CEYLON COLLEGE OF PHYSICIANS

MEDICINE UPDATE

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1.1 Is Chronic Idiopathic Urticaria (CIU) an autoimmune disease?.

CIU is defined by the presence of raised itchy lesions of at least 6 weeks duration with no identifiable trigger**.** 50% of them exhibit IgE antibodies or antibodies against IgE receptors on mast cells and basophils.

12,778 patients with CIU were analysed. Hypothyroidism was seen in 10% and hyperthyroidism in 2.6%. Type 1 diabetes, rheumatoid arthritis, celiac disease, lupus and Sjogren syndrome were significantly more common (OR 17.3). Women were significantly at greater risk for developing autoimmune diseases. 80% of the autoimmune diseases developed within 10 years of CIU diagnosis.

Comment: CIU is probably an autoimmune disease. All cases of CIU should be followed up long term to diagnose dangerous autoimmune diseases early. Since we are unable to prevent any of these autoimmune diseases, there is no point in routinely testing for autoimmune markers. However, if signs and symptoms point to the onset of an autoimmune disorder, then testing for the relevant antibodies is in order.

Ref: Confino – Cohen R. et al J.Allergy. Clin. Immunol 2012 May; 129: 1307.

1.2 Neuropsychiatric effects of glucocorticoids (GCs).

370,000 patients in a UK database, who had been exposed to glucocorticoids were compared with 1.2 million patients with similar diseases such as asthma, COPD and polymyalgia, who had not taken steroids. The overall incidence of neuropsychiatric effects that occurred within 3 months of exposure to GCs was 22.2 per 100 person years of exposure. The incidence of adverse effects were 3 fold higher for GC recipients than for non recipients and 4 – 6 fold for **suicidal behavior, mania, delirium or confusion**. The odds ratio for **panic disorder** and **depression** was 1.5. The incidence rose with prior history of neuropsychiatric disorder and with higher dosage of GCs, especially when the dose exceeded the equivalence of prednisolone 40mg daily.

Comment: Clinicians should consider these risks when prescribing GCs.

Ref: Fardet I et al Am.J.Psychiatry 2012 May 1; 169:491.

1.3 Is lumbar disc degeneration an association of obesity?.

Obese patients often complain of low back pain with normal spinal X'rays. This pain recedes after intentional weight loss either by medical means or after bariatric surgery. Sometimes however the pain persists even after weight loss. This may be due to permanent changes in the spine such as disc degeneration.

2,600 individuals (age range 21 – 63) underwent MRI of the lumbar spine. 73% of participants had at least minimal evidence of disc degeneration. The prevalence and severity of this degeneration increased progressively across 4 BMI categories – under weight, Normal weight, over weight and obese. Compared with under weight or normal weight subjects, obese participants were significantly

more likely (OR1.7) to have at least one level of degeneration, with the highest grade of abnormality being multilevel involvement.

Comment: In this cross sectional study, BMI was associated with intervertebral disc degeneration. Therefore obese patients have an elevated risk for chronic low back pain.

Ref: Samartzis D. et al Arthritis Rheum 2012 May; 64: 1488.

1.4 A new treatment for recurrent Urinary Tract Infections (UTIs) in women – Lactobacilli (L).

L can restore normal vaginal flora and thwart colonization by pathogenic bacteria. UTIs especially in females may be caused by invasion from the neighbouring genital tract.

252 post menopausal women with at least 3 symptomatic UTIs in the past year were randomized to either 480mg Cotrimoxazole nightly or standard dose of Lactobacillus rhamnosus and L. reuteri twice daily. The average number of UTIs in the past year for both groups was about 7. During the next 12 months, the number of symptomatic UTIs were decreased to a mean 2.9 in the Cotrim group and 3.3 in the L group. The difference was not statistically significant. Cotrim resistance was 20% at baseline and rose to 80% in one month and to 100% at 12 months.

Comment: Both Cotrim and Lactbacilli decrease the number of recurrent UTIs over one year but resistance rose with Cotrim over the year. There was apparent non inferiority of L treatment vs Cotrim, but the important advantage of L is that it does not cause resistance. L is therefore an acceptable alternative for women with recurrent UTIs, who prefer not to take antibiotics.

Ref: Beerepoot M.A.J. et al Arch Intern Med 2012 May 14; 172:704.

