 Statins and gall stones.**

Statins attenuate hepatic production of cholesterol. Their use might lower risk for cholesterol gall stones. 27,000 cholecystectomy patients were matched with 100,000 controls for Age and sex using a UK GP registry.

Current statin use was associated with a 22% reduction in risk for gall stones necessitating cholecystectomy. The odds ratio was 0.85 for 1-5 years of use and 0.64 for use for more than 5 years. The reduction was more pronounced for high dose than for low dose.

**Ref:** Bodmer M. et al JAMA 2009 Nov 11; 302: 2001.

#### **4.4 Revascularization for renal artery stenosis (RAS) of atherosclerotic origin.**

Revascularization of RAS can improve artery patency but is it associated with clinical benefit?. In a 5 year UK study, 806 patients with RAS and related clinical findings such as difficult to control hypertension or unexplained renal dysfunction – were randomized to medical management alone or to medical management + angioplasty (with stenting at the discretion of the physician). The median follow up was 34 months.

Compared with medical management alone, those assigned to combined treatment had only a borderline significant mean lower rate of disease progression. No differences in serum creatinine, systolic BP, adverse renal and cardiovascular events or death were seen between the two groups. Mean diastolic BP was significantly lower in the medical management only group. 23 patients suffered serious complications related to vascularization (2.5%).

**Comment:** Revascularization for RAS produced no benefit. People who required mandatory revascularization according to modern opinion with flash pulmonary oedema or acute renal injury or rapidly progressing disease were excluded in this study. This is the main limitation of this study. But for most people, revascularization for RAS does not appear to result in clinical benefit.

**Ref:** The ASTRAL investigators N.E.J.Med 2009 Nov 12; 361: 1953.

#### **4.5 Cervical radiculopathy (CR) , which is better – Cervical collar, physiotherapy or “wait and see”?**

CR manifests as pain from the neck to the arm and motor and sensory deficits of radicular distribution. Symptoms and signs resolve spontaneously in about 6 weeks, but pain during this period can be excruciating and debilitating. 205 patients with recent onset (<1month) CR were randomized to one of 3 treatment regimens.

1. Semi hard foam cervical collar with extra reinforcement (cerviflexS) + rest for 3-6 weeks.
2. 12 physiotherapy sessions (twice weekly) + home exercises for 6 weeks but no cervical traction.
3. Continued daily activities with analgesics only without specific treatment – “wait and see” controlled group.

After 6 weeks, mean pain scores in the collar and physiotherapy groups had diminished significantly more than scores in the “ wait and see” group. At 6 months however, median pain scores were low and not significantly different across the 3 groups.

**Comment:** This was an unblinded study and suggests that treatment with a semi hard collar or with physiotherapy is superior to a “wait and see” approach in patients with recent onset CR. The collar alleviates foraminal nerve root compression and inflammation by immobilizing the neck. Physiotherapy decreases pain by an unclear mechanism. The collar treatment is preferred as it is cheaper and involves less visits to the hospital. The results of cervical traction in patients with failed therapy while on any of the above 3 regimens are not available.

**Ref:** Kuijper B. et al B.M.J. 2009 Oct 7; 339: b3883.

#### **4.6 A new medical treatment for Schwannomas (S).**

S are found on the 8<sup>th</sup> nerve in neurofibromatosis Type 2. They possess receptors for Vaso Endothelial Growth Factor (VEGF). **Bevacizumab** is an antibody against VEGF. When administered to these patients, they shrunk the tumour and improved hearing loss. This is an alternative treatment when surgery is refused or contraindicated.

**Ref:** Plotlain et al NEJMed 2009 July 23<sup>rd</sup>; 361: 358 – 367.

#### **4.7 Treatment for Hepatitis C – Peginterferon Alpha 2b (PAb) + Ribavirin vs Peginterferon Alpha 2a (PAa) + Ribavirin.**

PAb dose 1.0 mcg/Kg/week + Ribavirin 800- 1400mg/d gave similar results to PAa 180mcg/week + Ribavirin 1000 – 1200mcg/d for 48 weeks gave viral RNA clearance in about 40%. RNA clearance at weeks 4 and 12 predicted a sustained virological response in about 80% of such patients.

**Ref:** IDEAL study team Mc Hutchison et al NEJ Med 2009 Aug 6<sup>th</sup>; 361 (16) : 580 – 593.

#### **4.8 Ultra sensitive Troponin assays.**

These are specific for cardiac myocyte injury. Positive values are those > 99 percentile in the general population. Older assays have sensitivity for myocyte injury at about 88% while the new assays have a sensitivity of about 95 %. The accuracy is increased within the first 3 hours after the onset of chest pain.

The increased sensitivity is at the expense of decreased specificity for ischaemic myocardial injury. Levels are also increased after myocarditis and traumatic cardiac injury. Renal failure prevents excretion of troponins leading to a false positive troponin test. Elevated levels of troponin are therefore not diagnostic of ischaemic injury. The diagnosis of acute coronary syndrome should be based both on clinical features and a positive troponin T. Cardiac MRI will complement ultra sensitive troponin assay for the diagnosis of MI.

**Ref:** Morrow D.A. et al NEJ Med 2009 Aug 27; 361 (9): 913 – 915.

#### **4.9 Dabigatran (D) vs Warfarin (W) for atrial fibrillation (AF).**

D is a direct thrombin inhibitor when used in 18,113 patients with AF in a dose of 110mg or 150mg and compared with dose adjusted W, the rates of stroke and systemic embolism were the same for both modalities of treatment. The rates of major haemorrhage was however significantly less with the 110mg/d dose of D whereas the 150mg dose gave the same rates of major haemorrhage as W.

**Comment:** D – a direct thrombin inhibitor is a useful replacement for W in the treatment of AF, as it doesn't require continuous Monitoring.

**Ref:** RE-LY investigators- Connolly S.J. et al NEJ Med 2009 Sept 17; 361 (12): 1139 – 1151.

#### **4.10 Coronary artery bypass grafting (CABG) – on pump vs off pump.**

At 30 days, there was no difference in the composite of death, complications, reoperation, cardiac arrest, coma, stroke, renal failure or mechanical support. At 1 year however, the composite outcomes of death, repeat revascularization or non fatal MI were more in those off pump. This may be due to the fact that the number of grafts originally intended could not be performed comprehensively during the off pump procedure.

**Ref:** ROOBY study group, Shroyer A.L. et al NEJ Med 2009 Nov 5; 361 (19): 1827 – 1837.

#### **4.11 Does Paracetamol lower response to childhood immunization?**

Some Practitioners prescribe prophylactic antipyretics after routine childhood immunizations because of concerns about febrile seizures.

459 healthy infants were randomized to receive prophylactic paracetamol, given immediately and twice more within 24 hrs or no antipyretic after each of their standard primary and booster immunizations during their first 15 months of life. Those receiving paracetamol had significantly lower primary antibody responses to H influenza, diphtheria, tetanus, pertussis and all 10 pneumococcal antigens and significantly lower booster antibody responses to tetanus and 9 pneumococcal antigens.

**Comment:** Paracetamol blocks a very early stage of the immune response. Later therapeutic use of antipyretics might not have the same effect. Prophylactic antipyretics seem to have little benefit and probably should not be prescribed routinely to healthy infants.

**Ref:** Prymula R. et al Lancet 2009 Oct 17; 374: 1339.

#### **4.12 What patients with non valvular atrial fibrillation (AF) benefit from anticoagulation?**

13,559 patients with non valvular AF were followed up for a mean 5 years. Net clinical benefit was defined as the annual combined rate of ischaemic stroke + systemic emboli that was prevented by warfarin, minus the annual rate of intracranial haemorrhages that were attributable to warfarin multiplied by 1.5( multiplier was included to give greater clinical weight to intracranial haemorrhage).

Net clinical benefit of warfarin was 0.68 annually. The benefit was higher for

1. Those with past ischaemic stroke.
2. Elders above age 85.
3. CHADS 2 risk score above 4 (1 point each for congestive heart failure, hypertension, age over 75 or diabetes and two points for past stroke).