1.5 Antidepressants for Parkinson's Disease (PD).

Patients with PD who also have depression are known to improve after cognitive behavioural therapy(Am.J.Psychiatry 2011 Oct ; 168:1066) and Nortriptyline (Neurology 2009; 72: 886).

115 patients with PD and major depression, Dysthymia or subsyndromal Depression (not dementia) were randomized to initial Paroxetine 10mg/d, Venlafaxine extended release 37.5mg or placebo. The doses of psychiatric drugs were then titrated upwards to a maximum dose of Paroxetine 40mg/d or Venlafaxine ER 225mg/d.

At week 12, all groups demonstrated reductions in the Hamilton Rating Scale for depression – Paroxetine - 13.0, Venlafaxine - - 11.0 and placebo - 6.8. The active drugs were equivalent to each other but statistically superior to placebo.

Comment: Tricyclic antidepressants like Nortriptyline have many side effects. SSRIs like Paroxetine and SSNRIs like Venlafaxine have less side effects. If response to SSRIs and SSNRIs are insufficient, then recourse to Nortriptyline or cognitive behavioural therapy is rational.

Ref: Richard I.H. et al Neurology 2012 Apr 17; 78: 1229.
Friedman J.H. and Weintraub D. IBID : 1198.

1.6 Is Aspirin useful in preventing Recurrent Unprovoked Venous Thrombo Embolism (RUVTE)?.

RUVTE is common after warfarin anticoagulation is stopped after initial treatment of VTE for 3 – 6 months. Warfarin may be restarted and continued for recurrence for many months or even years. The cumulative incidence of serious bleeding in such cases is high. Is aspirin a suitable alternative for such patients?.

Italian researchers identified 403 patients with first symptomatic VTE which was unprovoked. 63% had proximal DVT and 37% had Pulmonary Embolism (PE). After 6 – 18 months of treatment with warfarin, patients were randomized to either aspirin 100mg/d or placebo for 2 years.

The incidence of recurrent VTE was significantly lower in the aspirin group (6.6% for aspirin vs 11.2% for placebo annually, p = 0.02) . The frequency of bleeding events was identical in the two groups. Aspirin afforded protection both to patients whose index event was DVT and to those whose index event was PE.

Comment: For patient with unprovoked VTE, this trial provides persuasive evidence that aspirin lowers the incidence of recurrent VTE **after** conventional warfarin therapy. Aspirin is known to be less effective than warfarin, but bleeding risks are lower with aspirin. Newer oral anticoagulants such as Dabigatran and Rivaroxaban have also been studied for extended maintenance therapy after VTE - but are not yet FDA approved for this purpose.

Ref: Becattini C et al NEJ Med 2012 May 24; 366: 1959.

1.7 Should Probiotics be given along with antibiotics to prevent antibiotic associated diarrhoea (AAD).

Probiotics have been studied for treating and preventing AAD. A new meta analysis of 63 RCTs of probiotic use along with antibiotics was undertaken. The most commonly used probiotics were Lactobacillus and Saccharomyces.

The pooled relative risk for AAD when probiotics were given with antibiotics was 0.58. The NNT to prevent one case of AAD was 13. The results did not differ among age groups.

Comment: The consistent finding of lower risk in every sub group for AAD with probiotic use is striking. The most effective probiotic , optimal dose and duration of therapy was not determined. At a minimum, this therapy does no harm in otherwise healthy people.

Ref: Hempel S. et al JAMA 2012 May 9; 307 : 1959.

1.8 Dietary fats and cognition.

Unhealthy fats viz saturated fats and transfats – promote CVD. Healthy fats viz monounsaturated and polyunsaturated (MUFA and PUFA) prevent CV disease. What about the effect on cognition?.

The Women's Health Study (WHS) studied 6,183 older women with mean age of study entry 66, who provided detailed food histories and underwent repeated cognitive testing (general cognition, verbal memory and semantic fluency) for a period of 4 years.

It was found that higher saturated fat intake was associated significantly with worse global cognitive scores. In contrast, higher MUFA intake was associated with better global cognitive scores. Neither transfat content or PUFA content was associated with altered cognition scores.

Comment: This was not a randomized trial. Therefore the association cannot be considered causal but a RCT of this proportion is unlikely to be conducted. In the meantime recommending greater intake of MUFA in women over the age of 65 is advisable to prevent decline in cognition.

Ref: Okereke O I et al Ann. Neurol. 2012 May 17.

1.9 Which is best birth control method – Intra uterine Devices (IUDs), Implants, Depot Medroxy Progesterone Acetate (DMPA) or combined oral contraceptives (COCs)?.

7,846 women were studied.

1. COC users had failure rates at 1,2 and 3 years = 4.8%, 7.8% and 9.4% resp.
2. IUDs or implant users had failure rates of 0.3%, 0.6% and 0.9% ($p < 0.001$) at the same times resp.
3. DMPA users had similar low rates but only 43% were using them one year later.
4. The adjusted hazard ratio for unintended pregnancy in the COC users compared with IUD or implant users was 21.8.

Comment: IUDs and contraceptive implants appear to be the more successful forms of preventing unwanted pregnancies.

Ref: Winner B et al NEJ Med 2012 May 24; 366 : 1998.

1.10 Do Vitamin and mineral supplements lower cancer risk?.

In a large RPCT, in the US, 14,641 male physicians age > 50 (mean age 64), with relatively healthy life styles, mean BMI 26, 3.6% current smokers were followed up for a period of 11.2 yrs. The randomization was to a commercial multivitamin "Centrum Silver" or placebo. 2,669 incident cancers occurred during this study of which 50% were cases of prostate cancer. Total cancer incidence was lower in the multivitamin group vs placebo (17.6% vs 18.8%, $p = 0.04$). No significant risk reduction was noted for any **specific type** of cancer, **specific mortality,** or **all cause mortality.**

Comment: In this large rigorous trial, multivitamins modestly albeit significantly lowered cancer risk. The participants probably were at lower baseline risk than the general population, so the benefit in the general population might be greater. In addition, duration of follow up of 11.2 years might have been too short to show a mortality benefit. These results certainly will renew patient's enthusiasm for vitamin supplementation and provide another excuse of not adhering to the recommendation to increase vegetable and fruit intake.

Ref: Gaziano J.M. et al The Physicians Health Study, JAMA 2012 Oct 17.

1.11 Fungal meningitis.

An outbreak of fungal infection attributed to contaminated steroids was described in the US in October 2012 when 137 cases and 12 deaths were reported from 10 states. The first case was diagnosed with **Aspergillus fumigatus meningitis** 46 days after epidural steroid injection. Further 8 patients were detected subsequently. All the 9 patients had been injected with a preservative free methyl prednisolone acetate, 4 syndromes were recognized in a further 70 patients.

1. Insidious meningitis with minimal clinical signs.
2. Basilar stroke.
3. Spinal osteomyelitis or epidural abscess.
4. Septic arthritis following joint injection.

Time from last steroid injection to symptom onset ranged from 1 to 42 days (mean 15 days). Patients with meningitis had CSF pleocytosis with a median white cell count of 1,299/mic L, with predominant neutrophils, elevated protein levels and slightly decreased glucose levels. The fungal species identified was mainly Excerohilum spp and A fumigatus. Voriconazole and in some cases Liposomal amphotericin B was used in treatment.

Ref: CDC US MMWR Morb Mortal Wkly Rep 2012 Oct 12; 61: 1.

1.12 In Paroxysmal Atrial Fibrillation (PAF) - which is better – Radio Frequency Ablation (RFA) or Anti Arrhythmic Drugs (AAD)?.

RFA is moderately effective in treating patients with drug refractory AF. However its effectiveness as first line therapy for AF is unclear. In a multicenter, partially Industry supported trial, investigators randomized 294 patients, age <70 with PAF (defined as episodes of AF <7 days in duration) to treatment with RFA or AADs. Patients with left atrial diameter > 50mm and LV ejection fraction < 40% were excluded.

In the ablation group, the mean number of procedures was 1.6. In the AAD group, 36% ultimately underwent RFA. The primary end point of AF burden on 7 day Holter monitoring, did not differ between the two groups except at 24 months, when the burden was significantly lower in the ablation group. Symptom reduction and improvement in physical well being at 24 months was also

better in the RFA group. Serious adverse events did not differ significantly between the groups but included one procedure related death in the ablation group (1 out of 147).

Comment: In 2 year outcomes, the results of initial ablation was roughly equivalent to those on AADs. This cohort is highly selected and the results cannot be extrapolated to other types of patients who were excluded from randomization.

Ref: Nielsen J.C. et al NEJ Med 2012 Oct 25; 367: 1587.
Stevenson W.G. and Albert C.M. IBID : 1648.