**Comment:** The editorialist state that these results suggest that almost half of patients with AF of non valvular origin (especially those with single or no stroke risk factors ) will not benefit from anticoagulation. In contrast, benefits of anticoagulation is sizable for people at high risk for stroke.

**Ref:** Singer D.E. et al Ann. Intern. Med. 2009 Sept 1 ; 151: 297.

Hart R.G. et al IBID: 355.

#### **4.13 Radiofrequency catheter ablation (RCA) for primary paroxysmal atrial fibrillation (PPAF).**

PPAF is often not controlled by medical therapies. Reviewers analyzed 6 randomized trials and 2 comparative studies of RCA in patients (mean age 55, preserved LV ejection fraction, left atrial size about 5cms) with primarily paroxysmal AF that was uncontrolled by medications. Maintenance of sinus rhythm was superior with RCA vs medical treatment at 1 year. No associations were found between RCA and stroke incidence, changes in left atrial size or ejection fraction. Incidence of serious complications (pulmonary vein stenosis, stroke, peripheral vascular complications or atrio-oesophageal fistula was 5%.

**Comment:** RCA is an attractive treatment option because although it was invasive, it might allow patients to avoid anticoagulation or antiarrhythmic medications. Evidence supports its use as 2<sup>nd</sup> line therapy to maintain sinus rhythm in younger patients with preserved cardiac function.

**Ref:** Terasawa T. et al Ann. Intern. Med. 2009 Aug 6; 151: 191.

#### **4.14 Angiotensin receptor blockers (ARBs) for microalbuminuria.**

Telmisartan an ARB was compared with placebo in 5,927 adults (mean age 67) who could not tolerate ACEIs. The study was Industry sponsored and duration was 5 years. All had cardiovascular disease or diabetes but no macroalbuminuria or heart failure.

No significant difference was seen in the combined outcome of doubling of serum creatinine or dialysis. In fact doubling of serum creatinine and decreases from baseline in GFR was significantly more common with telmisartan than with placebo.

In 3 other 5 year International Industry sponsored trials of candisartan in normotensive with Type 2 diabetes and normoalbuminuria, candisartan did not lower risk of developing microalbuminuria in any of the trials.

**Comment:** These trials do not support ARBs to prevent renal disease among people with vascular disease or diabetes or to prevent microalbuminuria among those with diabetes and no macrovascular disease. ACE inhibitors however do prevent microalbuminuria in people with diabetes who are at high risk for vascular disease.

**Ref:** Mann. J.F.E et al Ann. Intern. Med 2009 July 7; 151: 1.

Bilous R. et al IBID: 11.

Parfrey P.S. IBID: 63.

#### **4.15 A non surgical treatment for Dupuytren's contractures (DC)**

Surgery is the only treatment option for patients with DC. A non surgical option is the injection of Collagenase (derived from *Clostridium histolyticum*) directly into the involved tissue.

308 patients with DC were randomized to collagenase injections or placebo injections. At 1 month, a proportion of joints that achieved the primary end points – reduction of contracture to full extension – was significantly greater in the collagenase than in the placebo group (64% vs 7%). Adverse events were injection site pain, swelling and contusions without further interventions. Tendon rupture occurred in 2 collagenase recipients.

**Comments:** Injected collagenase clearly provides short term improvement in DC.

**Ref:** Hurst L.C. et al NEJ Med 2009 Sept 3; 361: 968.

#### **4.16 Does inhaled steroid for COPD increase the risk for pneumonia – If so which steroid?.**

Several clinical trials, studies and meta analyses suggest that inhaled steroids increase the risk of pneumonia by as much as 70%. The two steroids commonly used are Budesonide or Fluticasone.

7,000 patients with COPD were randomized to Budesonide or placebo, with or without the long acting Beta 2 agonist Formoterol for 6 – 12 months. In both groups, 3% developed pneumonia. In 1% of Budesonide recipients and 2% on placebo, the pneumonia was severe.