1.13 Which is better for urgency incontinence – anticholinergic agents or Botulinum toxin?.

In a DB PCT, Federally funded investigators randomized women with urgency incontinency to either an oral anticholinergic agent – Solifenacin or a single cystoscopically delivered 100 unit injection of Ona Botulinum toxin A to the detrusor muscle. The initial 5 mg daily dose of Solifenacin was up titrated to 10mg and then changed to 60mg Trospium XR as needed. Incontinence episodes were assessed for 6 months, when oral medications were stopped. The mean daily incontinence episodes was 5.0 before treatment and the mean reduction in daily episodes was 3.4 and 3.3 resp for Solifenacin and Botulinum groups. Women assigned to Botulinum were more likely to report complete resolution of incontinence (27% vs 13% p = 0.003). Dry mouth was reported significantly more often in the Solifenacin group. Intermittent catheterization was recommended for Botulinum women in 3% at 4 months and 1% at 6 months. Urinary tract infections were more common in the Botulinum group.

Comment: Since anti cholinergic therapy has a benign adverse effect profile and Botulinum toxin has a need for cystoscopic administration and may require intermittent catheterization and has more UTIs – anti cholinergics are a sensible first line therapy for urgency incontinence. Botulinum injections may be reserved for women in whom anti cholinergics are ineffective, contraindicated or associated with intolerable adverse effects.

Ref: Visco A.G. et al N.E.J.Med 2012 Nov 8; 367: 1803.

1.14 What is the natural history of "migrainous vertigo" (MV) also called "Vestibular migraine"?.

The diagnostic criteria for MV include episodic vertigo plus migrainous symptoms such as headache, photophobia, phonophobia and visual auras during the vertigo attack.

During a follow up of 61 patients (54 women) for a mean 9 years – 87% were still symptomatic at the end of the follow up period, with attacks ranging from minutes to hours. Over time, the frequency of vertigo attacks decreased but headaches usually continued. Half of the patients had cochlear symptoms also such as tinnitus and aural fullness during the spells of vertigo and 77% had cochlear symptoms between spells. 28% had positional nystagmus. A few patients had peripheral vestibular symptoms such as vomiting and 50% exhibited high frequency hearing loss.

Comment: The differential diagnosis include Meniere's disease, vertebrobasilar transient ischaemic attacks and benign positional vertigo. None of these conditions have the headache of MV. Treatment of MV is the same as for any other attack of migraine**.**

Ref: Radtke A. et al Neurology 2012 Oct 9; 79: 1607.

1.15 What is the best initial treatment for early rheumatoid arthritis (RA)?.

In a 2 year manufacturer supported study, 755 patients with early RA were randomized to 4 treatment groups.

1. Methotrexate + Etanercept.
2. Oral triple therapy with Methotrexate + Hydroxy chloroquine + Sulphasalazine.
3. Methotrexate mono therapy with step up at 24 weeks + Etanercept.
4. Methotrexate monotherapy with step up at 24 weeks with oral triple therapy (2)

The end point was a standard disease activity score at base line and at weeks 48 to 102.

At week 24, both groups 1 and 2 had significantly better end point scores than the monotherapy Methotrexate groups 3 and 4. However between weeks 48 and 102, the disease activity score was the same in all 4 groups. The radiological study showed more improvement in the Etanercept groups 1 and 3 but did not reflect better clinical response.

Comment: Etanercept groups had better radiological improvement which was statistically significant but the clinical responses were the same. Since groups 2 and 4 are oral agents and are relatively cheap, these may be the better initial therapy in developing countries.

Ref: Moreland L.W. et al Arthritis Rheum 2012 Sept; 64: 2824.

1.16 Faecal occult blood testing (FOBT).

FOBT can be done by the Guaiac method (GM) or by the immuno chemical method(ICM). Their relative sensitivity and specificity in the detection of colorectal cancer and advanced adenoma was studied in 1,256 patients before they underwent screening colonoscopy.

Colonoscopy identified 0.6% with colorectal cancer and 9% with adenomas. At a cutoff value of 50ng/ml the ICM was positive in 10% of patients with a sensitivity and specificity of 38% and 93% resp for detecting advanced adenoma. The sensitivity was 88% and specificity was 91% for detection of colorectal cancer. The ICM detected proximal and distal colonic advanced neoplasia with equal sensitivity.