**Comment:** Budesonide is cleared more rapidly from the airways than Fluticasone. This might explain why pneumonia risk is not elevated with Budesonide whereas it seems to be increased with Fluticasone. The pneumonias which occurred were mainly mild ones. The benefit of inhaled steroids in COPD patients continue to out weigh the risks substantially.

**Ref:** Sin D.D. et al Lancet 2009 Aug 29; 374 : 712.  
Welte T IBID: 668.

#### 4.17 Syncope in elders.

This is a common problem in the elderly and finding the cause may be challenging. Many tests are done including the following. ECG, Telechest, cardiac enzymes, CT head, Echo, postural BP, carotid ultrasound, EEG, MRI of head and cardiac stress test. In a study of 1,900 consecutive patients (age >65) the commonest aetiologies were found to be vasovagal (22%), postural hypotension (13%) and arrhythmias (12%). In 47% of cases the cause was unknown. The cost effectiveness of the tests in descending order were Postural BP measurement, Telechest, ECG, Echo, cardiac stress test, and Head MRI.

**Ref:** Mendu [M.L.et](#) al Arch.Intern Med. 2009 July 27; 169 : 1299.

#### 4.18 A pleasant gift after an MI in a non diabetic – Chocolate.

Several studies suggest that chocolate which contain antioxidants, can protect the heart. 1,169 non diabetic patients who were hospitalized with initial non fatal MI were identified. Their food histories for the preceding 12 months and the following 8 years were analysed.

Compared with patients who never ate chocolate, **cardiac mortality** was

1. Reduced by 27% if chocolate was taken once monthly.
2. Reduced by 44% if chocolate was taken weekly.
3. Reduced by 66% if chocolate was taken twice or more times weekly.

Non fatal adverse cardiac events, strokes and total mortality were however not related clearly to chocolate consumption. Consumption of other sweets had no relationship to cardiac mortality.

**Comment:** The most interesting result of the study is that chocolate strongly protected against cardiac mortality but not against adverse cardiac events. The same finding has been reported for Omega 3 fatty acid supplements, which suggest that the primary beneficial effect of both chocolate and Omega 3 fatty acid supplements is in **suppressing arrhythmias**.

**Ref:** Janszky I et al J.Intern.Med.2009 Sept; 266:248.

#### 4.19 New treatment for head lice – Spinosad (S) cream.

Permethrin (P) is commonly applied for head lice. However, increasing resistance to this agent has been noted. S is a fermentation product of soil bacterium that causes CNS paralysis in insects.

391 households with 949 infected cases were randomized to treatment with 1% P cream rinse followed by nit combing and compared with S cream rinse without nit combing. Inspection was done 7 days after treatment was completed and retreatment done if still infected. Lice free status 14 days after the last treatment was assessed. S was significantly more likely to be nit free after one lice treatment (94 vs 68%) and 85% vs 45% 14 days after the last treatment. Both agents can cause ocular hyperaemia and application site irritation and erythema. The latter was commoner with P application.

**Comment:** S does not require nit combing and was more effective than P for treatment of head lice.

**Ref:** Stough D. et al Paediatrics 2009 Sept; 124.

#### **4.20 Treatment of hypertension – should the goal of systolic BP be 140 or 130 mm/Hg ?**

1,111 non diabetic hypertensive patients were randomized to either < 130mmHg or < 140mmHg systolic BP. The trial lasted 2 years. The primary end point was ECG evidence of LVH. More patients in the usual control group < 140mmHg than in the tight control group <130mmHg had new onset LVH (17% vs 11.4%) . Further the usual control group had a higher secondary composite end point of any of 9 adverse clinical cardiovascular outcomes.

**Comment:** According to this study, an aggressive approach to systolic BP reduction can be well tolerated and might lower the incidence of adverse CV outcomes. Patients in this group had at least 1 cardiovascular risk factor in addition to elevated systolic BP. LVH by ECG is not a clinical end point. Larger and longer studies will be required to test this hypothesis in patients at lower baseline risk.

**Ref:** Verdecchia P et al Lancet 2009 Aug 15; 374:525.

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