Comment: According to these findings, if patients were screened initially with a **single** ICM, most localized cancers and about 1/3rd of advanced adenomas would be detected and 90% of those who were negative would avoid colonoscopy. Annual ICM FOBT is atleast as cost effective as

colonoscopy every 10 years. However 30% of colorectal cancers arise through a genetic pathway characterized by hypermethylation. The precursors of these cancers are usually called sessile serrated adenomas and are located primarily in the proximal colon, have no vessels on their surface and may not bleed at all. Therefore FOBT will be negative. For these patients, **faecal DNA testing** rather than ICM is the preferred method. In other words, both ICM and faecal DNA testing will be the way forward to detect these adenomas and carcinomas.

Ref: de Wijkerslooth T.R. et al Am.J.Gastroenterol 2012 Oct; 107:1570.

1.17 The timing of cholecystectomy in patients with gall stone pancreatitis.

Traditionally surgeons perform cholecystectomy in patients with **mild** gall stone pancreatitis, after several days. However recently, researchers randomized 50 patients to early cholecystectomy (within 48 hrs) or delayed cholecystectomy and found that early procedure was safe.

Now, the same research group conducted a retrospective study of surgery timing in 303 patients at 2 medical centers. Patients with suspected cholangitis, marked dehydration or persistent common bile duct stones were excluded. The median length of hospital stay was significantly shorter in those who were operated within 48 hrs of admission than in those in the delayed group (3 vs 6 days). Complication and readmission rates were similar. No deaths occurred.

Comment: Physicians who diagnose mild gall stone pancreatitis should refer such patients to surgeons promptly.

Ref: Falor A.E. et al Arch. Surg. 2012 Nov; 147: 1031.

1.18 A new treatment for the constipation of irritable bowel syndrome (IBS) – Linaclotide (L).

L was recently FDA approved for 2 indications viz chronic idiopathic constipation and IBS constipation. The drug is minimally absorbed and acts by increasing intestinal luminal fluid secretion and intestinal transit.

Researchers have published the results of 2 trials in which 1,600 patients (90% women) with IBS constipation were randomized to receive 290 mcg of daily L or placebo. Enrollment criteria included a score of atleast 3 on a 10 point scale for daily abdominal pain, and an average of <3 spontaneous bowel movements weekly.

The combined primary end point of a 30% improvement in the abdominal pain score + > one additional complete spontaneous bowel movement weekly was seen more significantly frequently in the L recipients compared to placebo – in the first 12 weeks (34% vs 21%) and (34% vs 14%) in the first 26 weeks. Diarrhoea occurred in 20 % vs 3% in both the 12 weeks and 26 weeks trial. 5% of L recipients withdrew from the trials.

Comment: Linaclotide clearly improves symptoms in some patients with IBS – constipation but the modest differences between the L vs Placebo recipients means that 5-8 patients had to be treated to benefit one patient. The drug will be costly initially, and its cost effectiveness thus diminished.

Ref: Chey W.D. et al Am.J.Gastroenterol 2012 Nov; 107: 1702.

1.19 A new test for C. difficile infections – PCR assays.

Diagnosis of C.difficile infections has been hitherto been done by the enzyme immuno assay (EIA) method. Nowadays the polymerase chain reaction (PCR) assay has become more popular, because it is more reliable and has a better sensitivity of 50 – 80%. In those who are negative for PCR whose symptoms persist, it is reasonable to repeat the test in the next 14 days but the yield was low (3 – 5%).

Comment: PCR testing for C.difficile is reliable and generally does not require repetition.

Ref: Khanna S et al J.Clin. Gastroenterol. 2012 Nov/Dec; 46: 846.

1.20 Are steroids effective for dengue fever (DF)?.

Dengue's feared complication is dengue shock syndrome (DSS), vasculopathy, thrombocytopaenia, coagulopathy – all of which are atleast partly immune mediated. Would steroids help prevent DSS?.

Vietnamese researchers randomized 225 patients (age 5 – 20) with newly diagnosed DF to 3 days of low dose (0.5mg/Kg) or high dose (2mg/Kg) oral prednisolone or placebo. Neither steroid dose affected the incidence of DSS , need for intensive care unit admission, platelet count, or any other relevant clinical end point. Hyperglycaemia was somewhat more common in the high dose steroid group than in the other groups. All patients survived.

Comment: Even though steroids in early DF is expected to lower complication rate, they apparently do not. Whether they are effective or not when initiated at the onset of DSS was not studied.

Ref: Tam D.T.H. et al Clin. Infect. Dis. 2012 Nov 1; 55: 1216.

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